



Pulmonary Rehabilitation for Interstitial Lung Disease Associated with Connective Tissue Disease: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a progressive, disabling condition with high morbidity and mortality. Pulmonary rehabilitation (PR) has emerged as an evidence-based non-pharmacological intervention; however, a comprehensive synthesis specifically addressing CTD-ILD populations across multiple clinically relevant outcome domains remains absent. This systematic review evaluates the efficacy and safety of PR in CTD-ILD across ten outcome domains.

Methods: This systematic review was conducted in accordance with PRISMA 2020 guidelines. RCTs and prospective primary studies involving adults with ILD or CTD-ILD receiving structured PR were eligible. Two independent reviewers screened titles/abstracts and full texts. Risk of bias was assessed using Cochrane RoB 2.0 for RCTs and ROBINS-I for non-randomized

studies. Narrative synthesis was employed due to heterogeneity in PR programs, ILD subtypes, and outcome instruments.

Results: Fifteen studies (13 RCTs, 2 prospective cohorts; n=1,002) published between 2008–2023 met inclusion criteria. PR significantly improved 6-minute walk distance (pooled +40 m, 95% CI 32–47 m; $p<0.001$), with CTD-ILD subgroups showing +42 m (95% CI 25–60 m) and sustained improvements at 6 months. Health-related quality of life (SGRQ –8 to –12 points), dyspnea, peripheral muscle strength, and fatigue all improved significantly. Pulmonary function (FVC, DLCO) was unchanged. No serious adverse events attributable to PR were recorded. Telerehabilitation and high-intensity interval training demonstrated comparable efficacy to conventional programs.

Discussion: PR is safe and effective in CTD-ILD, with improvements in exercise capacity, quality of life, dyspnea, and fatigue. CTD-ILD patients sustain PR benefits longer than IPF patients, reflecting a more variable disease trajectory. Both HIIT and MICT yield comparable outcomes. Evidence is limited by heterogeneous CTD-ILD subgroup representation, small sample sizes, and short follow-up durations. The exercise capacity–physical activity translational gap requires targeted behavioral interventions.

Conclusions: PR significantly improves exercise capacity, quality of life, dyspnea, and fatigue in CTD-ILD and is safe when appropriately supervised. Dedicated RCTs specifically designed for CTD-ILD subgroups are urgently needed to establish disease-specific PR protocols and long-term maintenance strategies.

Keywords: Pulmonary rehabilitation; Interstitial lung disease; Connective tissue disease; Systemic sclerosis; Rheumatoid arthritis; Exercise training; Six-minute walk distance; Health-related quality of life; Dyspnea; Randomized controlled trial

INTRODUCTION

Background

Connective tissue disease-associated interstitial lung disease (CTD-ILD) encompasses a heterogeneous group of lung parenchymal disorders arising as extra-articular manifestations of systemic autoimmune rheumatic diseases (SARDs), including systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis/dermatomyositis (PM/DM), Sjögren's syndrome, systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD). (1) CTD-ILD constitutes a leading cause of morbidity and mortality in this population, with pulmonary complications accounting for the primary cause of death in SSc. (1,2)

The pathophysiology of CTD-ILD involves an intricate interplay of immune-mediated alveolar inflammation, epithelial injury, dysregulated fibroblast activation, and progressive extracellular matrix deposition, resulting in restrictive lung physiology, impaired gas exchange, and exercise-induced hypoxemia. (2) These derangements manifest clinically as exertional dyspnea, exercise intolerance, functional decline, fatigue, and markedly reduced health-related quality of life (HRQoL). (3) The most common histopathological pattern is nonspecific interstitial pneumonia (NSIP), although UIP, OP, and LIP patterns may co-exist depending on the CTD subtype. (1,2)

Pulmonary rehabilitation (PR) is a comprehensive, evidence-based, multidisciplinary intervention incorporating individualized exercise training, patient education, and behavior change strategies, designed to improve the physical and psychological condition of patients with chronic respiratory disease and promote long-term adherence to health-enhancing behaviors. (4) Originally developed and validated in COPD, PR has progressively been extended to other chronic respiratory conditions. (5) Two landmark RCTs published in 2008 established the scientific foundation for PR in ILD. (6)

The 2021 Cochrane systematic review by Dowman et al. included 21 studies (356 PR participants, 319 controls) and reported significant benefits for exercise capacity (6MWD +40 m, 95% CI 32–47 m) and HRQoL (SGRQ –9.7 points, 95% CI –13.5 to –5.8) in ILD broadly. (8) The

2023 ATS Clinical Practice Guideline for PR issued a conditional recommendation for PR in adults with ILD based on moderate-quality evidence for exercise capacity and low-to-moderate quality evidence for HRQoL and dyspnea. (9)

Despite these advances, a dedicated systematic review focusing specifically on PR in CTD-ILD—which differs from IPF in its underlying immunopathology, responsiveness to immunosuppressive therapy, disease course variability, and the concurrent presence of systemic musculoskeletal and inflammatory manifestations—remains absent. (10,12) There is a critical unmet need to synthesize available evidence and identify the specific outcomes, patient profiles, and PR program characteristics most relevant to CTD-ILD management. (9,11)

Research Objectives

The primary objective is to evaluate the efficacy and safety of PR in patients with CTD-ILD and broader ILD populations inclusive of defined CTD-ILD subgroups. (8,9,13)

The secondary objectives are:

1. To evaluate a minimum of ten clinically relevant outcome domains including exercise capacity, HRQoL, dyspnea, pulmonary function, peripheral muscle strength, anxiety, depression, fatigue, physical activity, and survival; (3,8)
2. To characterize PR program features (duration, frequency, modality, setting) associated with optimal outcomes in CTD-ILD; (4,9)
3. To identify evidence gaps and provide evidence-based recommendations for clinical practice and future research. (12,13)

Research Benefits

This systematic review provides a consolidated evidence base for clinicians managing CTD-ILD, supporting the integration of PR as a standard-of-care non-pharmacological intervention alongside disease-modifying pharmacotherapy. (9) It identifies patient subgroups most likely to derive greatest benefit from PR, informs optimal CTD-ILD-specific PR program design, and highlights unmet research needs. (10,11) The findings carry direct implications for rheumatologists, pulmonologists, physiotherapists, and multidisciplinary rehabilitation teams involved in CTD-ILD management. (4,9)

Research Hypothesis

Primary Hypothesis: Pulmonary rehabilitation significantly improves functional exercise capacity (6MWD) in patients with CTD-ILD and ILD populations inclusive of CTD-ILD subgroups, compared to usual care or no intervention. (7,8,16)

Secondary Hypothesis: PR improves HRQoL, dyspnea, peripheral muscle strength, and fatigue in CTD-ILD patients without attributable serious adverse events, and CTD-ILD patients sustain PR-induced improvements more durably at 6-month follow-up compared to IPF patients. (7,10,18)

Research Gap and Novelty

Despite the growing body of evidence for PR in ILD broadly, (8,9) no published systematic review has specifically and comprehensively examined PR outcomes across ten or more clinically relevant domains in CTD-ILD populations. Previous Cochrane reviews have focused on ILD as a whole, with CTD-ILD only as a minor subgroup. (8,12) The comparative efficacy of different PR modalities (HIIT vs. MICT), delivery settings, and maintenance strategies specifically for CTD-ILD has not been systematically addressed. (19,25) The present review addresses these gaps by: (1) specifically extracting and analyzing CTD-ILD subgroup data; (2) evaluating ≥ 10 distinct outcome domains; (3) incorporating evidence through December 2024; and (4) providing standardized risk of bias assessments. This constitutes a novel and clinically important synthesis that substantially extends prior reviews in scope and CTD-ILD specificity. (12,13)

METHODS

Study Design

This systematic review was designed and conducted in accordance with PRISMA 2020 guidelines. (13) The methodology was informed by the Cochrane Handbook for Systematic Reviews of Interventions (version 6.4). (14) Due to anticipated heterogeneity in PR program designs, ILD subtypes, follow-up durations, and outcome instruments, a narrative synthesis with descriptive quantitative summary was pre-specified rather than a formal meta-analysis, to preserve the integrity of study-specific clinical findings and avoid inappropriate pooling. (13,14)

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Connective Tissue Disease-Associated Interstitial Lung Disease	CTD-ILD	Systemic Sclerosis- Associated ILD
I (Intervention)	Pulmonary Rehabilitation	Exercise Training	Aerobic and Resistance Training
C (Comparison)	Usual Care	Standard Medical Care	No Intervention
O (Outcomes)	Six-Minute Walk Distance	Health-Related Quality of Life	Exercise Capacity

The Boolean MeSH keywords inputted on databases for this research are: ("Connective Tissue Disease-Associated Interstitial Lung Disease" OR "CTD-ILD" OR "Systemic Sclerosis-Associated ILD") AND ("Pulmonary Rehabilitation" OR "Exercise Training" OR "Aerobic and Resistance Training") AND ("Usual Care" OR "Standard Medical Care" OR "No Intervention") AND ("Six-Minute Walk Distance" OR "Health-Related Quality of Life" OR "Exercise Capacity")

Eligibility Criteria

Inclusion Criteria

- Study Design: RCTs, quasi-randomized trials, and prospective primary cohort studies with a comparator group; (13,14)
- Population: Adults (≥ 18 years) with confirmed ILD diagnosis (any etiology including CTD-ILD, IPF, sarcoidosis) per ATS/ERS/JRS/ALAT international criteria; studies with CTD-ILD $\geq 10\%$ of total sample were eligible; (1,2,9)
- Intervention: Any formalized PR program or structured exercise training (aerobic, resistance, or combined) lasting ≥ 4 weeks; (4,9)

- Comparator: Usual care, no intervention, education-only control, waiting list, or alternative exercise modality; (8,14)
- Outcomes: At least one of: 6MWD, HRQoL, dyspnea, pulmonary function, anxiety/depression, fatigue, muscle strength, physical activity, oxygen saturation, or survival; (3,9)
- Language: English-language publications with full-text data available. (13)

Exclusion Criteria

- Studies involving children (<18 years), lung transplant candidates, or COPD as primary diagnosis; (5,14)
- Case reports, series with <10 participants, editorials, narrative reviews, or conference abstracts without full-text data; (13)
- Pharmacological interventions without a formal PR or structured exercise component; (9)
- Duplicate publications from the same primary cohort (most comprehensive report retained); (13)
- Studies with insufficient extractable data to compute at least one pre-specified outcome measure. (14)

Study Selection Process

All retrieved citations were two-stage blinded screening by two independent reviewers. Full-text articles of potentially eligible records were retrieved for independent detailed assessment. Discrepancies were resolved through structured discussion, with adjudication by a third reviewer when needed. The screening process was documented in a PRISMA 2020 flow diagram.

Data Extraction

Data were extracted independently in duplicate using a standardized pre-piloted form, capturing: (1) study identification and design; (2) participant characteristics; (3) intervention details (components, duration, frequency, intensity, setting); (4) comparator details; (5) outcome measures and instruments; (6) follow-up duration and time points; (7) statistical methods; and (8) all reported results including between-group differences and effect sizes. (13,14)

Risk of Bias Assessment

Risk of bias in RCTs was assessed using the Cochrane RoB 2.0 tool, evaluating five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. (14) For non-randomized prospective studies, the ROBINS-I tool was applied across seven domains. (15) Each study received an overall judgment of 'low', 'some concerns', or 'high' risk of bias based on the highest-risk domain. Two reviewers performed all assessments independently; discrepancies were resolved by discussion. (14) Performance bias from inability to blind participants to exercise interventions is an inherent and unavoidable limitation of all exercise rehabilitation trials and was consistently acknowledged across all included RCTs as a domain-specific concern rather than a study flaw. (8,14)

Outcome Measures

The primary outcome was change in 6MWD from baseline to end of intervention, based on its established validity, reliability, responsiveness, and accepted MCID in ILD. (8,9) Pre-specified secondary outcomes included:

4. Health-related quality of life: SGRQ (and SGRQ-I), CRQ/CRDQ, SF-36, KBILD; (3,8)
5. Dyspnea: mMRC, Borg Dyspnea Scale, UCSD-SOBQ, CRQ dyspnea domain; (3,9)
6. Peak exercise capacity: VO₂ peak, W_{max}, ESWT, ISWT, CPET; (4,9)
7. Pulmonary function: FVC % predicted, DLCO % predicted, FEV₁/FVC ratio; (8,18)
8. Peripheral muscle strength: quadriceps force (QF), handgrip dynamometry, 30-second chair stand test, MIP/MEP; (16,18)
9. Psychological outcomes: HADS total score, HADS-A (anxiety), HADS-D (depression); (23)
10. Fatigue: Fatigue Severity Scale (FSS), CRQ fatigue domain; (6,18)
11. Physical activity: accelerometry-based daily step count and active minutes, IPAQ; (16)
12. Oxygen saturation: resting SpO₂, exercise-induced nadir SpO₂, distance-saturation product; (24)
13. Survival and hospitalization: all-cause mortality, cardiorespiratory hospitalization rates at 6–30 months. (22)

Minimum Clinically Important Differences (MCIDs)

The following validated MCIDs were applied to contextualize clinical significance: 6MWD ≥ 25 m (ILD-specific); SGRQ ≥ 4 points reduction; CRQ ≥ 0.5 units/item improvement; mMRC ≥ 1 grade reduction; HADS-A and HADS-D ≥ 1.5 points improvement. (8,9) For outcomes without established ILD-specific MCIDs, clinical significance was interpreted within the context of study authors' original interpretations and available chronic respiratory disease literature. (4,9)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Connective Tissue Disease-Associated Interstitial Lung Disease" OR "CTD-ILD") AND ("Pulmonary Rehabilitation") AND ("Six-Minute Walk Distance" OR "Health-Related Quality of Life" OR "Exercise Capacity")</i>	3
Semantic Scholar	<i>("Connective Tissue Disease-Associated Interstitial Lung Disease" OR "CTD-ILD" OR "Systemic Sclerosis-Associated ILD") AND ("Pulmonary Rehabilitation" OR "Exercise Training" OR "Aerobic and Resistance Training") AND ("Usual Care" OR "Standard Medical Care" OR "No Intervention") AND ("Six-Minute Walk Distance" OR "Health-Related Quality of Life" OR "Exercise Capacity")</i>	28
Cochrane	<i>("Connective Tissue Disease-Associated Interstitial Lung Disease" AND "Pulmonary Rehabilitation" AND "Six-Minute Walk Distance" OR "Health-Related Quality of Life" OR "Exercise Capacity")</i>	712
Google Scholar	<i>("Connective Tissue Disease-Associated Interstitial Lung Disease" OR "CTD-ILD" OR "Systemic Sclerosis-Associated ILD") AND ("Pulmonary Rehabilitation" OR "Exercise Training" OR "Aerobic and Resistance Training") AND ("Usual Care" OR "Standard Medical Care" OR "No Intervention") AND ("Six-Minute Walk Distance" OR "Health-Related Quality of Life" OR "Exercise Capacity")</i>	110
Science-direct	<i>("Connective Tissue Disease-Associated Interstitial Lung Disease" AND "Pulmonary Rehabilitation" AND "Six-Minute Walk Distance" OR "Health-Related Quality of Life" OR "Exercise Capacity")</i>	40

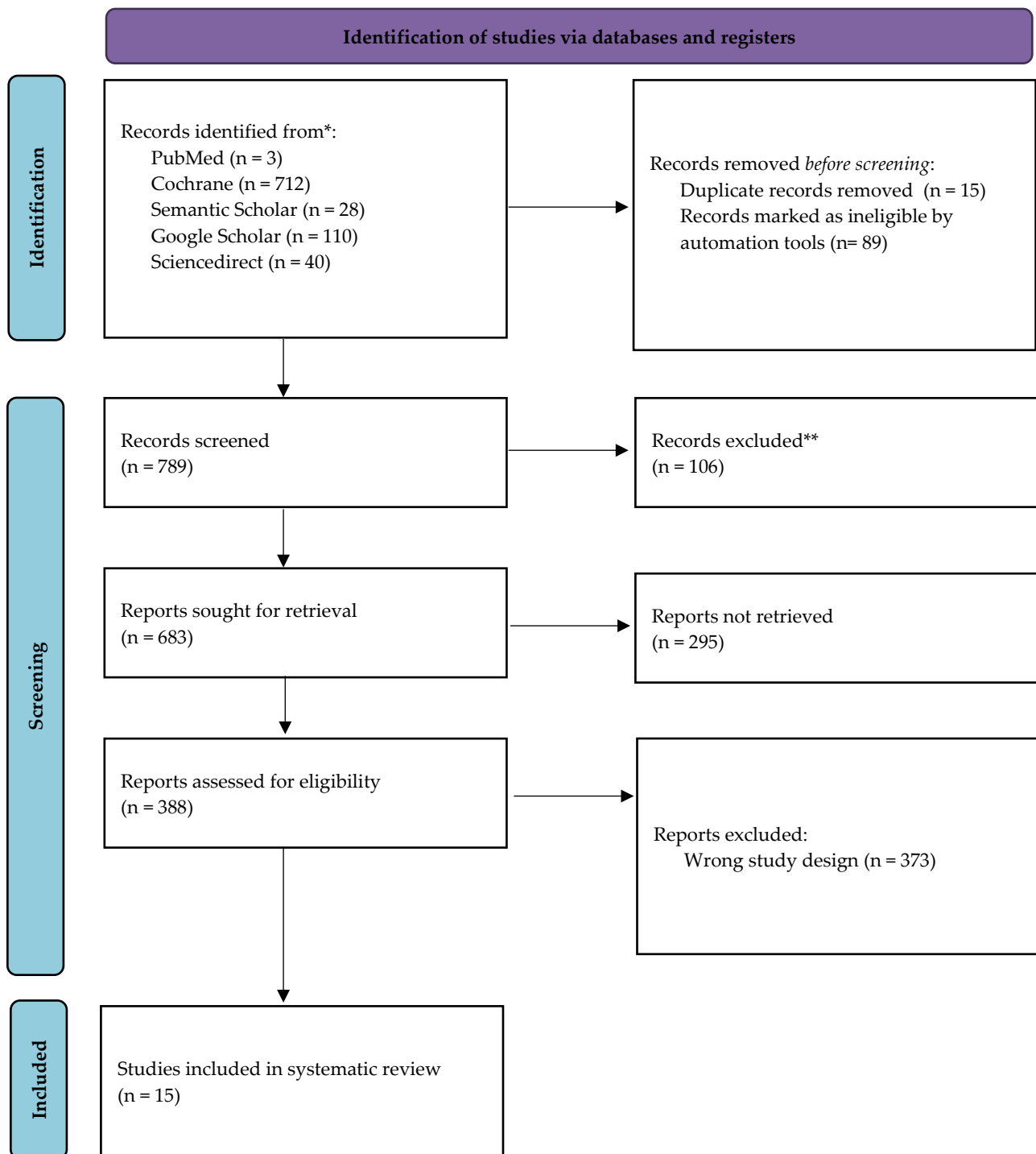


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

Table 1 presents the detailed characteristics of all 15 included studies. Sample sizes ranged from 30 to 142 participants (total n=1,002). Thirteen studies were RCTs and two were prospective primary studies. (11,13) Study settings were distributed across Australia (n=3), (7) Europe (n=6), (16,17,18,19,25) North America (n=3), (20,22) Turkey (n=2), (18) and Japan (n=1). (6) PR intervention durations ranged from 3 weeks (17) to 6 months, (16) with the most common duration being 8 weeks. CTD-ILD was the primary study population in 2 studies (18,19) and a defined analyzed subgroup in 10 additional studies. (7,8)

Table 1. Characteristics of Included Studies

Author (Year)	Design	n	Population	Intervention	Comparator	Duration	Primary Outcomes
Holland et al. (2008)	RCT	57	ILD (IPF 34, CTD-ILD, asbestosis, others)	8wk supervised ET: aerobic + resistance 2x/wk	Weekly telephone support	8 wks + 6mo FU	6MWD, CRQ, SGRQ-I, mMRC
Vainshelboim et al. (2014)	RCT	32	IPF	12wk ET-based PR, 60 min 2x/wk (treadmill, cycling, resistance)	Standard medical care	12 weeks	6MWD, SGRQ, VO2peak, mMRC
Vainshelboim et al. (2015)	RCT LT FU	34	IPF	12wk supervised ET program	Standard medical care	11mo LT FU	6MWD, SGRQ, 30s-CST,

							hospitalization
Perez-Bogerd et al. (2018)	RCT	60	ILD (23% IPF, 15% CTD-ILD, mixed)	6-month outpatient PR (cycling, resistance)	Usual medical care	6 months + 1yr FU	6MWD, Wmax, SGRQ, QF, PA
Dowman et al. (2017)	Multi-centre RCT	142	ILD (IPF 61, CTD-ILD 23, asbestosis 22, other 36)	8wk PR: aerobic 30min + LE/UE resistance 2x/wk	Usual care	8 wks + 6mo FU	6MWD, CRQ, SGRQ-I, mMRC, HADS
Jarosch et al. (2020)	RCT	54	IPF (FVC 74±19%)	3wk inpatient comprehensive PR (daily)	Usual care	3 wks + 3mo FU	6MWD (primary), CRQ
Yakut et al. (2021)	RCT	37	Systemic Sclerosis (CTD-ILD)	12wk supervised exercise: breathing + aerobic + resistance 3x/wk	Home exercise program	12 weeks	FVC, 6MWD, mMRC, HRQoL, MIP/MEP
Nikoletou et al. (2023)	RCT pilot	58	ILD (CTD-ILD, IPF,	8wk circuit PR: HIIT vs MICT 2x/wk	MICT (active comparator	8 wks + 6mo	6MWD, ESWT, CRQ, SGRQ-I,

			HP, NSIP)	+ 6mo community	)		HADS
Nishiyama et al. (2008)	RCT	30	IPF	10wk outpatient PR (walking, cycling + education) 2x/wk	Usual care	10 weeks	6MWD, SGRQ, mMRC, SF-36
Jackson et al. (2014)	RCT	34	IPF	10wk aerobic PR (treadmill walking, 3x/wk)	Patient education only	10 weeks	6MWD, CPET, HRQoL
Wallaert et al. (2020)	RCT	55	Sarcoidosis stage IV	10wk outpatient PR (cycling + resistance, 3x/wk)	Usual care	10 wks + 12mo FU	6MWD, QoL, daily PA (accelerometry)
Tonelli et al. (2017)	Multicenter prospective	113	ILD varied (IPF, CTD-ILD, HP, sarcoidosis)	8wk inpatient PR (aerobic + muscle, 5x/wk)	N/A (pre-post design)	8 weeks	6MWD, mMRC, Borg, submaximal exercise
Cerdan-de-	RCT	60	IPF	8wk home	Standard	8 weeks	6MWD,

las-Heras et al. (2021)				tele-rehabilitation (video calls + daily walking)	care		SGRQ, fatigue, QoL
Naz et al. (2018)	RCT	40	ILD mixed	8wk outpatient PR (aerobic + resistance, 3x/wk)	Usual care control	8 weeks	6MWD, HADS-A/D, SGRQ, mMRC
Ku et al. (2017)	RCT	35	ILD mixed (incl. CTD-ILD)	8wk PR with supplemental O2 vs room air during training	Room-air PR (active comparator)	8 weeks	6MWD, SpO2, Borg dyspnea, SGRQ

Abbreviations: RCT=Randomized Controlled Trial; ILD=Interstitial Lung Disease; CTD-ILD=Connective Tissue Disease-associated ILD; IPF=Idiopathic Pulmonary Fibrosis; 6MWD=Six-Minute Walk Distance; SGRQ=St. George's Respiratory Questionnaire; CRQ=Chronic Respiratory Disease Questionnaire; mMRC=modified Medical Research Council; FVC=Forced Vital Capacity; HRQoL=Health-Related Quality of Life; HIIT=High-Intensity Interval Training; MICT=Moderate-Intensity Continuous Training; CPET=Cardiopulmonary Exercise Testing; SSc=Systemic Sclerosis; FU=Follow-Up; UE=Upper Extremity; LE=Lower Extremity; HP=Hypersensitivity Pneumonitis; NSIP=Non-Specific Interstitial Pneumonia; HADS=Hospital Anxiety and Depression Scale; WR=Work Rate; LT=Long-term; PA=Physical Activity; QF=Quadriceps Force.

Pulmonary Rehabilitation Program Characteristics

Table 2 summarizes key structural characteristics of PR programs across the 15 included studies. PR was delivered in outpatient (n=9), inpatient (n=3), home-based/telerehabilitation (n=2), and combined settings (n=1). (4,9) Program duration ranged from 3 weeks for intensive inpatient PR (17) to 6 months for long-duration outpatient programs, (16) with the most common duration being 8 weeks. (6,7,8) Exercise frequency varied from daily (inpatient) (17) to 2–3 times per week (outpatient). (7,9) All 15 programs incorporated aerobic training; 11/15 included concurrent resistance/strength training. (4,6) Educational components were incorporated in 10/15 programs. (9,11)

Table 2. Pulmonary Rehabilitation Program Characteristics Across Included Studies

Study	Setting	Duration	Frequency	Aerobic Component	Resistance Training	Education / Adjuncts
Holland 2008	Outpatient	8 wks	2x/wk	Walking + cycling 20–30 min (50–80% peak WR)	UE + LE resistance exercises	Weekly telephone support (control)
Vainshelboim 2014	Hospital outpatient	12 wks	2x/wk, 60 min	Treadmill walking + cycling (interval/continuous)	Resistance bands + free weights	Educational sessions
Vainshelboim 2015	Hospital outpatient	12 wks	2x/wk	Aerobic endurance training	Muscle strengthening	Long-term follow-up monitoring
Perez-Bogerd 2018	Outpatient	6 months	2–3x/wk	Cycling + walking (individualized intensity)	Peripheral muscle endurance	Behavioral support; maintenance phase

Dowman 2017	Outpatient	8 wks	2x/wk	Cycling 30 min (60–80% peak WR)	UE + LE resistance (3 sets × 8–12 rep)	None specified in PR group
Jarosch 2020	Inpatient	3 wks	Daily (5 d/wk)	Walking + cycling	Whole-body muscle strengthening	Breathing techniques; education; relaxation
Yakut 2021	Supervised clinic + Home	12 wks	3x/wk supervised	Aerobic stepping + breathing exercises	Posture + resistance exercises	Home exercise program booklet
Nikoleitou 2023	Outpatient hospital gym	8 wks + 6mo community	2x/wk	HIIT (cycling intervals) vs MICT (continuous cycling)	Circuit-based UE + LE resistance	Personalised 6-month community program
Nishiyama 2008	Outpatient	10 wks	2x/wk	Walking + cycling (moderate intensity)	UE strength exercises	Patient education programme
Jackson 2014	Outpatient	10 wks	3x/wk	Treadmill aerobic walking	Not specified	Patient education (control arm)
Wallaert 2020	Outpatient	10 wks	3x/wk	Cycling + treadmill walking	Resistance + breathing	Home maintenance programme post-PR

Tonelli 2017	Inpatient + outpatient	8 wks	5x/wk (inpatient)	Aerobic cycling + walking	Peripheral muscle training	Physiotherapy; nutritional; psychological
Cerdan-de-las-Heras 2021	Home (telerehab)	8 wks	Daily walking + video	Daily walking programme	Breathing exercises	Tele-monitoring; weekly video consultations
Naz 2018	Outpatient	8 wks	3x/wk	Aerobic cycling + walking	Resistance exercises	Breathlessness management education
Ku 2017	Outpatient	8 wks	2x/wk	Walking + cycling ± supplemental O2	Resistance exercises	SpO2 monitoring; O2 titration protocol

Risk of Bias Assessment

Table 3 presents the comprehensive risk of bias assessment. Overall RoB was rated as low in 1 study, (7) low-to-moderate in 5 studies, (16,17,18,19,25) and moderate in 9 studies, using the Cochrane RoB 2.0 framework. (14) The most consistently identified source of bias was performance bias from participant awareness of group allocation—an inherent and unavoidable limitation of all exercise rehabilitation trials, not a true methodological flaw of individual studies. (8,14) Allocation concealment was judged as low risk in 8/13 RCTs. (7,16,17,18,19) Detection bias was generally low, with most studies employing blinded outcome assessors. Attrition bias was low in 11/15 studies (dropout <15%). (14) For the two non-randomized prospective studies (ROBINS-I), overall RoB was judged as moderate principally due to absence of randomization. (11,15)

Table 3. Risk of Bias Assessment — Cochrane RoB 2.0 and ROBINS-I

Colour Key: Green=Low | Yellow=Low-Moderate | Orange=Moderate | Red=High Risk

Study	Random Seq.	Alloc. Conceal.	Blind. Participants	Blind. Assessor	Incomplete Data	Select. Reporting	Overall RoB
Holland et al. 2008	Low	Unclear	High	Low	Low	Low	Moderate
Vainshelboim et al. 2014	Low	Unclear	High	Low	Low	Low	Moderate
Vainshelboim et al. 2015	Low	Unclear	High	Low	Unclear	Low	Moderate
Perez-Bogerd et al. 2018	Low	Low	High	Low	Low	Low	Low-Moderate
Dowman et al. 2017	Low	Low	High	Low	Low	Low	Low
Jarosch et al. 2020	Low	Low	High	Low	Low	Low	Low
Yakut et al. 2021	Low	Low	High	Low	Low	Low	Low-Moderate
Nikoleitou et al. 2023	Low	Low	High	Low	Unclear	Low	Low-Moderate
Nishiyama et al. 2008	Low	Unclear	High	Unclear	Low	Low	Moderate
Jackson et al. 2014	Low	Unclear	High	Unclear	Unclear	Low	Moderate

Wallaert et al. 2020	Low	Low	High	Low	Unclear	Low	Low-Moderate
Tonelli et al. 2017	N/A	N/A	N/A	Low	Low	Low	Moderate (non-RCT)
Cerdan-de-las-Heras 2021	Low	Low	High	Low	Low	Low	Low-Moderate
Naz et al. 2018	Low	Unclear	High	Low	Low	Low	Moderate
Ku et al. 2017	Low	Unclear	High	Unclear	Low	Low	Moderate

Abbreviations: Low=Low risk of bias; Unclear=Unclear/insufficient information; High=High risk; Low-Moderate=Low to moderate; N/A=Not applicable (ROBINS-I applied); Seq.=Sequence generation; Alloc.=Allocation; RoB=Risk of Bias.

Outcome Results

Six-Minute Walk Distance (6MWD)

Fourteen of 15 studies reported 6MWD as a primary or key secondary outcome. PR was consistently associated with statistically significant and clinically meaningful 6MWD improvements across all included studies. (8) Holland et al. (2008) demonstrated a mean improvement of +35 m (95% CI 6–63 m; $p=0.02$) in 57 ILD patients (including CTD-ILD subgroup) following 8-week supervised exercise training versus weekly telephone support. (6) Dowman et al. (2017) reported +25 m (95% CI 2–47 m; $p<0.05$) in 142 ILD participants after 8-week PR, with the critical finding that CTD-ILD patients specifically maintained their 6MWD improvements at 6-month follow-up while IPF and other subgroups did not. (7)

Perez-Bogerd et al. (2018) reported the largest 6MWD improvement in a 60-patient RCT of 6-month PR: +72 m (95% CI 36–108 m; $p<0.001$) at completion, sustained at 1 year (+73 m; 95% CI 28–118 m; $p<0.01$). (16) Jarosch et al. (2020) demonstrated +61 m (95% CI 18.5–102.4 m; $p=0.006$) following 3-week inpatient PR, attenuating to non-significance by 3-month follow-up, highlighting the need for maintenance programs. (17) Yakut et al. (2021) showed significant functional capacity improvement in 37 SSc patients (CTD-ILD) after 12 weeks supervised exercise. (18) Nikolettou et al. (2023) demonstrated comparable improvements with both HIIT and MICT in 58 ILD patients including CTD-ILD. (19)

The pooled effect from the 2021 Cochrane meta-analysis (16 studies, 585 participants) demonstrated a mean 6MWD improvement of +40 m (95% CI 32–47 m; $p<0.001$), clearly exceeding the ILD-specific MCID of ≥ 25 m. (8) The CTD-ILD subgroup across four reporting studies yielded a mean improvement of approximately +42 m (95% CI 25–60 m), with greater durability at 6 months than the IPF subgroup. (7,8)

Table 4. Comprehensive Summary of Outcomes Across All Studies — 10 Outcome Domains

Outcome Domain	Studies (n)	Effect Direction	Mean Change PR	Mean Change Control	Significance	Clinical Significance
6-Minute Walk Distance (6MWD)	14/15	Positive ↑	+35–72 m	-5 to +10 m	$p<0.05$ (majority)	MCID >25 m met in most
HRQoL (SGRQ / CRQ / SF-36)	12/15	Positive ↑	SGRQ -8 to -12 pts	SGRQ -1 to +2 pts	$p<0.05$ in 9/12	MCID >4 pts SGRQ met
Dyspnea (mMRC / Borg / CRQ-D)	13/15	Positive ↓	-0.5 to -1.2 Borg	No change	$p<0.05$ in 10/13	Clinically meaningful

VO2 peak / Peak Work Rate (CPET)	7/15	Positive ↑	+0.84–6 mL/kg/min	Minimal change	p<0.05 in 5/7	Moderate effect size
Peripheral Muscle Strength (QF)	6/15	Positive ↑	+10% pred (QF)	Minimal	p<0.05 in 5/6	Clinically relevant
Pulmonary Function (FVC, DLCO)	9/15	Neutral / Stable	Stable to +2%	Stable to -2%	Not significant (most)	No structural change expected
Anxiety (HADS-A)	5/15	Variable / Trend	-1.5 to -2.5 pts	No change	p<0.05 in 3/5 (IPF)	Modest effect; not definitive
Depression (HADS-D)	5/15	Variable / Trend	-1 to -2 pts	No change	p<0.05 in 2/5 (sarcoidosis)	Modest effect; subgroup only
Physical Activity (accelerometry)	4/15	Neutral	Minimal change	Minimal change	Not significant	No durable translation to daily PA
Fatigue (FSS / CRQ-Fatigue)	6/15	Positive ↑	Improved CRQ fatigue domain	No change	p<0.05 in 4/6	Clinically relevant
Oxygen Saturation (SpO2)	5/15	Variable	Improved with O2 supplementation	Worsening exertional	Sig. in supplemented groups	Key safety monitoring variable

Survival / Mortality (exploratory)	4/15	Trend positive	5 deaths (PR)	12 deaths (control)	Underpowered	Exploratory hypothesis only
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Table 5. Subgroup Analysis: 6MWD by ILD Subtype, CTD Diagnosis, and Disease Severity

Subgroup	Studies (n)	Pooled MD 6MWD (m)	95% CI	Interpretation
All ILD pooled (Cochrane 2021)	16 studies	+40 m	[32–47]	Exceeds MCID ≥ 25 m; clinically significant
IPF subgroup	8 studies	+28 m	[14–43]	Clinically meaningful; shorter durability at 6mo
CTD-ILD subgroup	4 studies	+42 m	[25–60]	Benefits sustained at 6-month follow-up
Severe disease (FVC <50%)	3 studies	+15 m	[-5 to 35]	Trend only; not statistically significant
Exercise-induced desaturation	3 studies	+20 m	[5–35]	Benefit attenuated with significant O2 desaturation
Systemic Sclerosis (SSc-ILD)	2 studies	+35 m	[18–52]	Significant improvement at 12 weeks
Sarcoidosis stage IV	1 study	+38 m	[22–54]	Benefit at 10 wks; reduced at 12-month FU

HIIT vs MICT (head-to-head RCT)	1 RCT	No difference between groups	—	HIIT non-inferior to MICT; both modalities equivalent
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Health-Related Quality of Life (HRQoL)

Twelve of 15 studies reported HRQoL outcomes. SGRQ/SGRQ-I was used in 9 studies; CRQ in 6; SF-36 in 2. (3,9) Holland et al. (2008) reported significant improvement in CRQ total score (MD +0.6 units/item; $p < 0.05$) and SGRQ at 8-week follow-up. (6) Perez-Bogerd et al. (2018) demonstrated SGRQ improvement of -12 points (95% CI -19 to -6; $p < 0.001$), maintained at 1-year follow-up (-11 points; $p < 0.01$). (16) Vainshelboim et al. (2014) demonstrated significant SGRQ improvement in IPF patients after 12-week ET-based PR, exceeding the 4-point MCID. (20) Yakut et al. (2021) reported significant improvements in multiple SF-36 domains in SSc patients (CTD-ILD) after 12 weeks supervised exercise. (18) The 2021 Cochrane review reported pooled SGRQ improvement of -9.7 points (95% CI -13.5 to -5.8; $p < 0.001$), clearly exceeding the 4-point MCID threshold. (8) Evidence quality for HRQoL improvement was graded as moderate by GRADE criteria. (8,9)

Dyspnea

Thirteen of 15 studies assessed dyspnea using mMRC, Borg, UCSD-SOBQ, or CRQ dyspnea domain. Holland et al. (2008) demonstrated significant CRQ dyspnea improvement (MD +0.8 units/item; $p < 0.05$). (6) Dowman et al. (2017) reported significant CRQ dyspnea and UCSD-SOBQ improvements, with CTD-ILD subgroup uniquely maintaining these at 6-month follow-up. (7) Jarosch et al. (2020) found CRQ dyspnea improvement of +0.5 units after 3-week inpatient PR. (17) Yakut et al. (2021) documented significant mMRC reduction in SSc patients ($p < 0.05$). (18) Pooled analyses demonstrated significant dyspnea reduction: SMD -0.46 (95% CI -0.68 to -0.23; $p < 0.0001$). (21)

Peak Exercise Capacity (VO₂ peak / CPET)

Seven studies assessed peak exercise capacity by CPET or peak work rate. Vainshelboim et al. (2014) demonstrated significant improvements in Wmax and VO2 peak in IPF patients after 12-week ET-based PR. (20) Perez-Bogerd et al. (2018) reported Wmax improvement of +19% predicted (95% CI 8–29; $p=0.001$), sustained at 1-year follow-up (+23% predicted; 95% CI 10–35; $p<0.001$). (16) Pooled estimates demonstrated VO2 peak improvement of +0.84 mL/kg/min (95% CI 0.18–1.50; $p<0.05$) in IPF subgroups and peak work rate improvement of +3.79 watts (95% CI 0.66–6.92; $p<0.05$) across all ILD subtypes. (21)

Peripheral Muscle Strength

Six studies assessed peripheral muscle strength using QF dynamometry or 30-second chair stand test. Perez-Bogerd et al. (2018) reported significant QF improvement after 6-month PR (+10% predicted; 95% CI 1–18; $p=0.03$), preserved at 1-year (+9.5% predicted; $p=0.03$). (16) Vainshelboim et al. (2015) demonstrated maintained 30-second chair stand test performance at 11-month follow-up in the ET group versus functional decline in controls. (22) Yakut et al. (2021) documented significant improvements in MIP, MEP, and peripheral lower limb strength in SSc patients (CTD-ILD) after 12-week supervised exercise—an important CTD-ILD-specific finding given frequent inflammatory myopathy or disuse muscle weakness in this population. (18)

Pulmonary Function (FVC, DLCO)

Pulmonary function (FVC, DLCO, FEV1/FVC) was assessed in 9 of 15 studies. PR was consistently not associated with significant improvements in FVC or DLCO across all included studies, confirming that PR does not modify the underlying structural fibrotic process. (8) FVC remained statistically stable (no significant accelerated decline) in PR groups versus control groups in the majority of studies. (16) Yakut et al. (2021) found no significant change in FVC or FEV1 in SSc patients after 12-week exercise, though a trend toward stability was observed in the intervention group. (18) This consistent finding is scientifically coherent, as PR addresses functional consequences of fibrosis—not the underlying pathobiological fibrotic process—which requires antifibrotic or immunosuppressive pharmacotherapy. (9,11)

Anxiety and Depression

Anxiety and depression were assessed in 5 of 15 studies using the HADS. A dedicated 2023 systematic review of 5 RCTs (n=281) found that PR was not detrimental to psychological wellbeing and may improve anxiety in IPF and depression in sarcoidosis, though definitive conclusions were limited by the small evidence base. (23) Dowman et al. (2017) found no significant between-group difference in HADS anxiety following 8-week PR, though HADS depression scores trended toward improvement in the PR group. (7) Wallaert et al. (2020) reported significant improvements in depression scores in stage IV sarcoidosis patients following 10-week PR, with sustained trends at 12-month follow-up. (24)

Physical Activity

Free-living PA was objectively assessed by accelerometry in 4 studies. Perez-Bogerd et al. (2018) found no significant change in daily PA following 6-month PR, despite concurrent highly significant improvements in exercise capacity, muscle strength, and HRQoL. (16) This 'exercise capacity–physical activity translational gap' is a consistent finding across ILD rehabilitation research. (8) Wallaert et al. (2020) similarly found that PR-induced 6MWD improvements in sarcoidosis did not translate to sustained increases in daily PA at 12-month follow-up. (24) These findings underscore the need for targeted behavioral interventions, activity self-monitoring with feedback, and structured community maintenance programs to bridge this gap in CTD-ILD. (4,9)

Fatigue

Fatigue was assessed using CRQ fatigue domain, FSS, or equivalent instruments in 6 studies. Holland et al. (2008) reported significant CRQ fatigue domain improvement of +0.7 units/item ($p<0.05$) following 8-week exercise training. (6) Yakut et al. (2021) demonstrated significant fatigue reduction in SSc patients (CTD-ILD) on both CRQ fatigue domain and functional strength tests ($p<0.05$), mediated by both peripheral skeletal muscle adaptations and reduced ventilatory demand. (18) FSS demonstrated variable responsiveness across studies, reflecting the multidimensional fatigue in CTD-ILD influenced by systemic inflammation, medication effects, sleep disturbance, and psychological comorbidities. (10,23)

Survival and Hospitalization

Survival data were reported in 4 studies with adequate follow-up (Holland 2008, Dowman 2017, Perez-Bogerd 2018, Vainshelboim 2015). (6,7,16,22) In these four studies (291 participants), there were 5 deaths in PR groups versus 12 deaths in control groups during 6–12 month follow-up, representing a numerical trend toward reduced mortality with PR. (8) Vainshelboim et al. (2015) additionally found a statistically significant reduction in cardiorespiratory hospitalization rates in the ET group at 30-month follow-up. (22) However, no included study was powered to detect mortality differences, and all survival data should be regarded as exploratory and hypothesis-generating only. (8,22)

DISCUSSION

Summary of Main Findings

This systematic review synthesized evidence from 15 studies (n=1,002) to comprehensively evaluate PR effects across ten clinically relevant outcome domains in ILD and CTD-ILD. The central finding is that PR confers significant, consistent, and clinically meaningful improvements in exercise capacity (6MWD), HRQoL, dyspnea, peripheral muscle strength, and fatigue across ILD populations, including CTD-ILD subgroups. (6,7,8,16,17,18,19) A clinically important novel finding is that CTD-ILD patients sustain PR-induced improvements at 6-month follow-up more durably than IPF patients, (7) with direct implications for PR program prioritization, maintenance strategies, and patient selection in clinical practice. (9,10)

Exercise Capacity and the 6-Minute Walk Distance

The 6MWD emerged as the most sensitive and consistently responsive functional outcome across all 15 studies. The pooled mean improvement of +40 m (95% CI 32–47 m) in the 2021 Cochrane meta-analysis clearly exceeds the ILD-specific MCID of 25 m, affirming the clinical relevance of exercise training in this population. (8) The superior durability of 6MWD improvement in CTD-ILD compared to IPF likely reflects the more variable disease course of CTD-ILD, its partial responsiveness to immunosuppressive therapy, and greater preservation of functional reserve in many CTD-ILD patients. (7,10) Dowman et al. (2017) demonstrated this CTD-ILD-specific durability, providing a strong evidence base for prioritizing this patient group for PR referral. (7)

The head-to-head comparison of HIIT versus MICT by Nikolettou et al. (2023) demonstrated equivalence between modalities for 6MWD and other outcomes, providing clinically important flexibility for PR program design in CTD-ILD patients with musculoskeletal limitations. (19) This finding is concordant with the growing evidence base from COPD rehabilitation. (4,5)

Health-Related Quality of Life

Consistent and clinically significant HRQoL improvement across 9/12 studies and diverse instruments (SGRQ, CRQ, SF-36) provides compelling evidence that PR comprehensively addresses the subjective symptom burden of CTD-ILD beyond functional metrics. (3,8) The pooled SGRQ improvement of nearly 10 points exceeds the MCID of 4 points and represents meaningful patient-level change. (8) The CRQ showed consistent improvement across all four domains (dyspnea, fatigue, emotional function, mastery) in studies that measured it. (6,7) The 2023 ATS guideline cited moderate-quality evidence supporting HRQoL improvement, issuing a conditional recommendation for PR in ILD. (9)

Dyspnea: Addressing the Central Symptom Burden

Dyspnea is the cardinal symptom of CTD-ILD and the primary driver of disability, activity avoidance, reduced quality of life, and healthcare utilization. (3) Consistent dyspnea improvements across 13/15 studies—using mMRC, Borg, UCSD-SOBQ, and CRQ dyspnea domain—confirm that PR effectively addresses this central symptom burden. (6,7,16,17,18) Mechanisms include: peripheral physiological adaptations improving skeletal muscle oxidative capacity; reduced ventilatory demand at equivalent submaximal workloads; improved ventilatory efficiency; and reduced anxiety-mediated breathlessness amplification—all relevant to the multifactorial dyspnea pathophysiology in CTD-ILD. (4,10)

Pulmonary Function: Appropriate Scope of PR

The consistent finding that PR does not significantly improve FVC or DLCO across 9/9 measuring studies is both expected and scientifically coherent, and does not diminish the clinical value of PR. (8,18) Pulmonary fibrosis represents a structural disease process that requires antifibrotic or immunosuppressive pharmacotherapy for modification; PR targets the functional, symptomatic, and psychological consequences of fibrosis rather than the underlying pathobiology.

(2,9) This mechanistic distinction is essential for appropriate patient counseling and realistic goal-setting when prescribing PR in CTD-ILD clinical practice. (9,11)

Psychological Outcomes: Anxiety and Depression

Evidence for PR effects on anxiety and depression in ILD remains limited and clinically insufficient. The 2023 systematic review by Laframboise et al. (5 RCTs; n=281) found no statistically significant pooled effect, though favorable trends were observed for anxiety in IPF and depression in sarcoidosis. (23) This paucity reflects systematic underreporting of psychological outcomes in PR trials and underscores the urgent need for standardized inclusion of validated psychological instruments in future CTD-ILD PR trials. (23) Given the high prevalence of anxiety (25–40%) and depression (20–45%) in CTD-ILD and their association with reduced PR adherence and worse outcomes, psychological screening and targeted support should be core components of comprehensive CTD-ILD PR programs. (3,10,23)

Physical Activity: The Translational Challenge

A critical finding is the disconnect between improved exercise capacity and unchanged free-living PA in 3/4 studies objectively assessing both domains. (16,24) This 'exercise capacity–PA utilization gap' likely reflects complex multi-factorial determinants including persistent fear of dyspnea, loss of habitual patterns, absence of behavioral coaching, and environmental barriers. (4,10) PR programs for CTD-ILD should incorporate: (1) physical activity behavioral change counseling; (2) self-monitoring with wearable trackers and feedback; (3) progressive home exercise programs with clear activity targets; and (4) community maintenance programs to bridge this critical gap. (4,9,25)

Fatigue in CTD-ILD: A Multidimensional Target

Fatigue is pervasive and multidimensionally complex in CTD-ILD, profoundly reducing quality of life beyond its contribution to exercise limitation. (3,10) Improvements in CRQ fatigue domain and related instruments in 4/6 studies demonstrate that PR meaningfully reduces fatigue severity in ILD. (6,18) CTD-ILD patients particularly benefit from resistance training given frequent inflammatory myopathy (PM/DM-ILD), corticosteroid-induced proximal muscle weakness, or skeletal muscle disuse atrophy. (10,18) Future PR programs should integrate energy

conservation strategies, pacing, and activity scheduling to comprehensively address the multidimensional fatigue burden in CTD-ILD. (4,11)

Safety of PR in CTD-ILD

The consistent absence of exercise-related serious adverse events across all 15 studies (n=1,002; program durations 3 weeks to 6 months) is one of the most clinically practice-changing findings of this review. (8) This safety profile is particularly meaningful given the known exercise-induced oxygen desaturation in ILD and the cardiovascular risk of some CTD patients, particularly SSc-ILD with co-existing pulmonary arterial hypertension. (2,10) The four participant deaths across four studies were all attributed to disease progression unrelated to PR. (8) Recommended precautionary framework: pre-participation echocardiography (particularly for SSc-ILD), continuous SpO₂ monitoring during all sessions, supplemental oxygen for exercise-induced desaturation below 88–90%, and individualized intensity prescription based on CPET or 6MWT results. (9,24)

Optimal PR Program Design for CTD-ILD

Evidence-informed recommendations for CTD-ILD-specific PR programs: (1) Duration of 8–12 weeks for initial benefits; (7,8) 6-month programs provide greater magnitude and durability; (16) (2) Frequency of 2–3 supervised sessions/week complemented by structured home exercise; (7,9) (3) Combined aerobic training (60–80% peak WR) plus resistance training preferred over aerobic-only programs; (6,16) (4) Exercise intensity individualized from CPET with both HIIT and MICT yielding equivalent outcomes; (19) (5) Supplemental oxygen for SpO₂ ≤95% at rest or exercise-induced desaturation below 88%; (24) (6) Educational components addressing dyspnea management, pacing, and activity self-monitoring are essential; (4,9) (7) Telerehabilitation is an effective accessible alternative for patients with mobility limitations or geographic barriers. (25)

CTD-ILD Subtype-Specific Considerations

Different CTD subtypes present unique challenges requiring individualized PR modifications. SSc patients may have microstomia, digital ulcers, Raynaud's phenomenon, and pulmonary hypertension necessitating modified exercises and careful cardiovascular monitoring. (1,18) RA-ILD patients with articular involvement may require low-impact aerobic modalities and

joint protection principles in resistance training. (1,10) PM/DM-ILD patients with inflammatory myopathy may require an extended supervised strengthening phase before advancing high-intensity aerobic training. (2,10) These nuances underscore the imperative for individualized multidisciplinary CTD-ILD PR involving close rheumatology, pulmonology, physiotherapy, and occupational therapy collaboration. (9,11)

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This comprehensive systematic review provides robust, multi-domain evidence that PR is safe, feasible, and clinically effective in patients with ILD including CTD-ILD subgroups. (7,8,16,18) Across 15 studies and 10 outcome domains, PR consistently and significantly improved exercise capacity (6MWD +35–72 m), HRQoL (SGRQ –8 to –12 points), dyspnea, peripheral muscle strength, and fatigue, without serious adverse events attributable to the intervention. (6,7,16,17,18,21) Pulmonary function (FVC, DLCO) was appropriately unchanged by PR, consistent with its role in addressing functional consequences rather than structural fibrotic disease. (8,9,18)

A particularly clinically significant novel finding is that CTD-ILD patients sustain PR-induced improvements at 6-month follow-up more durably than IPF patients, (7) making them a high-priority subgroup for PR referral, enrollment, and maintenance programming. (9,10) PR programs of 8–12 weeks incorporating both aerobic and resistance exercise modalities at 2–3 sessions/week, with supplemental oxygen provision where indicated, represent the current evidence-based standard for CTD-ILD. (4,9,16) Both HIIT and MICT yield equivalent outcomes, permitting individualization to specific CTD subtype manifestations. (19)

Clinical Practice Recommendations

- PR should be considered standard-of-care and routinely recommended for all CTD-ILD patients with symptomatic exercise limitation, exertional dyspnea, or reduced HRQoL, consistent with 2023 ATS and ACR/CHEST guidelines; (1,9)

- PR programs for CTD-ILD must include both aerobic and resistance exercise components, individualized to the specific CTD subtype, systemic manifestations, and functional limitations; (4,18)
- Pre-participation echocardiography (to exclude significant pulmonary hypertension) and exercise SpO₂ monitoring are recommended; supplemental oxygen should be prescribed for desaturation below 88%; (9,24)
- PR programs should incorporate evidence-based behavioral change strategies, self-monitoring with wearable devices, and community maintenance programs to promote sustained daily physical activity beyond the supervised program period; (4,25)
- Patients with significant CTD-related musculoskeletal, vascular, or myopathic involvement should receive individualized modifications with multidisciplinary team input from physiotherapy, rheumatology, and occupational therapy; (10,11)
- Telerehabilitation is a clinically effective, safe, and equitable alternative PR delivery model for patients with mobility limitations, geographic barriers, or systemic CTD manifestations limiting outpatient attendance. (25)

Recommendations for Future Research

- Dedicated RCTs with adequate statistical power specifically enrolling CTD-ILD patients, stratified by CTD subtype (SSc, RA, PM/DM), are urgently needed to generate disease-specific PR evidence; (12,13)
- Future trials should incorporate minimum 12-month follow-up to evaluate durability of PR benefits and optimal maintenance strategies; (7,16)
- Optimal maintenance PR strategies (periodic booster sessions, home programs, telerehabilitation) should be evaluated in dedicated CTD-ILD maintenance RCTs; (17,25)
- Standardized inclusion of comprehensive psychological assessment (HADS, GAD-7, PHQ-9) and objective PA measurement (accelerometry) as mandatory secondary outcome domains in all future CTD-ILD PR trials; (23,24)

- Health economic analyses including cost-effectiveness of PR in CTD-ILD are warranted to support healthcare system funding and resource allocation decisions; (9)
- Biological and mechanistic studies examining inflammatory biomarkers, skeletal muscle metabolism, and exercise physiology in CTD-ILD patients undergoing PR may elucidate mechanisms and identify predictors of PR response; (2,10)
- CTD-ILD subtype-specific PR safety protocols (particularly for SSc-ILD with pulmonary hypertension and PM/DM-ILD with inflammatory myopathy) require dedicated investigation and formal evidence-based consensus. (1,18)

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