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Improved functional exercise capacity after primary care pulmonary rehabilitation in patients with long COVID (PuRe-COVID): a pragmatic randomised controlled trial

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ABSTRACT

Background Pulmonary rehabilitation (PR) improves physical status and symptoms in patients with long COVID, but access to specialised hospital-based centres is challenging. This trial studied the effect of primary care PR on functional exercise capacity and symptoms in patients with long COVID.

Methods In this pragmatic randomised controlled trial (PuRe-COVID), patients with long COVID were randomised to a 12-week stepwise PR programme in primary care, or to a control group without PR. The primary end point was change in 6 min walk distance (6MWD) from baseline to 12 weeks. Additional outcomes, measured at 6, 12, 24 and 36 weeks, included patient-reported outcomes, physical activity, maximal inspiratory (MIP) and expiratory pressures and hand grip strength.

Results In total, 76 patients were randomised (PR/control group (n=39/37); mean age 49±13 years). The change in 6MWD at 12 weeks was estimated to be +39 m in the PR group compared with the control group (95% CI (18 to 59), p<0.001). Furthermore, a decrease in Checklist Individual Strength (CIS)-fatigue was found for the PR group (−6 points; 95% CI (−10 to −2), p=0.011). At 12 weeks, patients in the intervention group were more likely to have a clinically significant improvement in 6MWD (OR 5.7, 95% CI (2.0 to 16.1), p=0.001), CIS-fatigue (OR 3.8, 95% CI (1.2 to 12.0), p=0.020), MIP (OR 3.7, 95% CI (1.05 to 12.7), p=0.036) and modified Medical Research Council dyspnoea score (OR 5.2, 95% CI (1.6 to 16.4), p=0.003).

Conclusions Primary care stepwise individual PR may improve functional exercise capacity, fatigue and dyspnoea in patients with long COVID. It therefore may be a promising treatment option in primary care for patients with long COVID experiencing fatigue and/or respiratory symptoms.

Trial registration number NCT05244044.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ No existing randomised controlled trials (RCTs) on the effect of primary care pulmonary rehabilitation in patients with long COVID were found at the time of starting this PuRe-COVID RCT.

WHAT THIS STUDY ADDS

⇒ The PuRe-COVID trial, a pragmatic RCT, showed that a pulmonary rehabilitation programme with five phases in primary care could contribute to an improvement in functional exercise capacity, fatigue and dyspnoea.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research on the ideal training mode, intensity and duration, taking postexertional malaise into account and focussing on behaviour change is needed.

INTRODUCTION

Long COVID is a condition characterised by persistent symptoms post-COVID-19 infection that commonly include fatigue, postexertional malaise (PEM) and dyspnoea. PEM involves worsening of symptoms following physical, cognitive or emotional activity, typically 12–48 hours after an activity and lasting for days or even weeks.[1] However, long COVID is a heterogeneous condition with various symptomatic manifestations, suggesting the presence of different phenotypes.[2] This multisystemic disease significantly impacts health-related quality of life (HRQoL), leading to absenteeism, loss of productivity, increased healthcare expenditure and other costs, implying a high economic global impact.[3] The WHO guideline recommends integrated multidisciplinary rehabilitation services as treatment, including physiotherapy.[4]

Pulmonary rehabilitation (PR) has been proven safe and effective in enhancing physical functioning and quality of life in patients

with chronic respiratory diseases.[5] Consequently, experts have proposed using PR as a treatment component for patients with long COVID. Indeed, evidence on the effect of hospital-based PR in patients with long COVID has started to emerge, suggesting that PR has beneficial effects on the (functional) exercise capacity, muscle strength, symptom burden and HRQoL.[6–10] Guidelines of several countries, including Belgium, advise performing PR in patients with long COVID in primary care as it is more accessible and relieves the burden on hospitals and/or rehabilitation centres.[11] Previous studies have examined PR delivered in hospital settings or via telehealth, many of these involved group-based formats or unsupervised sessions.[12 13] Currently, only one RCT reported about primary care PR in patients with long COVID admitted to intensive care during the acute COVID-19 infection. However, their control group also received rehabilitation in primary care, limiting its interpretability.[14] To the best of our knowledge, no prior RCT has investigated the effect of PR in primary care on the functional exercise capacity in patients with long COVID—as compared with controls not undergoing rehabilitation. Moreover, the recommended stepwise approach[15] for PR has not been included into previous trials. Although the Belgian government actively promotes primary care physiotherapy for long COVID, no standardised, evidence-based protocol currently exists. Therefore, a study examining individually tailored, one-on-one physiotherapy in real-world primary care is needed. Such an approach enables personalised treatment, active coaching and close follow-up—elements often less achievable in remote or hospital-based rehabilitation programmes.

Therefore, we initiated a pragmatic RCT (PuRe-COVID), which aimed to assess the short-term and long-term effects of a stepwise 12-week PR programme in primary care on functional exercise capacity and symptoms in patients with long COVID.

METHODS

Trial design

This prospective, pragmatic, two-centre, parallel-group, open-label RCT (NCT05244044) was conducted between April 2022 and February 2024 in two hospitals in Belgium: Antwerp University Hospital (UZA, Edegem) and Ziekenhuis Oost-Limburg (ZOL, Genk). Patients were recruited through these two hospitals, referrals from general practitioners or other medical specialists and media outreach. The protocol of the trial was previously published.[16]

Participants

Adult patients (aged ≥18 years) were eligible if they had a confirmed COVID-19 infection >6 weeks ago, with persistent COVID-19-related symptoms. These were defined as: COPD Assessment Test (CAT) ≥10,[17] modified Medical Research Council (mMRC) dyspnoea scale ≥2,[18] Checklist Individual Strength (CIS)-fatigue ≥36[19] or post-COVID-19 Functional Status (PCFS) ≥2.[20] A complete overview of the eligibility criteria is listed in the published protocol.[16]

Interventions

After baseline assessments, patients were randomised to either a control group, receiving no PR, or an intervention group. The latter received a 12-week standardised but personalised PR programme, consisting of 36 individual 1:1 sessions (three 30 min sessions per week), supervised by a single personal primary care physiotherapist specialised in PR. The programme included the following components: information about long COVID, a healthy lifestyle and behaviour change towards a more active lifestyle, endurance training, strength training, breathing exercises and inspiratory muscle training (a Philips Respironics threshold IMT trainer was provided). The PR programme consisted of five consecutive phases with progressively increasing exercise intensity, as described by Salman *et al*.[15] Participating patients were asked to give a score for the recovery from the previous training session (perceived training recovery score (PTR score)) and the intensity of the current training session (perceived training intensity score (PTI score)), and a total score (total training score (TTS)) was calculated. This TTS was seen as an indicator whether to proceed to the next phase, remain in the current phase or return to the previous phase, thereby implementing shared decision-making and a staged care approach to prevent PEM. More information about the intervention is available in the published protocol and online supplemental e-appendix (E.1-E.3).[16] Follow-up assessments for all outcomes were performed at 6, 12 and 24 weeks after enrolment, and patient-reported outcomes were repeated remotely at 36 weeks. An overview of the frequency of all the assessments can be found in the online supplemental e-appendix (E.4,E.5).

Outcomes

The primary outcome was the change in functional exercise capacity, measured via the 6 min walk test (6MWT) from baseline to 12 weeks.[21] Two tests were administered at baseline; only the first test was used for analysis since no learning effect has been found in this population.[22] Reference values were used to calculate predicted values.[23]

Several secondary outcomes were assessed, such as CIS-fatigue score (subjective fatigue subscale of the CIS questionnaire),[19] CAT questionnaire[17] and EQ-5D-5L (utility index and visual analogue scale (VAS)).[24] Number of daily step counts was assessed using an accelerometer (Actigraph wGT3X-BT, Pensacola, Florida, USA). Patients wore the monitor continuously for 9 days after each hospital visit. The device was worn on the right hip while awake and the non-dominant wrist while asleep. Data were extracted in 60 s epochs (ActiLife V.6.13.5). Non-wear time was defined as periods of consecutive zero counts for 90 min.[25] A valid day was determined as having

at least 8 hours of wearing time between 7:00 and 22:00 hours.[26] The analysis prioritised the seven middle consecutive valid days (including 1 weekend day); if unavailable, the last day was included, and if not invalid, the first day was used.

Exploratory outcomes were PCFS,[20] Hospital Anxiety and Depression Scale (HADS),[27] mMRC,[18] Nijmegen questionnaire,[28] handgrip strength (HGS), maximal inspiratory (MIP) and maximal expiratory (MEP) pressure. HGS was measured using a handheld digital dynamometer (Jamar Smart, Preston, Michigan, USA).[29] The mean value of three maximal efforts was used for analysis and compared with normal values.[30] Spirometry, body plethysmography, diffusion capacity measurements, MIP and MEP were performed in accordance with the ATS/ERS recommendations (Jaeger Masterscreen, Würzburg, Germany).[31] Normal values were calculated accordingly.[32 33] The outcomes WPAI (collected in the context of a cost-effectiveness analysis) and sleep efficiency will be reported separately to allow for a more detailed analysis and discussion. Finally, demographic and medical data were recorded. Serious adverse events (SAEs) and intervention-related AEs were collected during the intervention period.

Sample size

At the time of sample size calculation, no RCT data on (primary care) PR were available in patients with long COVID. Therefore, the sample size calculation was based on PR in patients with COPD, using 80% power and an effect of 39 m in the change in 6MWD (with a two-sample t-test with an SD of 77 and 60 for the intervention and control groups, respectively), and accounting for a 23% dropout rate, leading to a target recruitment of 134 participants with long COVID.[16]

Randomisation and blinding

Included patients were 1:1 randomised to the intervention group or the control group.[16] Stratification was done based on acute COVID-19 hospitalisation (yes/no), 6MWD (<350 m, ≥350 m) and recruitment site. A minimisation procedure (biased coin randomisation) was used through QMinim, a web-based randomisation tool hosted by the Sponsor and accessible by authorised users. The trial was open-label, but the primary end point measurement (6MWD) was performed by a blinded assessor. Patients were instructed not to disclose their assigned group.

Statistical methods

Numeric variables are presented as means and SD or medians and IQRs; categorical variables as frequencies and proportions. Analyses were conducted in an intention-to-treat fashion (R, V.4.3.1).[34]

For the primary outcome analysis, a linear mixed model was fitted using all available 6MWD measurements over the 24-week period as the outcome. Time, treatment group and the interaction between time and treatment group were included as fixed effects, with subject as a random effect, assuming missing data were missing at random. If the interaction between time and treatment group was significant, the mixed model was used to estimate the treatment effect between the two groups at 12 weeks using a post hoc contrast. The treatment effect was studied overall (online supplemental e-appendix E.6) and with change from baseline (giving more insight into the net benefit). Different sensitivity analyses were conducted to assess the treatment effect and are reported in the online supplemental e-appendix E.7 for transparency. These results should be interpreted with caution, given the reduced sample size and associated limitations. The initial mixed model was extended by adding covariates like age, sex, body mass index (BMI), smoker status, time since COVID-19 infection, acute COVID-19 hospitalisation, asthma, diabetes, heart disease, as fixed effects in separate models to evaluate their individual effects while retaining time, group and their interaction. The site was added as an extra random intercept. This resulted in a reported model adjusted for age (significant in individual model), sex (known prognostic factor) and BMI (significant in individual model) as fixed effects and subject and site as random intercepts. As planned and defined in the study by Volckaerts *et al*,[16] the primary outcome was also studied in the per-protocol population, defined as a compliance rate of 70% (a minimum of 25 sessions) in the intervention group. For the case-control group, if patients started rehabilitation for long COVID at their own initiative, only eight sessions were allowed. For the secondary and exploratory outcomes, daily step counts, patient-reported outcomes, HGS, MIP and MEP, a linear regression model was used with the measurements at 12 weeks as outcome and the treatment and baseline measurements as independent variables. The percentage of patients with a significant improvement in 6MWD, CAT, EQ-5D-5L, CIS-fatigue, mMRC, HADS, HGS, PCFS, Nijmegen questionnaire and MIP was compared between the treatment groups using a χ^2 test (expected values all above five except for HGS where Fisher's exact test was used) and was reported as an OR on improvement for intervention compared with control group. The used minimal clinically important differences (MCID) were: 6MWD 30.5 m,[35] CAT two units,[36] EQ utility index 0.051,[37] EQ-5D-5L-VAS 6.9,[37] CIS-fatigue 10 units,[38] mMRC one point,[39] HADS subscales 1.6 points,[36] HGS 5 kg[40] and MIP 18 cmH_2O.[41] For PCFS, we considered decreasing one category as MCID, and for Nijmegen, going from a score of ≥23 to <23.

A responder analysis for 6MWD was prespecified. However, given the limited sample size (37 responders vs 31 non-responders), this analysis was exploratory. For transparency, logistic regression models including treatment group, each covariate and the treatment×covariate interaction were fitted; models without the interaction were also evaluated. Candidate covariates included baseline

CAT, mMRC, CIS-fatigue, 6MWD, acute COVID-19 hospitalisation and the above-mentioned confounders. These analyses were considered hypothesis-generating only and were not used to support confirmatory inferences. The proportions of responders by group and by stratum (based on dichotomised numeric variables) are provided in the online supplemental e-appendix E.8.

For the secondary and exploratory outcomes, the similar linear mixed model as for the primary outcome was considered. For all mixed models, the intervention effect at each time point was estimated (including week 36 for questionnaires). To correct for the fact that multiple time points are considered in the post hoc comparisons, a Bonferroni-Holm multiple testing correction was applied.

For all linear mixed models and linear regression models, necessary assumptions of homoscedasticity and normality of residuals were checked graphically in residual plots. For the logistic regression model, the Box-Tidwell and Hosmer-Lemeshow tests were used. For the models adjusting for age, sex, BMI and site, variance inflation factors were checked and found to be low.

A two-sided p value <0.05 indicated statistical significance.

Patient and public involvement

Patients from the Flanders Long COVID Association and UZA were consulted during the study design. A patient representative also participated in Trial Steering Committee meetings.

RESULTS

Between April 2022 and June 2023, 381 patients were prescreened. Of these, 81 patients were enrolled in the study, of whom five patients were classified as screen failure due to not meeting the symptom-related eligibility criteria. Consequently, 76 patients were randomised: 39 were allocated to the intervention group and 37 to the control group (figure 1). Because of a slower recruitment rate than expected, the target sample size of 134 patients was not reached.

Baseline characteristics are presented in table 1 for the intention-to-treat population (n=76). Patients had borderline normal 6MWD values (intervention group: 83.4±11.9% predicted, control group: 83.2±14.6% predicted). Overall adherence to the intervention was 81%, and nine patients completed all 36 sessions, while nine other patients did not reach 25 sessions (compliance threshold). Patients in the control group were asked at weeks 6 and 12 whether they had attended a physiotherapist since their previous visit. If they had, they were asked to specify the number of sessions and the reason for attending. Eight patients reported attending physiotherapy, with an average of 3.75 sessions each. However, none of these sessions specifically targeted long COVID.

In the intervention group, all patients (n=39) received education and endurance training (n=39); 95% of the patients performed strength training and IMT (n=37); 82% functional breathing exercises (n=32); 21% mucus clearance techniques (n=8); 54% relaxation exercises (n=21) and 8% received other physiotherapy treatment modalities (n=3). The mean perceived training intensity score at the end of a session was 2.9, while the mean perceived training recovery score at the beginning of a session was 3.8. Most sessions were conducted in phase III (29.3%) and 51.4% of patients reached the fifth phase by the end of the intervention (online supplemental e-appendix E.9,E.10). Among the nine participants excluded in the per-protocol analysis, the reasons for not reaching the predefined threshold of 25 sessions were: musculoskeletal problems unrelated to the intervention (n=2), unrelated illness (mental or physical, n=2), extended holiday (n=1), difficulty combining daily activities (n=1) and unknown reasons (n=3).

There were eight AEs (four PEM, two musculoskeletal issues, one nausea and one atypical chest pain) and one unrelated SAE (*Staphylococcus epidermidis* sepsis).

A highly significant interaction term between time and group was found (p<0.0001) revealing a statistically significant different evolution of the 6MWD for intervention and control groups (figure 2). The linear mixed model estimated the treatment effect at week 12 as +39 m (95% CI (18 to 59), uncorrected p<0.001). A significant difference between both groups was also observed at week 24 (+47 m; 95% CI (26 to 68); p<0.001). The per-protocol analysis showed similar results for the 6MWD at 12 weeks (+37 m; 95% CI (15 to 59); uncorrected p=0.001 (online supplemental e-appendix E.11). Mean 6MWD per time point per group can be found in online supplemental appendix E.12.

In the linear regression model with the 12-week outcome as dependent variable and adjusted for the corresponding baseline value, a significant intervention effect was found for the CAT (−3.4 points, 95% CI (−6.0 to −0.7), p=0.013), CIS-fatigue (−7.4 points, 95% CI (−12.5 to −2.4), p=0.004), CIS-activity (−2.2 points, 95% CI (−4.2 to −0.2), p=0.029), CIS-total (−10.5 points, 95% CI (−20.5 to −0.6), p=0.039) and mMRC (−0.5, 95% CI (−0.9 to −0.1), p=0.014) (online supplemental e-appendix E.13). After adjusting for confounders, these outcomes remained statistically significant, except for the CIS-total (p=0.052). With this adjusted model, significant intervention effects were also found for Nijmegen questionnaire (p=0.027), MIP (p=0.025) and MEP (p=0.044) (online supplemental e-appendix E.13). No significant intervention effect (p>0.05) was found on EQ-5D-5L utility index or VAS, PCFS, HADS anxiety or depression, HGS and daily step counts.

At 12 weeks, patients in the intervention group were more likely to have a clinically significant improvement in 6MWD (OR 5.7, 95% CI (2.0 to 16.1), p=0.001), CIS-fatigue (OR 3.8, 95% CI (1.2 to 12.0), p=0.020), mMRC (OR 5.2, 95% CI (1.6 to 16.4), p=0.003) and MIP (OR 3.7, 95% CI (1.05 to 12.7), p=0.036) (table 2) as compared with controls. None of the considered variables (baseline

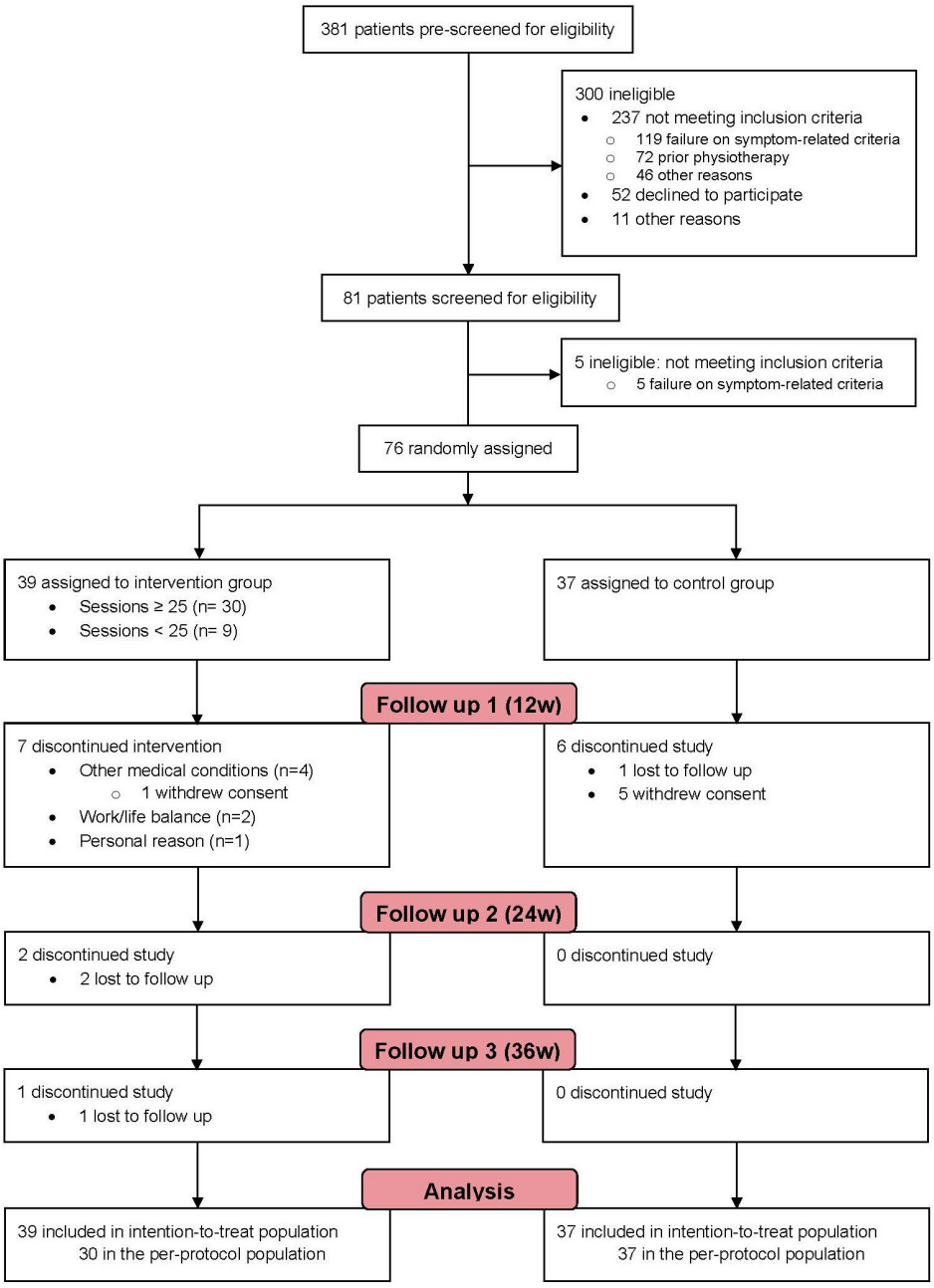

Figure 1 Consolidated Standards of Reporting Trials flow diagram of patients.

CAT, mMRC, CIS-fatigue, 6MWD, acute COVID-19 hospitalisation, age, sex, BMI, smoker status, time since COVID-19, asthma, heart disease) showed a significant association with the response in 6MWD at week 12 in the logistic regression models, where the group and each respective variable (one per model) was used as independent variables. In online supplemental e-appendix E.8, there was a tendency towards higher responder proportions with lower age and higher baseline CIS-fatigue values, although interpretation is limited by the small sample size.

The linear mixed model showed a significant interaction between time and group for CIS-fatigue (p=0.019) and for MIP (p=0.021). A post hoc test at each time point showed a treatment effect for CIS-fatigue at week 12 (p<0.05) and for MIP at week 24 (p<0.05) (table 3). No statistically significant difference was observed for CIS-fatigue at 36 weeks (figure 2).

DISCUSSION

This pragmatic RCT is the first to evaluate a 12-week stepwise primary care PR programme in patients with long COVID. Although the trial did not achieve the prespecified sample size and is therefore not definitive for any outcome, the results suggest significant improvements in the primary outcome, 6MWD and in CIS-fatigue compared with the control group. Additionally, patients

Table 1 Baseline characteristics of the intention-to-treat population per treatment group

Variables	Intervention N=39	Control N=37
Clinical characteristics		
Age, years	50.7±12.6	48.1±12.6
Female sex, n (%)	24 (61.5%)	25 (67.6%)
BMI (kg/m²)	27.7±4.6	27.9±5.6
Smoking status, n (%)		
Never smoked	28 (71.8%)	22 (59.5%)
Current smoker	3 (7.7%)	3 (8.1%)
Former smoker	8 (20.5%)	12 (32.4%)
Occupation, n (%)		
Employed (part-time or full-time)	27 (69.2%)	21 (56.8%)
Benefit for incapacity for work (part-time or full-time)	15 (38.5%)	14 (37.8%)
Other (unemployed, retired, student,…)	6 (15.4%)	7 (18.9%)
Charlson Comorbidity Index (total score)	1 (0–2)	1 (0–2)
Time since COVID-19 infection (days)	366 (189–633)	282 (196–477)
Hospitalisation during acute COVID-19 infection, n (%)*	3 (7.7%)	3 (8.1%)
≥Two vaccinations, n (%)	35 (89.7%)	35 (94.6%)
Site		
UZA	15 (38.5%)	19 (51.4%)
ZOL	24 (61.5%)	18 (48.6%)
Functional measures		
6MWD (m)*	562.2±87.3	557.7±122.2
Daily step counts (steps/day)†	7685.8±2697.9	7457.7±2203.7
Handgrip strength dominant side (% predicted)	107.7±27.0	101.4±20.3
MIP (cmH_2O)‡	68.0±33.5	66.9±27.7
FEV_1 (% predicted)	102.6±10.4	96.3±13.7
FVC (% predicted)	101.4±10.8	97.9±15.5
FEV_1/FVC ratio	80.7±5.5	79.4±6.4
RV (% predicted)	103.9±20.4	106.4±24.8
TLC (% predicted)	97.9±9.2	97.2±10.1
RV/TLC (%)	30.5±6.8	30.8±9.0
DLCO SB (TLCO) (% predicted)§	101.2±13.5	98.3±12.3
Patient-reported outcome measures		
CIS-fatigue (points)	45.1±7.7	48.2±5.6
CAT score (points)	18.8±6.8	20.2±7.0
mMRC dyspnoea (grade)	1 (1, 2)	2 (1, 2)
EQ-5D-5L index	0.8 (0.6, 0.9)	0.7 (0.6, 0.8)
EQ-5D-5L VAS (points)	51.8±19.1	49.5±14.9
PCFS score (grade)	2 (2, 3)	2 (2, 3)
Nijmegen questionnaire (points)	22.9±11.6	25.9±10.3
HADS anxiety (points)	7.3±4.5	8.8±4.7
HADS depression (points)	6.9±4.3	7.2±3.4

Summary statistics are presented as n (%), mean±SD or median (IQR). Occupation categories are not mutually exclusive.
*Minimisation variables, for baseline 6MWD category <350 m was empty (minimum for intervention group: 368 m and for control group: 365 m).
†Missing values n=37 available in intervention group and n=33 in control group.
‡One missing value in control group.
§One missing in intervention group.
BMI, body mass index; CAT, COPD Assessment Test; CIS, Checklist Individual Strength; DLCO SB, single-breath diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; HADS, Hospital Anxiety and Depression Scale; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council; 6MWD, 6 min walk distance; PCFS, post-COVID-19 Functional Status; RV, residual volume; TLC, total lung capacity; UZA, Antwerp University Hospital; VAS, visual analog scale; ZOL, Ziekenhuis Oost-Limburg.

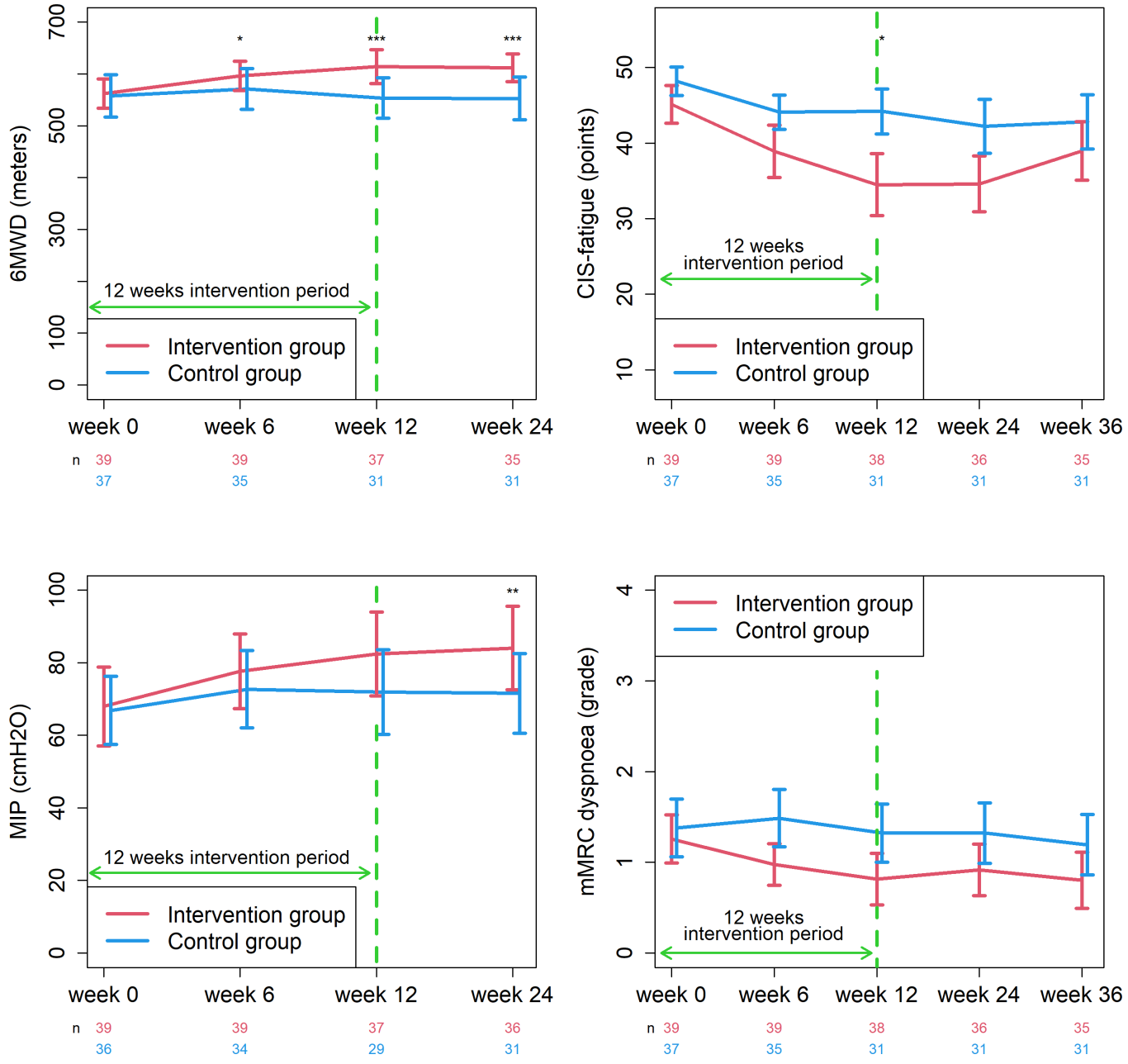

Figure 2 Mean 6MWD, CIS-fatigue, MIP and mMRC dyspnoea scale values over time with 95% CI per time point per group. P values from post hoc contrasts of change from baseline at each time point between groups, estimated with the linear mixed model (corrected for multiple testing using Bonferroni-Holm correction). 6MWD, 6 min walk distance; CIS, Checklist Individual Strength; MIP, maximal inspiratory pressure; mMRC: modified Medical Research Council. •P<0.1, *p<0.05, **p<0.01 and ***p<0.001.

in the PR group were more likely to achieve minimal clinically important improvements in 6MWD, CIS-fatigue, mMRC dyspnoea score and MIP compared with those in the control group. A linear regression model at 12 weeks also identified statistical significance in health status, dysfunctional breathing and expiratory muscle strength. Since this was not seen with the linear mixed model, these latter intervention effects should be confirmed in a trial powered for these outcomes.

The PuRe-COVID trial is the first RCT to examine the effects of a stepwise primary care PR programme, compared with a control group receiving no PR (unlike the trial by Romanet *et al*[14]), on the 6MWD in patients with long COVID. The intervention group showed a mean improvement (overall treatment effect) of 55 m (online supplemental e-appendix E.6) at 12 weeks compared with the control group. These findings align with a meta-analysis by Oliveira *et al*,[42] which reported an average improvement of 61 m in 6MWD with PR compared with control in patients with long COVID; however, important to note is that the interventions studied by Oliveira *et al* were tele-based or home-based interventions.

Table 2 Observed numbers and percentages of clinical improvement within group

Clinical improvement from baseline to week 12		Yes	P value χ^2 test	OR (95% CI)
6MWD	Control (n=31)	10 (32.3%)		
(increase of ≥30.5 m)	Intervention (n=37)	27 (73.0%)	**0.001**	5.67 (1.99 to 16.13)
CIS-fatigue	Control (n=31)	5 (16.1%)		
(decrease of ≥10 points)	Intervention (n=38)	16 (42.1%)	**0.020**	3.78 (1.19 to 11.99)
mMRC	Control (n=31)	5 (16.1%)		
(decrease of ≤1 point)	Intervention (n=38)	19 (50%)	**0.003**	5.20 (1.65 to 16.41)
MIP	Control (n=28)	4 (14.3%)		
(increase of ≥18 cmH_2O)	Intervention (n=37)	14 (37.8%)	**0.036**	3.65 (1.05 to 12.74)

P values <0.05 are in bold.
CIS, Checklist Individual Strength; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council; 6MWD, 6 min walk distance.

Our trial showed that primary care PR may decrease fatigue, compared with usual care. Similar results were found in other RCTs; however, different methodologies were employed to assess fatigue, such as varying scales and number of patients crossing a cut-off value. Additionally, the absence of a control group that received no therapy or information makes it more challenging to rule out the influence of spontaneous recovery.[6–8] CAT scores at week 12 showed significant improvements in our intervention group, compared with control. This is a novel finding as no other RCTs analysed this questionnaire yet in this population. This trial did not find significant differences in HRQoL between both groups, measured with EQ-5D-5L. Previous studies are not uniform on this outcome, as some RCTs report a statistically significant difference between groups on HRQoL effects,[6 7 9 14] while others do not.[8] For the daily step counts, no significant differences were found either, and to our knowledge, no other RCT included this parameter before.

One of the strengths of this trial is the pragmatic and unique approach of offering patient-tailored stepwise PR through primary care physiotherapists, focusing on different treatment components and starting with a low training modality, and making it easy to implement in a

Table 3 Results of linear mixed model in intention-to-treat population for 6MWD; CIS-fatigue and MIP

		Estimate of treatment effect (95% CI)	P value*	P value with Holm correction†
Linear mixed model				
6MWD (m)	Week 6	24.45 (4.47 to 44.42)	**0.016**	**0.016**
	Week 12	38.81 (18.17 to 59.45)	**<0.001**	**<0.001**
	Week 24	46.87 (26.05 to 67.70)	**<0.001**	**<0.001**
CIS-fatigue (points)	Week 6	−2.02 (−5.97 to 1.93)	0.316	0.632
	Week 12	−6.22 (−10.27 to −2.16)	**0.003**	**0.011**
	Week 24	−3.87 (−7.96 to 0.22)	0.064	0.191
	Week 36	−0.45 (−4.55 to 3.66)	0.831	0.831
MIP (cmH_2O)	Week 6	4.39 (−2.73 to 11.51)	0.227	0.227
	Week 12	8.39 (0.98 to 15.80)	**0.027**	0.053
	Week 24	11.13 (3.78 to 18.48)	**0.003**	**0.009**

6MWD: using n=284 observations (baseline (n=76), week 6 (n=74), week 12 (n=68) and week 24 (n=66)). CIS-fatigue: using n=352 observations (baseline (n=76), week 6 (n=74), week 12 (n=69), week 24 (n=67) and week 36 (n=66)). MIP: using n=281 observations (baseline (n=75), week 6 (n=73), week 12 (n=66) and week 24 (n=67)). A linear mixed model is fitted with time, treatment group, time×treatment group interaction as fixed effects and subject as random effect.
P values <0.05 are in bold.
*P values from post hoc contrasts of change from baseline at each time point between groups, estimated with the linear mixed model (uncorrected for multiple testing).
†P values from post hoc contrasts of change from baseline at each time point between groups, estimated with the linear mixed model (corrected for multiple testing using Bonferroni-Holm correction).
BMI, body mass index; CIS, Checklist Individual Strength; F, female; M, male; 6MWD, 6 min walk distance.

real-world setting. Another notable strength of the trial is the inclusion of a control group that did not receive an intervention, allowing for a clear assessment of the added value of the PR while accounting for spontaneous recovery.

However, it is important to acknowledge certain limitations. First, the trial was terminated before reaching the target sample size of 134 patients due to several factors, including declining COVID-19 infection rates, reduced diagnostic testing to confirm COVID-19, the introduction of reimbursement for primary care PR in Belgium (which led to more patients already having undergone the treatment and thus becoming ineligible) and budgetary constraints—rather than a lack of suitability for the intervention itself. This study was limited by its modest sample size, which reduces precision and reproducibility of the findings. Although statistically significant effects were observed, these results must be interpreted cautiously as the study was not powered for definitive conclusions. In addition, the responder analyses are descriptive and underpowered. Interaction tests and multivariable models were exploratory and intended to generate hypotheses for future adequately powered studies. Readers should interpret observed differences in responder proportion and subgroup patterns cautiously.

No significant between-group differences were found in HRQoL; however, the relatively high baseline EQ-5D-5L index in the intervention group (0.80) may have limited the ability to detect change. Interestingly, EQ-5D-5L VAS scores were lower, suggesting a mismatch between the index score and patients' perceived health status. This may indicate limited sensitivity of the EQ-5D-5L to capture long COVID-specific burden. Future studies might consider more comprehensive QoL tools. As no formal cost-effectiveness analysis was performed, and given the limited QoL effects, further research could be advised from a health economic perspective.

Furthermore, patients who had already completed one physiotherapy session for long COVID within the past 12 weeks, or more than eight sessions in total before the trial, could not participate to minimise the inclusion of potential non-responders; however, this may limit the generalisability of the findings to previously treated patients. Additionally, only patients accepting our intensive rehabilitation programme were included. Individuals with a high symptom burden or experiencing PEM likely chose not to participate due to concerns about the intensive nature of the programme. However, this reflects real-world situations. Given the diverse long COVID phenotypes and the selection criteria based on fatigue and/or respiratory symptoms, the PR programme's outcomes may not apply to patients with different symptom profiles. Furthermore, no validated questionnaire was used to screen for PEM, but physiotherapists were informed about it and were required to provide feedback regarding the occurrence of PEM signs by a binary (yes/no) question. Finally, the intervention consisted of individual, in-person physiotherapy in primary care, which reflects standard practice in Belgium, while PR is often delivered in group-based multidisciplinary settings in other countries. While other forms of rehabilitation, such as tele-rehabilitation or home-based programmes, can also be part of primary care, our approach differs in terms of supervision, intensity (stepwise approach) and therapist-patient interaction. These differences may affect outcomes and limit direct comparisons. As such, our findings are most generalisable to healthcare systems with similar models of one-to-one primary care rehabilitation. However, evidence is needed for all delivery formats, given the wide variability in primary care practice. Despite these limitations, the results may offer valuable insights, with the limitations unlikely to significantly compromise the validity or applicability of the conclusions.

Patients in this trial had normal baseline functional exercise capacity values but suffered from severe fatigue. Nevertheless, patients in the intervention group still significantly improved their functional exercise capacity. It is likely that, due to the COVID-19 infection and their long-lasting symptoms of fatigue and dyspnoea, patients became deconditioned, leading to a downward spiral of inactivity, decreased exercise tolerance, increased sedentary behaviour and as such further worsening of deconditioning and symptoms, speculating that their baseline 6MWD was reduced compared with their unknown pre-COVID-19 levels.[43] However, peripheral muscle limitations and decreased ventilatory efficiency have also been described in long COVID.[44] It is beyond the scope of this RCT to unravel the physiological changes contributed by PR, but the integration of various physical treatment modalities probably accounts for the observed improvements in functional exercise capacity, fatigue and dyspnoea. However, it remains unknown whether improvements in functional exercise capacity are the cause or consequence of reductions of fatigue and dyspnoea or vice versa.

Fatigue is known to be a complex and challenging symptom with diurnal variations. Various physical, psychological, behavioural and systemic factors can contribute to feelings of fatigue.[45] There is insufficient understanding of the underlying mechanisms of fatigue, including both physical and mental fatigue, in long COVID.[46] The potentially observed improvements in fatigue were not sustained at week 36, as fatigue levels increased again after the initial improvement observed at week 12. The intervention may not have sufficiently targeted behavioural change or self-management strategies needed to maintain long-term benefits, as reflected by the lack of change in daily step count. Other contributing factors are also possible. These observations highlight the complexity of fatigue in long COVID and suggest that future interventions should include long-term behavioural support and follow-up strategies to sustain improvements over time.

This pragmatic, patient-tailored intervention attempted to take PEM into account by informing the physiotherapist about PEM and implementing a five-phase training programme, despite the absence of established guidelines.

It is crucial to screen for PEM, either through clinical interviews or the DePaul Symptom Questionnaire-PEM (DSQ-PEM), and adjust the exercise training programme accordingly.[47] During the PuRe-COVID intervention, only four (10%) patients reported PEM during the whole programme, but none discontinued the intervention due to PEM, suggesting that this training programme may be achievable. Future trials should distinguish between patients with and without PEM. Additionally, further research should explore different training modalities and intensities, and be able to predict responders and non-responders. A multidisciplinary approach might be recommended to achieve even better results.

In conclusion, this PR programme in primary care, consisting of five phases, is a safe and effective intervention that may improve functional exercise capacity, fatigue and dyspnoea in patients with long COVID. Given its benefits, this programme may be a promising treatment option in primary care for patients with long COVID experiencing fatigue and/or respiratory symptoms.

Protocol

The full trial protocol can be assessed at *BMJ Open* (doi: 10.1136/bmjopen-2022-071098).[16]

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