--- ONLINE DATA SUPPLEMENT ---

The evidence of benefits if exercise training in interstitial lung disease: A Randomised Controlled Trial

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Methods

Participants

Participants were recruited through the hospitals respiratory and sleep medicine departments, the surrounding private respiratory clinics, the Australian idiopathic pulmonary fibrosis (IPF) registry and Maurice Blackburn and Slater & Gordon Law Firms. In IPF, the diagnostic criteria were consistent with those outlined in the International Consensus Statement.[4] A surgical lung biopsy was not required for entry into the study as it has been demonstrated that clinical and radiologic data are sufficient to distinguish between IPF and other ILDs in the hands of experienced clinicians.[5] Diagnosis of connective tissue disease was made according to the rheumatological criteria for that disease; ILD in this setting was diagnosed according to clinical/radiologic and lung function criteria, with lung biopsy in atypical cases. Dust-related ILD was confirmed according to accepted criteria that include significant exposure to an agent recognised to cause ILD and radiological confirmation on high resolution computed tomography of the chest, as determined by independent radiologists. Where needed, the diagnosis of ILD was confirmed through a multidisciplinary review. The presence of co morbidities, the use of oxygen and any pharmacological therapies were identified from the respiratory physician referral, the participants electronic medical record and by participant report during the baseline assessment and documented accordingly.

Components of the exercise training program

Aerobic Training. The aerobic exercise component consisted of 30 minutes of aerobic exercise, typically comprising 15 minutes each of stationary cycling and walking, either on the treadmill or along a corridor depending of the capability of the individual. The duration on each modality was adjusted if the participant was inhibited on a specific modality due to a

pre-existing co-morbidity, however the total exercise time still equated to 30 minutes. Interval training was also utilised if a participant was unable to tolerate continuous exercise.

Walking: The initial intensity for walking was 80% of the peak walking speed achieved on the 6-minute walk test (6MWT). The walking intensity was increased each week by 0.25km/h (treadmill walking) or 62m (corridor walking) for initial speeds of less than 3km/h or by 0.5km/h (treadmill walking) or 125m (corridor walking) for initial speeds equal to or greater than 3km/h. When the maximal walking speed (predominantly occurring at 4-5km/h) of the participants was reached, the speed was reduced 0.2-0.4km/h and a gradient of 1-2% was added. Subsequent weekly progressions involved an increase in gradient of 1-2%.

Cycling: The initial intensity for cycling was 70% of the maximum work rate estimated from their 6MWT.[1] The initial intensity was also adjusted accordingly, where needed, to elicit a rating of perceived exertion (RPE) of 12-14 on the 6-20 Borg scale and a dyspnoea score of 3-4 on the modified Borg scale. The cycling intensity was increased weekly by 15% of the initial work rate.

Resistance training. The resistance program comprised of three lower limb and four upper limb dumbbell exercises. The initial load corresponded to 10-12RM (repetition maximum) and a RPE of 12-14 on the 6-20 Borg scale. Lower limb resistance exercises were increased every 2 weeks by 1-3 kg in total prescribed according to a 12-14 on the Borg Rating of Perceived Exertion (RPE) Scale. Upper limb resistance exercises were increased by 2-5 repetitions until a total of 20 repetitions were reached. Weight was then increased by 0.5-1kg for each hand, the number of repetitions returned to 10 and a gradual increase in repetitions to 20 was repeated.

Home exercise. An unsupervised home exercise program was prescribed to achieve three additional exercise sessions per week. Participants were instructed to exercise at an intensity

that corresponded to dyspnoea score of 3-4 on the modified Borg scale and for a duration similar to that achieved in the supervised sessions. The home exercise was reviewed regularly to ensure the participants were exercising at level of exertion similar to that achieved in the supervised sessions and to implement progression. At the conclusion of the intervention, the participants were instructed to continue with their home exercise program for four to five times per week.[2,3]

Education component. Participants were also to encouraged to attend the face to face interactive group education sessions provided within the standard pulmonary rehabilitation program. These group education sessions were facilitated by a multidisciplinary team including a respiratory physician, respiratory scientist, respiratory nurse, physiotherapist, exercise physiologist, dietician, pharmacist, speech therapist and occupational therapist and involved the follow topics; Understanding lung disease, respiratory function tests, medications, home oxygen therapy, self-management including exacerbations, managing breathlessness, energy conservation, exercise and physical activity, stress and anxiety, nutrition and healthy eating, sexuality and intimacy, community resources, swallowing and chronic lung disease, continence and chronic lung disease and airway clearance.

Statistical Analysis

Linear mixed models

All the interactions (subgroup×group, subgroup×time, group×time, and subgroup×group×time) for the subgroup analyses were initially entered into the model. The interaction term with the highest p value greater than <0.05, and not forming a part of another interaction term was dropped and each time the model was re run in order to identify any significant interactions. The statistical comparisons were difference between groups, independent of time (group effect), change over time, independent of group (time effect), response over time between groups (group×time effect) and response to exercise according to subgroup with or without the presence of group, time or group×time effect (subgroup×group, subgroup×time, group×time, and subgroup×group×time).

Categorisation of exercise progression for per protocol analyses. Exercise training data for all participants was reviewed to determine if progression of exercise training was achieved over the duration of the intervention. Participants were initially categorised as i) progressed according to the protocol (consistent weekly progression of all three exercise modalities), ii) progressed slower than protocol (consistent weekly progression evident but lesser intensity than planned or progression was not evident on all modalities) and iii) not progressed. Participants who progressed slower than protocol were re-categorised as progressed according to protocol if consistent and substantial progressions were achieved on two out of the three modalities leading to final categorisation into two groups; yes - progressed per protocol or no - not progressed.

Stepwise multiple linear regression. Baseline variables of age, gender and previously documented markers of disease severity such as FVC, TLCO, PASP, TLC and

oxyhaemoglobin desaturation on baseline 6-minute walk test,[6-9] with a univariate relationship ($p<0.1$),using Pearson's r or Spearman's rho, to the dependent variables of change in 6 minute walk distance (6MWD), chronic respiratory disease questionnaire (CRDQ) dyspnoea and CRDQ fatigue were entered into a stepwise multiple linear regression model along subgroup and group allocation as categorical predictor variables. If two baseline variables were highly correlated (correlation coefficient >0.8), the variable with the strongest relationship to the dependent variable was entered into the model. Independent predictors of change in 6MWD, CRDQ dyspnoea and CRDQ fatigue were identified using the backward elimination method. All predictors were entered into the model and the predictor with the highest p value greater than 0.05 was removed for each step. The model was re run until all of the predictors in the model had $p<0.05$.

Receiver operating characteristic (ROC) curve analysis. Change in 6MWD, CRDQ dyspnoea and fatigue at nine weeks and six months were re categorised as change ≥ minimal important difference (MID) or < MID. The MID for 6MWD, CRDQ dyspnoea and fatigue domain were defined as a change of greater than or equal to 34 m,[10] 2.5 points[11] and 2.0 points[11] respectively. Baseline 6MWD was analysed against change in 6MWD at nine weeks and PASP and FVC was analysed against change in 6MWD at six months to identify suitable thresholds that predicted short term and long term benefit in 6MWD respectively. Baseline PASP was analysed against change in CRDQ fatigue and baseline TLCO was analysed against CRDQ dyspnoea to identify suitable thresholds that predicted long term symptom outcome.

Results

Baseline characteristics

Of the 22 participants with CTD ILD, eight had rheumatoid arthritis, four had scleroderma, four had undifferentiated CTD, three had lupus, two had anti-Jo-1 anti-synthetase syndrome, one had ankylosing spondylitis and one had Wegener's syndrome. Of those participants with other types of ILD, 13 had hypersensitivity pneumonitis (HP), eight had sarcoidosis, five had non-specific interstitial pneumonia, four had unclassifiable ILD, three had drug related ILD, two had lymphangioleiomyomatosis and one had lymphoid interstitial pneumonia.

Predictors of response to exercise

The CTD-ILD subgroup had a significantly greater proportion of participants above the 6MWD threshold (78%) compared to the asbestosis (41%, p 0.01) and IPF (33%, $p<0.001$) subgroup. The IPF subgroup had a greater proportion of participants above the PASP threshold (55%) compared to the asbestosis (35%, $p=0.2$) and CTD-ILD (35%, $p=0.1$) subgroup.

Table E1 Baseline characteristics of participants for entire ILD population

	Usual Care n=68	Exercise Training n=74	p value
Age	70 (11)	69 (11)	0.6
Gender -male	44 (65%)	43 (58%)	0.4
Oxygen Therapy			
Long Term	9 (13%)	3 (4%)	0.07
Exertional	19 (28%)	8 (11%)	**0.01**
Treatment			
Prednisolone	22 (32%)	25 (34%)	1.0
Immunosuppressant	6 (9%)	8(11%)	0.8
Pirfenidone	1 (1%)	1 (1%)	0.6
Nintedanib	0 (0%)	0 (0%)	
N-Acetylcysteine	2 (3%)	0 (0%)	0.2
FVC (%pred, n=141)	75 (20)	76 (18)	0.7
TLCO (%pred, n=141)	48 (14)	50 (16)	0.4
TLC (%pred, n=127)	80 (16)	80 (18)	0.8
PASP (mmHg, n=115)	34 (11)	32 (13)	0.4
6MWD (m)	441 (142)	477 (107)	0.2
Knee extensor strength	20 (7)	21 (6)	0.7
MMRC Dyspnoea	2 (1)	2 (1)	0.1
Total CRDQ Score	82 (21)	87 (19)	0.1
Total SGRQ-IPF Score	54 (19)	48 (18)	**0.03**
UCSD SOBQ Score	45 (21)	38 (22)	0.06
HADS Anxiety	7 (4)	6 (4)	0.1
HADS Depression	6 (4)	5 (3)	0.1
Comorbidities			
Hypertension	26 (28%)	23 (31%)	0.4
Ischaemic heart	14 (21%)	12 (16%)	0.5
Gastro-oesophageal	10 (15%)	14 (19%)	0.7
Osteoarthritis	22 (32%)	20 (27%)	0.6
Rheumatoid	8 (12%)	6 (8%)	0.6
Diabetes	17 (25%)	16 (22%)	0.7
Chronic back pain	6 (6%)	7 (10%)	1.0
Obstructive sleep	4 (6%)	6 (8%)	0.7
COPD	5 (7%)	3 (4%)	0.5
Osteoporosis	3 (4%)	4 (5%)	1.0

*Values are mean (SD) or n (%). Data are from all 142 participants except where indicated. *p<0.05, exercise vs control group*

6MWD, 6minute walk distance; %pred, per-cent predicted; COPD, chronic obstructive pulmonary disease; CRDQ, Chronic Respiratory Disease questionnaire; FVC, forced vital capacity ; HADS, Hospital Anxiety and Depression scale; MMRC, modified Medical Research Council dyspnoea scale; PASP, pulmonary artery systolic pressure; SGRQ-IPF, St George respiratory questionnaire idiopathic pulmonary fibrosis specific version; TLC, total lung capacity; TLCO, carbon monoxide transfer factor; UCSDSOBQ, University College of San Diego shortness of breath questionnaire

Table E2: Adherence to home exercise sessions in the exercise training group

	Adherence to home exercise (≥3 sessions)	Average sessions per week	Average duration per session (minutes)
All ILD	54%	2.4 (2.0)	22.6 (19.4)
IPF	50%	2.5 (2.2)	22.7 (20.4)
Dust	55%	2.2 (2.0)	21.7 (20.2)
CTD	54%	2.1 (1.5)	22.5 (17.6)

Values are mean (SD) or n (%)

Table E3 Effect of exercise training on anxiety for each subgroup

	HADS Anxiety								
	IPF n=61			DUST n=22			CTD n-23		
	No	Borderline	Case	No	Borderline	Case	No	Borderline	Case
Baseline									
Usual Care	21	4	4	8	2	1	6	3	3
Exercise	19	6	7	7	3	1	7	3	1
p value			**0.6**			**0.9**			**0.6**
9 weeks									
Usual Care	19	2	5	8	2	1	8	1	2
Exercise	23	4	4	8	3	0	7	3	0
p value			**0.7**			**0.5**			**0.2**
6 months									
Usual Care	17	4	2	7	3	1	8	1	3
Exercise	17	4	6	7	2	2	9	1	0
p value			**0.4**			**0.8**			**0.2**

Data are n participants in each category, p value represents difference between groups at each time point

No case corresponds to HADS scores of 0-7, borderline corresponds to scores of 8-10 and case corresponds to scores of 11-21 for the anxiety subscale of HADS

HADS, hospital and anxiety depression scale

Table E4 Effect of exercise training on depression for each subgroup

	HADS Depression								
	IPF n=61			DUST n=22			CTD n=23		
	No	Borderline	Case	No	Borderline	Case	No	Borderline	Case
Baseline									
Usual	21	3	5	8	3	0	8	3	1
Exercise	25	6	1	7	4	0	8	3	0
p value			**0.1**			**0.6**			**0.6**
9 weeks									
Usual Care	21	2	3	8	2	1	10	1	0
Exercise	25	4	2	10	1	0	8	2	0
p value			**0.7**			**0.5**			**0.5**
6 months									
Usual Care	18	2	3	9	1	1	10	1	1
Exercise	20	3	4	8	3	0	10	0	0
p value			**0.9**			**0.4**			**0.4**

Data are n participants in each category, p value represents difference between groups at each time point.

No case corresponds to scores of 0-7, borderline corresponds to scores of 8-10 and case corresponds to scores of 11-21 for the depression subscale of HADS

HADS, hospital and anxiety depression scale

Table E5 Per protocol analysis between group differences following the intervention

	Entire Sample n=142	IPF n=61	Asbestosis n=22	CTD n=23
CRDQ Dyspnoea				
ITT	2.5 (0.9)	3.0 (1.6)	1.0 (1.8)	2.7 (2.6)
PP Completion	3.0 (1.0)	3.3 (1.6)	1.9(2.2)	5.7 (2.5)
PP Progression	3.6 (1.0)	4.4 (1.6)	1.9(2.2)	5.7 (2.5)
CRDQ Fatigue				
ITT	2.6 (0.8)	2.0 (1.2)	4.1 (1.5)	-0.3 (1.9)
PP Completion	3.2 (0.8)	2.2 (1.4)	4.5 (1.8)	1.8 (2.1)
PP Progression	3.8 (0.8)	3.3 (1.3)	4.5 (1.8)	1.8 (2.1)
CRDQ Emotion function				
ITT	3.3 (1.2)	2.9 (1.9)	5.4 (3.1)	-1.4 (2.7)
PP Completion	4.2 (1.3)	4.4 (2.2)	5.8 (3.0)	-0.2 (3.5)
PP Progression	4.4 (1.3)	4.5 (2.2)	5.8 (3.0)	-0.2 (3.5)
CRDQ Mastery				
ITT	3.4 (1.1)	3.7 (1.8)	5.1 (3.0)	-2.0 (2.6)
PP Completion	4.2 (1.3)	5.0 (1.8)	5.2 (2.4)	-1.1 (2.7)
PP Progression	4.6 (1.3)	5.8 (1.7)	5.2 (2.4)	-1.1 (2.7)
SGRQ-IPF Symptoms				
ITT	-9.0 (3.3)	-3.4 (4.5)	-20.2 (8.4)	-9.2 (8.7)
PP Completion	-8.4 (3.6)	-3.2 (5.7)	-20.3 (7.6)	-3.5 (8.8)
PP Progression	-8.2 (3.7)	-2.8 (5.6)	-20.3 (7.6)	-3.5 (8.8)
SGRQ-IPF Activity				
ITT	-5.9 (2.7)	-7.5 (4.6)	-14.8 (6.1)	0.6 (5.7)
PP Completion	-6.2 (2.9)	-6.9 (4.7)	-13.3 (6.4)	-2.4 (7.4)
PP Progression	-6.6 (2.7)	-7.0 (4.3)	-13.3 (6.4)	-2.4 (7.4)
SGRQ-IPF Impact				
ITT	-6.4 (2.5)	-6.4 (3.9)	-6.8 (5.0)	-2.3 (4.4)
PP Completion	-7.2 (2.7)	-7.5 (4.0)	-7.9 (5.3)	-1.2 (6.2)
PP Progression	-7.9 (2.7)	-8.0 (4.0)	-7.9 (5.3)	-1.2 (6.2)
SGRQ-IPF Total				
ITT	-5.8 (2.0)	-5.6 (3.1)	-9.4 (3.4)	-2.8 (3.7)
PP Completion	-6.1 (2.1)	-6.0 (3.3)	-9.6 (4.0)	-2.4 (4.6)
PP Progression	6.7 (2.1	-6.5 (3.0)	-9.6 (4.0)	-2.4 (4.6)

Values are mean difference (SE). Data are exercise group – control group. Positive increase represents improvement except for MMRC, UCSDSOBQ and SGRQ IPF where a reduction represents an improvement

CRDQ, Chronic Respiratory Disease questionnaire; ITT, intention to treat; PP, per protocol; SGRQ-IPF, St George respiratory questionnaire IPF specific version

Table E6 Baseline characteristics for successful and unsuccessful program completion and exercise progression

	Entire ILD population		IPF		CTD ILD	
	Non Completer n=28	**Completer n=46**	**Non Completer n=17**	**Completer n=15**	**Non Completer n=5**	**Completer n=6**
Age (years)	66 (10)	70 (11)	68 (9)	73 (10)	66 (11)	60 (10)
FVC (%pred)	78(17)	75 (18)	79 (17)	70 (18)	77 (18)	80 (17)
TLCO (%pred)	53 (14)	48 (18)	54 (14)	47 (21)	44 (14)	61 (19)
PASP (mmHg)	33 (11)	31 (14)	35 (14)	35 (19)	30 (5)	28 (7)
6MWD (m)	480 (99)	469 (109)	478 (112)	435 (140)	490 (97)	557 (33)
Nadir SpO2 (%)on 6MWT	88 (7)	86 (6)	88 (7)	85 (9)	87 (8)	92 (4)
	Not Progressed n=29	**Progressed n=45**	**Not Progressed n=16**	**Progressed n=16**	**Not Progressed n=5**	**Progressed n=6**
Age (years)	66 (12)	70 (10)	69 (9)	72 (10)	66 (11)	60 (10)
FVC (%pred)	73 (16)	78 (18)	72 (15)	76 (20)	77 (18)	80 (17)
TLCO (%pred)	52 (17)	49 (16)	55 (18)	46 (17)	44 (14)	61 (19)
PASP (mmHg)	34 (11)	31 (14)	37 (14)	33 (19)	30 (5)	28 (7)
6MWD (m)	476 (114)	471 (100)	468 (137)	447 (117)	490 (97)	557 (33)
Nadir SpO2 (%) on 6MWT	87 (9)	87 (5)	86 (10)	88 (5)	87 (8)	92 (4)

Values are mean (SD). Asbestosis is not included as only one participant did not complete the program or progress their exercise intensity

6MWT, 6 minute walk test; 6MWD, 6minute walk distance; %pred, per cent predicted; FVC, forced vital capacity; PASP, pulmonary artery systolic pressure; TLCO, carbon monoxide transfer factor

Table E7 Univariate relationships between baseline predictors and response to rehabilitation

	Short term response			Long term response		
	Change in 6MWD	**Change in CRDQ dyspnoea**	**Change in CRDQ fatigue**	**Change in 6MWD**	**Change in CRDQ dyspnoea**	**Change in CRDQ fatigue**
Age (years)	-0.07	0.10	-0.04	-0.14	**-0.31***	-0.20
TLC (%pred)	-0.05	0.01	0.04	**0.34***	0.18	0.03
FVC (ml)	0.02	-0.15	0.01	**0.32***	-0.01	-0.10
FVC (%pred)	0.05	-0.02	-0.04	**0.36***	0.08	-0.07
TLCO (%pred)	-0.15	0.04	0.12	0.16	**0.30***	0.07
PASP (mmHg)	-0.02	0.02	-0.16	**-0.27†**	-0.07	**-0.38***
Nadir SpO_2 (%) on 6MWT	0.06	0.13	0.26	**0.29***	**0.28†**	**0.26†**
Baseline 6MWD (m)	**-0.28†**	-0.16	-0.11	0.12	0.03	-0.03
Baseline CRDQ dyspnoea		**-0.35***	-0.22		**-0.30***	0.04
Baseline CRDQ fatigue		-0.22	**-0.52***		**-0.28†**	**0.40***

*Data are Pearson's r, except for short-term (nine weeks) and long term (six months) 6MWD response and short term (nine weeks) CRQ dyspnoea response which are Spearman's rho, *p<0.05, † p<0.01*

6MWT, 6-minute walk test; 6MWD, 6minute walk distance; %pred, per- cent predicted; CRDQ, Chronic Respiratory Disease questionnaire; FVC, forced vital capacity; Nadir SpO_2, oxyhaemoglobin saturation on baseline 6-minute walk test; PASP, pulmonary artery systolic pressure; TLC, total lung capacity; TLCO, carbon monoxide transfer factor

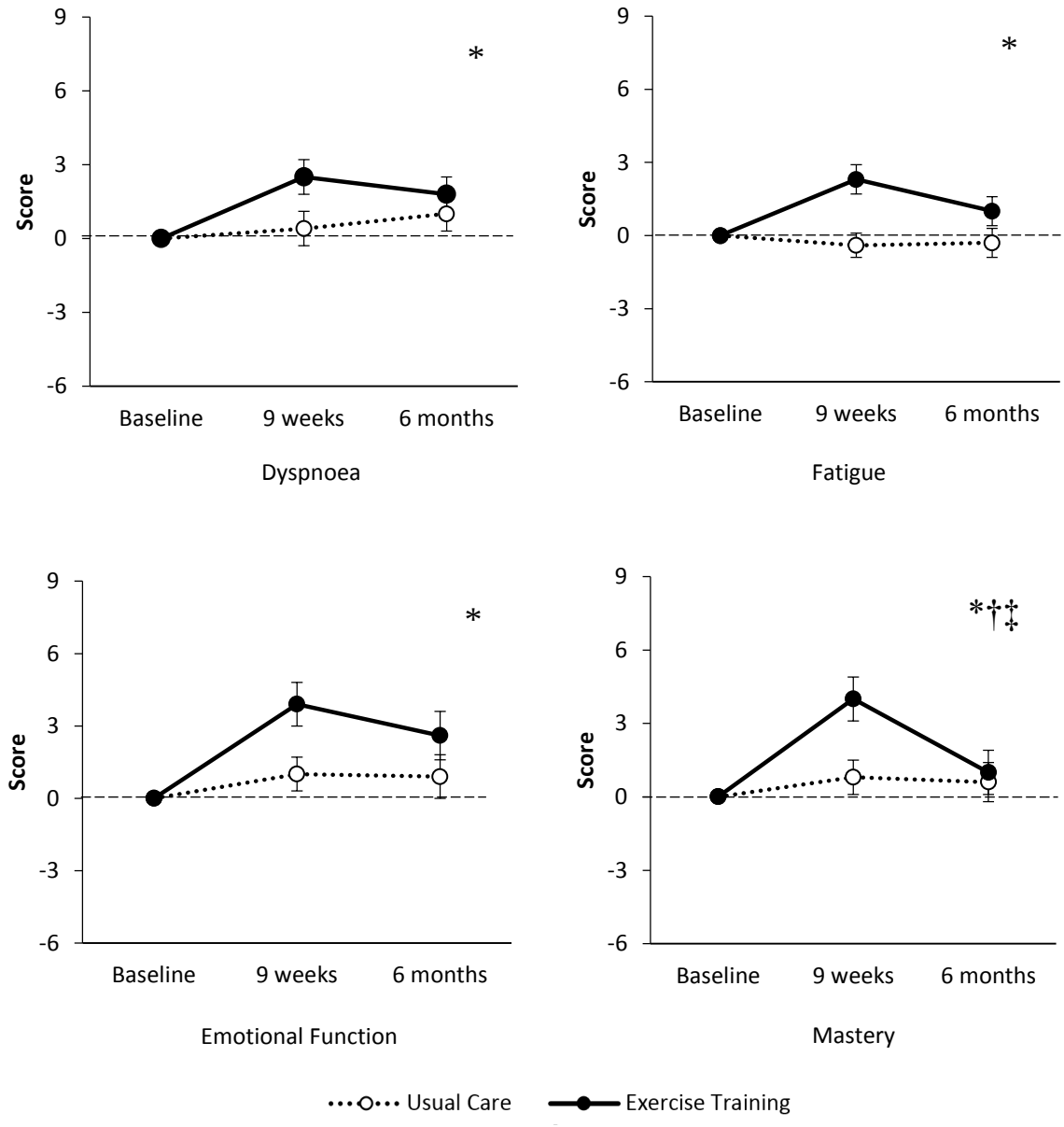
Table E8 Stepwise multiple linear regression model for change in dyspnoea and fatigue following intervention

	B	SE of B	Standardised	P value	R^2
Change from baseline to 9 weeks					
CRDQ Dyspnoea					
Constant	7.507	1.702		**<0.001**	
Group	2.675	1.100	0.223	**0.02**	
Baseline CRDQ	-0.436	0.098	-0.409	**<0.001**	20%
CRDQ Fatigue					
Constant	6.608	1.352		**<0.001**	
Group	2.218	0.832	0.234	**0.009**	
Baseline CRDQ	-0.416	0.079	-0.466	**<0.001**	26%
Change from baseline to 6months					
CRDQ Dyspnoea					
Constant	3.546	2.313		0.129	
Baseline CRDQ	-0.432	0.102	-0.413	**<0.001**	
TLCO (%pred)	0.096	0.038	0.245	**0.014**	19%
CRDQ Fatigue					
Constant	10.596	1.959		**<0.001**	
Baseline CRDQ	-0.365	0.090	-0.400	**<0.001**	
PASP	-0.129	0.037	-0.341	**0.001**	27%

Group, exercise vs usual care with usual care group as reference category;

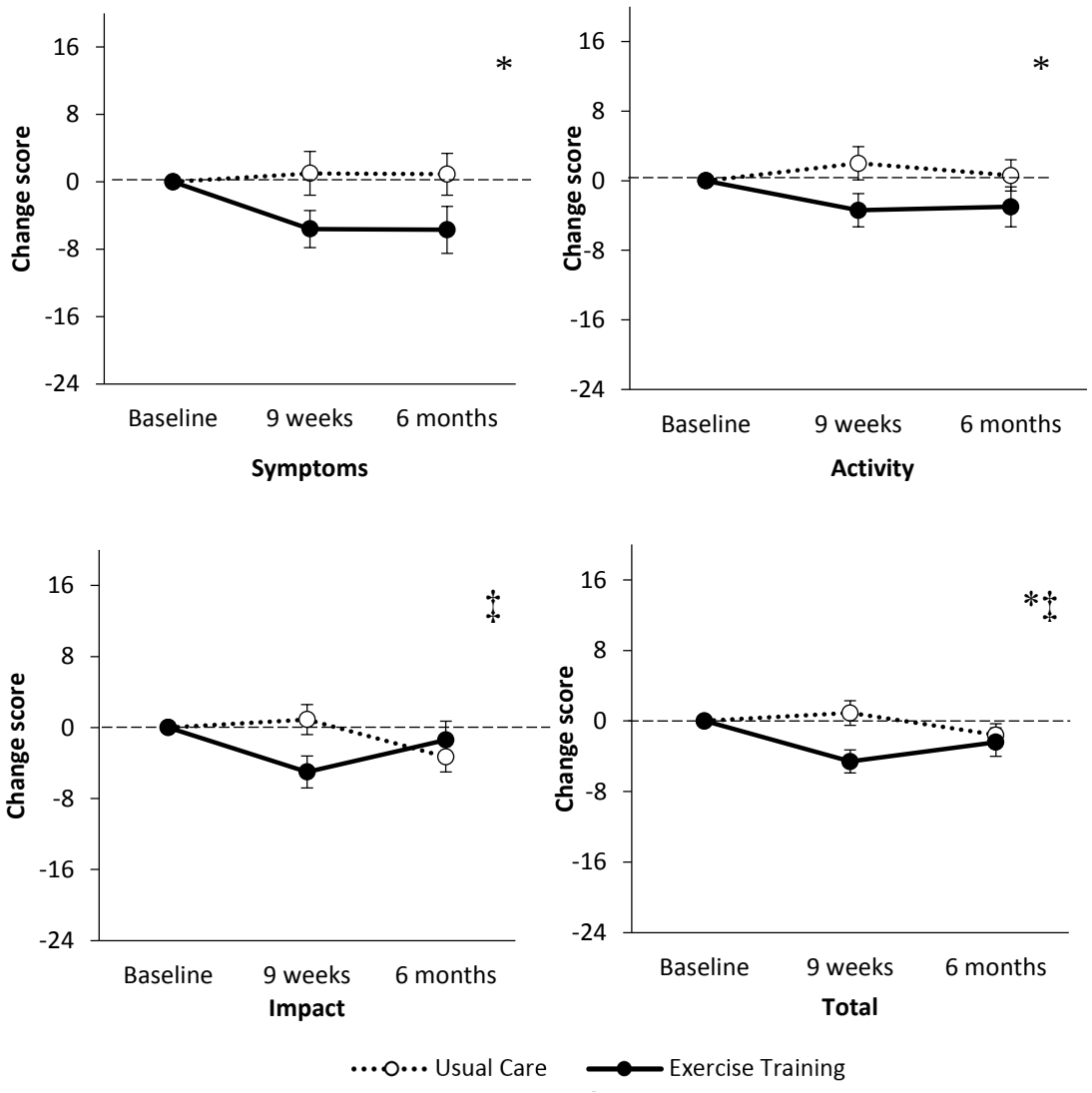
6MWD, 6-minute walk distance; %pred, per cent predicted; B, unstandardised coefficient; CRDQ, Chronic Respiratory Disease questionnaire; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PASP, pulmonary artery systolic pressure; R^2, R square - proportion of variation in change in 6MWD explained by the model. SE, standard error

Figure E1 Change in health-related quality of life (CRDQ)



*Data are raw mean (SE). *p<0.05, exercise vs control group, †p<0.05, time effect, ‡ p<0.05, group×time interaction*

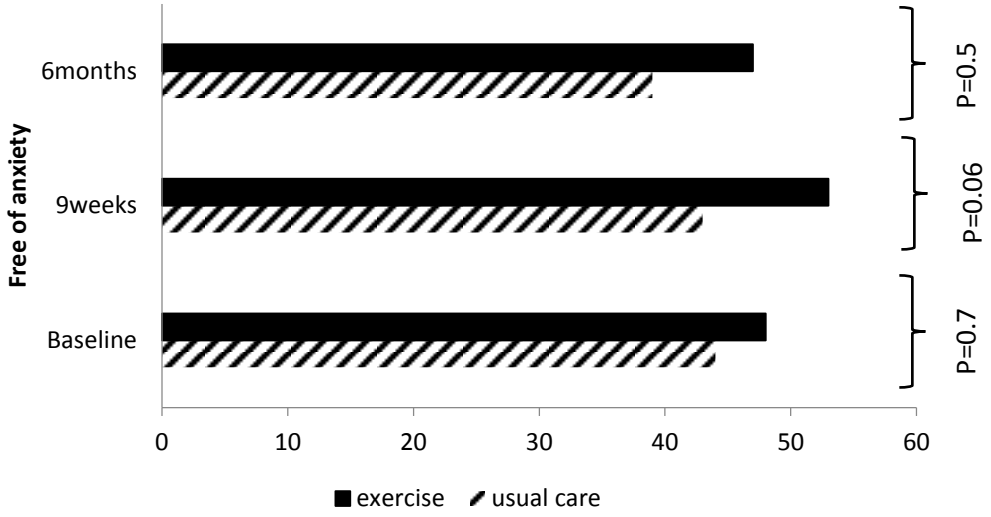
Figure E2 Change in health-related quality of life (SGRQ IPF)



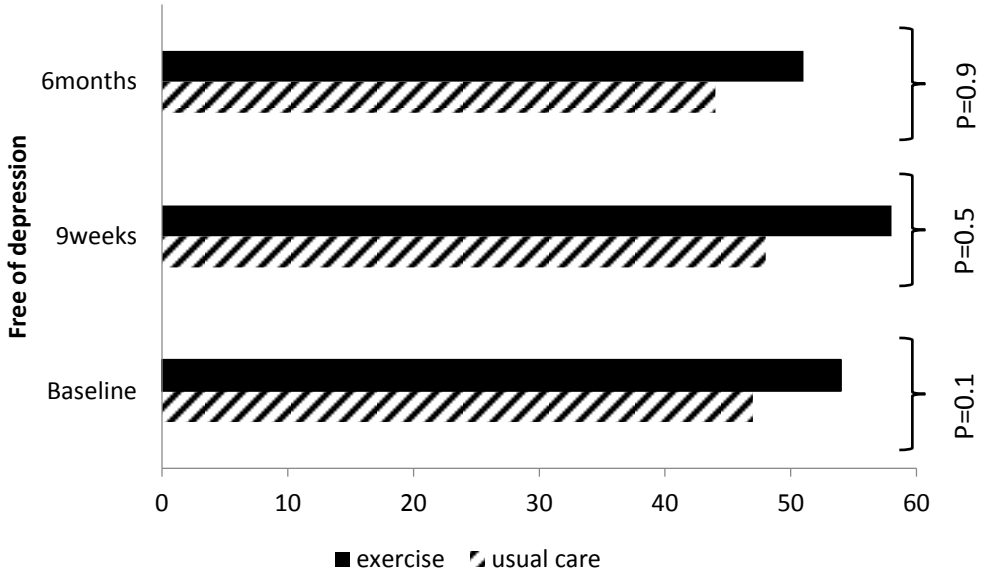
*Data are raw mean (SE). *p<0.05, exercise vs control group, †p<0.05, time effect, ‡ p<0.05, group×time interaction *p<0.05, exercise vs control group, a reduction in scores represents an improvement*

Figure E3 Effect of exercise training on anxiety and depression

a. Anxiety



b. Depression

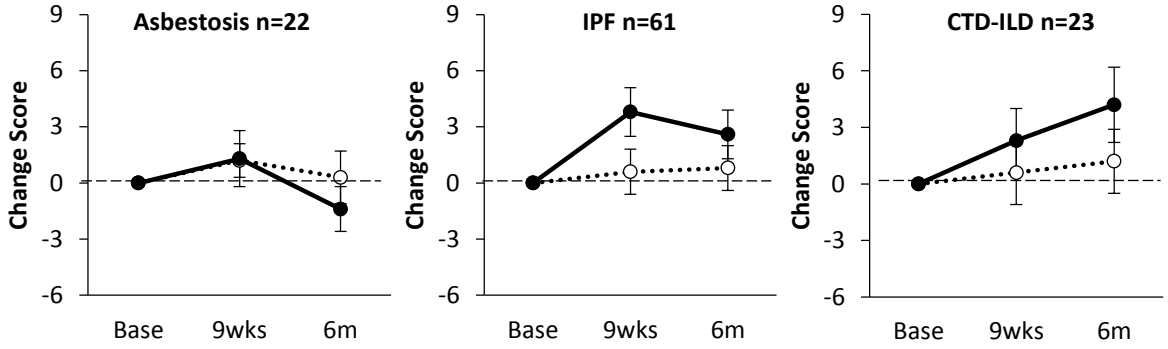


Data are n participants, p value represents difference between groups at each time point.

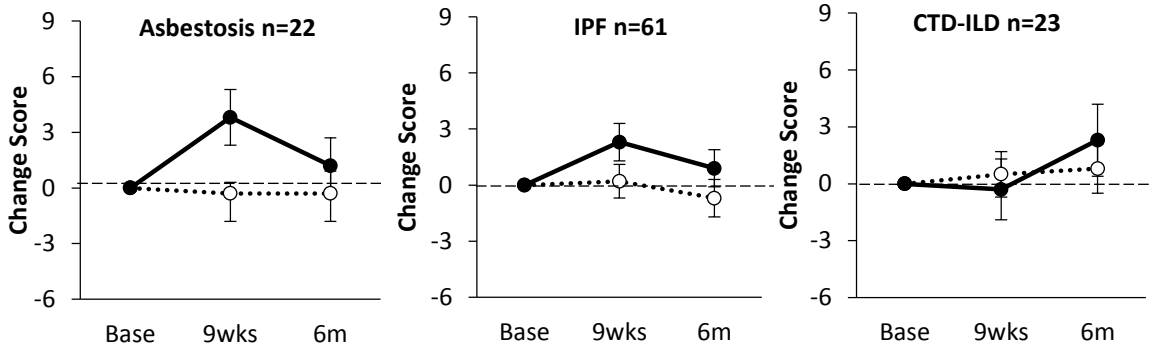
Free of anxiety corresponds to scores of 0-7 on hospital and anxiety depression scale (HADS)

Figure E4 Change in health-related quality of life (CRDQ) for each subgroup

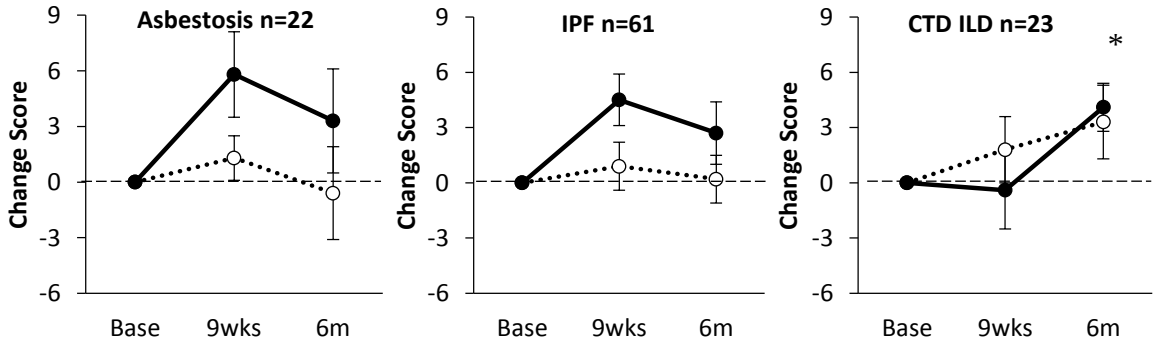
a. Dyspnoea



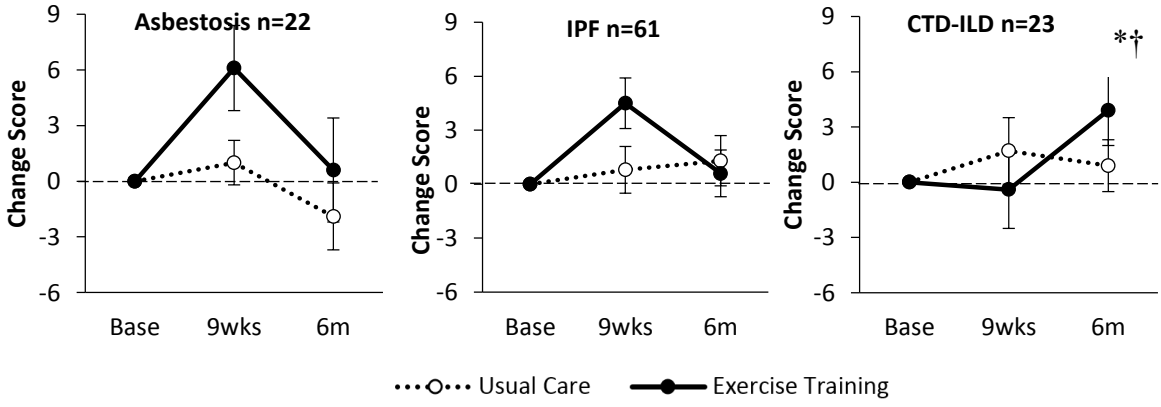
b. Fatigue



c. Emotional Function

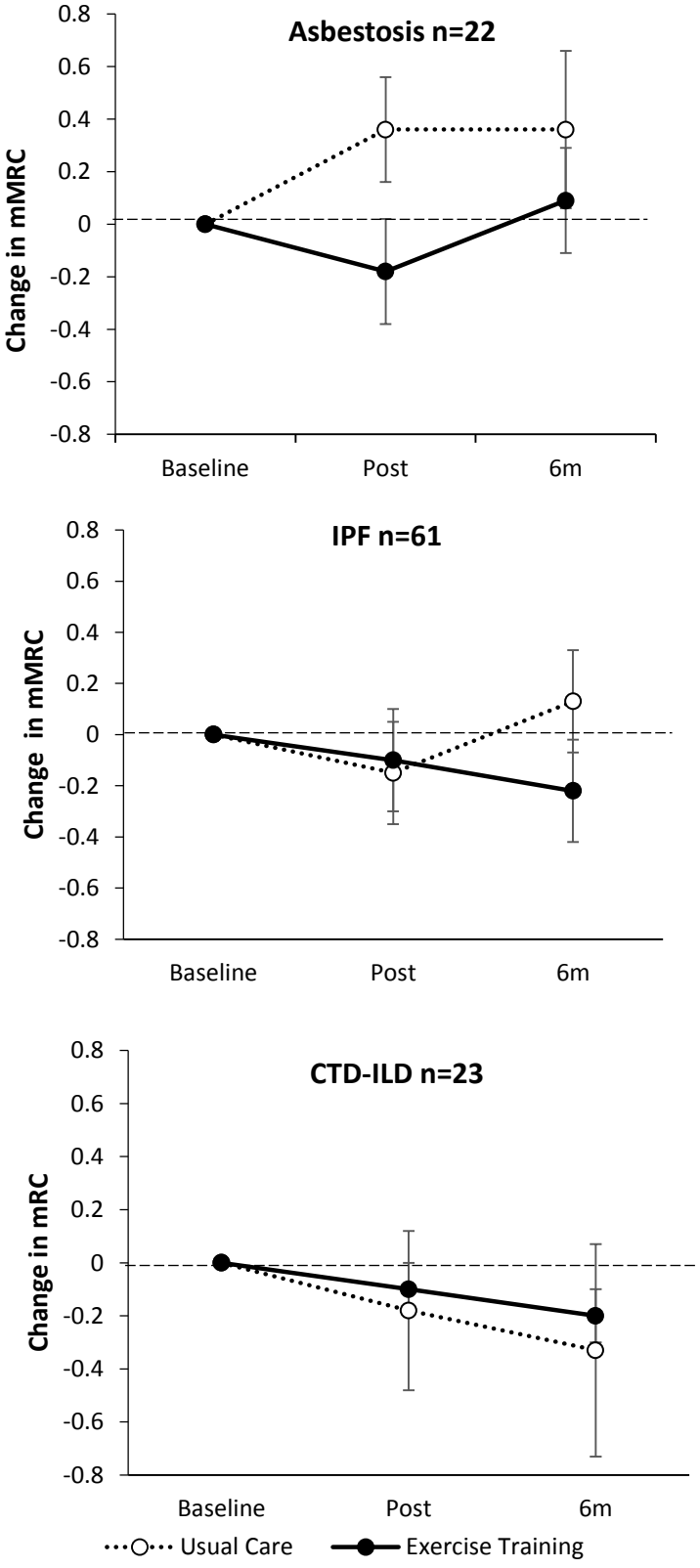


d. Mastery



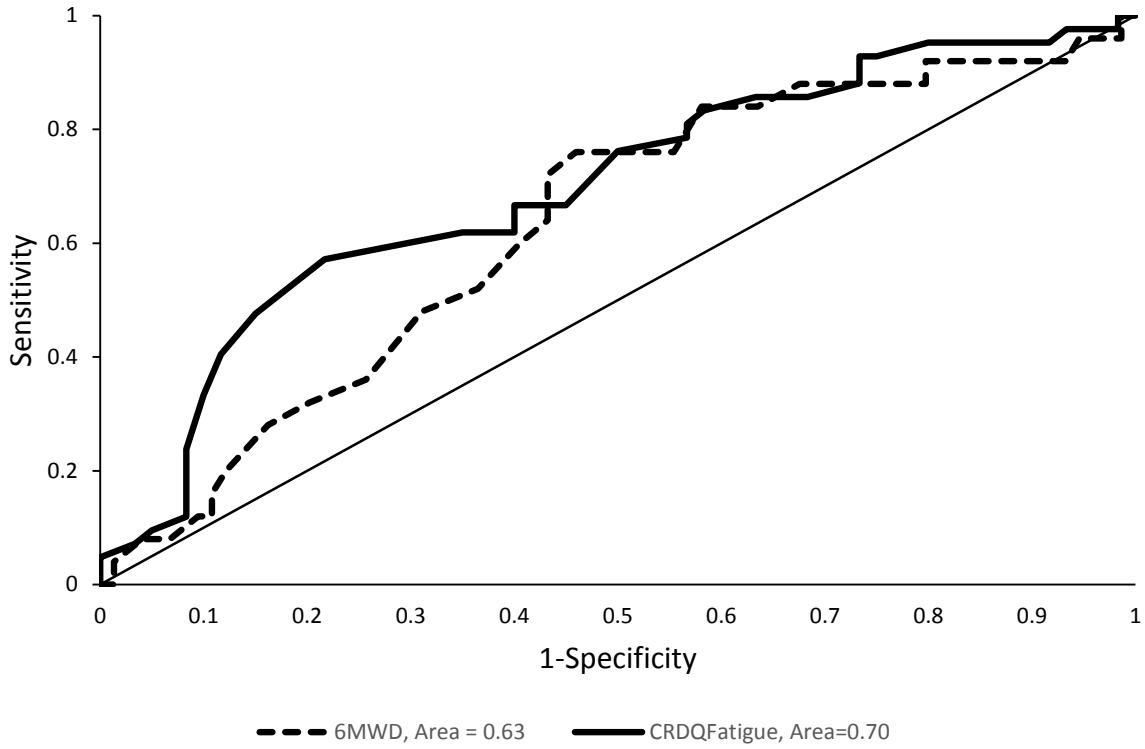
*Data are raw mean (SE), *p<0.05, subgroup× time interaction † p<0.05 subgroup×group×time interaction*

Figure E5 Change in dyspnoea (MMRC) for each subgroup



Data are raw mean (SE), a reduction in scores represents an improvement, no significant difference between subgroups

Figure E6 ROC curves for thresholds of clinical efficacy



6MWD, 6-minute walk distance; CRDQ, chronic respiratory disease questionnaire; Area, area under the curve

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