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Original Research

# The presence of extra-pulmonary treatable traits increases the likelihood of responding to pulmonary rehabilitation

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ABSTRACT

*Introduction:* Studies suggest that people with chronic obstructive pulmonary disease (COPD) who are worse at baseline respond better to pulmonary rehabilitation (PR). Identifying treatable traits (TTs) may help to distinguish responders from non-responders. We explored the impact of PR on extra-pulmonary traits of people with COPD and whether the presence of TT influences the type of response to PR.
*Methods:* A comprehensive assessment of 9 TT including symptoms (dyspnoea, fatigue, anxiety and depression), functional capacity, deconditioning, balance, impact of the disease and health-related quality of life was conducted before and after a 12-week community-based PR programme. Pre-post differences between people with or without each TT at baseline were compared with independent samples t-tests or Mann-Whitney U tests. Proportion of responders between groups were explored with chi-square tests and odds ratio.
*Results:* 102 people with COPD were included (70 [65; 75] years old, 78% male, $FEV_1$ 47 [36; 60] %predicted). They had a median of 3 (out of 9) TTs per person and each patient responded on average to 5 (out of 9) outcomes of PR. People with TT were more responsive than those without them in all outcomes ($p < 0.05$) except for the 1-min sit-to-stand test. The presence of TT increased 4 to 20 times the likelihood of being a good responder.
*Conclusions:* Identification of baseline extra-pulmonary TT in people with COPD showed the potential to inform on PR responsiveness and might therefore be an important strategy for patient prioritization, treatment personalisation (i.e., activation of the most suitable components) and optimisation.

## 1. Introduction

A treatable traits strategy has been advocated for people with chronic respiratory diseases, to personalise medicine to the individual's needs and therefore, improve outcomes of interventions [1,2]. In general, only necessary treatments are provided according to the identified treatable traits. This strategy has been shown to be more effective than usual care in improving health-related quality of life and asthma control in patients with asthma [3].

Pulmonary rehabilitation (PR) provides a unique opportunity to address various treatable traits simultaneously and to implement person-centred treatments in chronic respiratory diseases, namely chronic obstructive pulmonary disease (COPD). In fact, it is a multicomponent intervention moving towards more personalised care where ideally the best strategies are activated according to patients' needs [4].

PR has multiple benefits (e.g., less symptoms, better exercise tolerance, improved health-related quality of life) for people with COPD [5,6]. However, there are non-responders in one or more outcomes

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(e.g., anxiety, fatigue, functional status) and the magnitude of response to PR has been found to be greater in people who are worse at baseline (e.g., higher symptom burden) [7–10]. Additionally, despite its comprehensiveness, a recent systematic review has shown that treatable traits have been poorly addressed in PR trials [11].

Hence, identifying treatable traits might help to better personalise PR (e.g., select the most appropriate components for each treatable trait), and distinguish responders from non-responders, which could aid optimisation of the intervention in the future.

This study aimed to explore the impact of PR on extra-pulmonary treatable traits of people with COPD and to explore the influence of the presence of these traits on being a responder or non-responder to PR.

## 2. Materials and methods

This was a retrospective study of data collected between October 2017 and November 2021 and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. The study was approved by the Ethics Committees of Administração Regional de Saúde do Centro (Ref. 73/2016, 16/2020, 85/2018), and Centro Hospitalar do Baixo Vouga (15-05-2019, 086,892). Participants needed to have a diagnosis of COPD (post bronchodilator forced expiratory volume in the first second [$FEV_1$]/forced vital capacity $<0.70$), be clinically stable in the previous month (i.e., no hospital admissions, acute exacerbations or changes in medication) and have participated in PR to be included. Exclusion criteria comprised the presence of other respiratory diseases or any clinical condition that precluded participation in the assessment (i.e., signs of cognitive impairment or presence of a significant cardiovascular, neurological, musculoskeletal, immunological, or infectious disease). Eligible participants were identified during routine appointments at a hospital or primary healthcare centres. All participants provided written informed consent.

### 2.1. Data collection and intervention

A comprehensive assessment was performed. Sociodemographic (age and sex), anthropometric (height and weight to compute body mass index) and general clinical data (smoking status, comorbidities through the Charlson comorbidity index [CCI], use of long-term oxygen therapy and non-invasive ventilation, and number of acute exacerbations of COPD in the previous year) were collected. Activity-related dyspnoea was assessed with the modified Medical Research Council dyspnoea scale (mMRC), fatigue with the functional assessment of chronic illness therapy fatigue subscale (FACIT-F), and symptoms of anxiety and depression with the hospital anxiety and depression scale (HADS). Functional capacity was assessed with the 1-min sit-to-stand test (1-min STS) and deconditioning with the 6-min walk test (6MWT). Handgrip strength and quadriceps maximal isometric voluntary contraction (QMVC) were measured using a handheld dynamometer (microFET2, Hoggan Health, The best Salt Lake City, Utah and W50174, Baseline, UK, respectively). Balance was assessed with the Brief balance evaluation systems test (Brief-BESTest). Self-reported physical activity was measured with the brief physical activity assessment tool (BPAAT), the impact of disease/health status with the COPD assessment test (CAT) and health-related quality of life with the Saint George's respiratory questionnaire (SGRQ).

People with COPD underwent a conventional 12-week community-based PR programme. The programme was not designed considering the prevalence of treatable traits. The exercise training was personalised to each person (e.g., functional and muscle strength capacity), but all patients received the same PR components. It consisted of exercise training (aerobic and resistance training) twice per week and education and psychosocial support once every 2 weeks. Each session lasted approximately 60 min. A multidisciplinary team of physiotherapists, medical doctors, nurses, psychologists, dietitians, and social workers provided the programme. Details of the programme have been published elsewhere [13].

Extra-pulmonary treatable traits and responders and non-responders to PR were identified for each outcome measure. Nine treatable traits were defined based on previously established cut-offs and responders and non-responders to PR were defined based on published minimal clinical important differences (Table 1).

### 2.2. Data analysis

A multivariate imputation by chained equations was performed as some variables (i.e., HADS, FACIT-F) had more than 5% but less than 30% of missing data [14]. A sensitivity analysis with the original dataset (not imputed) was performed to check if results were similar to the ones of our main analysis.

Descriptive statistics were used to characterise the sample. Effects of PR were explored using paired samples t-tests or Wilcoxon signed-rank tests. Differences in mean/median between people with COPD with or without the treatable trait were explored using independent samples t-tests or Mann-Whitney U tests. Responders with or without the treatable trait were compared using chi-square tests for two proportions.

Odds ratios were computed to explore the probability of being a responder in each outcome, by having the presence of each treatable trait.

Adherence of responders was compared with the adherence of non-responders considering the absence or presence of the treatable traits using non-parametric two-way ANOVA. Normality of residuals was explored with Shapiro-Wilk test and homogeneity of variance with Levene's test.

All statistical analysis were performed in R (v. 4.1.2).

## 3. Results

Of the initial 140 database entries, 102 people with COPD were included. 38 entries were excluded after applying inclusion and exclusion criteria (repeated PR programmes, $FEV_1$/FVC $>70\%$ predicted). No differences were found in the interpretation of results between imputed or

**Table 1**
Cut-offs and minimal important clinical differences used to define treatable traits and response to pulmonary rehabilitation in each outcome measure in people with chronic obstructive pulmonary disease.

| Treatable trait | Cut-off used for the treatable trait | Minimal clinical important difference |
|---|---|---|
| Severe dyspnoea | mMRC ≥2 points [22] | Difference in mMRC ≥1 point [23] |
| Clinically relevant fatigue | FACIT-F ≤43 points [24] | Difference in FACIT-F ≥4.7 points |
| Symptoms of anxiety | HADS sub score ≥8 points [25] | Difference in HADS ≥1.5 points [26] |
| Symptoms of depression | HADS sub score ≥8 points [25] | Difference in HADS ≥1.5 points [26] |
| Poor functional capacity | 1-min STS <70% predicted [27] | Difference in 1-min STS ≥3 repetitions [28] |
| Deconditioning | 6MWT <70% predicted [27] | Difference in 6MWT ≥30 m [29] |
| Poor balance | Brief-BESTest ≤16.5 points [30] | Difference in Brief-BESTest ≥3 points [31] |
| Poor health status | CAT ≥18 points [32] | Difference in CAT ≥2 points [33] |
| Poor health-related quality of life | SGRQ ≥46 points [32] | Difference in SGRQ ≥4 points [34] |

mMRC: Medical Research Council dyspnoea scale (mMRC); FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: 1-min sit-to-stand test; 6MWT: 6-min walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

non-imputed data (analysis with the original dataset provided in Supplementary material).

Patients were mostly male (78%), had a median $FEV_1$ of 47% predicted, and were predominantly from GOLD grades 2 and 3 (43%, 42% respectively) and group B (57%). Patients had 85 ± 14.3% adherence to the PR sessions. Full characteristics of the sample are presented in Table 2.

Overall, PR was effective in improving all outcomes ($p < 0.05$) (Table 2).

At baseline, people with COPD had a median [min-max] of 3 [0–7] extra-pulmonary treatable traits per person, and responded on 5 [0–9] outcomes of PR.

People with the presence of treatable traits responded to a greater extent than those without treatable traits in all outcomes except for the 1-min STS (Table 3). Indeed, the pre-post mean differences of each outcome were significantly higher in those with a baseline mMRC ≥2 points ($p < 0.001$), FACIT-F ≤43 points ($p < 0.001$), HADS ≥8 points ($p < 0.001$ both anxiety and depression symptoms), 6MWT <70% predicted ($p = 0.005$) and Brief-BESTest <16.5 points ($p < 0.001$), CAT ≥18 points ($p < 0.001$), and SGRQ ≥46 points ($p = 0.005$). Accordingly, people with the treatable trait were more frequently responders than those without the treatable trait (Table 3 and Fig. 1). There was a significantly higher proportion of responders to mMRC ($p = 0.003$), FACIT-F ($p < 0.001$), HADS ($p < 0.001$, $p = 0.001$), 6MWT ($p = 0.009$), Brief-BESTest ($p < 0.001$), CAT ($p < 0.001$) and SGRQ ($p = 0.003$), in people with the respective treatable trait - severe dyspnoea, clinically relevant fatigue, symptoms of anxiety and depression, deconditioning, poor balance, poor health status and poor health-related quality of life - compared to those without the treatable trait at baseline (Table 3 and Fig. 1). People with the treatable traits were more likely responders than those without the treatable traits (OR = 4.25–19.95) with the exception of people with less than 70% predicted in the 1-min STS (Table 3).

No significant differences were found between responders and non-responders nor in the interaction between the 2 factors (i.e., treatable trait, no treatable trait; responder, non-responder) for all outcomes ($p > 0.05$). A significant difference was found in adherence rates between people with or without depression symptoms ($p = 0.013$).

## 4. Discussion

This study showed that PR was generally effective in addressing extra-pulmonary traits of people with COPD, and that people who exhibit treatable traits at baseline are more responsive than those without the treatable traits.

Our findings are consistent with several recent studies which demonstrated that people with COPD who are clinically worse at baseline are usually those responding better to the intervention [7–9,15]. This might be due to having more room for improvement in those more severe, and an absence of abnormal values in some measures or a delayed response to PR in people that are functionally better at baseline. Therefore, early identification of these patients and referral to PR considering their treatable traits seems to be of paramount importance.

A recent study has demonstrated different stakeholders to believe that when necessary people with chronic respiratory diseases who are more symptomatic and with worse functional status should be prioritised for PR [16]. Considering these findings and the present study, it might be appropriate to prioritise patients who exhibit a higher number of treatable traits. Nonetheless, this requires further investigation.

Overall, for most outcomes, the group of patients with absence of each treatable trait did not achieve clinically relevant benefits (within the established minimal clinical important differences) with PR. Therefore, it seems crucial to conduct a comprehensive assessment at baseline to identify the multiple treatable traits of each person and only activate the necessary PR components (e.g., exercise, education, psycholog-

**Table 2**
Baseline characteristics and outcomes of pulmonary rehabilitation in people with chronic obstructive pulmonary disease (n = 102).

| | Baseline | Post | $Mean/Median_{diff}$ | 95% CI | p-value |
|---|---|---|---|---|---|
| Age, years | 69.5 [65.0; 75.0] | N.A. | N.A. | N.A. | N.A. |
| Sex, n (%) | | | | | |
| Female | 23 (22.5) | N.A. | N.A. | N.A. | N.A. |
| Male | 79 (77.5) | N.A. | N.A. | N.A. | N.A. |
| Smoking status, n (%) | | | | | |
| Never smoker | 21 (20.6) | N.A. | N.A. | N.A. | N.A. |
| Former smoker | 65 (63.7) | N.A. | N.A. | N.A. | N.A. |
| Current smoker | 16 (15.7) | N.A. | N.A. | N.A. | N.A. |
| Pack-years, n | 30.0 [9.4; 57.0] | N.A. | N.A. | N.A. | N.A. |
| $FEV_1$, % predicted | 47.0 [36.0; 60.0] | N.A. | N.A. | N.A. | N.A. |
| GOLD grade, n (%) | | | | | |
| 1 | 7 (7.0) | N.A. | N.A. | N.A. | N.A. |
| 2 | 43 (42.6) | N.A. | N.A. | N.A. | N.A. |
| 3 | 42 (41.6) | N.A. | N.A. | N.A. | N.A. |
| 4 | 9 (8.9) | N.A. | N.A. | N.A. | N.A. |
| GOLD group, n (%) | | | | | |
| A | 27 (26.5) | N.A. | N.A. | N.A. | N.A. |
| B | 58 (56.9) | N.A. | N.A. | N.A. | N.A. |
| C | 2 (2.0) | N.A. | N.A. | N.A. | N.A. |
| D | 15 (14.7) | N.A. | N.A. | N.A. | N.A. |
| CCI, total | 4.0 [3.0; 5.0] | N.A. | N.A. | N.A. | N.A. |
| LTOT, n (%) | 10 (9.8) | N.A. | N.A. | N.A. | N.A. |
| NIV, n (%) | 13 (12.7) | N.A. | N.A. | N.A. | N.A. |
| No. AECOPD previous 12 months, n | 0.0 [0.0; 1.0] | N.A. | N.A. | N.A. | N.A. |
| BMI, $kg/m^2$ | 26.4 ± 4.8 | N.A. | N.A. | N.A. | N.A. |
| mMRC, score | 2.0 [1.0; 3.0] | 1.0 [1.0; 2.0] | 0.0 [-1.0; 0.0] | N.A. | <0.001 |
| FACIT-F, total score | 36.1 ± 9.0 | 39.3 ± 8.5 | 3.2 ± 6.7 | 1.9; 4.5 | <0.001 |
| HADS, Anxiety score | 5.9 ± 4.1 | 5.2 ± 3.7 | −0.7 ± 3.2 | −1.3; −0.1 | 0.02 |
| HADS, depression score | 6.0 [3.0; 9.8] | 6.0 [3.0; 8.0] | −1.0 [-3.0; 1.0] | N.A. | <0.001 |
| 1-min STS, repetitions | 22.5 [18.3; 27.8] | 26.0 [21.0; 31.0] | 4.0 [0.0; 6.0] | N.A. | <0.001 |
| 6MWT, m | 405.1 ± 127.3 | 448.8 ± 123.1 | 43.7 ± 61.9 | 31.5; 55.9 | <0.001 |
| Handgrip strength, Kg | 34.0 [26.0; 40.0] | N.A. | N.A. | N.A. | N.A. |
| QMVC, Kg/F | 30.7 ± 7.9 | 33.2 ± 8.4 | 2.5 ± 6.2 | 1.2; 3.7 | <0.001 |
| Brief-BESTest, score | 18.0 [15.0; 22.0] | 21.0 [18.0; 23.0] | 3.0 [0.0; 4.0] | N.A. | <0.001 |
| BPAAT, score | 0.0 [0.0; 2.8] | 4.0 [2.0; 6.0] | 2.0 [1.0; 4.0] | N.A. | <0.001 |
| CAT, total score | 14.7 ± 8.0 | 11.6 ± 7.1 | −3.1 ± 6.1 | −4.3; −1.9 | <0.001 |
| SGRQ, total score | 46.0 [28.4; 59.5] | 40.0 [20.1; 51.8] | −7.5 [-14.3; 0.5] | N.A. | <0.001 |

N.A. Not applicable; $FEV_1$: forced expiratory volume in the first second; GOLD: Global initiative for chronic obstructive lung disease; CCI: Charlson comorbidity index; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation; BMI: body mass index; mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: 1-min sit-to-stand test; 6MWT: 6-min walk test; QMVC: quadriceps maximal isometric voluntary con-

traction; Brief-BESTest: Brief balance evaluation systems test; BPAAT: brief physical activity assessment tool; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

ical support, and/or balance training) accordingly. Indeed, designing the PR programme for each individual based on the treatable traits that need to be targeted could enhance the programme personalisation and cost-effectiveness, especially considering the lack of resources commonly available [5]. Healthcare professionals should be however aware of the need of a multidimensional assessment, as narrow baseline assessments may lead to a misinterpretation of the lack of need of PR for some patients. In fact, it is unlikely for a person with COPD to exhibit no treatable traits [17,18], and therefore to have no need to be integrated, at least partially, in PR.

The present study did not aim to explore the effectiveness of a treatable trait strategy for PR. Similar to a randomized controlled trial of a treatable traits strategy vs. usual care in asthma [3], future studies could compare conventional PR with a treatable traits based programme in terms of their effectiveness for people with COPD.

Even though most responders were those who had the treatable traits at baseline, our findings still showed a large proportion of people with the treatable traits who did not respond to PR. We found no influence between adherence to PR and responding to the intervention, independently of the presence or absence of treatable traits. Therefore, whether these patients are truly non-responders or if a higher intensity or frequency of treatment is necessary, requires further research.

In our sample the response in the 1-min STS was not significantly different between those with or without the treatable trait. Most of our patients were responders in this outcome and therefore this fact is likely to have impacted the group comparisons. Nevertheless, responders to PR in the 1-min STS have been found to exhibit a lower capacity at baseline than non-responders [8]. Therefore, similar to other outcomes, a pattern of better response to PR with the presence of poor functional capacity in the 1-min STS at baseline is expected.

Although we identified multiple traits through a comprehensive assessment, it might also be important to identify other treatable traits that are relevant for PR, such as respiratory muscle dysfunction, lack of disease-specific knowledge, poor nutritional status, and poor social status, to decide the most suitable PR path for each patient. A recent study has provided a clinical decision tree for the quick allocation of people with COPD to a profile, which might enable a fast decision on the best treatment regimens, following the profile's treatable traits [18]. Future studies could also develop a PR-specific clinical decision tool to rapidly decide the PR components to be activated for each patient according to their treatable traits (based on a comprehensive treatable trait assessment).

Our sample was mainly composed of men and elderly people. Studies have shown women to have a higher prevalence and more severe treatable traits than men with COPD, which also seem to increase with

**Table 3**
Response to pulmonary rehabilitation defined by the minimal important clinical differences of each outcome measure, according to the presence or absence of each treatable trait in people with chronic obstructive pulmonary disease (n = 102).

| Treatable trait | Mean/Median$_{diff}$ | p-value | Non-responders, n (%) | Responders, n (%) | p-value | OR [95%CI] | Non-responders % adherence | Responders % adherence | p-value[a] |
|---|---|---|---|---|---|---|---|---|---|
| mMRC, score | | | | | | | | | |
| <2 points | 0.0 [0.0; 0.0] | <0.001 | 29 (76.3) | 9 (23.7) | 0.003 | 4.14 [1.69; 10.15] | 88.0 [71.0; 92.0] | 100.0 [83.0; 100.0] | 0.182 |
| **≥2 points (severe dyspnoea)** | −1.0 [-1.0; 0.0] | | 28 (43.8) | 36 (56.3) | | | 81.0 [74.0; 89.0] | 88.0 [75.0; 96.0] | |
| FACIT-F, score | | | | | | | | | |
| **≤43 points (clinically relevant fatigue)** | 5.0 [0.0; 8.8] | <0.001 | 40 (48.8) | 42 (51.2) | <0.001 | 19.95 [2.55; 156.05] | 88.0 [75.0; 96.0] | 85.5 [72.0; 95.0] | 0.819 |
| >43 points | 0.0 [-3.0; 1.2] | | 19 (95.0) | 1 (5.0) | | | 88.0 [77.0; 92.0] | 67.0 [67.0; 67.0] | |
| HADS, Anxiety score | | | | | | | | | |
| <8 points | 0.0 [-2.0; 2.0] | <0.001 | 50 (73.5) | 18 (26.5) | <0.001 | 6.67 [2.67; 16.62] | 88.0 [75.0; 96.0] | 88.0 [73.0; 94.3] | 0.362 |
| **≥8 points (symptoms of anxiety)** | −2.5 [-5.0; 0.0] | | 10 (29.4) | 24 (70.6) | | | 79.0 [69.0; 94.3] | 81.0 [70.0; 89.0] | |
| HADS, Depression score | | | | | | | | | |
| <8 points | 0.0 [-2.0; 2.0] | <0.001 | 41 (69.5) | 18 (30.5) | 0.001 | 4.25 [1.84; 9.82] | 88.0 [83.0; 96.0] | 88.0 [75.0; 95.0] | 0.767 |
| **≥8 points (symptoms of depression)** | −3.0 [-4.0; −1.0] | | 15 (34.9) | 28 (65.1) | | | 79.0 [67.5; 88.0] | 81.0 [70.0; 95.3] | |
| 1-min STS, % predicted | | | | | | | | | |
| **<70% (poor functional capacity)** | 4.0 [2.0; 7.0] | 0.046 | 21 (39.6) | 32 (60.4) | 0.245 | 1.72 [0.78; 3.78] | 79.0 [71.0; 88.0] | 88.0 [81.0; 96.0] | N.A. |
| ≥70% | 2.0 [-1.0; 5.0] | | 26 (53.1) | 23 (46.9) | | | 90.0 [79.0; 96.0] | 83.0 [71.0; 93.0] | |
| 6MWT, % predicted | | | | | | | | | |
| **<70% (deconditioning)** | 81.0 [43.5; 117.0] | 0.005 | 4 (17.4) | 19 (82.6) | 0.009 | 4.87 [1.52; 15.62] | 81.0 [79.0; 86.3] | 83.0 [71.0; 94.0] | 0.729 |
| ≥70% | 29.6 [2.5; 65.4] | | 40 (50.6) | 39 (49.4) | | | 83.0 [74.0; 93.0] | 88.0 [75.0; 95.0] | |
| Brief-BESTest | | | | | | | | | |
| **<16.5 points (poor balance)** | 4.0 [3.0; 6.0] | <0.001 | 9 (21.4) | 33 (78.6) | <0.001 | 6.81 [2.75; 16.89] | 83.0 [75.0; 88.0] | 83.0 [71.0; 95.0] | 0.251 |
| ≥16.5 points | 1.0 [0.0; 3.0] | | 39 (65.0) | 21 (35.0) | | | 88.0 [73.0; 92.0] | 92.0 [79.0; 100.0] | |
| CAT, score | | | | | | | | | |
| <18 points | −1.6 ± 6.0 | <0.001 | 32 (46.4) | 37 (53.6) | <0.001 | 8.65 [2.41; 31.03] | 88.0 [79.0; 97.0] | 88.0 [71.0; 96.0] | 0.281 |
| **≥18 points (poor health status)** | −6.2 ± 5.1 | | 3 (9.0) | 30 (90.9) | | | 79.0 [77.0; 85.5] | 81.0 [71.0; 92.0] | |
| SGRQ, score | | | | | | | | | |
| <46 points | −6.0 [-11.4; 4.0] | 0.005 | 37 (72.5) | 14 (27.5) | 0.003 | 9.27 [1.98; 43.32] | 92.0 [80.0; 100.0] | 83.0 [75.0; 92.0] | 0.193 |
| **≥46 points (poor health-related quality of life)** | −10.4 [-15.4; −5.1] | | 2 (4.0) | 49 (96.1) | | | 91.5 [87.3; 95.8] | 88.0 [71.0; 95.0] | |

[a]p-value of ANOVA for differences between responders and non-responders; no interaction effects found for all variables. Results are presented as mean ± SD, median [1st; 3rd quartile] or n (%). The presence of the treatable trait is presented in bold. mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: 1-min sit-to-stand test; 6MWT: 6-min walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire; N.A.: Not applicable.

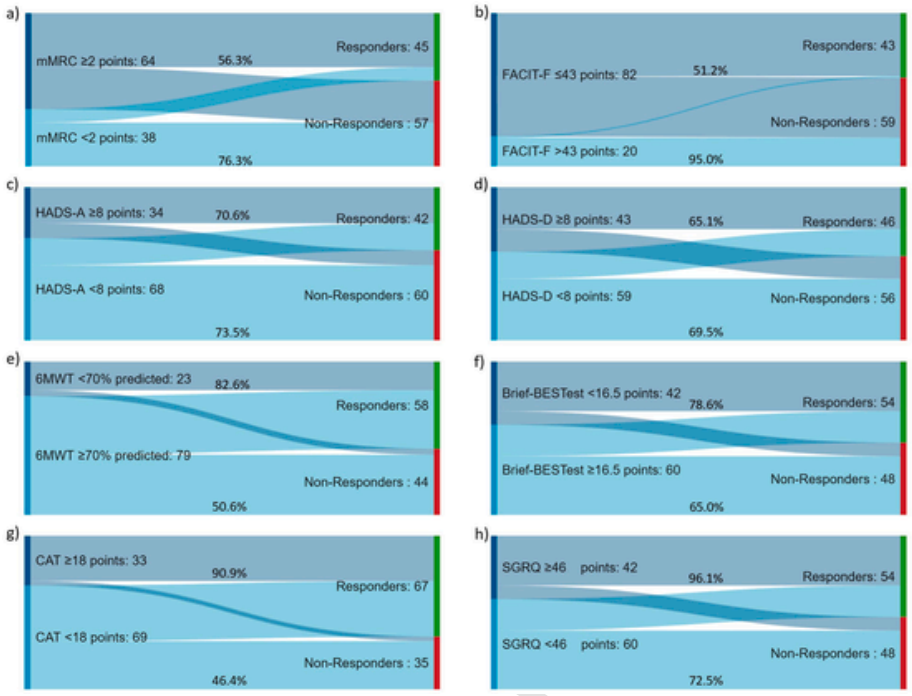


**Fig. 1.** Flow of responders and non-responders to pulmonary rehabilitation with or without each treatable trait a) treatable trait – severe dyspnoea mMRC ≥2 points; b) treatable trait – clinically relevant fatigue FACIT-F ≤43 points; c) treatable trait – symptoms of anxiety HADS ≥8 points; d) treatable trait – symptoms of depression HADS ≥8 points; e) treatable trait - deconditioning 6MWT <70% predicted; f) treatable trait – poor balance Brief-BESTest <16.5 points; g) treatable trait poor health status CAT≥18 points; h) treatable trait - poor health-related quality of life SGRQ ≥46 points . Dark blue represents people with the treatable trait and light blue people without the treatable trait. Green represents responders and red represents non-responders. Percentages are represented for responders with the treatable trait and non-responders without the treatable trait.
mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 6MWT: 6-min walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

progression of disease [19]. Hence, comparison of the impact of PR on the treatable traits of men versus women, and also in younger and less severe samples should be further explored. Holland and colleagues concluded that treatable traits have been poorly addressed in PR trials [11]. However, most of the traits were identified based on previous literature [20] and were non-relevant outcomes for PR, such as emphysema or persistent systemic inflammation. Future studies need to identify rehabilitation-specific treatable traits for which patients and clinicians can expect improvements [21]. Finally, the cut-offs used to define the treatable traits in this study seem to be suitable to differentiate responders from non-responders to PR, but they should be externally validated .

## 5. Conclusions

Identification of extra-pulmonary treatable traits in people with COPD showed the potential to inform on PR responsiveness and might therefore be an important strategy for patient prioritization (when/if needed), treatment personalisation and optimisation. Future trials are needed to compare the use of a treatable traits' strategy within PR (identification of each patient's treatable traits to trigger the most suitable PR components accordingly) with conventional PR.

## CRediT authorship contribution statement

**Sara Souto-Miranda :** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Vânia Rocha :** Conceptualization, Visualization, Writing – review & editing. **Maria Aurora Mendes :** Resources, Validation, Writing – review & editing. **Paula Simão :** Resources, Validation, Writing – review & editing. **Vitória Martins :** Resources, Validation, Writing – review & editing. **Martijn A. Spruit :** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing. **Alda Marques :** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.107086.

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