High-intensity interval and resistance training programme improves pain and fatigue outcomes in people with systemic sclerosis: a European multicentre randomised controlled trial

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A high-intensity interval and resistance training programme improves pain and fatigue outcomes in people with systemic sclerosis: A European multi-centre randomised controlled trial.

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Abstract

Background

Pain and fatigue are among the most debilitating symptoms of systemic sclerosis (SSc), severely impairing quality of life (QoL). Pharmacological management is often inadequate, and evidence on exercise is limited. This study aimed to evaluate the effects of a tailored exercise programme on pain and fatigue in people with SSc (PwSSc).

Methods

This European multicentre RCT (n=6) recruited 170 PwSSc (89% limited cutaneous SSc), randomised to an exercise intervention group (EIG) or usual care group (UCG). The EIG completed a 12-week, twice-weekly supervised programme combining 30 minutes of high-intensity interval training (HIIT) and 15 minutes of resistance training (RT), in addition to usual care. The UCG received usual care alone. Outcomes were assessed at baseline, 12 weeks (primary endpoint), and 24 weeks, with pain and fatigue as primary outcomes, and QoL, depression, functional ability, musculoskeletal strength/endurance, and cardiorespiratory fitness as secondary outcomes.

Results

At 12 weeks, the mean group differences for the primary-, fatigue [-10.4 (95% CI 19.4, -1.4), p<0.05] and pain [0.48 (95% CI 0.21, 0.76), p<0.05], secondary-, depression (p<0.001), QoL and self-reported function (p<0.05) and exploratory outcomes musculoskeletal strength and endurance (p<0.01), and cardiorespiratory fitness (p<0.001) were significantly improved in EIG compared to UCG.,

Conclusion

A 12-week supervised combined upper body exercise programme can improve pain, fatigue, depression, QoL, function, strength, and cardiorespiratory fitness in PwSSc. HIIT combined with RT is safe for the study population and may serve as an effective non-pharmacological adjunct to pharmacotherapy to manage SSc symptoms and enhance QoL.

Trial registration: ClinicalTrials.gov (NCT number): NCT05234671, January 14, 2022.

Keywords: systemic sclerosis, pain, fatigue, exercise, high-intensity interval training, quality of life, aerobic, muscular function

What is already known on this topic - Pain and fatigue are two of the most debilitating symptoms in systemic sclerosis, and current medical treatments alone are often insufficient.

What this study adds - A 12-week supervised, individualised exercise programme adjunct to pharmacotherapy can improve pain, fatigue, and other SSc-related symptomatology in people with systemic sclerosis.

How this study might affect research, practice or policy - The exercise prescription of a combined training programme could be implemented as part of the clinical care in people with systemic sclerosis to support disease management.

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by complex pathology[1] and a high prevalence of pain, [2]reported in 63%-93% of people with SSc (PwSSc)[2]. Pain is among the most debilitating symptoms, significantly affecting quality of life (QoL)[3]. It commonly arises from joint and musculoskeletal involvement (including arthritis)[3], Raynaud's phenomenon (RP), and skin ulcers[4]. [2]

Fatigue in SSc is defined as abnormal tiredness disproportionate to activity and not improved by rest[5]. Similarly to pain, it is among the most common and disabling symptoms[6], with a prevalence of 50%-90%[6]. Fatigue is strongly linked to depression, pain, and sleep disorders severely affecting QoL in PwSSc[6].

Medical treatment has shown limited effectiveness for alleviating pain and fatigue in PwSSc. Pain is commonly managed with nonsteroidal anti-inflammatory drugs, opioids, and/or low-dose glucocorticoids, while therapies [7]such as tocilizumab[7] and L-thyroxine have not improved fatigue[8]. In addition, medications including opioids, antidepressants, immunosuppressants, and cardiovascular drugs may alleviate certain symptoms but often exacerbate fatigue[9]. These limitations highlight the need to explore non-pharmacological approached such as exercise[10].

Increased physical activity levels in PwSSc have been correlated with lower levels of fatigue compared to inactive individuals[11]. Moreover, PwSSc who were interviewed following a 12-week combined high intensity interval (HIIT) and resistance training (RT) programme reported feeling more energetic stronger and noted improvements in fitness and social life[12]. Although this evidence is promising, definitive randomised controlled trials (RCT) that assess the effects of exercise on pain and fatigue quantitively in PwSSc are warranted.

Building on existing evidence[12-14], this European multi-centre RCT is the first to assess the effects of a combined and RT programme on pain and fatigue in PwSSc. We hypothesised that the intervention would significantly reduce pain and fatigue compared to usual care and would

also improve secondary outcomes such as physical function and cardiorespiratory fitness. The interactions between key SSc symptoms (e.g., pain, fatigue, depression, physical dysfunction) and fitness components (e.g., musculoskeletal strength and endurance, and cardiorespiratory fitness) remain poorly understood. Identifying predictors and exploring these relationships could provide valuable insights into the mechanisms underlying the exercise responses.

Methods

Study design

Our study was a multi-centre (n=6) randomised (1:1 ratio), parallel-group, superiority, single-blinded (i.e., assessor- and statistician-blinded), controlled clinical trial. One hundred and seventy PwSSc were recruited across six European research institutions (Figure 1). Following the eligibility criteria confirmation, participants provided informed consent and were randomly assigned via stratified (by research centre, SSc-type, disease duration and severity) block randomisation remotely by an independent statistician to either exercise (supervised combined exercise for 12 weeks, twice/week adjunct to usual care) or control (usual care alone) groups. Both groups continued receiving their usual medical as well as non-pharmacological treatment (if applicable) throughout the study. Following the 12-week exercise intervention period, the exercise intervention group (EIG) was encouraged to continue exercising independently (either at home or at local health clubs) by replicating their individualised programme according to available resources. The baseline assessments were repeated at 12- (primary endpoint) and 24 weeks. The study's protocol and registration were published on ClinicalTrials.gov (NCT number: NCT05234671). Medical (where applicable) or non-medical ethical approval was granted by each research centre locally.

Participants

Adults with SSc and able to perform exercise were recruited. Individuals with active exacerbations (e.g., digital ulcers), and advanced cardiac (e.g., NYHA class 3 or 4) and severe/uncontrolled pulmonary involvement (e.g., severe pulmonary arterial hypertension) were excluded. Except PwSSc, who did not present with severe symptoms (e.g., dyspnoea at rest, syncope, chest pain, and extreme fatigue) and was cleared for exercise following a clinical appraisal by the rheumatologists.

Eligibility criteria were standardised across study sites; however, the final appraisal of suitability was made by the local rheumatologist, which could occasionally introduce variation in interpretation. This ensured that clinical judgment was applied alongside the protocol to safeguard patient safety and appropriateness for participation.

Patient and public involvement

A patient and public involvement and engagement (PPIE) group contributed to the study design, outcome selection, and interpretation of results.

A detailed study's methodology and reporting according to the CONSORT guidelines for RCTs on non-pharmacological interventions can be found in Supplementary File 1.

Baseline assessments

Demographics

A detailed medical history including current medication was recorded. Stature (cm), weight (kg) and body composition (e.g., percentage of fat and muscle masses) via bioelectrical impedance analysis were performed. The demographics are presented in Table 1.

Primary outcomes

Pain (overall and digital)

Overall pain was assessed using the visual analogue scale (VAS) scores (0-3 scale) included in the scleroderma health assessment questionnaire (SHAQ; Supplementary File 2)[15]. Digital pain was assessed using a unidimensional measure of pain intensity, widely used in diverse adult populations, including rheumatic diseases[16]. Lower score indicates less pain.

Fatigue

Fatigue was assessed using the 40-item functional assessment of chronic illness therapy—fatigue (FACIT-F, version 4; Supplementary File 3) that assesses self-reported fatigue and its impact upon daily activities and function. Higher scores indicate less fatigue.

Secondary outcomes

Self-reported quality of life, functional ability and Depressive Symptoms

SSc-related QoL and self-reported functional ability were assessed using the SScQoL and SHAQ questionnaires[15,17], respectively (Supplementary Files 4 and 2). As included in SHAQ the VAS- breathing, intestinal, and overall disease activity were also assessed. The Centre for Epidemiologic Studies Depression Scale (CES-D; Supplementary File 5)[18] was used to assess the depressive symptoms. Lower scores indicate higher level of QoL, functional ability, and lower level of depression, respectively.

Exploratory Outcomes

Cardiorespiratory fitness

The cardiorespiratory fitness was assessed via a peak oxygen uptake (VO_{2peak}) test, performed on an arm crank ergometer. Throughout the test, gas exchange was collected and analysed by an online breath-by-breath analysis system. Heart rate (HR), ratings of perceived exertion (BORG-RPE; 6-20 points) and the electrocardiogram (ECG) were continuously monitored.

Peak power output (PPO) was measured in watts and was utilised as a critical component for the individualised exercise prescription.

Upper body musculoskeletal strength and endurance

The upper body strength was assessed using the Southampton handgrip strength test protocol[19]. The endurance was assessed via the 30-second biceps curl test of the dominant arm[20]. The detailed protocols are described in supplementary file 1.

Exercise programme

The exercise programme, including the FITT (frequency, intensity, time and type) and training (i.e., specificity, overload, progression, initial values, reversibility, and diminishing returns) principles, has been reported according to the position statement on exercise dosage in rheumatic and musculoskeletal diseases (Supplementary File 1)[21].

Exercise intervention group (EIG)

The exercise programme was performed by the EIG adjunct to usual care. The programme consisted of a 12-week training period, twice per week and all exercise sessions were supervised by a qualified health care professional. The exercise protocol (~ 60mins duration) consisted of upper body HIIT (30-min; 30 s at 100% of PPO and 30-s passive recovery) and RT (upper body circuit weight training at 75–80% of one repetition maximum performing 10 repetitions of each exercise interspersed by 20–30)[13].

Disease-specific exercise modifications were applied only when participants presented with musculoskeletal limitations that restricted performance.

Safety monitoring

Participant safety was prioritised throughout the trial. Eligibility criteria and medical history were carefully reviewed prior to enrolment, and all participants completed a baseline

cardiopulmonary exercise test (CPET) to identify any abnormal responses to exercise stress. During the intervention, participants were instructed to fast for at least 2–3 hours before each session. Prior to exercise, heart rate, blood pressure, and potential symptoms (e.g., dizziness) were assessed at rest, and during each session heart rate, rating of perceived exertion (RPE), and vital signs were continuously monitored.

Usual care group (UCG)

Participants in the UCG continued with their standard management as directed by their treating rheumatology team. This typically included routine or as-needed clinic visits, during which pharmacological and/or non-pharmacological treatments (e.g., physio- and occupational therapy, patient education and self-management) were prescribed according to individual clinical needs. None of the participants engaged in structured high-intensity interval training (HIIT) or resistance training (RT) before or during the study.

Statistical analysis

Data were analysed using SPSS (IBM, New York, USA). Descriptive statistics are presented as mean (SD) for normally distributed data. Normality and homogeneity of variance were tested using the Kolmogorov-Smirnov test ($n > 50$) and Levene's test, respectively. Between-group comparisons for primary outcomes (pain, fatigue) and physical fitness measures (VO_2peak, handgrip strength, biceps curl) used independent t-tests, Wilcoxon, Mann-Whitney U, Chi-squared, or Kruskal-Wallis tests, as appropriate. Missing data were addressed using maximum likelihood estimation. Effect sizes (Cohen's d) were reported for significant results (small = 0.2, medium = 0.5, large = 0.8). Significance was set at $p \leq 0.05$.

Correlations and regressions assessed associations between outcomes at 12 weeks. Spearman correlations quantified strength and direction (0.00–0.10 negligible, 0.10–0.39 weak, 0.40–

0.69 moderate, 0.70–0.89 strong, 0.90–1.00 very strong). Multiple linear regression identified predictors of pain and fatigue. Stepwise regression (exercise group only) examined predictors of 12-week pain (VAS-Pain) and fatigue (F-Scale 13-Item), including QoL (SScQoL), depression, disease severity (VAS), fatigue, pain, functional ability (SHAQ), strength/endurance (handgrip, biceps curl), and cardiorespiratory fitness (VO_2peak in ml/kg/min and L/min).

Sample size calculation

The primary outcome was the VAS-digital pain. For our calculations, we used commercial software (G*Power 3.1.7, HHU of Düsseldorf) by using data from two studies that examined the exercise training effects on SSc-QoL including digital pain following a 12-week exercise intervention (mean RP pain, 1.8 ± 0.6)[12,13]. Based on those calculations, we required no more than 90 patients in each group (180 in total) to detect a difference in RP's pain at 3 months (significance level = 0.05; power =80%) accounting also for an estimated 15% dropout and 5% site effect.

Results

Recruitment, randomisation and dropouts

A total of 874 PwSSc were screened for eligibility, of whom 170 were eligible, willing to participate and were randomly allocated to receive a 12-week exercise intervention adjunct to usual (n=86) care or usual care alone (n=84; Figure 1). Three participants per group were lost at 12 weeks assessment, and further two from the EIG and four from the UCG were lost at 24 weeks assessment. The mean age of dropouts was 53 ± 15 years, with 80% female and most presenting mild disease severity, reflecting the overall study population (Table 1).

Demographics

The demographics (e.g., population characteristics, SSc-type, clinical profile and medical history) are demonstrated in Table 1.

Table 1. Baseline demographics, clinical profile, medical history and treatment of participants in a randomised controlled trial on a 12-week exercise intervention.

Baseline characteristics	**N**	**Intervention group (n=86)**	**N**	**Usual Care group (n=84)**	**Total (n=170)**
Female gender, n (%)	86	68/86 (79.1)	84	73/84 (86.9)	141/170 (82.9)
Age, years, mean [SD]	86	58.3 [11.3]	84	60.5 [12.6)]	59.4 [12.0]
Weight, kg, mean [SD]	86	67.5 [12.2]	84	68.1 [11.9]	67.8 [12.1]
Body Mass Index, kg/m^2), mean [SD]	86	25.1 [4.6]	84	25.8 [4.6]	25.4 [4.6]
Lean Muscle Mass, % [SD]	86	53 [17.7]	84	51 [17.5)]	52 [17.6]
Fat Mass, % [SD]	86	33 [8.6]	84	34.5 [8.7]	33.7 [8.6]
Smoking status	65		62		
Current, n (%)		9 (13.8)		11 (17.7)	20 (15.7)
Never smoked, n (%)		56 (86.2)		51 (82.3)	107 (84.3)

SSc Type	86		84		
Limited, n (%)		77 (89.5)		74 (88.1)	151 (88.8)
Diffuse, n (%)		9 (10.5)		10 (11.9)	19 (11.2)
Clinical Profile					
ANA Positive, n (%)	80	62 (72.1)	77	66 (78.6)	128 (75.3)
ACA Positive, n (%)	80	27 (33.8)	78	24 (30.8)	51 (32.3)
Anti-Scl-70 Positive, n (%)	80	29 (36.3)	77	32 (41.6)	61 (38.9)
ESR (mm/hr), mean [SD]	61	18.2 [14.3]	61	21.6 [18.8]	19.9 [16.7]
CRP (mg/L), mean [SD]	76	2.4 [2.8]	69	2.9 [5.7]	2.6 [4.4]
FEV_1 (%), mean [SD]	71	91.1 [15.5]	68	88.6 [21.7]	89.9 [18.8]
DLCO (%) Predicted, mean [SD]	73	70.4 [14.6]	73	68.1 [15.9]	69.3 [15.3]
Duration of SSc (years), mean [SD]	74	10.0 [7.4]	72	10.7 [7.7]	10.3 [7.5]
Hyperlipidaemia, n (%)	68	25 (36.8)	74	29 (39.2)	54 (38)
Hypertension, n (%)	79	19 (24.1)	82	26 (31.7)	45 (28)
Pulmonary Hypertension, n (%)	80	4 (5)	82	4 (4.9)	8 (4.9)
Pulmonary Fibrosis, n (%)	82	34 (41.5)	80	30 (37.5)	64 (39.5)

Oesophageal Involvement, n (%)	80	40 (50)	82	39 (47.6)	79 (48.8)
Medication					
Steroids, n (%)	78	20 (25.6)	79	34 (43)	54 (34.4)
Anti-hypertensives, n (%)	78	20 (25.6)	79	24 (30.4)	44 (28)
Calcium channel blockers, n (%)	78	47 (60.3)	79	43 (54.4)	90 (57.3)
Anti-hypercholesterolaemia, n (%)	78	18 (23.1)	79	22 (27.8)	40 (25.5)
Immunosuppressives, n (%)	78	46 (59)	79	49 (62)	95 (60.5)
PDE Inhibitors, n (%)	77	7 (9.1)	78	12 (15.4)	19 (12.3)
NSAIDS, n (%)	60	2 (3.3)	59	3 (5.1)	5 (4.2)
Comorbidities					
Osteoporosis, n (%)	50	9 (18.0)	55	8 (14.5)	16.2
Sjogren's, n (%)	50	10 (20.0)	55	7 (12.7)	16.2
Chronic kidney disease, n (%)	50	1 (2)	55	2 (3.6)	3 (2.9)
Biliary Cirrhosis, n (%)	50	2 (4.0)	55	4 (7.3)	6 (5.7)
Osteoarthritis, n (%)	60	10 (16.7)	61	10 (16.4)	20 (16.5)

ACA; anticentromere antibody, ANA; antinuclear body, CRP; C-reactive protein, DLCO; diffusing capacity for carbon monoxide, ESR; erythrocyte sedimentation rate, FEV_1; forced expiratory volume in one second, NSAIDS; nonsteroidal anti-inflammatory drugs, PDE; phosphodiesterase.

Primary Outcomes

Pain

At 12 weeks (based on Independent T-tests), the EIG demonstrated a significant reduction in VAS-Pain ($p<0.001$, effect size (ES)=0.6), and VAS-RP ($p<0.001$, ES=0.55) but not for VAS-digital pain ($p>0.05$) compared to the UCG (Table 2). The within-group differences (based on Paired-Samples T-Test) when the 12 weeks were compared to baseline demonstrated that VAS-pain, RP and digital pain were significantly improved ($p<0.001$) for the EIG. The within group differences for the UCG at 12 weeks compared to baseline showed no significant chance for the VAS digital pain and VAS-pain, but a significant worsening for the VAS-RP ($p<0.01$). At 24 weeks, the groups differences were maintained for VAS-pain ($p<0.01$) and VAS digital pain ($p>0.05$), but not for the VAS RP ($p>0.05$).

A general linear model including baseline pain, SSc subtype, disease duration, centre and group allocation explained 54 % of the variance in 3-month pain scores ($F(5,107)=25.49$, $p<.001$; adjusted $R^2=.522$). Baseline pain was the strongest predictor ($F(1,107)=90.21$, $p<.001$). Group assignment remained significantly associated with pain after adjustment ($F(1,107)=9.23$, $p=.003$), with participants in the EIG reporting lower adjusted pain scores than the UCG (Table 2). SSc subtype ($p=.343$), disease duration ($p=.302$) and centre ($p=.365$) were not significant predictors.

In a model including sex and group, the group effect remained significant ($F(1,134)=10.59$, $p=.001$), whereas no overall difference in pain at 12 weeks between males and females was observed ($p=.314$) indicating that the intervention effect did not differ by sex.

Table 2. Visual Analogue Scales (VAS) for pain, RP, and digital pain at baseline, 12- and 24 weeks for the exercise intervention and usual care groups. Between- and within group differences are presented as means (SD) and mean changes (95% CI).

	Exercise Intervention group			**Usual care group**			**Intervention vs usual care group**
	Baseline Mean (SD)	**12 Weeks Mean (SD)**	**Mean change (95% CI)**	**24 Weeks Mean (SD)**	**Baseline Mean (SD)**	**12 Weeks Mean (SD)**	**Mean change (95% CI)**	**24 Weeks Mean (SD)**	**Mean difference in change scores between groups at 12 weeks (95% CI)**
N	86	83		81	84	81		77	
VAS Pain	0.81 ± 0.81	0.54 ± 0.73	-0.27 (-0.42, -0.13)	0.69 ± 0.71	0.96 ± 0.83	1.02 ± 0.88	0.09 (-0.08, 0.25)	1.05 ± 0.86	0.48 (0.21, 0.76)
VAS RP	0.88 ± 0.88	0.61 ± 0.75	-0.27 (-0.42, -0.12)	0.72 ± 0.80	0.84 ± 0.87	1.11 ± 1.05	0.27 (0.10, 0.44)	1.05 ± 1.07	0.50 (0.19, 0.81)
VAS digital pain	1.19 ± 1.04	0.88 ± 0.91	-0.32 (-0.45, -0.18)	1.01 ± 0.93	0.99 ± 0.94	0.97 ± 0.98	0.07 (-0.08, 0.21)	1.03 ± 1.01	0.08 (-0.23, 0.40)

RP; Raynaud's phenomenon, VAS; visual analogue scale. Range: 0.00 (No Involvement/Pain) 3.00 (Severe Involvement/Pain)

Fatigue

The 40-item FACIT-F total score was significantly better ($p<0.05$, Cohen's D = 0.36) at 12 weeks for the EIG compared to the UCG, based on Independent T-test. The 13-item fatigue scale did not demonstrate any significant differences between the two groups at 12 weeks ($p = 0.56$, Cohen's D = 0.3) and 24 weeks. All the fatigue-related sub-scales (e.g., physical, social, emotional, and functional wellbeing) were significantly ($P<0.05$) improved at 12 weeks for the EIG compared to the UCG. These differences were not maintained at 24 weeks except of the fatigue-related subscale social wellbeing (Table 3).

A general linear model including baseline fatigue, SSc subtype, disease duration, centre and group allocation explained 63 % of the variance in 12 weeks fatigue scores ($F(5,133)=44.88$, $p<.001$; adjusted $R^2=.614$). Baseline fatigue was the strongest predictor ($F(1,133)=206.68$, $p<.001$). Group assignment remained significantly associated with fatigue after adjustment ($F(1,133)=10.50$, $p=.002$), with participants in the EIG reporting lower adjusted fatigue scores than the UCG (Table 3). SSc subtype ($p=.315$), disease duration ($p=.632$) and centre ($p=.611$) were not significant predictors.

In a model including sex and group, group assignment was significantly associated with 12 weeks fatigue ($F(1,161)=5.01$, $p=.027$), whereas no overall difference between males and females was observed ($p=.792$) indicating that the intervention effect did not differ by sex.

Table 3. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) version 4 including Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Between- and within group differences at baseline, 12- and 24 weeks are presented as means (SD) and mean changes (95% CI).

	Exercise Intervention Group (n=86)				**Usual care group (n=84)**				**Intervention vs usual care group**
	Baseline	**12 Weeks**	**Mean change (95% CI)**	**24 Weeks**	**Baseline**	**12 Weeks**	**Mean change (95% CI)**	**24 Weeks**	**Mean difference in change scores between groups at 12 weeks (95% CI)**
N	86	83		81	84	81		77	
FACIT_F Total (Score range: 0-160)	110.2 ± 25.6	118.2 ± 25.9	9.4 (6.4, 12.3)	113.5 ± 27.7	109.2 ± 29.4	107.8 ± 32.2	-1.9 (-6.7, 2.9)	104.5 ± 31.2	-10.4 (-19.4, -1.4)
Fatigue 13-Item Scale (Score range: 0-52)	34.7 ± 11.3	36.9 ± 10.6	2.8 (1.6. 4.0)	35.6 ± 11.6	34.9 ± 12.2	33.6 ± 11.6	-1.5 (-3.0, 0.02)	33.4 ± 11.8	-3.3 (-6.8, 0.1)
Physical WB (Score range: 0-28)	20.7 ± 5.9	22.3 ± 5.2	1.9 (0.9, 2.9)	21.3 ± 6.2	20.6 ± 6.2	20.5 ± 6.0	-0.1 (-0.9, 0.6)	20.8 ± 6.0	-1.8 (-3.5, -0.1)
Social WB (Score range: 0-28)	20.3 ± 5.2	21.5 ± 4.9	1.4 (0.7, 2.1)	21.1 ± 5.4	19.9 ± 5.9	18.8 ± 5.8	-1.2 (-2.1, -0.3)	18.5 ± 5.9	-2.7 (-4.3, -1.0)

Emotional WB (Score range: 0-24)	17.5 ± 4.0	18.1 ± 4.1	0.8 (0.08, 1.5)	17.6 ± 4.1	16.9 ± 5.3	16.7 ± 7.0	-0.4 (-1.2, 0.4)	16.7 ± 4.6	-1.4 (-2.8, -0.03)
Functional WB (Score range: 0-28)	17.3 ± 5.3	18.9 ± 5.6	1.8 (1.1, 2.5)	18.0 ± 5.9	17.4 ± 6.7	16.7 ± 7.0	-0.8 (-1.6, -0.02)	16.9 ± 6.9	-2.3 (-4.2, -0.3)

WB; wellbeing. Lower scores indicate worse fatigue.

Secondary Outcomes

Quality of Life, symptoms of depression, and self-reported functional ability

The QoL was significantly improved at 12 weeks for the EIG ($p<0.05$, Cohen's D = 0.34) compared to the UCG using Independent T-test (Table 4). Symptoms of depression was significantly improved at 12 weeks for the EIG ($p<0.001$, Cohen's D = 0.55) compared to the UCG. The difference between the groups for depression was maintained at 24 weeks (Cohen's D = 0.41).

Concerning the self-reported functional ability activities at 12 weeks (Table 4), the EIG was found to be statistically improved in the eating disability index (DI; $p<0.05$, Cohen's D = 0.34), walking DI ($p<0.01$, Cohen's D = 0.39), hygiene DI ($p<0.05$, Cohen's D = 0.30), reach and grip DI ($p<0.01$, Cohen's D = 0.40), activities DI ($p<0.01$, Cohen's D = 0.41), and overall DI ($p<0.05$, Cohen's D = 0.34) compared to the UCG, assessed via Independent T-tests..

At 12 weeks, the EIG demonstrated improvements in VAS-Intestinal ($p<0.05$, ES=0.31), VAS-Breathing ($p<0.001$, ES=0.62), and VAS-Overall disease activity ($p<0.001$, ES=0.59) when compared to the UCG.

At 24 weeks, some of the improvements were maintained for the EIG except for hygiene DI, grip DI, VAS- intestinal, breathing, and overall disease activity.

Table 4. Quality of life (SScQoL), depression (CES-D), and self-reported functional ability (SHAQ) – Between- and within group differences at baseline, 12- and 24 weeks are presented as means (SD) and mean changes (95% CI). The higher scores indicate worsening for all three questionnaires.

	Exercise Intervention Group (n=86)				Usual Care group (n=84)				**Intervention vs usual care group**
	Baseline	12 Weeks	**Mean change (95% CI)**	24 Weeks	Baseline	12 Weeks	**Mean change (95% CI)**	24 Weeks	**Mean difference in change scores between groups at 12 weeks (95% CI)**
N	86	83		81	84	81		77	
SSc QoL (Score range: 0-29)	10.3 ± 7.5	9.2 ± 7.0	-1.4 (-2.1, -0.6)	10.0 ± 7.5	11.3 ± 7.3	11.6 ± 7.2	0.3 (-0.6, 1.2)	11.8 ± 7.2	2.4 (0.2, 4.7)
CES-D (Score range: 0-60)	13.2 ± 8.8	11.4 ± 8.5	-1.9 (-3.6, -0.3)	13.2 ± 9.2	15.3 ± 11.2	16.9 ± 11.2	1.7 (0.03, 3.3)	17.5 ± 11.8	5.5 (2.4, 8.6)
Dressing & Grooming DI	0.44 ± 0.56	0.39 ± 0.55	-0.04 (-0.11, 0.03)	0.40 ± 0.56	0.49 ± 0.64	0.54 ± 0.58	0.08 (-0.01, 0.17)	0.54 ± 0.58	0.2 (-0.03, 0.3)

Arising DI	0.41 ± 0.62	0.41 ± 0.62		0.33 ± 0.53	0.46 ± 0.56	0.47 ± 0.56		0.53 ± 0.63	0.05	(-0.1, 0.2)
Eating DI	0.44 ± 0.61	0.39 ± 0.6	-0.05 (-0.12, 0.01)	0.38 ± 0.62	0.52 ± 0.57	0.60 ± 0.61	0.10 (0.02, 0.18)	0.57 ± 0.61	0.2	(0.02, 0.4)
Walking DI	0.40 ± 0.6	0.31 ± 0.5	-0.09 (-0.18, -0.01)	0.37 ± 0.53	0.44 ± 0.53	0.51 ± 0.56	0.08 (-0.004, 0.16)	0.56 ± 0.53	0.2	(0.04, 0.4)
Hygiene DI	0.37 ± 0.53	0.31 ± 0.47	-0.06 (-0.14, 0.02)	0.41 ± 0.57	0.43 ± 0.48	0.45 ± 0.52	0.04 (-0.03, 0.12)	0.52 ± 0.56	0.2	(-0.01, 0.3)
Reach DI	0.51 ± 0.72	0.42 ± 0.64	-0.08 (-0.2, 0.03)	0.50 ± 0.71	0.66 ± 0.75	0.68 ± 0.7	0.04 (-0.1, 0.2)	0.68 ± 0.7	0.3	(0.05, 0.5)
Grip DI	0.37 ± 0.53	0.31 ± 0.46	-0.06 (-0.13, 0.02)	0.34 ± 0.53	0.45 ± 0.54	0.51 ± 0.57	0.1 (-0.02, 0.15)	0.47 ± 0.56	0.2	(0.04, 0.4)
Activities DI	0.52 ± 0.64	0.39 ± 0.56	-0.06 (-0.1, 0.02)	0.46 ± 0.64	0.6 ± 0.7	0.65 ± 0.7	0.1 (-0.03, 0.2)	0.68 ± 0.68	0.3	(0.06, 0.5)
Overall DI	0.41 ± 0.52	0.35 ± 0.47	-0.04 (-0.07, -0.003)	0.39 ± 0.54	0.49 ± 0.51	0.51 ± 0.49	0.05 (0.02, 0.09)	0.56 ± 0.51	0.2	(0.01, 0.3)
VAS Intestinal	0.84 ± 0.96	0.80 ± 1.22	-0.04 (-0.28, 0.19)	0.8 ± 1.2	1.1 ± 1.3	1.2 ± 1.4	0.08 (-0.10, 0.26)	1.2 ± 1.3	0.41	(-0.04, 0.86)

VAS Breathing	0.59 ± 0.71	0.43 ± 0.65	-0.16 (-0.26, -0.06)	0.6 ± 0.8	0.8 ± 0.9	0.9 ± 0.9	0.12 (-0.00, 0.25)	0.9 ± 1.0	0.50 (0.23, 0.77)	
VAS Overall disease activity	0.98 ± 0.88	0.77 ± 0.7	-0.22 (-0.38, -0.06)	1.0 ± 0.9	1.1 ± 0.8	1.3 ± 0.9	0.15 (0.02, 0.29)	1.3 ± 1.0	0.48 (0.20, 0.76)	

53 CES-D; Centre for Epidemiologic Studies Depression Scale, DI; Disability Index.

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Exploratory Outcomes

Musculoskeletal and cardiorespiratory fitness

Table 5. illustrates that at 12 weeks, the EIG statistically improved the handgrip left arm ($p<0.01$, Cohen's D=0.43), biceps curl ($p<0.01$, Cohen's D=0.45), VO_{2peak} L/min ($p<0.001$, Cohen's D=0.71), VO_{2peak} ml/kg/min ($p<0.001$, Cohen's D=0.73), HR_{peak} ($p<0.01$, Cohen's D=0.48), peak power output ($p<0.001$, Cohen's D=0.79) when compared to the UCG. At 24 weeks, handgrip strength right- ($p<0.01$, Cohen's D=0.37) and left arm ($p<0.05$, Cohen's D=0.37), and biceps curl ($p<0.01$, Cohen's D=0.38) was higher for the EIG compared to the UCG (Table 5), as those assessed via independent t tests. The differences between the cardiorespiratory fitness components were not maintained between the two groups at 24 weeks.

Table 5. Musculoskeletal and cardiorespiratory fitness outcomes- Between- and within group differences at baseline, 12- and 24 weeks are presented as means (SD) and mean changes (95% CI).

	Exercise Intervention Group (n=86)				**Usual Care Group (n=84)**				**Intervention vs usual care group**
	Baseline	**12 weeks**	**Mean change (95% CI)**	**24 weeks**	**Baseline**	**12 weeks**	**Mean change (95% CI)**	**24 weeks**	**Mean difference in change scores between groups at 12 weeks (95% CI)**
N	86	83		81	84	81		77	
Handgrip right arm (kg)	24.9 ± 9.3	26.1 ± 9	1.2 (-0.3, 2.6)	25.1 ± 8.5	23.5 ± 6.7	24.2 ± 17.6	0.7 (-2.7, 4.2)	21.8 ± 9.2	-1.9 (-6.2, 2.4)
Handgrip left arm (kg)	23.5 ± 9.5	25.2 ± 9.4	1.6 (0.3, 3.0)	24.4 ± 9	22.7 ± 6.6	21.3 ± 8.8	-1.4 (-2.7, -0.04)	21.1 ± 9.1	-3.9 (-6.7, -1.1)
Biceps curl (reps)	18.3 ± 6.8	21.9 ± 6.9	3.6 (2.3, 5.0)	21 ± 8	19.1 ± 6.4	18.7 ± 7.1	-0.5 (-1.8, 0.8)	18 ± 7	-3.2 (-5.3, -1.0)
VO_{2peak} (L/min)	0.93 ± 0.32	1.1 ± 0.37	0.14 (0.08, 0.2)	0.94 ± 0.36	0.90 ± 0.24	0.84 ± 0.21	-0.06 (-0.1, -0.00)	0.84 ± 0.24	-0.2 (0.1, -0.3)

VO_{2peak} (ml/kg/min)	13.5 ± 4.4	15.5 ± 5.1	2.0 (1.1, 3.0)	13.6 ± 4.9	13.2 ± 3.6	12.2 ± 3.0	-1.0 (-1.8, -0.1)	12 ± 3.4	-3.1 (-4.6, -1.6)
HR_{peak} (bpm)	132.8 ± 23.4	133.3 ± 23.9	0.5 (-3.5, 4.5)	132 ± 24	126.7 ± 20.2	122.4 ± 21.5	-4.2 (-8.5, -0.01)	121 ± 23	-10.9 (-18.8, -3.0)
Peak power output (watts)	43 ± 17.7	53 ± 20	10 (4.4, 15.5)	47 ± 20	37.1 ± 13.1	38.2 ± 13.6	1.2 (-2.7, 5.0)	40 ± 19	-14 (-21.4, -6.6)

78 VO_{2peak}; peak oxygen uptake, HR; heart rate.

Regression Analysis

The findings in Table 6 indicate that for pain (VAS-Pain), higher disease severity is associated with higher reported pain levels, while worse depressive symptoms are modestly but significantly linked to higher pain ratings.

The depressive symptoms (CES-D) are significantly associated with greater fatigue (FACIT-F), with higher depression scores predicting lower FACIT-F scores (i.e., more fatigue). Additionally, perceived disease severity (VAS-Disease Severity) is also a strong predictor of fatigue, independently contributing to lower FACIT-F scores.

87 **Table 6.** Stepwise regression analysis to explore predictors of fatigue and pain at 12 weeks for the exercise group.

Dependent Variable: F-Scale 13-Item					95% Confidence Interval for B	
Model		**Unstandardised B**	**Coefficients Standard Error**	**P Values**	**Lower Bound**	**Upper Bound**
1	CES-D	-1.2	0.2	<0.001	-1.6	-0.8
2	CES-D	-0.8	0.2	<0.001	-1.2	-0.4
	VAS-Disease Activity	-7.9	2.4	<0.01	-12.7	-3.0
Dependent Variable: VAS-Pain						
1	VAS-Disease Activity	0.9	0.1	<0.001	0.7	1.2
2	VAS-Disease Activity	1.2	0.2	<0.001	0.8	1.5
	CES-D	-0.03	0.01	<0.05	-0.06	-0.006

88 CES-D; Centre for Epidemiologic Studies Depression Scale, VAS; visual analogue scale.

Correlations

The majority of the correlations between the patient-reported outcomes were higher than between the objective measured physical functional tests. VAS disease severity had strong correlations to VAS pain, FACIT-F and SScQol. CES-D had strong correlation to FACIT-F, moderate correlation to SSc-QoL and weak correlation to VAS-pain (Table 7).

Table 7. Spearman's correlation for pain, fatigue, and QoL at 12 weeks for the exercise group.

Exercise Group		VAS_Pain	VAS Disease Severity	SScQoL	F-Scale 13-Item	FACIT-F	CES-D	SHAQ DI	Handgrip LA	Biceps curl	VO2peak (ml/kg/min)
VAS Pain	Correlation Coefficient	1.0	0.77	0.62	-0.55	-0.64	0.59	0.59	0.04	-0.46	-0.21
	Sig. (2-tailed)		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	>0.05	<0.001	>0.05
FACIT-F Total Score	Correlation Coefficient	-0.64	-0.72	-0.80	0.88	1.0	-0.45	-0.45	-0.002	0.40	0.23
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	>0.05	<0.001	>0.05
SScQoL	Correlation Coefficient	0.62	0.71	1.0	-0.74	-0.80	0.52	0.52	0.06	-0.30	-0.15
	Sig. (2-tailed)	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	>0.05	<0.05	>0.05

FACIT-F; Functional Assessment of Chronic Illness Therapy-Fatigue, SScQoL; systemic sclerosis quality of life questionnaire, VAS; visual analogue scale.

Adverse events

One participant in the EIG experienced a moderate, expected epileptic seizure before the start of the exercise program and required hospitalization. The participant was already receiving treatment for this condition. This was a one-time event and thus it was deemed unrelated to the exercise intervention in overall. No major and/or minor exercise-related side effects occurred.

Discussion

This large multi-centre European definitive RCT is the first study to demonstrate the benefits of a combined exercise programme on debilitating symptoms (e.g., pain and fatigue) including QoL, self-reported functional ability and depression in PwSSc. Namely, our exercise programme was shown to be safe (i.e., no adverse events) and effective in improving at 12 weeks overall pain and fatigue, QoL, depression, self-reported functional ability, and overall fitness including cardiorespiratory fitness, and upper body musculoskeletal strength and endurance.

Pain

Baseline pain levels were mild in both groups. Exercise may reduce pain in SSc, commonly cause by inflammatory arthritis, by improving vascular tone, modulating immune responses, decreasing inflammation[22-24] reducing disease activity, and strengthening the musculature system[25].

At 12 weeks, the EIG improved by 0.27 VAS units from baseline and 0.46 units compared to UCG, a change meeting the reported minimal clinically important differences (MCID) of 0.2 to 0.3 units for PwSSc[26].

VAS digital pain did not differ between groups following the exercise intervention, likely reflecting a ceiling effect due to low baseline scores. Previously, VAS digital pain was

improved following an exercise intervention in PwSSc; however, baseline values were higher (2.2 ± 1.2)[12] compared with the current study (1.19 ± 1.04). Numerous psychosocial risk factors (e.g., emotional health including depression, perceived physical health, and social support) have also been identified as predictors of pain[27]. Regression analyses showed that reductions in depression and disease severity predicted pain improvement, suggesting psychological and disease-activity pathways may mediate the exercise effect.

Fatigue

The FACIT-F total score which includes sub-sections on physical function, social well-being, and daily activities, improved significantly in the EIG at 12 weeks compared with the UCG. Our group has previously shown that exercise could improve energy levels and social profile in PwSSc[12].

The 13-item fatigue scale demonstrated a non-significant statistical improvement for the EIG compared to the UCG at 12 weeks. This finding could be attributed to an insufficient exercise dose-response for this fatigue scale. A higher exercise dose (e.g., thrice weekly) and/or a whole-body exercise instead of upper body alone could have contributed to a significant change for this outcome.

In addition, our participants at baseline presented on average with mild fatigue (i.e., score: 31-40) for both groups, and a ceiling effect is possible to have restricted significant improvements[28].

The MCID for the 13-item fatigue scale over a 12-month follow-up in PwSSc indicates that a change of -3 points reflects deterioration and +4 points reflects improvement[29]. In our study, after only 12 weeks, the EIG improved by +2.2 points from baseline, while the UCG deteriorated by -1.3 points. Although this difference did not reach clinical significance, the magnitude and direction of change achieved in just 12 weeks suggest a potentially meaningful

clinical effect for PwSSc that would warrant confirmation in longer trials. Previous studies report similar findings, an 8-week, thrice-weekly aerobic and muscle endurance programme in a small PwSSc sample (n=4) showed fatigue improvement[30], and other exercise[31] and Tai Chi[32] studies reported benefits however, both studies presented methodological limitations (e.g., absence of exercise dosage)[33].

Our protocol may reduce fatigue through both psychological (reduced depression) and physical (lower perceived disease impact) pathways, supported by regression analyses showing CES-D and VAS-disease activity as meaningful fatigue predictors.

Quality of life, depression, and self-reported functional ability

The QoL (SScQoL) improved significantly in the EIG compared with the UCG at 12 weeks, in agreement with previous systematic reviews and RCTs demonstrating exercise benefits in PwSSc[34,35]. Lower limb muscle strength has strongly correlated with QoL in PwSS[36]. In our study, a weak correlation between upper body strength and QoL was reported, potentially because lower limb strength is closely linked to mobility, independence in daily living and physical functioning scales included within QoL questionnaires.

Depressive symptoms (CES-D) also improved significantly at 12 weeks in the EIG compared with the UCG. Depression in PwSSc may have psycho-neuro-immunological origins[37], with chronic pain, fatigue, body-image dissatisfaction, and functional disability[38] promoting negative emotions and pro-inflammatory cytokines release (e.g., IL-6)[39]. Exercise may counteract this by increasing brain serotonin via the 5-HT3-IGF-1 mechanism leading to antidepressant effects[40] and reduce inflammation[35].

The MCID for SHAQ-DI in PwSSc is 0.2 to 0.25 units[26]. In our study, the between group difference at 12 weeks was 0.16 units, just below the MCID threshold. A higher exercise dose

(e.g., thrice weekly) or an extended exercise period (e.g., 24 weeks) could have contributed to a MCID.

A MCID for the CES-D 20 items questionnaire has not been established. Applying a 10% change (as used in lupus exercise studies[41]), the EIG improved by 14.4% from baseline and 38.9% compared with the UCG, suggesting a clinically meaningful reduction in depression.

Visual Analogue Scales

The VAS- intestinal, -breathing, -RP, and -disease activity improved significantly in the EIG compared with the UCG at 12 weeks. Although baseline symptom burden was mild, these changes are important given the lack of medical cure for SSc. Gastrointestinal, pulmonary, RP and overall disease activity manifestations in SSc are underlined by vascular changes, alteration of innate immunity, inflammatory responses and the process of fibrosis[42]. Exercise has demonstrated that is able to improve the microvasculature[13] and lung function[43], and to reduce inflammation[35] in PwSSc.

Musculoskeletal and cardiorespiratory fitness

Cardiorespiratory and musculoskeletal improvements in the EIG at 12 weeks were lost by 24 weeks, most likely due to physical deconditioning. The physiological mechanisms underlying these improvements have been described previously[13,14].

Right-hand grip strength did not differ significantly between groups post-intervention, and baseline strength was similar between hands. Hand dominance and habitual use can influence muscle adaptation to RT[44], which may explain the limited improvement in the dominant arm compared to the non-dominant arm.

A systematic review reported MCID for grip strength ranging from 0.04 to 6.5 kg across clinical populations[45], reflecting heterogeneity in both populations and MCID calculation

methods. In our study, the left-hand grip strength difference between groups was 3.9 kg above the midpoint of this reported range. Based on the 10% change to account for a significant MCID used when no established value exists[41], our study, demonstrated an 8.5% difference between groups which is slightly below the 10% MCID. his may reflect that the biceps curl test was performed only in the dominant arm, where strength adaptations after resistance training are often smaller than in the non-dominant arm[44].

The MCID for VO_2peak is generally considered 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ [46]. In our study, the mean between-group difference at 12 weeks was 3.1 $mL \cdot kg^{-1} \cdot min^{-1}$, approaching but not reaching this threshold. This may partly reflect the use of upper-limb exercise, which recruits smaller muscle groups and imposes less cardiovascular stress than lower-limb modalities. In a previous study, our group showed that arm-crank ergometry elicited a VO_2peak about 29% lower than cycling in $L \cdot min^{-1}$ and 41% lower when adjusted for body weight, reflecting reduced muscle mass involvement. Given the strong links between VO_2peak and mortality, physical function, and symptom management in chronic disease, enhancing VO_2peak should remain a key target in exercise programmes for PwSSc.

Participant eligibility and recruitment considerations

A notable number of patients (704 of 874 screened) were not included in the trial. Of these, 413 were excluded mainly due to disease exacerbations (e.g., active digital ulcers, uncontrolled renal crisis) or severe complications such as advanced pulmonary arterial hypertension (PAH). Although exercise is not generally contraindicated in PAH[47], our protocol was designed at an individualised high intensity to target pain and fatigue, and we excluded patients with severe cardiopulmonary involvement for safety. Future studies should explore more exercise protocols to improve inclusivity. Additionally, 206 eligible patients declined participation;

understanding barriers and facilitators to exercise uptake through qualitative research will be important for developing tailored referral strategies in PwSSc.

Strengths and Limitations

Strengths of the study include a large sample size, which enhances generalizability, and the potential clinical benefit of our exercise protocol. The multi-centre design also allowed resource sharing and improved networking.

Some limitations of our study were the use of different equipment for the physiological assessments (potentially increasing data variability) and the fact that could not be blinded due to the nature of the intervention (i.e., risk of intervention-driven bias). However, these limitations it is unlikely that have impacted our results due to the large sample size, strict adherence to standardized procedures across centres, and consistent use of the same equipment (at the respective site) and blinded assessors, ensuring data validity and reliability. In addition, all the patient-reported questionnaires and assessments have previously been validated in PwSSc. In addition, we did not systematically collect detailed data on other non-pharmacological treatments (e.g., physical or occupational therapy, counselling) that participants may have used alongside usual care. However, the relatively large sample size (n = 170) and the randomised design, with both groups equally able to access such adjunctive treatments, likely mitigated potential confounding and supports the robustness of our findings.

Conclusion

Our European multi-centre definitive RCT demonstrated that a 12-week supervised combined upper body exercise program (aerobic and resistance training) twice weekly significantly improved pain, fatigue, depression, SSc-related quality of life, and physical fitness compared to the control group. Improvements were also observed within the exercise group from baseline, while the control group showed slight deterioration, suggesting that exercise may not

only alleviate symptoms but also help prevent disease progression. These findings support incorporating exercise as a non-pharmacological adjunct to pharmacotherapy for managing symptoms and enhancing quality of life in PwSSc. A long-term RCT is warranted to investigate the feasibility, implementation and the efficacy of a whole-body exercise program integrated with education on healthy lifestyles and behavioural support.

Conflict of Interest

The authors declare no conflicts of interest for this research.

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Data availability statement

All data obtained during the process have been disclosed in this article, and there is nothing else to share.

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