Mood disorder in idiopathic pulmonary fibrosis: response to pulmonary rehabilitation

George D. Edwards[1], Oliver Polgar[2], Suhani Patel[1,2], Ruth E. Barker[1,2,3], Jessica A. Walsh[2], Jennifer Harvey[2,4], William D-C. Man [1,2,4,5,7] and Claire M. Nolan [2,6,7]

[1]National Heart and Lung Institute, Imperial College London, London, UK. [2]Harefield Respiratory Research Group, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, London, UK. [3]Wessex Academic Health Science Network, Southampton, UK. [4]Harefield Pulmonary Rehabilitation Unit, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, London, UK. [5]Faculty of Life Sciences and Medicine, King's College London, London, UK. [6]Brunel University London, College of Medicine, Health and Life Sciences, Department of Health Sciences, London, UK. [7]These authors contributed equally.

Corresponding author: Claire M. Nolan (claire.nolan@brunel.ac.uk)

Shareable abstract (@ERSpublications)
In people with idiopathic pulmonary fibrosis and suggestive or probable mood disorder, pulmonary rehabilitation reduces anxiety and depression. Mean MID estimates for HADS-Anxiety and HADS-Depression were −2 and −1.2, respectively. https://bit.ly/42SWFrf

Cite this article as: Edwards GD, Polgar O, Patel S, *et al*. Mood disorder in idiopathic pulmonary fibrosis: response to pulmonary rehabilitation. *ERJ Open Res* 2023; 9: 00585-2022 [DOI: 10.1183/23120541.00585-2022].

Received: 1 Nov 2022
Accepted: 23 March 2023

Abstract

Background Pulmonary rehabilitation improves mood disorder in COPD, but there are limited data in idiopathic pulmonary fibrosis (IPF). The aims of this cohort study were to investigate whether pulmonary rehabilitation reduces mood disorder in IPF, and estimate the minimal important difference (MID) of the Hospital Anxiety and Depression Scale (HADS).

Methods HADS and core pulmonary rehabilitation outcomes were measured in 166 participants before and after an 8-week, in-person, outpatient pulmonary rehabilitation programme. Anchor- and distribution-based methods were used to calculate the MID of HADS-Anxiety (A) and HADS-Depression (D).

Results Suggestive or probable anxiety and depression (HADS ⩾8) were present in 35% and 37% of participants, respectively, at baseline, and this reduced significantly following pulmonary rehabilitation (post-pulmonary rehabilitation: HADS-A 23%, HADS-D 26%). Overall, there was a significant reduction in HADS-D (mean change −1.1, 95% CI −1.6– −0.5), but not HADS-A (−0.6, −1.3–0.15) with pulmonary rehabilitation. Subgroup analysis of those with HADS ⩾8 revealed significant improvements in HADS domains (mean change: HADS-A −4.5, 95% CI −5.7– −3.4; median change: HADS-D −4.0, interquartile range −6.0– −1.0). The mean (range) MID estimates for HADS-A and HADS-D were −2 (−2.3– −1.7) and −1.2 (−1.9– −0.5), respectively.

Conclusion In people with IPF and suggestive or probable mood disorder, pulmonary rehabilitation reduces anxiety and depression.

Introduction

Idiopathic pulmonary fibrosis (IPF) is characterised by a progressive decline in respiratory and physical functioning [1, 2]. Anxiety and depression are common in people with IPF; point prevalence rates range between 21% and 98% [3–10] and 14% and 100% [3–12] for anxiety and depression, respectively. Mood disorder in IPF is attributed to multiple factors, including the variable disease trajectory of IPF, uncertainty and fear around disease progression [12, 13], treatment (*e.g.* supplemental oxygen [4]), symptom burden (*e.g.* dyspnoea, cough [4, 5, 12]), loss of physical function [5] and independence, and social isolation [12], which have a detrimental impact on health-related quality of life [4, 12].

However, mood disorders are undertreated, with 75–84% [4, 11] of people with mood disorder not prescribed medication. Similarly, nonpharmacological management is limited to studies demonstrating minimal impact on mood disorders in IPF with palliative care [14] or disease management interventions (educational sessions designed to enable people with IPF learn about their disease) [7].

Pulmonary rehabilitation, an exercise and education programme for people with chronic lung disease, improves symptoms of mood disorder in people with COPD [15–17] and bronchiectasis [18]. A recent Cochrane review investigated the effects of pulmonary rehabilitation on exercise capacity, breathlessness, health-related quality of life and survival in people with interstitial lung disease (ILD) (including an IPF subgroup), but not mood disorder [19]. Data on the effect of pulmonary rehabilitation on mood disorder in IPF-specific populations are limited, and restricted to small studies that are underpowered to detect change [20–23]. Furthermore, the minimal important difference (MID) of the most commonly used mood disorder outcome measure in IPF [3–6, 20, 21, 23, 24], the Hospital and Anxiety Depression Scale (HADS) [25], is not known in this population. Therefore, the primary aim of this study was to determine the effects of pulmonary rehabilitation on anxiety and depression in people with IPF, with particular focus on those presenting with suggestive or probable mood disorder. The secondary aim was to estimate the MID of the HADS questionnaire. We hypothesised that pulmonary rehabilitation would reduce symptoms of mood disorder in IPF.

Materials and methods

Study design and participants

Participants were recruited to this cohort study between August 2012 and October 2017. Inclusion criteria were a primary diagnosis of IPF determined by a specialist multidisciplinary team; referred for a pulmonary rehabilitation assessment with the Harefield Pulmonary Rehabilitation Unit (London, UK); ability to walk 5 m independently (with or without a mobility aid) and ability to provide informed consent. The exclusion criteria were the presence of significant nonrespiratory comorbidities that would affect participants' ability to walk and therefore participate in pulmonary rehabilitation (*e.g.* leg amputation) or any other conditions that could cause the participant to be unsafe during exercise (*e.g.* unstable heart condition). All participants provided written informed consent, and the study was approved by the West London and London-Riverside research ethics committees (11/LO/1780, 14/LO/2247).

Methods

Participants underwent an outpatient pulmonary rehabilitation programme, which comprised two supervised sessions of exercise and education and one unsupervised home-based exercise session per week for 8 weeks. The programme, which included an education session on psychological wellbeing, is described in the supplementary material and elsewhere [26, 27]. Completion of this programme was determined to be attendance of a minimum of eight sessions and the post-pulmonary rehabilitation assessment [27].

Symptoms of mood disorder were measured using the HADS questionnaire, which has 14 items with two subscales: anxiety (HADS-A) and depression (HADS-D) [25]. Each item is scored from 0 to 3 with each subscale score ranging from 0 to 21 (low scores indicate fewer symptoms). For both subscales, HADS $\leqslant$7 indicates no symptoms, HADS $\geqslant$8 is suggestive of mood disorder and HADS $\geqslant$11 signifies probable mood disorder [28]. HADS, spirometry, incremental shuttle walk test (ISW) [29], King's Brief Interstitial Lung Disease Questionnaire (KBILD) [26], Chronic Respiratory Questionnaire (CRQ) [30] and Medical Research Council dyspnoea scale (MRC) [31] were completed before and after the pulmonary rehabilitation programme.

Analysis

Baseline characteristics were reported using descriptive statistics (normally distributed data: mean±SD, non-normally distributed data: median (interquartile range (IQR)), categorical data: number (%)). The relationship between HADS-A and HADS-D with other outcome measures and number of pulmonary rehabilitation sessions attended was analysed using Pearson's correlation coefficient (or Spearman's rank correlation coefficient for non-normally distributed data). ANOVA (or Kruskal–Wallis for non-normally distributed data) compared the between-group baseline differences according to HADS-A and HADS-D categories. Paired t-test (or Wilcoxon signed-rank test for non-normally distributed data) analysed response to pulmonary rehabilitation (*i.e.* change pre- to post-pulmonary rehabilitation). Chi-squared test for trend compared HADS categories before and after pulmonary rehabilitation. A pre-specified analysis investigating the response to pulmonary rehabilitation in participants with baseline HADS-A or HADS-D $\geqslant$8 was performed.

MID analysis

Multiple anchor- and distribution-based approaches were used to estimate the MID of HADS-A and HADS-D. For anchor-based methods, the following external anchors were selected because they are known to be responsive to pulmonary rehabilitation in people with IPF: MRC, ISW, CRQ (domains and total score) and KBILD (domains and total score). The *a priori* criteria for establishing the validity of external

anchors were a statistically significant correlation at the 5% level and a correlation coefficient >0.3 [32]. For external anchors fulfilling these criteria, linear regression was used to estimate change in HADS-D corresponding to the established MID for the relevant external anchors [33]. Additionally, receiver operating characteristic (ROC) curves provided MID estimates with the highest equal sensitivity and specificity to discriminate between those who improved the external anchor by the established MID and those who did not [34]. The distribution-based methods used to estimate the MID included 0.5×SD change and SEM (SD × $\sqrt{1}$ – test–retest reliability of HADS (test–retest reliability 0.86)). Data analyses were performed using GraphPad Prism 9 (GraphPad Software, USA) and SPSS version 26 (IBM, USA). Statistical significance was considered at $p<0.05$.

Regarding the sample size calculation, for anchor-based approaches of determining the MID, a minimum correlation of r>0.3 between the outcome of interest and external anchor is required [32]. To show a correlation of r>0.3 between change in HADS and change in CRQ or ISW with 95% power at the 0.05 significance level would require a minimum of 138 participants completing pulmonary rehabilitation.

Results

Baseline characteristics

In total, 261 people with IPF were referred to Harefield Pulmonary Rehabilitation Unit. Of these, 20 declined to participate in the study and six failed to meet the inclusion criteria: unstable cardiac condition (n=2), foot-drop (n=2) and unable to walk 5 m (n=2) (figure 1). 235 people were recruited to the study and 166 (64%) completed the pulmonary rehabilitation programme; participants attended a mean±SD 10±6 pulmonary rehabilitation sessions. There was no difference in baseline HADS scores between completers and noncompleters (mean±SD completers *versus* noncompleters: HADS-A 5.9±4.6 *versus* 6.7±4.6, p=0.07; HADS-D 6.5±3.9 *versus* 7.3±4.3, p=0.08).

The baseline characteristics of the whole cohort are described in table 1 and categorised according to HADS-A and HADS-D categories in the supplementary material (supplementary tables S1 and S2). With higher HADS-A and HADS-D (increasing severity of anxiety and depression), there was a significant worsening of disease severity (forced vital capacity (FVC) % predicted), respiratory disability (MRC), exercise capacity (ISW) and health-related quality of life (CRQ, KBILD).

For baseline HADS-A, there were moderate significant correlations with HADS-D (r=0.63) and CRQ-Emotion (r= −0.50) (figure 2) and significant but weak correlations with the other CRQ domains

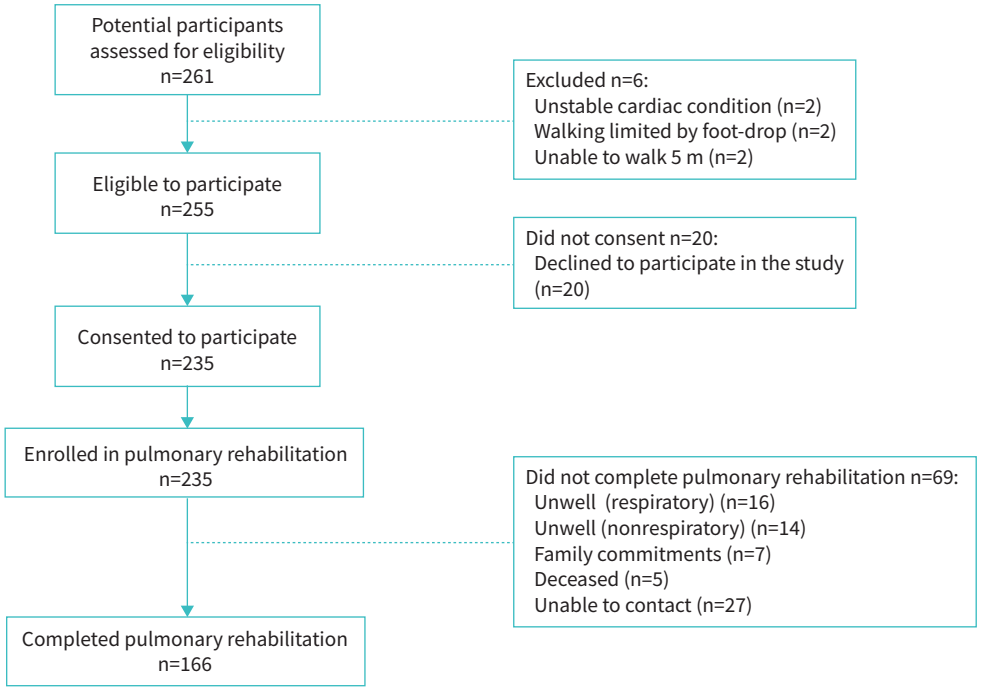

FIGURE 1 Study flow diagram.

TABLE 1 Baseline characteristics of the whole cohort

Participants	235
Male	163 (69)
Age (years)	73±9
FVC (L)	2.18±0.8
FVC (% pred)	68.8±21.6
FEV_1/FVC	0.81 (0.75–0.87)
MRC	3 (2–4)
BMI ($kg \cdot m^{-2}$)	26.8 (24.0–30.3)
Ischaemic heart disease	34 (15)
Pulmonary hypertension	17 (7)
Prescribed antifibrotic therapy	26 (11)
Prescribed medication for anxiety	1 (0.4)
Prescribed medication for depression	10 (4)
Long-term oxygen therapy	28 (12)
Ambulatory oxygen therapy	34 (15)
HADS-A	5.9±4.6
HADS-A ⩽7	154 (66)
HADS-A 8–10	44 (19)
HADS-A ⩾11	37 (16)
HADS-D	6.5±3.9
HADS-D ⩽7	149 (63)
HADS-D 8–10	47 (20)
HADS-D ⩾11	39 (17)
ISW (m)	235±171
CRQ-Dyspnoea	15.5±6.2
CRQ-Mastery	18.2±6.0
CRQ-Fatigue	13.8±5.5
CRQ-Emotion	31.6±9.4
CRQ-Total	79.2±23.2
KBILD-Psychological	56.0±17.2
KBILD-Breathlessness and Symptoms	40.0 (30.3–50.2)
KBILD-Chest	63.6±20.8
KBILD-Total	54.8±11.2

Data are presented as n, n (%), mean±SD or median (interquartile range). FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MRC: Medical Research Council dyspnoea scale; BMI: body mass index; HADS-A/D: Hospital Anxiety and Depression Scale – Anxiety/Depression; ISW: incremental shuttle walk test; CRQ: Chronic Respiratory Questionnaire; KBILD: King's Brief Interstitial Lung Disease Questionnaire.

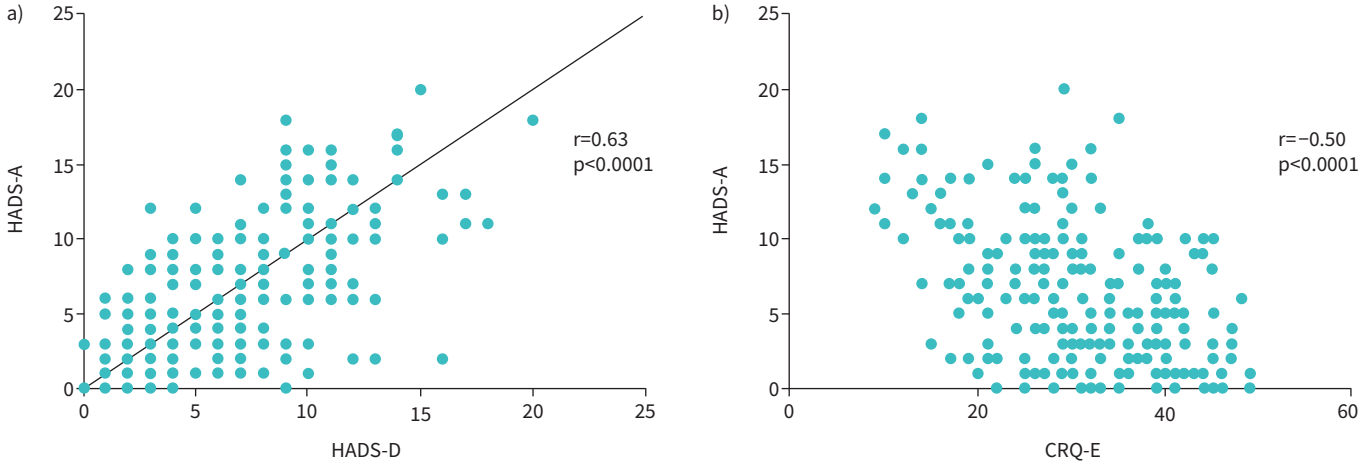

FIGURE 2 Relationship between Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and a) HADS-Depression (D) and b) Chronic Respiratory Questionnaire-Emotion (CRQ-E).

and KBILD (supplementary table S3). There was no correlation with number of pulmonary rehabilitation sessions attended. For baseline HADS-D, there were significant strong correlations with CRQ-Emotion (r= −0.79), CRQ-Mastery (r= −0.71) and CRQ-Total (r= −0.74) (figure 3); moderate correlations with HADS-A (0.63), CRQ-Fatigue (r= −0.57), KBILD-Psychological (r= −0.59), KBILD-Chest (−0.50), KBILD-Total (−0.56) and significant but weak correlations with FVC % pred, MRC, ISW, CRQ-Dyspnoea, KBILD-Breathlessness and symptoms and number of pulmonary rehabilitation sessions attended (supplementary table S3).

Response to pulmonary rehabilitation

For the whole cohort, there were significant and clinically meaningful improvements in the core pulmonary rehabilitation outcomes of exercise capacity, breathlessness and health-related quality of life, with no change in FVC % pred following completion of pulmonary rehabilitation (table 2). There was a significant reduction in the proportion of participants with suggestive or probable anxiety and depression following pulmonary rehabilitation (figure 4) (pre-pulmonary rehabilitation *versus* post-pulmonary rehabilitation: HADS-A 35% *versus* 23%, p≤0.01; HADS-D 37% *versus* 26%, p≤0.01). In the whole cohort, there was no statistically significant reduction in HADS-A scores with pulmonary rehabilitation (mean −0.6, 95% CI −1.3–0.15), but significant improvement in HADS-D (mean −1.1, 95% CI −1.6– −0.5). There was no correlation between the number of pulmonary rehabilitation sessions attended and change in HADS-A (r=0.08, p=0.30) or HADS-D (r= −0.14, p=0.09) scores. Participants with baseline HADS-A ⩾8 showed a significant improvement in HADS-A (mean change −4.5, 95% CI −5.7– −3.4) and HADS-D (mean change −1.7, 95% CI −2.8– −0.6) with pulmonary rehabilitation (table 3). Similarly, participants with baseline HADS-D ⩾8 demonstrated significant improvements in HADS-A (mean change −1.5, 95% CI −2.0– −1.0) and HADS-D (median change −4.0, IQR −6.0– −1.0; p<0.001) with pulmonary rehabilitation (table 3).

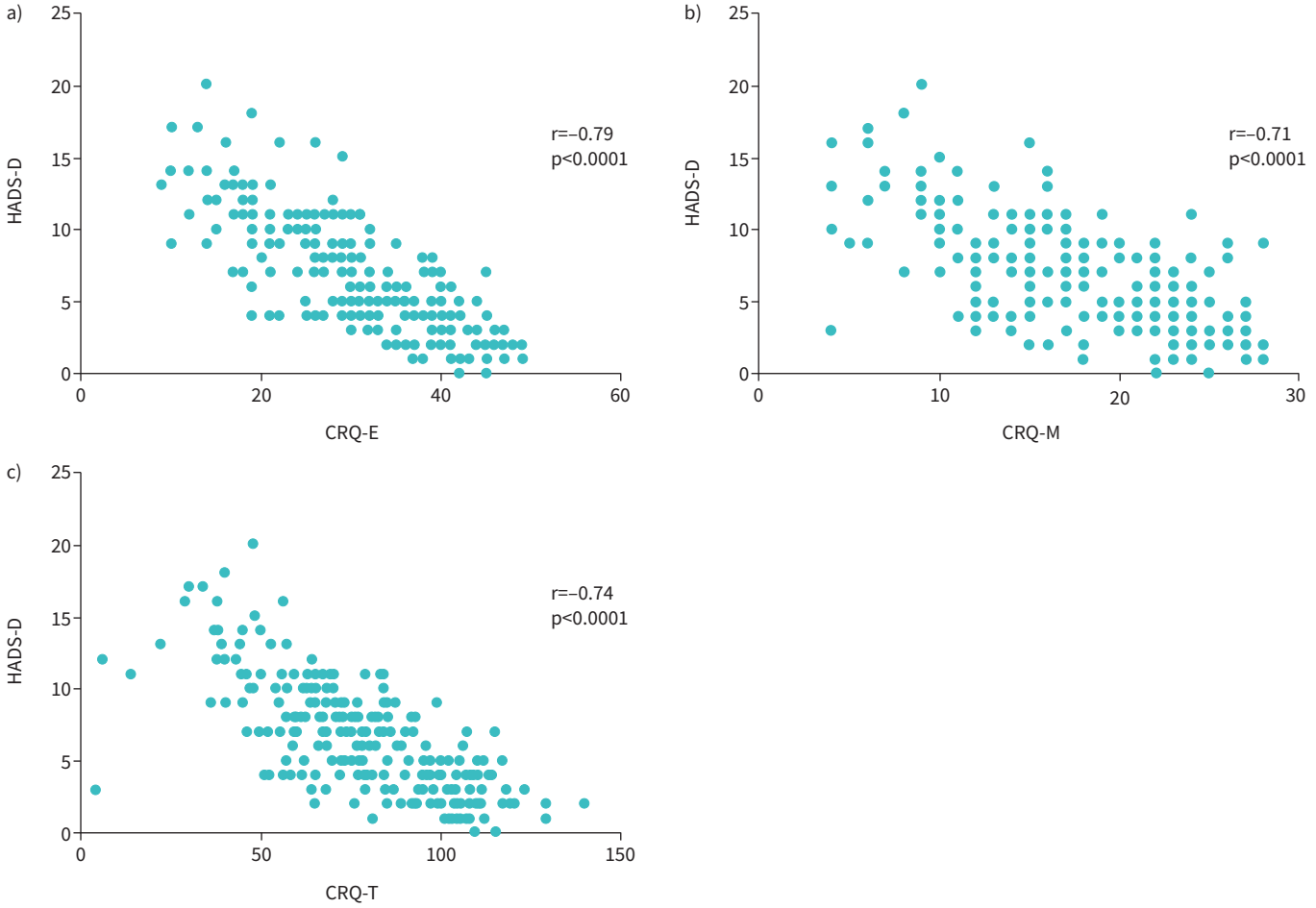

FIGURE 3 Relationship between Hospital Anxiety and Depression Scale-Depression (HADS-D) and a) Chronic Respiratory Questionnaire-Emotion (CRQ-E) and b) CRQ-Mastery (M) and c) CRQ-Total score (T).

TABLE 2 Baseline characteristics and response to pulmonary rehabilitation (n=166)

	Baseline characteristics	Post-pulmonary rehabilitation	Response to pulmonary rehabilitation	p-value
FVC (L)	2.20±0.80	2.20±0.83	0.1 (−0.1–0.4)	0.23
FVC (% pred)	70.5±21.9	70.6±23.1	2.9 (−3.9–9.8)	0.39
FEV_1/FVC	0.81 (0.76–0.87)#	0.80±0.09	0.01 (−0.09–0.09)#	0.96
MRC	3 (2–4)	2 (2–3)	−1 (−2–0)	<0.01
BMI ($kg \cdot m^{-2}$)	26.8 (24.0–30.3)#	26.7 (23.9–29.9)#	−0.8 (−4.2–4.6)#	0.71
HADS-A	5.5±4.5	4.9±3.7	−0.6 (−1.3–0.15)	0.12
HADS-D	6.1±3.7	5.0±3.4	−1.1 (−1.6– −0.5)	<0.01
ISW (m)	267±174	317±184	51 (39–63)	<0.01
CRQ-Dyspnoea	15.9±5.9	20.2±6.2	4.3 (3.3–5.3)	<0.01
CRQ-Mastery	19.0±5.6	20.4±5.3	1.2 (0.5–2.0)	<0.01
CRQ-Fatigue	14.4±5.2	16.7±4.6	2.4 (1.6–3.1)	<0.01
CRQ-Emotion	32.4±8.9	35.0±8.6	2.6 (1.5–3.7)	<0.01
CRQ-Total	81.7±21.5	92.2±20.6	10.5 (7.6–13.4)	<0.01
KBILD-Psychological	57.9±16.7	63.1±17.1	6.8 (4.1–9.5)	<0.01
KBILD-Breathlessness and Symptoms	41.9 (33.1–50.2)#	47.4 (37.8–55.2)#	6.0 (0.0–12.6)#	<0.01
KBILD-Chest	64.5±20.3	70.7±20.2	6.7 (2.8–10.6)	<0.01
KBILD-Total	55.9±11.0	59.3±10.3	4.4 (2.7–6.1)	<0.01

Data are presented as mean±SD or mean (95% CI) change, unless otherwise stated. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MRC: Medical Research Council dyspnoea scale; BMI: body mass index; HADS-A/D: Hospital Anxiety and Depression Scale – Anxiety/Depression; ISW: incremental shuttle walk test; CRQ: Chronic Respiratory Questionnaire; KBILD: King's Brief Interstitial Lung Disease Questionnaire. #: data are presented as median (interquartile range).

MID estimation

The correlations between change in HADS-A and HADS-D and change in MRC, ISW, CRQ and KBILD are reported in supplementary table S4). As the *a priori* criteria for establishing the validity of external anchors, a statistically significant correlation at the 5% level and a correlation coefficient >0.3 [32], were not achieved for HADS-A, we were unable to use this approach to estimate the MID for this domain. Using two distribution-based methods, the mean MID estimate was −2.0 (MID method and estimate: 0.5×SD −2.3; SEM −1.7).

For HADS-D, only the correlation with change in MRC, CRQ domains and total score and KBILD-Psychological met the *a priori* criteria for an external anchor. For these external anchors, linear

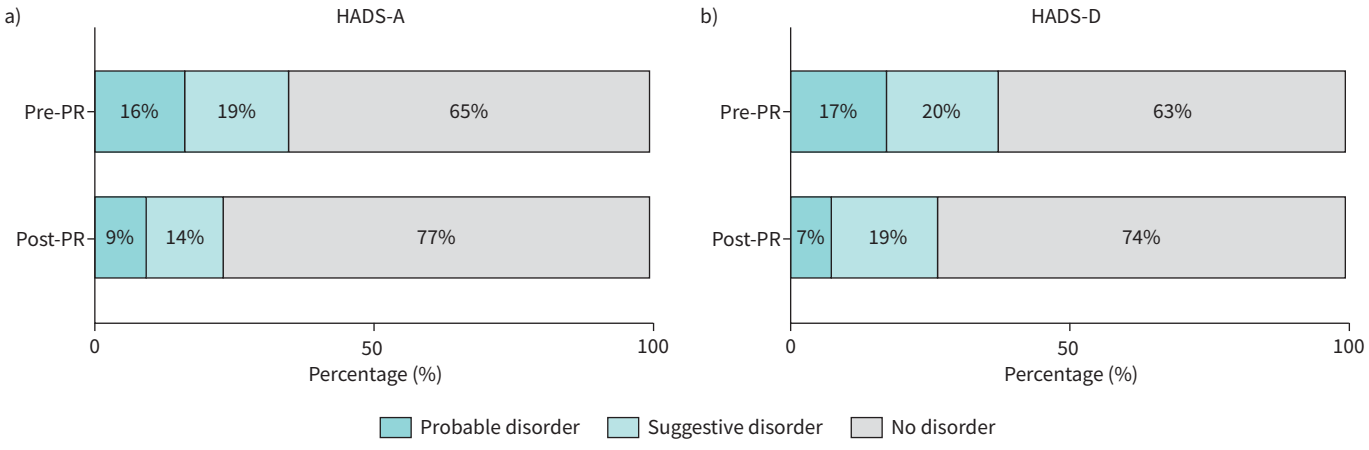

FIGURE 4 Prevalence of symptoms of mood disorder before and after pulmonary rehabilitation (PR) for a) Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and b) HADS-Depression (D). No disorder: HADS-A/D ⩽7; suggestive disorder: HADS-A/D 8–10; probable disorder: HADS-A/D ⩾11.

TABLE 3 Response to pulmonary rehabilitation in participants with Hospital Anxiety and Depression Scale-Anxiety (HADS-A) ⩾8 and HADS-Depression (HADS-D) ⩾8

	HADS-A ⩾8			HADS-D ⩾8		
	Baseline	Response to pulmonary rehabilitation	p-value	Baseline	Response to pulmonary rehabilitation	p-value
Participants		81			86	
MRC	4 (3–5)	−1 (−2–0.0)	<0.001	4 (2–4)	−1 (−1–−1)#	<0.001
BMI (kg·m^{-2})	27.5 (24.1–30.7)	1.5 (−5.6–7.5)	0.46	27.2 (24.0–30.6)	0.3 (−5.3–4.7)	0.98
HADS-A	11.2±2.8	−4.5 (−5.7–−3.4)#	<0.001	9.1±4.8	−1.5 (−2.0–−1.0)#	0.04
HADS-D	9.1±3.9	−1.7 (−2.8–−0.6)#	<0.01	10.0 (9.0–12.0)	−4.0 (−6.0–−1.0)	<0.001
ISW (m)	180 (75–280)	30 (0–65)	<0.001	175 (80–270)	50 (0–100)	<0.001
CRQ-Dyspnoea	14.0±6.0	4.2 (2.6–5.8)#	<0.001	13.4±5.2	5.3 (3.5–7.1)#	<0.001
CRQ-Mastery	15.1±6.1	1.3 (0.0–2.6)#	0.04	13.7±5.4	2.4 (1.1–3.7)#	<0.001
CRQ-Fatigue	11.7±5.1	2.1 (0.8–3.4)#	<0.01	10.7±4.1	4.0 (2.8–5.1)#	<0.001
CRQ-Emotion	26.4±9.1	1.8 (−0.0–3.7)#	0.052	23.3±6.7	5.2 (3.1–7.3)#	<0.001
CRQ-Total	67.3±22.5	9.4 (4.6–14.2)#	<0.001	60.9±17.2	17.0 (11.8–22.2)#	<0.001
KBILD-Psychological	49.1 (41.5–56.6)	4.1 (−1.1–9.2)	0.17	45.1 (38.5–50.5)	6.6 (1.7–15.7)	<0.01
KBILD-Breathlessness and Symptoms	34.7±14.4	6.9 (3.0–10.8)#	<0.01	32.9±14.7	7.7 (4.0–11.4)#	<0.001
KBILD-Chest	54.6±22.3	7.6 (1.6–13.6)#	0.01	52.0±21.6	9.7 (3.6–15.7)#	<0.01
KBILD-Total	49.7 (44.6–56.4)	3.9 (−0.5–7.0)	0.31	47.2 (43.2–54.8)	5.4 (0.0–12.2)	<0.001

Data are presented as n, median (interquartile range) or mean±SD, unless otherwise stated. MRC: Medical Research Council dyspnoea scale; BMI: body mass index; HADS-A/D: Hospital Anxiety and Depression Scale-Anxiety/Depression; ISW: incremental shuttle walk test; CRQ: Chronic Respiratory Questionnaire; KBILD: King's Brief Interstitial Lung Disease Questionnaire. #: data are presented as mean (95% CI) change.

regression and ROC plots were used to estimate change in HADS-D corresponding to the established MID of the anchors [33]: MRC −1, CRQ-Dyspnoea 2.5, CRQ-Fatigue 2, CRQ-Emotion 3.5, CRQ-Mastery 2, CRQ-Total 10 [35] and KBILD-Psychological 5.4 [26] (supplementary table S5). For linear regression and ROC plot analysis, the respective range of MID estimates was −1.2– −0.6 and −1.5– −0.5 (range: area under the curve 0.57–0.72; sensitivity 59–72%; specificity 53–72%). The distribution-based MID estimates were 0.5×SD −1.5 and SEM −1.9. In total, we provided 16 estimates of the MID of HADS-D (supplementary table S5). The mean (range) of these estimates was −1.2 (−1.9– −0.5).

Discussion

To the best of our knowledge, this study comprises the largest cohort of IPF participants undergoing pulmonary rehabilitation**.** We identified that mood disorder symptoms were present in a significant proportion of participants, and demonstrated a significant worsening of FVC % pred, core pulmonary rehabilitation outcomes and symptoms of depression (HADS-A cohort) and anxiety (HADS-D cohort) with increasing severity of mood disorder symptoms. Following pulmonary rehabilitation, there was a significant reduction in symptoms of depression, but not anxiety. Subgroup analysis of participants with suggestive or probable mood disorder at baseline assessment demonstrated significant reductions in symptoms of anxiety and depression following pulmonary rehabilitation. Mean MID estimates of HADS-A and HADS-D were −2 and −1.2, respectively.

Prior literature

Our study is the first to report that increasing symptoms of mood disorder is associated with worsening disease severity, respiratory disability, exercise capacity, health-related quality of life and symptoms of depression (HADS-A cohort) and anxiety (HADS-D cohort) in an IPF cohort referred for pulmonary rehabilitation. This contrasts with data in IPF outpatients which demonstrated that increasing mood disorder symptoms were not associated with exercise capacity or disease severity [5]. These disparities may be explained by differences in sample size and population: our study *versus* HOLLAND *et al.* [5]: n=235 *versus* n=124; pulmonary rehabilitation population *versus* ILD outpatient clinic population; 69% male *versus* 52% male; exercise capacity 235 m (ISW) *versus* 427 m (6-min walk test).

There are conflicting data regarding the effect of pulmonary rehabilitation on mood disorder symptoms in IPF despite all studies reporting similar baseline mean HADS scores. Three studies (two IPF-specific [22, 23], one ILD [20]) reported no change in mood disorder following pulmonary rehabilitation. In contrast, DENIZ *et al.* [21] demonstrated a significant reduction in symptoms of anxiety and depression in ILD

(n=81, of which n=38 IPF). Our study demonstrated significant reductions in symptoms of depression, and a trend towards reduction in anxiety. These differences may be because our study included a larger sample size, an IPF-specific population and a cohort where the majority did not have any suggestive or probable mood disorder. One study has investigated the response of mood disorder in people with IPF with baseline mood disorder symptoms and reported no change following pulmonary rehabilitation [23]. In contrast we demonstrated a significant reduction in these symptoms. This difference may be due to the duration of the intervention (our study 8 weeks *versus* 3 weeks in the study by Jarosch *et al.* [23]).

Our study is the first to report MID estimates of HADS following pulmonary rehabilitation in IPF. Our estimates of −2 and −1.2 for HADS-A and HADS-D, respectively, are similar to data reported in other chronic lung disease populations, which provides confidence in our results: HADS-A: COPD −1.5 [15], −2– −1.1 [16]; bronchiectasis with HADS-A ⩾8: −2 [18]; HADS-D: COPD −1.5 [15], −1.8– −1.4 [16]; and bronchiectasis with HADS-D ⩾8: −2 [18].

Clinical significance

This study demonstrated that suggestive or probable anxiety and depression were present in 35% and 37%, respectively, of people with IPF referred to pulmonary rehabilitation. In our study, <5% of participants with mood disorder symptoms were prescribed medication for these conditions (similar to IPF outpatients [11]) and indicates that mood disorder may be underrecognised and undertreated

Anxiety symptoms did not reduce with pulmonary rehabilitation in the whole cohort, possibly because the sample size was underpowered or the cohort included a significant proportion without significant anxiety, *i.e.* low baseline HADS-A scores. Additional reasons may include anxiety about IPF, *e.g.* disease trajectory and prognosis or components of pulmonary rehabilitation. Future research should corroborate or refute these data and explore the experience of people with IPF and anxiety undergoing pulmonary rehabilitation.

Participants with HADS ⩾8 at baseline achieved statistically and clinically significant (MID achieved) reductions in HADS-A and HADS-D following pulmonary rehabilitation; however, 23% and 26% still showed a HADS-A and HADS-D ⩾8, respectively. Future research should investigate interventions that improve symptom burden.

Our study provides MID estimates of HADS-A and HADS-D in response to pulmonary rehabilitation. This may help healthcare professionals evaluate whether their pulmonary rehabilitation programme provide clinically meaningful results in IPF in terms of mood disorder. In addition, it may aid researchers in evaluating the efficacy of interventions on mood disorder in IPF.

Strengths and limitations

This study has multiple strengths. To the best of our knowledge, it is the largest study to investigate the response of HADS to pulmonary rehabilitation and the first to provide MID estimates in IPF, which provides confidence in our results. Mood disorder was measured using a validated outcome measure (HADS) and pulmonary rehabilitation was performed in line with national guidance. However, a limitation was the absence of a control group; the ethics committees did not consider it ethical to deny participants with IPF the opportunity of pulmonary rehabilitation, given its recommendation in national clinical guidance documents [36]. Another limitation is that the HADS was primarily designed as a screening tool, and not as a longitudinal tool to assess the effects of intervention. However, the HADS has been widely used to investigate longitudinal change [37] and response to interventions in various populations including medication (tocilizumab) for people living with rheumatoid arthritis [38], self-management tools for the management of spinal pain [39], cardiac rehabilitation [40] and pulmonary rehabilitation [15, 16, 18]. Pulmonary rehabilitation is a complex intervention which includes exercise, educational and social components (group-based programme). However, the study was not designed to understand the component of pulmonary rehabilitation that is most influential on mood disorder symptoms. Furthermore, we are unable to comment on the long-term effects of pulmonary rehabilitation on mood disorder.

In conclusion, we have demonstrated that mood disorder is present in a significant proportion of people with IPF referred for pulmonary rehabilitation. Following pulmonary rehabilitation, there was a significant reduction in symptoms of depression, but not anxiety. Subgroup analysis of participants with baseline mood disorder demonstrated significant considerable reductions in both symptoms of anxiety and depression following pulmonary rehabilitation. Mean MID estimates of HADS-A and HADS-D were −2 and −1.2, respectively.

Provenance: Submitted article, peer reviewed.

Acknowledgements: We would like to express our gratitude to the patients involved in this study and the staff of the Harefield Pulmonary Rehabilitation Unit for providing the pulmonary rehabilitation intervention.

Author contributions: Concept and design of study: C.M. Nolan and W.D-C. Man; acquisition of data: O. Polgar, S. Patel, R.E. Barker, J.A. Walsh, J. Harvey and C.M. Nolan; analysis of data: G.D. Edwards, O. Polgar and C.M. Nolan; drafting of manuscript: all authors; revision of manuscript critically for important intellectual content: all authors; approval of final manuscript: all authors.

Support statement: This study was funded by a National Institute for Health Research Doctoral Research Fellowship (2014-07-089) and Medical Research Council New Investigator Research Grant (98576). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: G.D. Edwards, O. Polgar, S. Patel, R.E. Barker, J.A. Walsh and J. Harvey report no competing interests. W.D-C. Man reports personal fees from Jazz Pharmaceuticals, Mundipharma and Novartis, grants from Pfizer, nonfinancial support from GSK, and grants from the National Institute for Health Research and British Lung Foundation, outside the submitted work; and is an associate editor of this journal. C.M. Nolan reports personal fees from Novartis and consultancy work (not reimbursed) with Vicore Pharma outside the submitted work.

References

1 King CS, Nathan SD. Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. *Lancet Respir Med* 2017; 5: 72–84.
2 Fell CD. Idiopathic pulmonary fibrosis: phenotypes and comorbidities. *Clin Chest Med* 2012; 33: 51–57.
3 Bae W, Cho J, Lee J, *et al.* Longitudinal comparison of anxiety and depression between idiopathic pulmonary fibrosis (IPF) and non-IPF interstitial lung disease: a prospective cohort study. *Am J Respir Crit Care Med* 2019; 199: A3364.
4 Glaspole IN, Chapman SA, Cooper WA, *et al.* Health-related quality of life in idiopathic pulmonary fibrosis: data from the Australian IPF Registry. *Respirology* 2017; 22: 950–956.
5 Holland AE, Fiore JF, Bell EC, *et al.* Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. *Respirology* 2014; 19: 1215–1221.
6 Lee YJ, Choi SM, Lee YJ, *et al.* Clinical impact of depression and anxiety in patients with idiopathic pulmonary fibrosis. *PLoS One* 2017; 12: e0184300.
7 Lindell KO, Olshansky E, Song M-K, *et al.* Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart Lung* 2010; 39: 304–313.
8 Matsuda T, Taniguchi H, Ando M, *et al.* Depression is significantly associated with the health status in patients with idiopathic pulmonary fibrosis. *Intern Med* 2017; 56: 1637–1644.
9 Yalnız E, Polat G, Demirci F, *et al.* Are idiopathic pulmonary fibrosis patients more anxious and depressive than patient's with other interstitial lung disease? *Sarcoidosis Vasc Diffuse Lung Dis* 2019; 36: 294–301.
10 Yenibertiz D, Özyürek BA, Aydin MS, *et al.* Evaluation of anxiety and depression in idiopathic pulmonary fibrosis. *Middle Black Sea J Health Sci* 2020; 6: 333–339.
11 Akhtar AA, Ali MA, Smith RP. Depression in patients with idiopathic pulmonary fibrosis. *Chron Respir Dis* 2013; 10: 127–133.
12 Tzouvelekis A, Karampitsakos T, Kourtidou S, *et al.* Impact of depression on patients with idiopathic pulmonary fibrosis. *Front Med* 2020; 7: 29.
13 Lindell KO, Liang Z, Hoffman LA, *et al.* Palliative care and location of death in decedents with idiopathic pulmonary fibrosis. *Chest* 2015; 147: 423–429.
14 Janssen K, Rosielle D, Wang Q, *et al.* The impact of palliative care on quality of life, anxiety, and depression in idiopathic pulmonary fibrosis: a randomized controlled pilot study. *Respir Res* 2020; 21: 2.
15 Puhan MA, Frey M, Büchi S, *et al.* The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes* 2008; 6: 46.
16 Smid DE, Franssen FM, Houben-Wilke S, *et al.* Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: a prospective analysis. *J Am Med Dir Assoc* 2017; 18: 53–58.
17 Yohannes AM, Casaburi R, Dryden S, *et al.* The effectiveness of pulmonary rehabilitation on chronic obstructive pulmonary disease patients with concurrent presence of comorbid depression and anxiety. *Respir Med* 2022; 197: 106850.
18 Wynne SC, Patel S, Barker RE, *et al.* Anxiety and depression in bronchiectasis: response to pulmonary rehabilitation and minimal clinically important difference of the Hospital Anxiety and Depression Scale. *Chron Respir Dis* 2020; 17: 1479973120933292.
19 Dowman L, Hill CJ, May A, *et al.* Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* 2021; 2: CD006322.

20 Dowman LM, McDonald CF, Hill CJ, *et al.* The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017; 72: 610–619.
21 Deniz S, Şahin H, Yalnız E. Does the severity of interstitial lung disease affect the gains from pulmonary rehabilitation? *Clin Respir J* 2018; 12: 2141–2150.
22 Swigris JJ, Fairclough DL, Morrison M, *et al.* Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care* 2011; 56: 783–789.
23 Jarosch I, Schneeberger T, Gloeckl R, *et al.* Short-term effects of comprehensive pulmonary rehabilitation and its maintenance in patients with idiopathic pulmonary fibrosis: a randomized controlled trial. *J Clin Med* 2020; 9: 1567.
24 Glaspole IN, Watson AL, Allan H, *et al.* Determinants and outcomes of prolonged anxiety and depression in idiopathic pulmonary fibrosis. *Eur Respir J* 2017; 50: 1700168.
25 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361–370.
26 Nolan CM, Birring SS, Maddocks M, *et al.* Kings Brief Interstitial Lung Disease questionnaire: responsiveness and minimum clinically important difference. *Eur Respir J* 2019; 54: 1900281.
27 Nolan CM, Polgar O, Schofield SJ, *et al.* Pulmonary rehabilitation in idiopathic pulmonary fibrosis and COPD: a propensity-matched real-world study. *Chest* 2022; 161: 728–737.
28 Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes* 2003; 1: 29.
29 Nolan CM, Delogu V, Maddocks M, *et al.* Validity, responsiveness and minimum clinically important difference of the incremental shuttle walk in idiopathic pulmonary fibrosis: a prospective study. *Thorax* 2018; 73: 680–682.
30 Williams JE, Singh SJ, Sewell L, *et al.* Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). *Thorax* 2001; 56: 954–959.
31 Bestall JC, Paul EA, Garrod R, *et al.* Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54: 581–586.
32 Revicki D, Hays RD, Cella D, *et al.* Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008; 61: 102–109.
33 Kon SS, Canavan JL, Jones SE, *et al.* Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *Lancet Respir Med* 2014; 2: 195–203.
34 Kon SS, Dilaver D, Mittal M, *et al.* The Clinical COPD Questionnaire: response to pulmonary rehabilitation and minimal clinically important difference. *Thorax* 2014; 69: 793–798.
35 Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; 10: 407–415.
36 National Institute for Health and Care Excellence. Idiopathic Pulmonary Fibrosis in Adults: Diagnosis and Management. 2013. www.nice.org.uk/guidance/cg163/ Date last accessed: 10 January 2019. Date last updated: 23 May 2017.
37 Chan KS, Friedman LA, Bienvenu OJ, *et al.* Distribution-based estimates of minimal important difference for hospital anxiety and depression scale and impact of event scale-revised in survivors of acute respiratory failure. *Gen Hosp Psychiatry* 2016; 42: 32–35.
38 Traki L, Rostom S, Tahiri L, *et al.* Responsiveness of the EuroQol EQ-5D and Hospital Anxiety and Depression Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. *Clin Rheumatol* 2014; 33: 1055–1060.
39 Strøm J, Nielsen CV, Jørgensen LB, *et al.* A web-based platform to accommodate symptoms of anxiety and depression by featuring social interaction and animated information in patients undergoing lumbar spine fusion: a randomized clinical trial. *Spine J* 2019; 19: 827–839.
40 Lemay KR, Tulloch HE, Pipe AL, *et al.* Establishing the minimal clinically important difference for the hospital anxiety and depression scale in patients with cardiovascular disease. *J Cardiopulm Rehabil Prev* 2019; 39: E6–E11.