Determinants of health-related quality of life in a multinational systemic sclerosis inception cohort

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ABSTRACT

Objective. *To evaluate health-related quality of life (HRQoL) and its determinants in a systemic sclerosis (SSc) multinational inception cohort. We performed a meta-analysis of data from individual countries, and compared the meta-analysis to individual country results by pooling data from each of the countries.*

Methods. *SSc patients within 2 years of disease onset were recruited from 5 countries participating in the International Systemic Sclerosis Inception Cohort (INSYNC). Data from each country's database were exported for analysis using a harmonised platform. HRQoL was assessed using the Medical Outcomes Short Form-36 (SF-36). Multivariate linear regression assessed associations between HRQoL and predictors in cohorts separately and meta-analysed to generate pooled estimates. The analyses were repeated using individual patient data.*

Results. *Of the 637 SSc patients recruited, the majority was female (80.2%-83.3%), aged between 52.4-56.7 years with limited cutaneous disease subtype (48.6%-66.7%). HRQoL scores were lower for SSc patients than the general population (SF-36 physical component summary (PCS) score (36.4-39.6), mental component summary (MCS) score (41.0-46.4)). Determinants of SF-36 PCS by meta-analysis included increasing age (β=-0.1, 95%CI -0.2, -0.01), diffuse cutaneous disease subtype (β=-8.4, 95%CI -10.6, -6.3), and pulmonary arterial hypertension (β=-10.9, 95%CI -16.6, -5.3). Increasing age (β=0.09, 95%CI 0.0, 0.18) was the only variable associated with SF-36 MCS. Analyses using individual patient data revealed similar results to those of the meta-analysis of cohort data.*

Conclusion. *Our study provides estimates of HRQoL in a large inception SSc cohort and provides evidence that individual patient data analysis is valid in the INSYNC dataset.*

Introduction

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease characterised by vasculopathy and excessive collagen production leading to skin and internal organ fibrosis (1). It is commonly classified into two distinct subtypes based on the degree of skin fibrosis, namely limited (lcSSc) and diffuse cutaneous (dcSSc) subsets.

The heterogeneous nature of SSc is highlighted by its protean clinical manifestations including sclerodactyly, synovitis, joint contractures, Raynaud's phenomenon, digital ulceration, gastroesophageal reflux disease, renal insufficiency, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Morbidity and irreversible organ damage in SSc can occur early within the first two years of disease onset (2) causing significant functional limitation, which impact on employment, self-care and completion of household tasks (3, 4). Furthermore, SSc is associated with an altered physical appearance, pain and psychological consequences including depression, anxiety and diminished health-related quality of life (HRQoL) (5-7).

Despite an improvement over the last three decades, morbidity and mortality in SSc remain high with an age- and sex-adjusted standardised mortality ratio (SMR) of 4.06 for newly diagnosed SSc patients (8). These parameters, however, are not sufficient to capture the disease as experienced by patients and for this reason, more attention has been focused on patient reported outcomes such as HRQoL. SSc treatment

focuses to a large extent on addressing HRQoL by reducing symptoms and disability. In order to improve HRQoL, we must first determine the key drivers of poor HRQoL in SSc.

The literature to date indicates that SSc patients experience poor HRQoL, well below that of the general population and on par or lower than other chronic conditions, including rheumatic conditions (2, 9, 10). For example, SSc patients with joint involvement have poorer functional scores measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI) than patients with psoriatic arthritis and higher visual analog scale pain scores than rheumatoid arthritis (11).

However, studies assessing HRQoL in SSc have been performed in prevalent SSc patient cohorts. Therefore, this burden may be underestimated by survival bias whereby patients who survive the early years of disease are more likely to have better functional outcomes. No study has evaluated HRQoL in an inception SSc cohort where patients are recruited close to disease onset, allowing quantification of the impact of disease early in the course, before adaptation and acceptance of disability has occurred.

The International Systemic Sclerosis Inception Cohort (INSYNC) study was established in 2014 in order to facilitate multinational research in incident SSc. Currently, six countries are contributing data (Canada, Australia, Spain, Netherlands, Sweden and USA). Each country has harmonised its data collection thereby reducing any differences in variable categorisation. Harmonisation also occurs on data export making INSYNC the first harmonised data collection platform in SSc.

The purpose of this study was twofold: (i) to evaluate HRQoL and its determinants in a large multi-national study of SSc patients recruited within two years of their disease onset using meta-analysis of cohort data, and (ii) to compare results of the meta-analysis to results of individual patient data analysis.

Methods

Study design and patient cohorts

Subjects from the Australian Scleroderma Cohort Study (ASCS), the Canadian Scleroderma Research Group (CSRG) cohort study, the Leiden Combined Care In Systemic Sclerosis cohort (Leiden CCIS cohort), Spain (the Hospital Universitario 12 de Octubre of Madrid Scleroderma Cohort) and Sweden (The Systemic sclerosis cohort at the Rheumatology Unit, Skane University Hospital, Lund) were included. US data from a single centre in Utah was not included because SF-36 data is not collected in that cohort. The ASCS is a multi-centre study of risk and prognostic factors for cardiopulmonary outcomes in SSc established in 2007, and is approved by the human research ethics committees of all participating Australian centres. Subjects in the CSRG are recruited from 15 sites across Canada. They must have a diagnosis of SSc verified by a rheumatologist according to ACR/EULAR classification criteria and be fluent in English or French. Over 98% of the CSRG cohort meets the 2013 ACR/EULAR classification criteria for SSc (12). Ethics committee approval for the CSRG was obtained at McGill University (Montreal, Canada) and at all participating CSRG sites. The Leiden CCIS cohort is a prospective cohort study established in 2009 enrolling SSc patients within 2 years of disease onset and each participating in an annual comprehensive care program. The ethics committees of all participating Dutch centres approve the Leiden CCIS. The SSc cohort study in Lund, Sweden recruited SSc patient who fulfilled the ACR classification criteria for SSc (13) and provided written consent to participate. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the regional ethical committee in Lund. Ethics committee approval for the Spanish cohort was obtained at Hospital Universitario 12 de Octubre (Madrid, Spain).

All patients provide written informed consent to participate at recruitment. No specific treatment algorithm was used in the five cohorts and subjects were followed up at least once a year.

International Systemic Sclerosis Inception Cohort (INSYNC) harmonised platform

Variables from each study cohort were harmonised to ensure consistency in the merged dataset. The process of harmonisation involved mapping variables in each study cohort. Investigators from all cohorts then met multiple times to confer in person and by teleconferencing about how to transform existing variables into common INSYNC variables. The harmonised dataset is hosted on the REDCap platform (Vanderbilt University, Nashville Tennessee).

Inclusion and exclusion criteria

The INSYNC cohort includes adult (≥18 years) SSc subjects who had at least one visit in the ASCS between January 2007 and March 2016, in the CSRG cohort between January 2005 and March 2016, in the Dutch cohort between September 2009 and September 2015, in the Spanish cohort between January 2000 and March 2016 and in the Swedish cohort between January 2010 and May 2011. All patients were recruited within two years of onset of their first non-Raynaud symptom attributable to SSc.

Outcome measure

The Medical Outcome Short Form-36 (SF-36) is a validated instrument for measuring HRQoL in SSc (11). It consists of a 36-item scale, which measures eight domains of health status including physical functioning, role limitation because of physical health problems, bodily pain, social functioning, general mental health, role limitations because of emotional problems, vitality and general health perceptions (14). These eight domains can be summarised into a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score. A final score for each domain is provided between 0-100, with 0 being the worst possible health and 100 the best possible health. The score is standardised against normative population data, where the mean score ± SD of 50±10 is the population normative score. A score above 50 indicates better HRQoL than the normative general population, while a score below 50 indicates worse HRQoL than the normative general population, and each 10 points represents one standard deviation (11). SF-36 scores from baseline study visits were considered the outcome of interest.

Definition of disease manifestations
Patient demographics, clinical variables, autoantibodies, cardiac and pulmonary assessments were obtained from each country's respective database at the baseline study visit. Sex, age, ethnicity, tertiary education and employment status were patient reported at enrolment. Tertiary education was classified as yes if any further education following the successful completion of secondary school was completed. Patients were considered employed if they were working part- or full-time at baseline study visit. Clinical manifestations were physician-reported and defined as present if present ever from the onset of SSc. Extent of skin involvement was determined using the modified Rodnan skin scores (mRSS), a widely used clinical assessment where the examining physician records the degree of skin thickening ranging from 0 (no involvement) to 3 (severe thickening) in 17 areas (total score range 0–51). Physician classification of patients into lcSSc and dcSSc was confirmed by reviewing recorded mRSS scores. lcSSc was defined as skin involvement distal to the elbows and knees with or without facial involvement; dcSSc was defined as skin involvement proximal to the elbows and knees, with or without truncal involvement. Pulmonary involvement was assessed by pulmonary function tests (PFTs), high-resolution computer tomography (HRCT) lung, chest radiograph and/ or physical examination findings of bilateral fine pulmonary crackles. PAH was diagnosed on right heart catheterisation (RHC) according to international criteria (15). In the absence of a consensus definition for scleroderma renal crisis, physician reports were used as the surrogate. Gastrointestinal tract (GIT) involvement included the presence of any of reflux oesophagitis and/or oesophageal stricture on endoscopy, bowel dysmotility defined on barium and/or nuclear medicine studies, antibiotic response to diarrhoea and/or foecal incontinence. Musculoskeletal (MSK) manifestations were defined as the presence of any one of the following variables: synovitis, joint contractures and tendon friction rub.

Global disease activity, damage and severity were measured using physician-rated estimates on scales ranging from 0-10, with 0 being no activity/damage/severity and 10 being very severe activity/damage/severity (16).

Statistical analysis
Baseline characteristics are presented using summary statistics (mean ± standard deviation (SD) for continuous variables and as number (percentage) for categorical variables). Associations between SF-36 and predictors of interest were assessed by multivariate linear regression in the cohorts separately, and then meta-analysed to generate pooled estimates. The dependent variables were the SF-36 PCS and MCS. We investigated the following independent predictors: age, gender, race, disease subset (diffuse *vs*. limited), PAH and interstitial lung disease (ILD). Additional sub-group analyses including gastrointestinal (GIT) manifestations, employment status and tertiary education were performed using the Australian and Canadian patients as these variables were not available from the other cohorts. Between-cohort heterogeneity was evaluated by Q-test (p-value <0.05 indicating heterogeneity) and I^2 statistics (0–40%: heterogeneity might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity) (17). The analyses were repeated using individual patient data, instead of meta-analysis of cohort level data. Results obtained from meta-analysis of cohort data were visually compared to results of individual patient data analysis. Two-tailed p-values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SAS 9.4 and R 3.2.0

Results

Patient characteristics
A total of 637 SSc patients were recruited within two years of their SSc disease onset and were included in this study. Of these, 294 were Canadian, 203 were Australian, 105 were Dutch, 29 were Spanish and 6 were Swedish. The majority of patients were female (80.2–83.3%), white (83.3–100%), had lcSSc (48.6–66.7%) and were aged between 52.4–56.7 years. Patient characteristics and clinical manifestations are summarised in Table I. Interestingly, the frequency of ILD varied by country with the lowest frequency in Australian SSc patients (21.6%) and the highest frequency in Swedish SSc patients (50.0%). The frequency of PAH, according to international criteria (15), was similar among SSc patients in Canada (2.9%), Australia (4.9%), the Netherlands (3.8%) and Spain (3.5%). It was higher in Sweden (16.7%), but this was based on only 1 of 6 patients. Using physician reported global assessments ranging from 0-10, patients had moderate disease activity (range 4.0–5.3), disease damage (range 3.1–3.6) and disease severity (range 3.7–4.8).

HRQoL and its determinants
Regardless of the country of origin, the mean HRQoL scores for all SSc patients were lower than the general population normative scores of 50 (± 10). This was particularly evident for the SF-36 physical component summary (PCS) score, which ranged from 36.4–39.6. This represents, on average, 1.0 to 1.5 standard deviation lower scores compared to the general population. Impairments of similar magnitude were reported in several domains of physical status, notably physical function (36.0–41.4), role physical (32.5–42.5) and general health (36.5–38.8). The SF-36 mental component summary (MCS) score was also consistently lower than the general population normative score ranging from 41.0-46.4. SF-36 scores are summarised in Table II.
Determinants of SF-36 PCS and SF-36 MCS using multivariable linear regression was performed separately in all cohorts except the Swedish cohort, which had insufficient data for this set of analyses. Results are summarised in Table III. The presence of dcSSc was a determinant of worse SF-36 PCS in Canadian, Australian and Dutch patients (β ranging from -6.8 (95% CI -11.8, -1.7) to -12.5 (95% CI -17.3, -7.6)), but not in the Spanish patients (β=-3.3, 95% CI –15.9, 9.4). The

Table I. Patient characteristics by study cohort (n=637).

Variables	CSRG (n=294)		ASCS (n=203)		Netherlands (n=105)		Spain (n=29)		Sweden (n=6)	
	n (%) or Mean (SD)	NA	n (%) or Mean (SD)	NA	n (%) or Mean (SD)	NA	n (%) or Mean (SD)	NA	n (%) or Mean (SD)	NA
Female, %	239 (81.3%)	0	162 (80.2%)	1	86 (81.9%)	0	24 (82.8%)	0	5 (83.3%)	0
Age, years	54.5 (12.5)	0	53.5 (13.7)	3	53.5 (15.9)	0	52.4 (13.9)	0	56.7 (13.0)	0
White	229 (86.4%)	29	179 (91.8%)	8	85 (83.3%)	3	27 (93.1%)	0	6 (100%)	0
Diffuse subtype, %	151 (51.4%)	0	91 (44.8%)	0	29 (27.6%)	0	11 (37.9%)	0	2 (33.3%)	0
Modified Rodnan skin score (0-51)	14.4 (11.8)	3	13.0 (11.4)	17	6.4 (7.9)	0	12.4 (13.1)	0	7.0 (4.9)	0
ILD, %	89 (30.6%)	3	41 (21.6%)	13	50 (47.6%)	0	9 (31.0%)	0	3 (50.0%)	0
PAH, %	8 (2.9%)	13	10 (4.9%)	0	4 (3.8%)	0	1 (3.5%)	0	1 (16.7%)	0
SRC, %	19 (6.5%)	1	5 (2.6%)	7	2 (1.9%)	0	0	0	0	0
Global severity (0-10)	3.7 (2.4)	2	4.1 (2.3)	108	-	-	4.8 (2.8)	0	-	-
Global activity (0-10)	4.0 (2.6)	2	4.2 (2.3)	107	-	-	5.3 (3.1)	0	-	-
Global damage (0-10)	3.6 (2.5)	2	3.5 (2.0)	108	-	-	3.1 (2.8)	0	-	-
GIT manifestations*	211 (71.8%)	0	96 (47.3%)	0	-	-	-	-	-	-
Tertiary education	132 (49.8%)	29	81 (48.8%)	37	-	-	-	-	-	-
Employment	139 (52.1%)	27	105 (53.3%)	6	-	-	-	-	-	-
Antinuclear Antibody, %	178 (96.2%)	109	187 (94.9%)	6	-	-	-	-	-	-
Anti-centromere, %	70 (30.2%)	62	67 (34.4%)	8	-	-	-	-	-	-
Anti-topoisomerase, %	46 (19.8%)	62	42 (21.7%)	9	-	-	-	-	-	-
Anti-RNA polymerase III, %	57 (24.6%)	62	28 (20.4%)	66	-	-	-	-	-	-
Musculoskeletal involvement	191 (65.0%)	0	104 (51.2%)	0	-	-	-	-	-	-
Raynaud's phenomenon	275 (94.5%)	3	201 (99.0%)	0	-	-	-	-	-	-
Digital ulcers	20 (6.8%)	0	54 (27.4%)	6	-	-	-	-	-	-

ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; NA: non applicable; SD: standard deviation; CI: confidence interval; NA: not available; n: patient number (n).
*differences in frequency of GIT manifestations between groups may be due to the definition of oesophageal involvement requiring endoscopy in the ASCS cohort.

Table II. HRQoL determined by SF-36 domain and summary scores according to study cohort.

SF-36 domains	CSRG (n=294)		ASCS (n=203)		Netherlands (n=105)		Spain (n=29)		Sweden (n=6)	
	Mean (SD)	NA	Mean (SD)	NA	Mean (SD)	NA	Mean (SD)	NA	Mean (SD)	NA
Physical function	36.0 (12.6)	29	37.8 (12.6)	85	39.4 (12.2)	1	39.5 (15.7)	0	41.4 (13.0)	0
Role physical	38.2 (12.7)	28	32.5 (15.6)	85	40.3 (11.8)	3	42.5 (12.4)	0	34.7 (11.0)	0
Bodily pain	42.5 (10.3)	28	44.7 (11.8)	85	41.2 (11.0)	3	43.1 (13.1)	0	46.8 (11.8)	0
General health	38.8 (10.8)	28	38.1 (10.7)	86	36.5 (10.1)	1	37.2 (8.5)	0	37.4 (11.9)	0
Vitality	43.5 (10.8)	28	41.9 (11.8)	84	38.1 (10.6)	1	39.9 (15.1)	0	35.2 (19.9)	0
Social function	42.1 (12.6)	28	41.4 (11.1)	88	40.1 (12.8)	3	41.0 (15.1)	0	43.2 (11.0)	0
Role emotional	41.9 (13.6)	28	37.5 (18.0)	83	44.9 (13.2)	5	43.9 (13.7)	0	36.8 (14.9)	0
Mental Health	46.1 (11.9)	28	44.4 (11.2)	84	44.1 (10.8)	1	43.3 (13.4)	0	47.6 (9.7)	0
PCS	36.9 (11.4)	28	37.7 (13.3)	93	38.4 (11.5)	7	39.6 (12.9)	0	36.4 (6.3)	0
MCS	46.6 (12.4)	28	43.7 (12.9)	93	44.2 (12.2)	7	43.7 (15.3)	0	41.0 (12.4)	0
Pooled PCS (95% CI)					37.6 (36.5, 38.7)					
Pooled MCS (95% CI)					44.9 (43.2, 46.6)					

SF-36 scores scores range from 0-100. Scores below 50 indicate worse HRQoL than the population normative score and every 10 points indicates 1 standard deviation.
PCS: physical component score; MCS: mental component score; SD: standard deviation; NA: not available; n: patient number.

presence of PAH was a determinant of worse SF-36 PCS in all four cohorts, and this was statistically significant in the Canadian (β=-8.1, 95% CI -15.7, -0.4) and Australian (β=-15.4, 95% CI -26.5, -4.3) cohorts. White race was associated with better SF-36 PCS scores in Dutch patients only (β=-6.9, 95% CI 0.9, 12.9). In the Canadian cohort, ILD was the only statistically significant predictor of SF-36 MCS (β=-3.5, 95% CI -6.9, -0.1).

Meta-analysis

We undertook a meta-analysis to generate pooled estimates of the determinants of SF-36 PCS and MCS (Table IV). Older age had a small but significant negative effect on SF-36 PCS (β=-0.1, 95%CI -0.2, -0.01). dcSSc (β=-8.4, 95%CI -10.6, -6.3) and PAH (β=-10.9, 95%CI -16.6, -5.3) had large and significant negative effects on SF-36 PCS. Other variables including female gender, ethnicity and ILD had small effects and were not independent determinants of SF-36 PCS (Table IV). All of the variables examined had small effects, but only older age (β=0.09, 95%CI 0.0, 0.18) reached statistical significance as

Table III. Correlates of SF-36 PCS and SF-36 MCS determined by multivariable linear regression models.

PCS	CSRG (n=251)		ASCS (n=100)		Netherlands (n=96)		Spain (n=29)	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI))	*p*-value
Age	-0.1 (-0.2, 0.1)	0.16	-0.1 (-0.3, 0.1)	0.16	-0.1 (-0.2, 0.1)	0.45	-0.2 (-0.6, 0.2)	0.29
Female	0.1 (-3.4, 3.6)	0.95	-1.1 (-6.9, 4.8)	0.71	3.7 (-2.3, 9.6)	0.22	2.6 (-11.3, 16.5)	0.70
White	-0.5 (-4.4, 3.4)	0.79	2.4 (-8.3, 13.2)	0.66	6.9 (0.9, 12.9)	0.02	1.5 (-17.7, 20.8)	0.87
Diffuse subtype	-7.9 (-10.7, -5.2)	<0.001	-12.5 (-17.3, -7.6)	<0.001	-6.8 (-11.8, -1.7)	0.01	-3.3 (-15.9, 9.4)	0.59
PAH	-8.1 (-15.7, -0.4)	0.04	-15.4 (-26.5, -4.3)	0.01	-14.8 (-30.3, 0.8)	0.06	-8.2 (-35.5, 19.2)	0.54
ILD	0.2 (-2.8, 3.1)	0.91	-0.4 (-6.2, 5.4)	0.89	-2.1 (-6.6, 2.5)	0.36	-9.3 (-22.6, 4.0)	0.16
MCS	CSRG (n=251)		ASCS (n=100)		Netherlands (n=96)		Spain (n=29)	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI))	*p*-value
Age	0.1 (-0.1, 0.2)	0.18	0.1 (-0.1, 0.3)	0.57	0.1 (-0.1, 0.3)	0.16	-0.1 (-0.5, 0.4)	0.79
Female	-2.8 (-6.8, 1.2)	0.17	0.1 (-6.6, 6.7)	0.98	-3.3 (-10.3, 3.6)	0.34	5.0 (-12.7, 22.8)	0.56
White	2.5 (-2.1, 7.0)	0.29	-8.8 (-21.0, 3.4)	0.16	2.8 (-4.2, 9.7)	0.43	-0.9 (-25.5, 23.8)	0.94
Diffuse subtype	-0.4 (-3.6, 2.8)	0.79	2.5 (-3.0, 8.0)	0.37	-5.2 (-11.0, 0.7)	0.08	3.2 (-13.0, 19.4)	0.69
PAH	3.9 (-5.0, 12.8)	0.39	-7.7 (-20.4, 5.0)	0.23	0.6 (-17.4, 18.6)	0.95	24.5 (-10.5, 59.5)	0.16
ILD	-3.5 (-6.9, -0.1)	0.05	4.3 (-2.3, 10.9)	0.19	-1.2 (-6.5, 4.0)	0.72	5.9 (-11.1, 22.9)	0.48

ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; CI: confidence interval.

an independent predictor of SF-36 MCS. We obtained highly consistent results to those of the meta-analysis after pooling individual patient data (Table V).

Subgroup analysis

The presence and impact of Raynaud's phenomenon (RP), digital ulceration (DU), MSK and GIT manifestations, employment status and tertiary education on HRQoL were further evaluated in the Australian and Canadian SSc patients as these data were not available from the other cohorts.

In a meta-analysis of Australian and Canadian cohort data (Table VI), dcSSc (β=-6.6, 95%CI -9.0, -4.2), PAH (β=-8.6, 95%CI -14.6, -2.7), GIT manifestations (β=-4.1, 95%CI -6.6, -1.6), and MSK manifestations (β=-4.6, 95%CI -7.1, -2.2) were important predictors of worse SF-36 PCS. In addition, remaining in employment was protective of SF-36 PCS (β=6.7, 95%CI 9.1, 4.3). Of all the variables evaluated, only the presence of MSK manifestations (β=-3.5, 95%CI -6.6, -0.5) was significantly associated with SF-36 MCS. Again, we obtained highly consistent results to those of the cohort meta-analysis after pooling individual Canadian and Australian patient data (Supplementary Table I).

Table IV. Meta-analysis of determinants of HRQoL in SSc patients using cohort-level data.

PCS	β (95% CI)	Q-test	I^2 (CIs)
Age	-0.09 (-0.16, -0.01)	0.8545	0% (0%, 41.0%)
Female	0.65 (-1.94, 3.25)	0.6714	0% (0%, 70.3%)
White	1.77 (-1.29, 4.84)	0.2344	29.6% (0%, 74.3%)
Diffuse subtype	-8.44 (-10.55, -6.33)	0.2661	24.2% (0%, 88.4%)
PAH	-10.94 (-16.59, -5.29)	0.6910	0% (0%, 68.6%)
ILD	-0.77 (-2.99, 1.46)	0.4762	0% (0%, 81.6%)
MCS	β (95% CI)	Q-test	I^2 (CIs)
Age	0.09 (0.0, 0.18)	0.8897	0% (0%, 27.0%)
Female	-2.04 (-5.06, 0.97)	0.7126	0% (0%, 66.5%)
White	1.39 (-2.41, 5.18)	0.3683	4.9% (0%, 85.4%)
Diffuse subtype	-0.59 (-3.05, 1.85)	0.2720	23.2% (0%, 88.2%)
PAH	1.04 (-5.52, 7.61)	0.2390	28.9% (0%, 73.8%)
ILD	-1.44 (-4.02, 1.14)	0.1597	42.0% (0%, 80.5%)

ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; CI: confidence interval.

Discussion

This is the first study to collect and analyse harmonised multinational data to further our understanding of disease characteristics and patient reported outcomes in incident SSc. The pooling of inception cohort data among countries is particularly important for facilitating research in rare diseases such as SSc. Data from different countries is not always collected in the same way. Our results demonstrate that pooling multinational harmonised data is a valid method of analysing INSYNC data. In addition, the results of the meta-analysis were consistent with those of pooled individual patient data, suggesting that the latter analytical approach is valid in this setting.

Furthermore, by combining multinational data we were able to highlight the exceptionally poor HRQoL reported by patients living with incident SSc in five different countries. Our mean SF-36 PCS for an inception SSc cohort ranged between 36.4-39.6, which is, on average, 1.0-1.5 standard deviations below that of the general population. SSc patients living in Sweden had the lowest reported SF-36 PCS, followed closely by those living in Canada, Australia, the Netherlands and Spain (36.4, 36.9, 37.7, 38.4, 39.6 respectively). Our SF-36 PCS is lower than the SF-36 PCS of 43.3±23.4 found in a recent large international study assessing HRQoL in SSc patients with a mean disease duration of 13±12 years (18), but consistent with the pooled SF-

Table V. Correlates of HRQoL in SSc patients determined by multivariable linear regression in pooled individual patient data.

Variables	SF-36 PCS		SF-36 MCS	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Age	-0.1 (-0.2, 0.0)	0.01	0.1 (0.0, 0.2)	0.05
Female	0.8 (-1.7, 3.4)	0.53	-1.6 (-4.6, 1.4)	0.29
White	1.5 (-1.6, 4.5)	0.34	0.6 (-2.9, 4.2)	0.72
Diffuse subtype	-8.4 (-10.4, -6.4)	<0.001	0.3 (-2.1, 2.7)	0.82
PAH	-10.1 (-15.5, -4.7)	<0.001	2.0 (-4.4, 8.4)	0.53
ILD	-1.2 (-3.4, 0.9)	0.27	-1.0 (-3.6, 1.4)	0.39

PCS: physical component score; MCS: mental component score; GIT: gastrointestinal; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; CI: confidence interval.

Table VI. Meta-analysis of determinants of HRQoL in Canadian and Australian SSc patients using cohort-level data.

Outcome PCS	β (95% CI)	Q-test	I^2
Age	0 (-0.10, 0.10)	0.7039	0%
Female	0.14 (-2.70, 2.99)	0.9762	0%
White	-2.12 (-5.66, 1.43)	0.6533	0%
Diffuse subtype	-6.59 (-9.02, -4.16)	0.4731	0%
PAH	-8.61 (-14.52, -2.69)	0.7221	0%
ILD	-0.01 (-2.51, 2.50)	0.8054	0%
GIT manifestations	-4.09 (-6.61, -1.57)	0.6056	0%
Tertiary Education	0.77 (-1.59, 3.13)	0.6802	0%
Employment	6.69 (4.26, 9.11)	0.1834	43.5%
Musculoskeletal involvement	-4.63 (-7.07, -2.19)	0.7301	0%
Raynaud's phenomenon	0.96 (-4.21, 6.12)	0.9073	0%
Digital ulcers	-2.35 (-6.16, 1.47)	0.8716	0%
Outcome MCS	**β (95% CI)**	**Q-test**	**I^2**
Age	0.12 (-0.01, 0.24)	0.9228	0%
Female	-2.25 (-5.81, 1.31)	0.5817	0%
White	0.87 (-3.54, 5.28)	0.1689	47.2%
Diffuse subtype	1.59 (-1.45, 4.64)	0.1794	44.5%
PAH	1.27 (-6.16, 8.70)	0.3300	0%
ILD	-2.30 (-5.43, 0.82)	0.0937	64.4%
GIT manifestations	-2.63 (-5.79, 0.53)	0.8719	0%
Tertiary Education	0.20 (-2.75, 3.16)	0.7245	0%
Employment	2.64 (-0.39, 5.77)	0.7532	0%
Musculoskeletal involvement	-3.51 (-6.56, -0.45)	0.6359	0%
Raynaud's phenomenon	1.20 (-5.22, 7.62)	0.5736	0%
Digital ulcers	-1.77 (-6.59, 3.06)	0.8120	0%

PCS: physical component score; MCS: mental component score; GIT: gastrointestinal; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; CI: confidence interval.

36 PCS of 33.4-43.8 from nine studies addressing HRQoL in SSc cohorts with disease duration ranging from 2.2-9.1 years evaluated in a systematic review (19). These results highlight that reduced HRQoL scores occur early in SSc (within two years of disease onset in our cohort) and remain low without improvement as the disease progresses. The perplexing disparity between SF-36 PCS and SF-36 MCS seen in the literature (2, 10, 18) and hypothesised to be due to the ability of SSc patients to adapt over time to their progressive disease despite significant physical disability (20), was also seen in our study. The SF-36 MCS in our study is 0.5-1.0 standard deviations below that of the general population and substantially lower than the pooled SF-36 MCS in a systematic review (19), perhaps reflecting that our cohort may not have yet adjusted to their expectations in line with the progressive changes of their new disease.

We found that increasing age, dcSSc and PAH were determinants of low SF-36 PCS. Despite increasing age being a significant determinant of SF-36 PCS (p=0.01) in our study, the mean difference of - 0.1 (-0.2–0.0) is below the minimal important clinical difference (MICD) of 2.5–5.0 (20) adding to the conflicting results on the impact of age on HRQoL in SSc reported in the literature (18, 21, 22). dcSSc, on the other hand, was associated with a clinically significant mean difference in SF-36 PCS of -8.2 (-10.2, -6.1, p<0.001) compared to patients with lcSSc in our study, which meets the MICD and has been observed previously (18, 19, 23). Notwithstanding, in a study assessing time trade off in exchange for perfect health, both dcSSc and lcSSc patients were ready to give up a similar amount of time of their life expectancy in exchange for perfect health (median 12% of their life expectancy) (23) despite the lower HRQoL reported by dcSSc patients.

Finally, due to the incurable loss of exercise capacity and unpredictability of PAH, it is no surprise that SSc patients living with PAH have significantly lower HRQoL scores than SSc patients without PAH (24, 25), which was again highlighted in our study results.

Less is known about the determinants of SF-36 MCS in SSc. We were only able to identify age as a determinant of SF-36 MCS, which has been shown in the literature previously, in addition to the presence of anti-Scl70 antibody and a non-European origin (18).

Other psychosocial and clinical manifestations that have previously been reported in the literature to be associated with reduced HRQoL in SSc, that we were unable to test for in our study, include the presence of depression, fear and anxiety (26, 27), fatigue (28), pain (29) and pruritus (30). In our subgroup of Canadian and Australian SSc patients, we found that the presence of MSK and GIT manifestations negatively impacted on HRQoL, which has been shown before (11, 31), particularly in patients with lower GIT symptoms (32). Furthermore, we found that being employed was associated with better HRQoL, consistent with our previous studies that have also shown an association between better HRQoL and work productivity (31, 33).

We acknowledge that there are limitations to our study including its cross-sectional assessment of HRQoL and the definition of disease manifestations as present if present ever during the course of SSc. Furthermore we were only able to analyse the association of GIT manifestations and tertiary education in two of the five SSc cohorts as these data were not available for the other three cohorts. While our findings do not specify clinical care, this paper highlights the need to target patients with new onset disease in clinical trials of novel therapies to inform clinical care in new onset disease, before adaptation and acceptance of disability has occurred. Moreover, routine collection of patient reported outcomes (PROs) measures in clinical practice, such as HRQoL, is an important component of patient-centered care and has been shown to improve patient-provider communication and patient satisfaction (34) which are particularly important for physicians caring for scleroderma (SSc) patients where no cure and limited treatment options are available. Strengths of our study include a large sample size of SSc subjects with new onset disease, patient representation from five different countries across the world and a harmonised data collection and export platform.

Conclusion

Our study highlights the benefits of analysing harmonised multinational data and provides evidence of the presence and magnitude of impairment in HRQoL in an inception SSc cohort. HRQoL studies, such as ours, are essential for clinicians, researchers and health policy makers in order to characterise the burden of disease and to guide the development of tailored interventions and policies designed to improve patient care and reduce the long-term impact of this relatively rare but devastating disease.

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Competing interests

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