ORIGINAL ARTICLE

The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial

Leona M Dowman,[1,2,3,4] Christine F McDonald,[3,4,5] Catherine J Hill,[2,4] Annemarie L Lee,[4,6] Kathryn Barker,[7] Claire Boote,[7] Ian Glaspole,[8,9] Nicole S L Goh,[3,4,8] Anne M Southcott,[10] Angela T Burge,[1,4,6] Rebecca Gillies,[1,4] Alicia Martin,[7] Anne E Holland[1,4,6]

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For numbered affiliations see end of article.

Correspondence to
Leona M Dowman, La Trobe University/Alfred Health Clinical School, Level 4, The Alfred Centre, 99 Commercial Rd, Prahran, VIC 3181, Australia; leona.dowman@austin.org.au

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ABSTRACT

Background Uncertainty exists regarding the clinical relevance of exercise training across the range of interstitial lung diseases (ILDs).

Objective To establish the impact of exercise training in patients with ILDs of differing aetiology and severity.

Methods 142 participants with ILD (61 idiopathic pulmonary fibrosis (IPF), 22 asbestosis, 23 connective tissue disease-related ILD (CTD-ILD) and 36 with other aetiologies) were randomised to either 8 weeks of supervised exercise training or usual care. Six-minute walk distance (6MWD), Chronic Respiratory Disease Questionnaire (CRDQ), St George Respiratory Questionnaire IPF-specific version (SGRQ-I) and modified Medical Research Council dyspnoea score were measured at baseline, 9 weeks and 6 months.

Measurements and main results Exercise training significantly increased 6MWD (25 m, 95% CI 2 to 47 m) and health-related quality of life (CRDQ and SGRQ-I) in people with ILD. Larger improvements in 6MWD, CRDQ, SGRQ-I and dyspnoea occurred in asbestosis and IPF compared with CTD-ILD, but with few significant differences between subgroups. Benefits declined at 6 months except in CTD-ILD. Lower baseline 6MWD and worse baseline symptoms were associated with greater benefit in 6MWD and symptoms following training. Greater gains were seen in those whose exercise prescription was successfully progressed according to the protocol. At 6 months, sustained improvements in 6MWD and symptoms were associated with better baseline lung function and less pulmonary hypertension.

Conclusions Exercise training is effective in patients across the range of ILDs, with clinically meaningful benefits in asbestosis and IPF. Successful exercise progression maximises improvements and sustained treatment effects favour those with milder disease.

Trial registration number Results, ACTRN12611000416998.

Key messages

What is the key question?

- Does the aetiology and severity of disease impact the response to exercise training in patients with interstitial lung disease (ILD) and is there an optimal time for exercise training to occur to achieve maximal benefit?

What is the bottom line?

- Exercise training delivers clinically meaningful improvements in exercise capacity and quality of life for patients across the range of ILDs, especially those with asbestosis and idiopathic pulmonary fibrosis, with more lasting effects in those with milder disease.

Why read on?

- This is the first study to establish the effect of disease aetiology and markers of severity on response to exercise training in ILD, providing high-quality evidence supporting the role of exercise training in the clinical management of all patients with ILD.

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INTRODUCTION

Interstitial lung disease (ILD) is a disabling group of chronic lung conditions comprising over 200 different disease entities.[1] They are typically associated with interstitial inflammation,[2] and fibrosis as well as aberrant wound healing responses which appear to drive disease progression.[3] The clinical course is heterogeneous, but it is generally characterised by progressive morbidity[2 4] which can be chronic, irreversible and fatal.[5 6] Distressing dyspnoea, profound fatigue and reduced exercise tolerance are common[7] with consequent reductions in health-related quality of life (HRQoL).[8] Pulmonary hypertension, skeletal muscle dysfunction, arrhythmia and exercise-induced hypoxaemia can further complicate the clinical picture.[7 9 10] Treatment options are often limited and patients may eventually require lung transplantation.

Exercise training offers promise as a beneficial therapy for patients with ILD, with improvements in six-minute walk distance (6MWD), dyspnoea, HRQoL and peak exercise capacity.[11–13] Changes in 6MWD exceeded the minimal important difference (MID), suggesting benefits are clinically meaningful.[11] Nonetheless, recommendations for exercise training in clinical guidelines remain weak.[5 6] Existing randomised controlled trials

(RCTs) are small with methodological limitations, particularly with regard to lack of blinding and loss to follow-up. There are opposing views regarding which patients benefit most;[14 15] two studies suggest greater treatment effects in those with less functional impairment[14 16] while others[15 17] found greater improvements in those with more severe impairment. Furthermore, it has been suggested that patients with idiopathic pulmonary fibrosis (IPF) may improve less from exercise training than patients with other disease aetiologies.[11 14] In an uncontrolled study[14] patients with non-IPF ILD benefitted regardless of disease severity and were more likely to achieve longer-term symptomatic benefit than those with IPF. Therefore, the benefit of exercise training could vary according to disease severity and aetiology, and the timing of exercise training may matter for particular types of ILD.

Robust, adequately powered studies addressing the effects and timing of exercise training on ILD of different aetiologies are lacking. The primary aims of this study were to establish the impact of aetiology and severity of ILD on response to exercise training. The secondary aim was to identify an optimal time for exercise training to achieve maximal benefit.

METHODS

Study design and participants

This multicentre randomised, assessor-blinded, controlled trial, conducted at three tertiary hospitals in Melbourne, Australia, recruited patients with documented ILD who were clinically stable, ambulant, and reported dyspnoea on exertion despite maximal medical treatment (see online supplement). Exclusion criteria were concurrent and predominant respiratory disease other than ILD, a history of syncope on exertion, and any comorbidities that preclude exercise or participation in a supervised exercise programme within the previous 12 months. Participants were randomly allocated using consecutively numbered, sealed opaque envelopes to receive usual care or exercise training for 8 weeks. Randomisation was stratified according to four subgroups: IPF, dust-related ILD, connective tissue disease-related ILD (CTD-ILD) and other ILD. Those with IPF were further stratified for carbon monoxide transfer factor (TLCO) ≥ or <40%.[5 6] A researcher independent of the study completed the block randomisation using a web-based sequence generator (http://www.randomization.com). The study was registered (ACTRN12611000416998) and the protocol published.[18]

Intervention

Participants in the intervention group attended a twice-weekly supervised outpatient exercise training programme consisting of 30 min of aerobic exercise, cycling and walking, plus upper and lower limb resistance training.[18] Initial intensity for walking was 80% of peak walking speed achieved on the 6MWT, cycling at 70% of maximum work rate estimated from the 6MWT and resistance training at an initial load that corresponded to 10–12 RM (repetition maximum).[18] Exercise was progressed weekly and a home exercise programme prescribed. Supplemental oxygen was provided during training if necessary to maintain SpO_2 ≥88% and used during home exercise in participants prescribed ambulatory oxygen. The exercise training was conducted within the hospitals' pulmonary rehabilitation (PR) programmes which also included an education component that was available and recommended to all participants. The control group received once weekly telephone calls for general support. A detailed description of the intervention is in the online supplement.

Measurements

The primary outcome measure was change in 6MWD. The secondary outcome measures were knee extensor and elbow flexor strength (hand held dynamometry[19]), HRQoL (Chronic Respiratory Disease Questionnaire (CRDQ)[8] and St George Respiratory Questionnaire IPF specific version (SGRQ-I)[20]), dyspnoea (University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ)[21] and Modified Medical Research Council dyspnoea (MMRC) scale[22]), anxiety and depression (Hospital Anxiety and Depression Scale (HADS)[23]) and global rating of change. These were assessed at baseline, 9 weeks and 6 months by an assessor blinded to group allocation. Spirometry, TLCO, lung volumes and echocardiographic assessment of pulmonary artery systolic pressure (PASP) were measured at baseline. Spirometry and TLCO were repeated at 6 months. Current comorbidities, the use of oxygen or pharmacological therapies were also documented (see online supplement).

Statistical analysis

Based on effects seen in our previous study,[24] 22 participants with dust-related ILD and 22 with CTD-ILD were required to detect a mean (SD) difference in 6MWD with 80% power between groups of 52 (40) m and 38 (30) m respectively.[24 25] For participants with IPF, to detect differences of 29 or 34 m (SD 43 m) with 80% power, representing the upper and lower limits of the MID in IPF[25] required 72 and 54 participants respectively. Patients with other ILD diagnoses were also recruited for a total of 142 participants. Data analysis was according to intention-to-treat (ITT) principles. Between-group differences were evaluated using linear mixed models with three fixed effects: group (exercise or control), time (baseline, 9 weeks and 6 months), and a group×time interaction. Baseline data were used as a covariate. Subgroup analyses were performed with addition of a subgroup category (IPF, dust-related ILD and CTD-ILD) and all possible interactions. Analysis of the other ILD subgroup was not performed as it represented a heterogeneous group of disease entities and not a distinct ILD subtype. Two per-protocol analyses were defined a priori including (1) those who completed the programme (attendance at 12 out of 16 sessions)[24] and (2) those whose exercise training prescription was progressed according to the protocol. Categorical data were analysed using the Pearson χ^2 test. Stepwise multiple linear regression was undertaken using backward elimination to identify independent predictors of change in 6MWD and symptoms. Receiver operating characteristic (ROC) curve analysis identified thresholds at which exercise training became less effective, using established MIDs for change in 6MWD,[25] CRDQ dyspnoea and fatigue.[26] All analyses were performed using SPSS V.20 (SPSS, Chicago, Illinois, USA). A $p<0.05$ was considered statistically significant. Further statistical details are described in the online supplement.

RESULTS

Between November 2011 and June 2014, 296 patients with ILD were screened and 142 were randomised (figure 1). Sixty-one participants had IPF, 22 had dust-related ILD (all asbestosis), 23 had CTD-ILD and 36 had other diagnoses (see online supplement). Forty-nine (66%) participants in the intervention group completed the exercise programme. No adverse events occurred during exercise training. Follow-up data were available for 95% and 88% of participants at 9 weeks and 6 months respectively.

There were no baseline differences between the intervention and control groups for the entire ILD population, except for

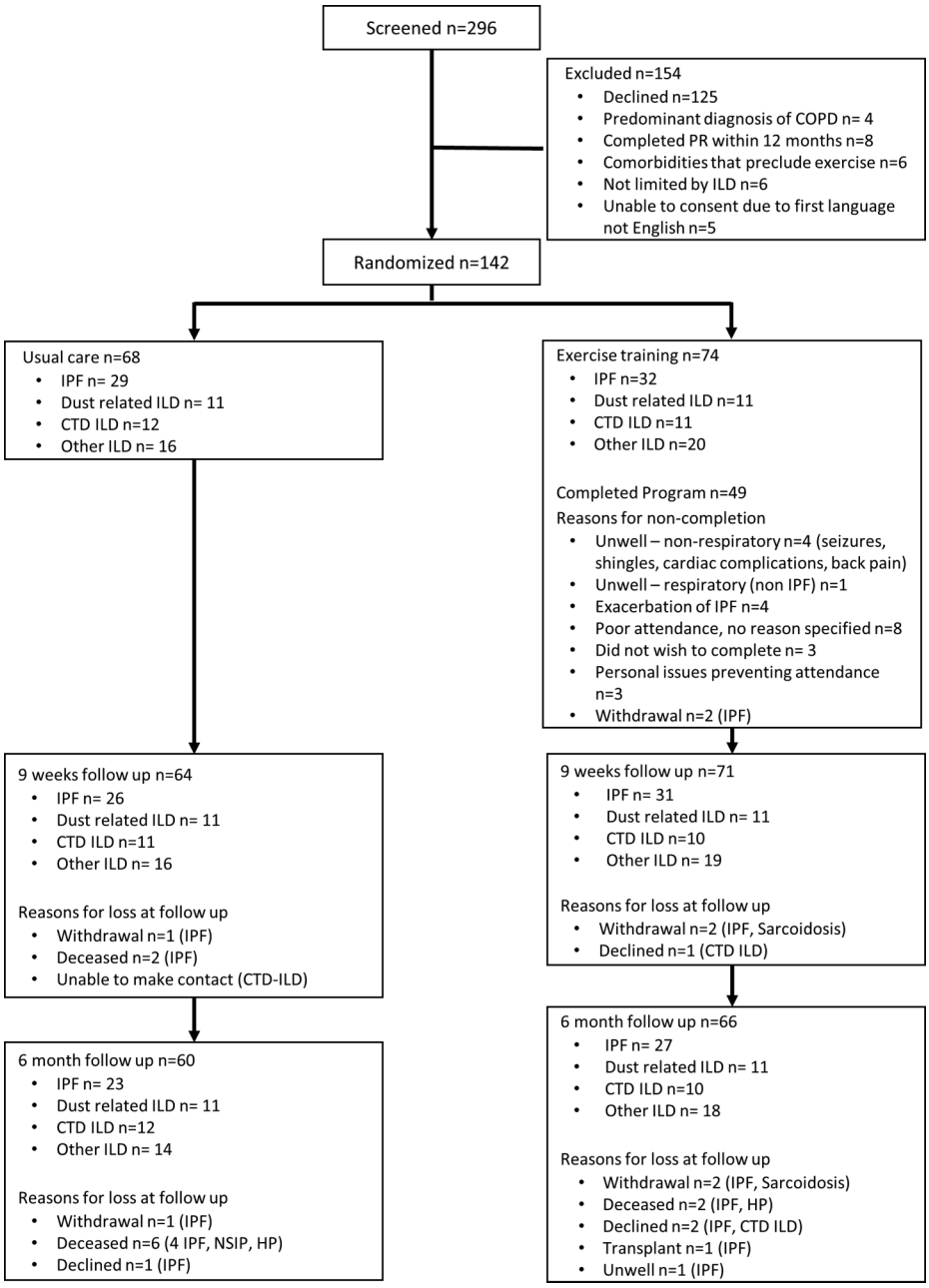

Figure 1 Flow of participants through the study. CTD-ILD, connective tissue disease-related ILD; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia.

HRQoL and use of exertional oxygen (table E1, online supplement), or across subgroups, except for MMRC dyspnoea (table 1). Those with IPF had lower baseline 6MWD (mean (SD): 430 (128) m) than those with asbestosis (475 (93) m) or CTD-ILD (505 (88) m, p=0.02). A small, non-significant, reduction in pulmonary function occurred at 6 months in the entire ILD population and the IPF subgroup (table 2). Twenty-seven (38%) participants received supplemental oxygen during exercise training and SpO_2 was maintained above 88% in 22 (81%) participants. Home diary review revealed that 40 (54%) participants in the intervention group achieved the three recommended home exercise sessions per week, averaging 2.4 sessions per week and 22 min per session. A similar pattern was demonstrated across the subgroups (table E2 in online supplement).

Clinical outcomes: all ILD

The 6MWD significantly improved following exercise training with a mean difference to control (95% CI) of 25 m (2 to 47 m). This improvement was not sustained at 6 months (table 3), with a significant decline in both groups (figure 2). The intervention group demonstrated significant short-term improvements in all CRDQ and SGRQ-I domains, except SGRQ-I impact score (table 3). A significant decline from 9 weeks to 6 months was seen in CRDQ mastery, SGRQ-I impact and SGRQ-I total in the exercise group (figures E1 and E2, online supplement). There was a trend towards reduced anxiety in the intervention group at 9 weeks (p=0.06) that was lost at 6 months (figure E3a, online supplement). There was no significant change in depression (figure 3B, online supplement). Only 8% and 16% of participants respectively had clinically significant depression and anxiety at baseline (HADS score ≥11).[27] No significant differences between groups were evident for dyspnoea, knee extensor or elbow flexor strength (table 3). The global rating of change showed that perceived walking ability improved in 50% of intervention participants and 17% in the control group following the intervention period (p<0.001), with a similar response for symptom improvement (50% vs 12%, p<0.001).

Table 1 Baseline characteristics of participants for each subgroup

	IPF			Asbestosis			CTD-ILD		
	Usual care n=29	Exercise training n=32	p Value	Usual care n=11	Exercise training n=11	p Value	Usual care n=12	Exercise training n=11	p Value
Age (years)	73 (9)	70 (10)	0.4	72 (9)	72 (7)	0.1	65 (11)	63 (10)	0.6
Gender, male	20 (69%)	21 (66%)	0.8	11 (100%)	11 (100%)		3 (25%)	1 (9%)	0.3
Oxygen therapy									
Long term	4 (14%)	2 (6%)	0.4	0 (0%)	0 (0%)		1 (8%)	0 (0%)	1.0
Exertional	10 (35%)	5 (16%)	0.1	2 (18%)	0 (0%)	0.2	1 (8%)	1 (9%)	1.0
Treatment									
Prednisolone	10 (35%)	5 (16%)	0.1	0 (0%)	0 (0%)		6 (50%)	7 (64%)	0.7
Immunosuppressant	3 (10%)	0 (0%)	0.1	0 (0%)	0 (0%)		2 (17%)	5 (46%)	0.2
Pirfenidone	1 (3%)	1 (3%)	1.0	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Nintedanib	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
N-Acetylcysteine	2 (7%)	0 (0%)	0.2	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
FVC (%pred)	78 (19)	74 (18)	0.4	78 (14)	85 (19)	0.3	71 (26)	78 (16)	0.5
TLCO (%pred)	49 (11)	50 (17)	0.1	54 (15)	54 (12)	1.0	51 (14)	53 (18)	0.7
TLC (%pred)	77 (13)	75 (15)	0.6	80 (17)	91 (22)	0.2	78 (17)	82 (19)	0.7
PASP (mm Hg)	37 (11)	35 (16)	0.4	34 (12)	28 (12)	0.3	30 (10)	28 (6)	0.7
6MWD (m)	398 (166)	456 (126)	0.1	498 (113)	453 (67)	0.3	486 (99)	526 (74)	0.3
Knee extensor strength (kg)	19 (7)	21 (6)	0.2	24 (7)	20 (4)	0.05	18 (5)	20 (5)	0.5
MMRC dyspnoea	2 (1)	2 (1)	0.3	2 (0.7)	1 (0.5)	0.5	2 (0.7)	1 (0.4)	**0.04**
Total CRDQ score	83 (23)	83 (22)	1.0	82 (15)	90 (21)	0.3	87 (16)	96 (19)	0.2
Total SGRQ-I score	55 (19)	49 (18)	0.2	53 (17)	45 (17)	0.3	48 (20)	41 (16)	0.1
UCSD SOBQ score	47 (20)	39 (23)	0.2	41 (19)	37 (24)	0.6	43 (25)	28 (16)	0.1
HADS anxiety	6 (4)	6 (4)	0.9	7 (2)	6 (4)	0.4	8 (5)	6 (4)	0.3
HADS depression	6 (4)	5 (3)	0.2	5 (3)	6 (3)	0.7	6 (3)	4 (3)	0.3
Comorbidities									
Hypertension	11(38%)	10 (34%)	0.6	6 (55%)	4 (36%)	0.7	6 (50%)	2 (18%)	0.2
Ischaemic heart disease	8 (28%)	5 (16%)	0.4	2 (18%)	5 (46%)	0.4	0 (0%0	0 (0%)	
Gastro-oesophageal reflux	3 (10%)	8 (25%)	0.2	1 (9%)	0 (0%)	1.0	3 (25%)	2 (18%)	1.0
Osteoarthritis	10 (35%)	10 (31%)	1.0	3 (27%)	3 (27%)	1.0	2 (17%)	2 (18%)	1.0
Rheumatoid arthritis	1 (3%)	1(3%)	1.0	0 (0%)	0 (0%)		5 (42%)	5 (46%)	1.0
Diabetes	10 (35%)	7 (22%)	0.4	4 (36%)	3 (27%)	1.0	1 (8%)	2 (18%)	0.6
Chronic back pain	2 (7%)	3 (9%)	1.0	2 (18%)	1 (9%)	1.0	2 (17%)	0 (0%)	0.5
Obstructive sleep apnoea	2 (7%)	4 (13%)	0.7	1 (9%)	0 (0%)	1.0	0 (0%)	0 (0%)	
COPD	3 (10%)	1 (3%)	0.3	0 (0%)	0 (0%)		1 (8%)	0 (0%)	1.0
Osteoporosis	2 (7%)	1 (3%)	0.6	0 (0%)	0 (0%)		1 (8%)	1 (9%)	1.0

Values are mean (SD) or n (%).
6MWD, six-minute walk distance; %pred, per cent predicted; CRDQ, Chronic Respiratory Disease Questionnaire; CTD, connective tissue disease; HADS, Hospital Anxiety and Depression Scale; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MMRC, Modified Medical Research Council; PASP, pulmonary artery systolic pressure; SGRQ-I, St George Respiratory Questionnaire IPF specific version; TLC, total lung capacity; TLCO, carbon monoxide transfer factor; UCSD SOBQ, University College of San Diego Shortness of Breath Questionnaire.

Table 2 Change in pulmonary function over the duration of study

	FVC %pred				TLCO %pred			
	Baseline	6 months	Change	p Value	Baseline	6 months	Change	p Value
ILD n=142	76.3 (18.3)	74.9 (19.7)	−1.4	0.1	50.7 (14.9)	50.3 (16.5)	−0.4	0.6
IPF n=61	76.9 (17.4)	75.4 (20.3)	−1.6	0.3	49.5 (15.0)	48.5 (16.5)	−1.0	0.5
Asbestosis n=22	76.4 (20.0)	81.5 (16.5)	5%	0.09	54.5 (15.4)	55.6 (13.0)	1.1	0.7
CTD-ILD n=23	75.5 (22.0)	78.9 (20.4)	0.3	0.08	53.6 (15.8)	54.7 (17.2)	1.1	0.6

Values are mean (SD).
CTD, connective tissue disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; %pred, % predicted; TLCO, carbon monoxide transfer factor.

Impact of disease aetiology

The largest changes following the intervention occurred in those with asbestosis for 6MWD (figure 3), SGRQ-I (figure 4), all CRDQ domains except dyspnoea (figure E4, online supplement) and MMRC dyspnoea (figure E5, online supplement), followed by those with IPF, with the smallest

Table 3 Differences between exercise and control groups following the intervention

	9 week follow-up		p Value		
	Mean difference (95% CI)	6 month follow-up	Group	Time	Group×time
6MWD (m)	25 (2 to 47)	21 (−3 to 44)	**0.03**	**<0.001**	0.7
Knee extensor strength (kg)	1.3 (−0.1 to 2.6)	0.8 (−0.7 to 2.2)	0.1	0.5	0.5
Elbow flexor strength (kg)	0.3 (−0.7 to 1.3)	−0.2 (−1.2 to 0.8)	0.9	**0.003**	0.4
CRDQ Dyspnoea	2.5 (0.6 to 4.3)	1.2 (−0.7 to 3.1)	**0.02**	0.7	0.2
CRDQ Fatigue	2.6 (1.1 to 4.1)	1.4 (−0.3 to 2.9)	**0.003**	0.1	0.1
CRDQ Emotional function	3.3 (1.0 to 5.6)	2.0 (−0.3 to 4.4)	**0.008**	0.2	0.3
CRDQ Mastery	3.3 (1.4 to 5.2)	0.4 (−1.5 to 2.3)	**0.02**	**0.004**	**0.01**
SGRQ-I Symptoms	−9.0 (−15.4 to −2.5)	−9.0 (−15.5 to −2.2)	**0.001**	1.0	1.0
SGRQ-I Activity	−5.9 (−11.2 to −0.4)	−4.0 (−9.5 to 1.5)	**0.04**	0.8	0.5
SGRQ-I Impact	−6.4 (−11.4 to −1.4)	0.6 (−4.5 to 5.7)	0.2	0.9	**0.006**
SGRQ-I Total	−5.8 (−9.7 to −1.9)	−1.4 (−5.4 to 2.7)	**0.04**	1.0	**0.04**
UCSD SOBQ	3.2 (−2.7 to 9.1)	−0.007 (−6.0 to 6.0)	0.6	0.01	0.2
MMRC dyspnoea scale	−0.3 (−0.5 to 0.04)	−0.2 (−0.5 to 0.05)	**0.06**	0.6	1.0

Data are estimated marginal means, exercise group – control group derived from linear mixed models. p Values are for group effect (between-group difference independent of time), time effect (change over time independent of group) and group×time interaction.
p Values <0.05 were considered statistically significant.
Positive increase represents improvement except for MMRC, UCSD SOBQ and SGRQ-I.
6MWD, six-minute walk distance; CRDQ, Chronic Respiratory Disease Questionnaire; IPF, idiopathic pulmonary fibrosis; MMRC, Modified Medical Research Council; SGRQ-I, St George Respiratory Questionnaire IPF-specific version; UCSD SOBQ, University College of San Diego Shortness of Breath Questionnaire.

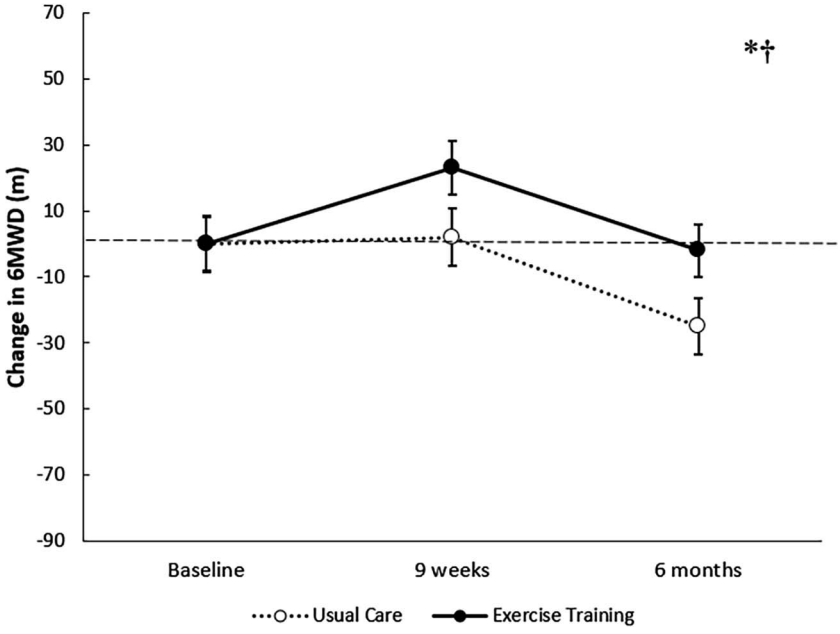

Figure 2 Change in six-minute walk distance. Data are raw mean (SE), *p<0.05, exercise versus control group, †p<0.05, significant change over time, no significant group×time interaction.

benefit often seen in those with CTD-ILD. Those with asbestosis and CTD-ILD had significantly greater improvements in the SGRQ-I symptoms compared with those with IPF (table 4). Regardless of group allocation, those with CTD-ILD had significantly better SGRQ-I impact and total scores at 9 weeks (table 4) and 6 months (figure 4). The 6MWD (figure 3) and CRDQ (figure E4, online supplement) improved at 6 months in those with CTD-ILD but declined in those with IPF and asbestosis; this different response over time reached significance only for CRDQ emotional function and mastery (table 4). There were no other significant differences between subgroups (table 4), including anxiety and depression (tables E3 and E4, online supplement). The CTD-ILD subgroup had a greater percentage of participants (50%) who did not improve in 6MWD than those with IPF (30%) and asbestosis (18%), with a similar trend for CRDQ fatigue (50% vs 33% vs 27%). There were no significant baseline differences between those who improved and those who did not improve in any subgroup.

Programme completion and exercise progression

A per-protocol analysis that included only those participants in the intervention group who completed the programme showed a greater increase in 6MWD (mean 27 m (95% CI 2 to 52 m, figure 5A). However, a per-protocol analysis including only those participants who were able to progress their exercise intensity according to the protocol showed a larger improvement in 6MWD (37 m, 95% CI 11 to 64 m, figure 5B). A similar pattern was demonstrated within diagnostic subgroups (table 5), and for HRQoL (table E5, online supplement). There were no significant differences between those who successfully completed the programme or progressed their exercise intensity and those who did not (table E6, online supplement).

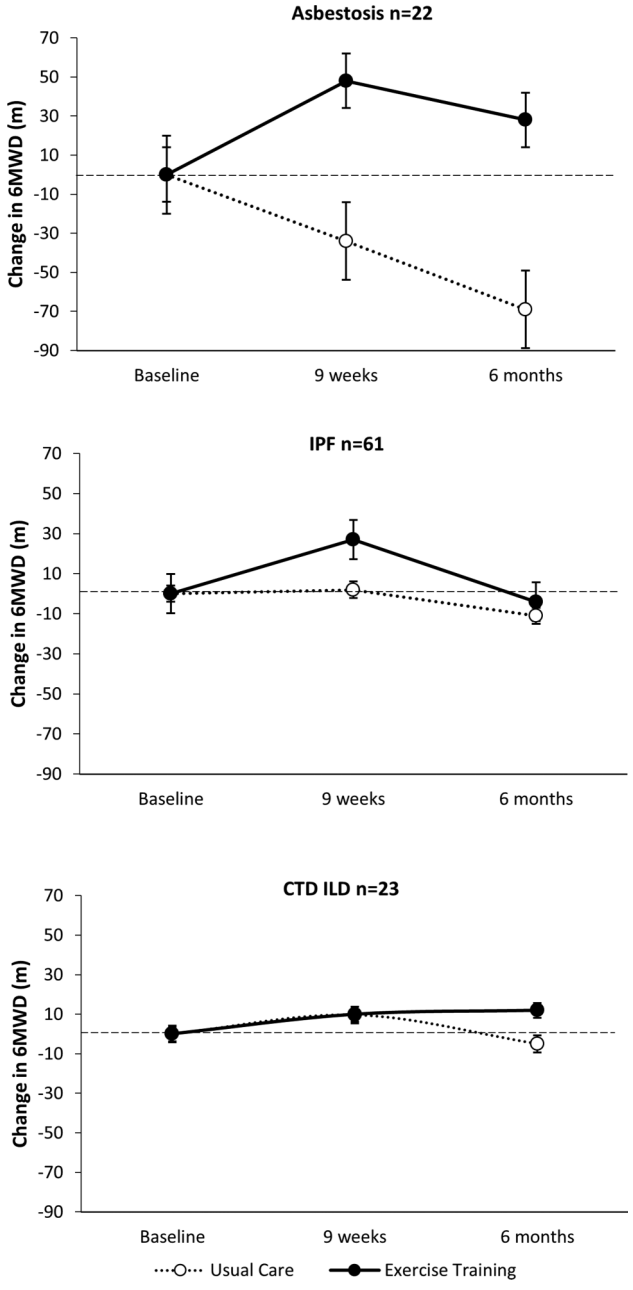

Figure 3 Change in six-minute walk distance for each subgroup. Data are raw mean (SE), no significant difference between subgroups or subgroup×group×time interactions.

Predictors of response to exercise

In a stepwise multiple regression model that included subgroup, group allocation and baseline variables with a significant relationship to change in 6MWD (table E7, online supplement), lower baseline 6MWD and allocation to exercise training predicted greater improvement in 6MWD at 9 weeks (table 6). For every 10 m increase in baseline 6MWD, the gain in 6MWD at 9 weeks declined by 1.4 m. Better physiological markers of disease severity predicted long-term gains in 6MWD, with no effect of group allocation. For every 10 mm Hg decrease in PASP or 100 mL increase in FVC, 6MWD increased at 6 months by 15 or 2.1 m respectively. These models explained 15% and 13% of the variation in exercise response at 9 weeks and 6 months respectively (table 6). A similar pattern was seen for change in symptoms (table E8, online supplement).

The ROC curve analysis indicated a baseline 6MWD threshold of 477 m above which exercise training was less likely to achieve 6MWD improvements exceeding the MID[27] (sensitivity 75%, specificity 55%, area under the curve (AUC) 67%, p=0.005). A PASP threshold ≥31.5 mm Hg predicted less likelihood of achieving the MID at 6 months (sensitivity 76%, specificity 54%, AUC 63%, p=0.05). A PASP ≥31.5 mm Hg (p=0.001) also predicted, with better accuracy, less impact of exercise training on CDRQ fatigue (figure E6, online supplement). The ROC analysis could not identify a suitable threshold for lung function to predict long-term outcome in 6MWD or symptoms. The CTD-ILD and the IPF subgroup, respectively, had the greatest percentage of participants above the 6MWD (78%) and the PASP (55%) thresholds (see online supplement).

DISCUSSION

This is the largest RCT of exercise training in ILD and the first to establish the impact of aetiology and disease severity on response to exercise training. We demonstrated clinically important improvements in 6MWD, symptoms and HRQoL following exercise, strengthening previous findings[11–13] and providing convincing evidence for exercise training to be adopted as a recommended treatment for all patients with ILD. We confirmed that people with asbestosis and IPF, and to a lesser extent CTD-ILD, receive clinically meaningful benefits and that disease severity predicts long-term benefit with sustained treatment effects favouring milder disease. A further novel finding was that successful adherence to exercise progression maximises the benefits.

The overall mean 6MWD improvement of 25 m was smaller than the MID (30–33 m) for people with ILD[25] and smaller than previously reported, (35 m)[24] despite equivalent disease severity and proportion of IPF participants. This could be attributed to the greater proportion of participants with CTD-ILD who experienced minimal change in 6MWD. Nonetheless improvements in CRDQ dyspnoea, fatigue and emotional function exceeded the MID.[26] The MID for the SGRQ-I-specific version has not been established; however, improvements in SGRQ-I symptoms and activity exceeded the MID for the standard SGRQ for IPF.[28] Together with the global rating of change scores, this suggests the impact of exercise training on health status was clinically significant and improvements were important to patients.

Despite the known diversity between ILD subgroups, the exercise response was not decidedly heterogeneous. Improvements achieved in those with asbestosis exceeded the MID for 6MWD,[25] symptoms and HRQoL[26 28 29] and were comparable to previous reports in a combined cohort of dust-related pleural and interstitial respiratory diseases.[13] Participants with IPF experienced smaller gains, in accordance with previous investigations[11 14 24] but improvements achieved fell within the MID range for 6MWD[25] and exceeded the MID for HRQoL,[26 28] suggesting that exercise training is equally effective in IPF. The mean 6MWD improvement of 31 m was less than previously reported (46 and 81 m),[12 30] however this could be attributed to the lack of blinding and ITT analyses in these studies, resulting in an overestimation of treatment effect. Additionally, our study may not have been optimally powered for IPF, as we did not achieve the larger sample size needed to detect mean effects equivalent to the lower estimates of the MID for 6MWD. Despite the limited improvement in those with CTD-ILD, some symptomatic benefit was achieved with changes in CRDQ dyspnoea and SGRQ-I symptoms exceeding

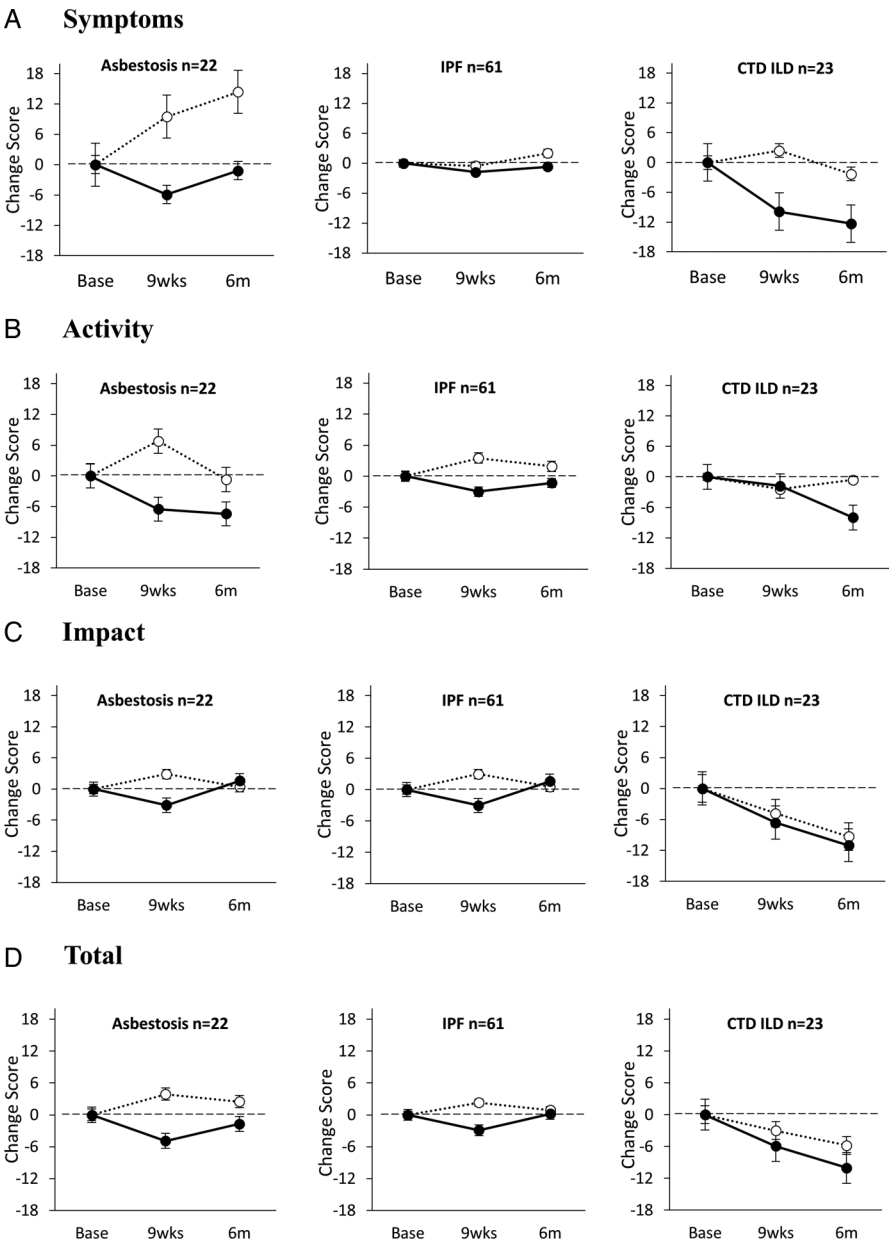

Figure 4 Change in health-related quality of life (St George Respiratory Questionnaire IPF specific version, SGRQ-I) for each subgroup. Data are raw mean (SE), *p<0.05, significant difference between subgroups, no significant subgroup×group×time interactions, a reduction in scores represents an improvement.

the MID.[26 28] Additionally, aetiology or severity of ILD did not predict short-term improvement in 6MWD or symptoms. This suggests that exercise training may be efficacious across the entire spectrum of disease in achieving short-term improvements.

Patients with high baseline 6MWDs received less benefit following exercise training, consistent with previous studies.[15] This could be regression to the mean, although the RCT design and ITT analyses would mitigate this effect.[31 32] Alternatively, a ceiling effect of the 6MWT may have masked the efficacy of exercise training in these patients. A ceiling effect has been previously documented in 6MWDs above 450 m in patients with pulmonary hypertension.[33] This is consistent with our ROC analysis which identified a baseline 6MWD threshold ≥477 m where exercise training became less effective. Therefore, an alternate measure of functional capacity with a higher ceiling effect such as incremental shuttle walk test[34 35] may be more sensitive in detecting change in people with high baseline 6MWDs.

Markers of disease severity were the only predictors of 6MWD at 6 months. This is consistent with previous reports[14] which found greater and more sustained benefits of exercise training in milder disease. As such, engaging in exercise training when the impact of the disease on physiological parameters is milder may assist in preserving benefits. This does not imply that exercise training is ineffective in more severe disease. Our sample, although consisting largely of those with moderate disease, included a wide range of disease severity; yet respiratory or circulatory impairment did not predict short-term benefits. In addition, the baseline threshold beyond which exercise training became ineffective was weak for PASP and indeterminate for FVC. We therefore do not advocate the use of any specific lung function, symptom severity or ROC thresholds to exclude patients from PR. Additionally, patients awaiting lung transplantation, including those with advanced ILD, can achieve gains with PR,[36] and post-transplant PR can further improve patients' exercise capacity and functional outcomes.[37 38] Therefore, all patients with ILD should be provided with the

Table 4 Between-group differences following the intervention for each subgroup

	Mean difference (95% CI)			p Value			
	Asbestosis n=22	IPF n=61	CTD-ILD n=23	Group	Time	Subgroup	Group×Subgroup×Time
6MWD (m)							
9 weeks	68 (10 to 124)	31 (−5 to 66)	3 (−53 to 60)	**0.006**	**0.008**	0.73	0.18
6 months	92 (36 to 148)	0.9 (−36 to 38)	21 (−35 to 77)				
CRDQ Dyspnoea							
9 weeks	1.5 (−3.1 to 6.2)	3.1 (0.1 to 6.0)	2.8 (−2.0 to 7.5)	**0.05**	0.59	0.27	0.61
6 months	−0.2 (−4.9 to 4.5)	1.5 (−1.5 to 4.6)	3.6 (−1.1 to 8.2)				
CRDQ Fatigue							
9 weeks	4.1 (0.4 to 7.7)	2.0 (−0.3 to 4.3)	−0.4 (−4.1 to 3.4)	**0.05**	0.46	0.99	0.17
6 months	1.4 (−2.2 to 5.1)	1.1 (−1.3 to 3.5)	1.8 (−1.9 to 5.4)				
CRDQ Emotion function							
9 weeks	5.3 (−0.5 to 11.0)	3.0 (−0.7 to 6.6)	−0.8 (−6.7 to 5.1)	**0.05**	0.79	0.88	0.18*
6 months	4.6 (−1.1 to 10.4)	1.2 (−2.6 to5.0)	1.9 (−3.9 to 7.7)				
CRDQ Mastery							
9 weeks	4.9 (0.4–9.5)	3.7 (0.8 to 6.5)	−2.0 (−6.8 to 2.6)	**0.07**	0.05	0.99	**0.005***
6 months	2.2 (−2.4 to 6.8)	−0.7 (−3.7 to 2.3)	3.1 (−1.5 to 7.7)				
SGRQ-I Symptoms							
9 weeks	−19.8 (−37.3 to −3.4)	−3.9 (−13.4 to 5.6)	−9.9 (−25.4 to 5.6)	**<0.001**	0.67	**0.03**	0.50
6 months	−19.9 (−37.5 to −3.2)	−4.7 (−14.8 to 5.4)	−9.9 (−25.1 to 5.3)				
SGRQ-I Activity							
9 weeks	−14.6 (−30 to −0.9)	−7.2 (−15.6 to 1.1)	0.1 (−13.6 to 13.8)	**0.03**	0.29	0.42	0.65
6 months	−8.0 (−21.4 to 5.4)	−3.0 (−11.8 to 5.8)	−8.2 (−21.6 to 5.2)				
SGRQ-I Impact							
9 weeks	−7.4 (−18.4 to 3.7)	−6.4 (−13.3 to0.5)	−2.0 (−13.2 to 9.3)	0.22	0.72	**0.003**	0.50
6 months	0.1 (−11.1 to 10.9)	0.8 (−6.5 to 8.1)	−2.7 (−13.7 to 8.4)				
SGRQ-I Total							
9 weeks	−9.6 (−18.3 to −0.4)	−5.7 (−11.1 to 0.3)	−2.8 (−11.6 to 6.0)	**0.01**	0.78	**0.004**	0.56
6 months	−5.0 (−13.6 to 3.7)	−0.8 (−6.5 to 5.0)	−4.6 (−13.3 to 4.1)				
MMRC Dyspnoea scale							
9 weeks	−1.0 (−1.7 to −0.3)	0.009 (−0.4 to 0.5)	−0.1 (−0.8 to 0.6)	**0.03**	0.81	0.31	0.36
6 months	−0.7 (−1.4 to −0.005)	−0.3 (−0.8 to 0.1)	−0.06 (−0.8 to 0.7)				
UCSD SOBQ							
9 weeks	−13.5 (−27.9 to 0.9)	6.5 (−2.5 to 15.6)	13.5 (−1.2 to 28.2)	0.94	0.23	0.31	0.13
6 months	−7.5 (−21.8 to 6.9)	−0.2 (−9.7 to 9.2)	−0.4 (−14.9 to 14.2)				
Knee extensor strength (kg)							
9 weeks	−0.6 (−4.1 to 2.8)	2.0 (−0.1 to 4.2)	0.7 (−2.7 to 4.2)	0.46	0.99	0.73	0.5
6 months	−1.8 (−5.2 to 1.5)	1.0 (−1.3 to 3.3)	2.1 (−1.3 to 5.5)				
Elbow flexor strength (kg)							
9 weeks	−1.8 (−4.1 to 0.6)	1.0 (−0.5 to 2.5)	0.04 (−2.3 to 2.4)	0.62	0.03	0.52	0.37
6 months	−0.2 (−2.5 to 2.2)	−0.3 (−1.8 to 1.3)	−0.5 (−2.8 to 1.9)				

Data are estimated marginal means for exercise group – control group derived from linear mixed models. p Values are for group effect (between-group difference independent of time), time effect (change over time independent of group), subgroup (differences in subgroups independent of time and group) and subgroup×group×time interaction.
p Values <0.05 were considered statistically significant.
*p<0.05 subgroup×time. There were no significant group×time or group×subgroup interactions. Positive increase represents improvement except for MMRC, UCSD SOBQ and SGRQ-I.
6MWD, six-minute walk distance; CRDQ, Chronic Respiratory Disease Questionnaire; CTD, connective tissue disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MMRC, Modified Medical Research Council; SGRQ-I, St George Respiratory Questionnaire IPF-specific version; UCSD SOBQ, University College of San Diego Shortness of Breath Questionnaire.

opportunity to undertake exercise training, although an early referral is recommended to promote longer-lasting effects. Other strategies such as a longer-term intervention, maintenance exercise programmes or recurrent bouts of exercise training may also promote longer-lasting improvements but further research is needed in this important area.

The lack of improvement in 6MWD seen in people with CTD-ILDs was disappointing but could be attributed to the 6MWT's ceiling effect. The CTD-ILD subgroup had higher baseline 6MWDs and a greater percentage of participants above the 6MWD threshold. Additionally, the CTD-ILDs are commonly associated with systemic manifestations such as joint pain, joint swelling, muscle weakness and muscle pain.[4] Despite some clinically meaningful benefits in HQRoL, there was limited change in majority of outcomes, therefore the standard exercise training principles used in COPD may be less effective in minimising the impact of these systemic manifestations. Other modalities such as hydrotherapy or resistance training may be more suitable in achieving benefits, neither of which has been investigated in ILD or CTD-ILD.

The progression of exercise training loads is crucial if physiological adaptations are to occur. Improvement in exercise

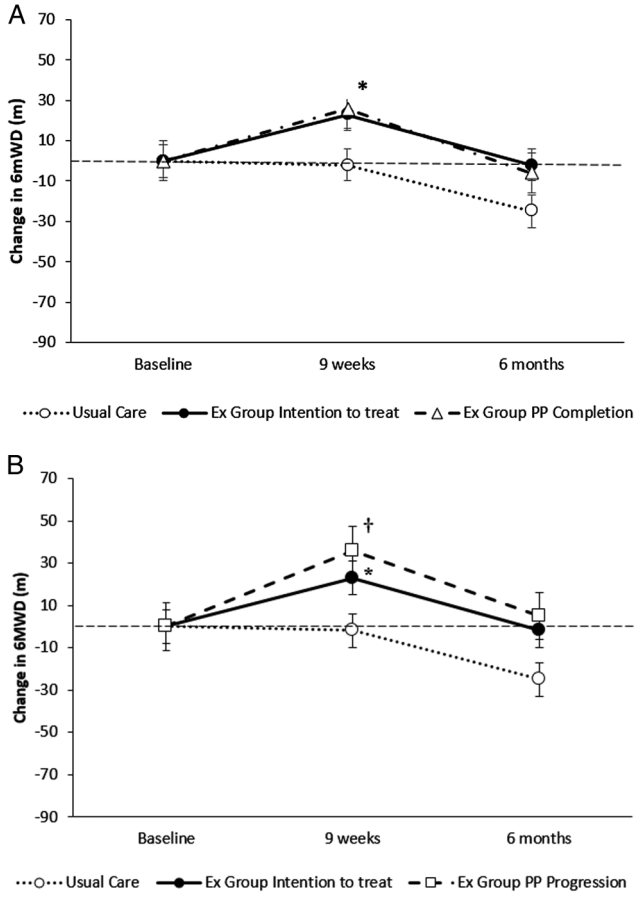

Figure 5 Comparison of change in six-minute walk distance (6MWD) between intention to treat analysis and (A) per-protocol analysis for programme completion; (B) per-protocol analysis for exercise progression. Data are raw mean (SE). *p<0.05, †p<0.01, exercise versus control group. PP, per-protocol.

Table 5 Comparison of change in 6MWD between intention to treat and per protocol analyses for each subgroup

	Mean difference (95% CI)	
	9 week follow-up	6 month follow-up
IPF		
ITT n=29/32	31 (−5 to 66)	0.9 (−36 to 38)
PP Completion n=29/15	26 (−14 to 67)	−18 (−63 to 26)
PP Progression n=29/16	55 (13–97)	15 (−30 to 60)
Asbestosis		
ITT n=11/11	68 (10 to 124)	92 (36 to 148)
PP Completion n=11/10	75 (19 to 132)	93 (38 to148)
PP Progression n=11/10	75 (19 to 132)	93 (38 to148)
CTD-ILD		
ITT n=12/11	3 (−53 to 60)	21 (−35 to 77)
PP Completion n=12/6	14 (−50 to 78)	38 (−25 to 101)
PP Progression n=12/6	14 (−50 to 78)	38 (−25 to 101)

Values are mean difference (SE). Data are exercise group − control group. n=number of participants in usual care group/exercise training group for the corresponding analysis.
6MWD, six-minute walk distance; CTD, connective tissue disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ITT, intention to treat; PP, per protocol.

Table 6 Stepwise multiple linear regression model for change in 6MWD following intervention

	B	SE of B	Standardised β	p Value	R^2 (%)
Change from baseline to 9 weeks					
Constant	58.468	21.572		**0.008**	
Group	36.595	11.722	−0.296	**0.002**	
Baseline 6MWD (m)	−0.141	0.045	0.297	**0.002**	15
Change from baseline to 6 months					
Constant	−12.182	36.166		0.737	
PASP (mm Hg)	−1.544	0.637	−0.266	**0.018**	13
FVC (mL)	0.021	0.010	0.224	**0.044**	

p Values <0.05 were considered statistically significant.
6MWD, six-minute walk distance; B, unstandardised coefficient; Group, exercise versus usual care with usual care group as reference category; PASP, pulmonary artery systolic pressure; R^2, R square—proportion of variation in change in 6MWD explained by the model.

capacity is directly related to training frequency,[39] with three to five sessions per week being optimal and fewer than two sessions being unlikely to produce meaningful change.[39] As expected, larger changes in 6MWD were evident in those who attended 12 or more sessions; however successful exercise progression led to much larger changes. This reinforces that exercise training is a critical component of PR for improving functional capacity and HRQoL in ILD. In addition, this suggests that improvements can still be achieved when attendance is less than 75% if progression of exercise intensity is achieved. There were no significant baseline differences between those who completed the programme or progressed their exercise and those that did not. Therefore, factors such as self-motivation or efficacy, fear of adverse events or comprehension may impact the ability to tolerate exercise training. Further investigation is required in identifying factors that influence non-adherence to exercise progression.

Limited changes were seen in dyspnoea, strength, anxiety and depression. The changes in strength may not have been larger enough to overcome measurement variation between the two raters[21] or the resistance training may not have been delivered at an adequate intensity to achieve significant changes in strength.[39] The limited change in anxiety and depression was likely attributed to the low numbers of participants with clinically significant anxiety and depression at baseline. This study may not have been adequately powered to see an effect on MMRC dyspnoea, or this measure may not be sensitive enough to detect changes following exercise.[40] Surprisingly the UCSD SOBQ worsened following exercise, except in those with asbestosis, despite improvements beyond the MCID in CRDQ dyspnoea.[26] Additional research is required to clarify the utility of the UCSD SOBQ in measuring change in dyspnoea in ILD.

This study had some limitations. The 'other ILD' subgroup included a diverse range of diagnoses, however the sample sizes were insufficient to allow detailed subgroup analyses of these entities. Given the small number of participants requiring long-term or exertional oxygen therapy, these results might not be generalisable to those with more advanced disease. Additionally, we did not assess whether the standard education component of PR, which was included in the intervention, was associated with comparable or greater clinical outcomes compared with exercise training alone.

In conclusion, this study demonstrates exercise training is effective for people with ILD and strengthens the rationale for exercise training to be recommended as a standard treatment.

Magnitude of change is greater in those with asbestosis compared with IPF, but both groups obtain clinically meaningful improvements. Individuals with a range of severity stand to benefit, however longer-lasting effects may occur in milder disease. Progression of exercise intensity and participation in exercise training earlier in the disease course are crucial to optimise and sustain physiological benefits. Further research is needed to determine the optimal exercise training strategy for CTD-ILD and to identify strategies that maximise long-term benefit.

Author affiliations
[1]Discipline of Physiotherapy, La Trobe University, Alfred Centre, Prahran, Victoria, Australia
[2]Department of Physiotherapy, Austin Health, Heidelberg, Victoria, Australia
[3]Department of Respiratory & Sleep Medicine, Austin Health, Heidelberg, Victoria, Australia
[4]Institute for Breathing and Sleep, Heidelberg, Victoria, Australia
[5]Department of Medicine, University of Melbourne, Parkville, Victoria, Australia
[6]Department of Physiotherapy, Alfred Health, Prahran, Victoria, Australia
[7]Department of Physiotherapy, Western Health, Footscray, Victoria, Australia
[8]Allergy, Immunology & Respiratory Medicine Department, Alfred Health, Melbourne, Victoria, Australia
[9]Department of Medicine, Central Clinical School, Monash University, Melbourne, Victoria, Australia
[10]Department of Respiratory & Sleep Disorders Medicine, Western Health, Footscray, Victoria, Australia

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