Early View

Original research article

Inspiratory Muscle Training Enhances Recovery Post COVID-19: A Randomised Controlled Trial

Melitta A McNarry, Ronan M G Berg, James Shelley, Joanne Hudson, Zoe L Saynor, Jamie Duckers, Keir Lewis, Gwyneth A Davies, Kelly A Mackintosh

Inspiratory Muscle Training Enhances Recovery Post COVID-19: A Randomised Controlled Trial

Melitta A McNarry[1], Ronan M G Berg[2], James Shelley[1], Joanne Hudson[1], Zoe L Saynor[3], Jamie Duckers[4], Keir Lewis[5,6], Gwyneth A Davies[6], [6], Kelly A Mackintosh[1]

[1] Applied Sports, Technology, Exercise and Medicine Research Centre, Swansea University, Swansea, UK.

[2] Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Centre for Physical Activity Research, and Department of Clinical Physiology and Nuclear Medicine, University Hospital Copenhagen – Rigshospitalet, Denmark.

[3] Physical Activity, Health and Rehabilitation Thematic Research Group Lead, School of Sport, Health and Exercise Science, Faculty of Science and Health, University of Portsmouth, Portsmouth, UK.

[4] All Wales Adult CF Centre, Cardiff and Vale University Health Board, Cardiff, UK.

[5] Hywel Dda University Health Board, UK.

[6] School of Medicine, Swansea University, Swansea, UK.

Correspondence to: Professor Melitta McNarry. Applied Sports, Technology, Exercise and Medicine Research Centre, Swansea University, Swansea, UK. Email: m.mcnarry@swansea.ac.uk. Tel: (+44) 01792 513069. ORCID ID: 0000-0003-0813-7477

SUMMARY

- IMT can significantly improve breathlessness and respiratory muscle function in people with Long COVID and represents an effective, home-based rehabilitation strategy that could be widely implemented as part of COVID-19 recovery strategies.

ABSTRACT

Background: Many people recovering from COVID-19 experience prolonged symptoms, particularly breathlessness. We urgently need to identify safe and effective COVID-19 rehabilitative strategies. The aim of the current study was to investigate the potential rehabilitative role of inspiratory muscle training (IMT).

Methods: 281 adults (46.6 ± 12.2 years; 88% female) recovering from self-reported COVID-19 (9.0 ± 4.2 months post-acute infection) were randomized 4:1 to an eight-week IMT or a "usual care" wait list control arm. Health-related quality of life and breathlessness questionnaires (King's Brief Interstitial Lung Disease (KBILD) and Transition Dyspnoea Index (TDI)), respiratory muscle strength and fitness (Chester Step Test) were assessed pre- and post-intervention. The primary endpoint was KBILD total score, with the KBILD subdomains and TDI being key secondary outcomes.

Results: According to intention to treat (ITT), there was no difference between groups in KBILD total score post-intervention (Control: 59.5 ± 12.4; IMT: 58.2 ± 12.3; $P<0.05$) but IMT elicited clinically meaningful improvements in the KBILD subdomains of breathlessness (Control: 59.8 ± 12.6; IMT: 62.2 ± 16.2; $P<0.05$) and chest symptoms (Control: 59.2 ± 18.7; IMT: 64.5 ± 18.2; $P<0.05$), along with clinically meaningful improvements in breathlessness according to TDI (Control: 0.9 ± 1.7 vs. 2.0 ± 2.0; $P<0.05$). IMT also improved respiratory muscle strength and estimated aerobic fitness.

Conclusions: IMT may represent an important home-based rehabilitation strategy for wider implementation as part of COVID-19 rehabilitative strategies. Given the diverse nature of long-COVID, further research is warranted on the individual responses to rehabilitation - the withdrawal rate herein highlights that no one strategy is likely to be appropriate for all.

Keywords: Long COVID; breathlessness; dyspnoea; fitness; physical activity; post-COVID; quality of life

INTRODUCTION

As of 31st January 2022, Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected all but four countries globally, with >364 million cases and 5.63 million deaths [1]. COVID-19 is a multisystem disease, with a non-linear evolution and potential long-term implications [2]. The persistence of COVID-19-related symptoms was noted in May 2020, with long COVID now defined as ongoing or new symptoms ≥four-weeks post-infection [3]. 1.9% of the United Kingdom (UK) population alone are estimated to be living with long COVID [4], which will increase as infections continue. Nonetheless, no clear rehabilitative pathway has been identified.

Over 200 different symptoms are associated with long COVID [5], with people experiencing symptoms for >six months still experiencing ~14 symptoms [5]. One of the top three most debilitating symptoms associated with a poor quality of life was dyspnoea (breathlessness) [5, 6]. Whilst the aetiology of dyspnoea in long COVID is unknown, in other chronic respiratory conditions the association between breathlessness and vicious cycles of physical, cognitive/emotional and functional deterioration [7], often referred to as the spiral of disability [8], is well-evidenced. With the potential deleterious consequences of this downward spiral in people living with long COVID, the need for safe and effective rehabilitation strategies to help combat this global health and economic crisis cannot be overstated.

Numerous non-pharmacological interventions have been highly effective at managing breathlessness in other chronic respiratory conditions [8]. Although pulmonary rehabilitation is effective at improving physical performance and quality of life following hospitalisation [9, 10], current worldwide availability of pulmonary rehabilitation services is alarmingly low [11]. Furthermore, these conventional approaches, almost without exception, are limited in the context of COVID-19 by their intensive, predominantly in-person, hospital- and/or group-based delivery formats, which present significant transmission risks and time and resource burdens on overstretched healthcare systems Inspiratory muscle training (IMT) utilises restricted airflow breathing to challenge the respiratory muscles, eliciting a hypertrophic response equivalent to that observed in the peripheral musculature following a strength training programme [12] and can be carried out independently at home. IMT has elicited clinically meaningful improvements in dyspnoea and quality of life in chronic obstructive

pulmonary disease (COPD)[13] and has been well tolerated and perceived as beneficial in bronchiectasis [14]. As respiratory muscle weakness predicts poor outcomes following COVID-19 infection [15], IMT could represent a feasible initial step towards a whole-body rehabilitation programme. We hypothesised that IMT may be an effective home-based, unsupervised rehabilitation strategy for adults with long COVID, eliciting clinically meaningful reductions in breathlessness and improvements in quality of life and functional capacity.

METHODS

Participants

281 adults (46.6±12.2 years; 88% female; 9.0±4.2 months post-acute COVID-19; **Table 1**) were recruited through social media, online COVID-19 support groups, or following hospital discharge. Inclusion criteria comprised: prior self-reported COVID-19 infection; primary symptom of breathlessness; aged ≥18 years. Standard pulmonary rehabilitation exclusion criteria were applied, excluding individuals with: i) dementia meaning they could not follow commands/training; ii) unstable cardiac disease, myocardial infarction or non-ST-elevation myocardial infarction within six weeks; and/or iii) high risk of falls.

Study Design

This two-arm, randomised control trial compared eight-weeks IMT with a "usual care" wait list control to which, following informed consent, participants were randomised using a computer-generated allocation on a 4:1 basis, respectively. The study was conducted entirely remotely via video-conferencing software (Zoom Communications Technology Company, San Jose, US), with pre- and post-intervention measures collected during one-to-one calls. Institutional (Ref: 2020-037) and NHS Research Ethics Committees (Ref: 20/HRA/3536) approved the study, which was conducted in accordance with the Declaration of Helsinki and registered on the Health and Care Research Wales Research Directory (Ref: 48075).

IMT Intervention

The PrO2^{TM} (PrO2Fit Health Incorporated, RI, USA), a handheld inspiratory flow resistive device that wirelessly syncs to a computer, smartphone, or tablet via an App to provide users with graphical biofeedback during and following each inspiratory effort, was used. Participants were trained on its set-up and use during the first session.

Intervention participants were asked to perform three unsupervised IMT sessions/week, on non-consecutive days, for eight weeks, as in previous studies [16]. Before each session, participants performed a maximal inspiratory effort from residual volume to determine sustained maximal inspiratory pressure (SMIP), with training subsequently requiring >80% SMIP to be maintained. This reassessment prior to each session ensured individually optimised training loads, accounting for the relapsing and remitting nature of long COVID. Each session involved up to six blocks of six inspirations, with the rest periods interspersing

each inspiration progressively decreasing from 40-10 seconds with each block, producing maximum session durations of 20 minutes. Participants completed as many inspirations as they could prior to failure, defined as not achieving 80% SMIP on three consecutive breaths. Data from all sessions was automatically uploaded to a secure cloud server, enabling remote adherence monitoring.

Primary outcomes

The primary outcome was health-related quality of life, as estimated by the 15-item KBILD Questionnaire, with a seven-point Likert scale [17], and three domains: Psychological, Breathlessness and Activities, and Chest Symptoms. The domain raw scores and total score were converted to logit scores using Rasch analysis then transformed to a 0–100 scale, with 100 representing the best health status [18]. The minimal clinically important difference (MCID) for the logit-transformed total score is 5, with 6, 7 and 11 representing the MCID for the Psychological, Breathlessness and Activities and Chest Symptoms domains, respectively [18].

Secondary outcomes

Perceived breathlessness was assessed by the Baseline Dyspnoea Index (BDI) and Transition Dyspnoea Index (TDI). These clinically validated questionnaires assess three domains (functional impairment, magnitude of task, and magnitude of effort) that quantify dyspnoea-related limitations [19]. One unit change in the TDI is considered the MCID [20].

Inspiratory muscle strength was assessed using the $PrO2^{TM}$ device. Following device familiarisation, participants performed a maximal sustained inspiratory effort following a full expiration to residual volume to provide measures of maximal inspiratory pressure (MIP), SMIP, inspiratory duration and the Fatigue Index Time (FIT).

Exploratory outcomes

The Chester Step Test, with standardised instructions and a demonstration of the initial step rate, was used to evaluate fitness [21]. Participants stepped on and off a 15-30 cm step at a metronome-dictated rate that progressively increased every two minutes until they reached 80% maximum-predicted heart rate or withdrew. Estimated maximal oxygen uptake ($\dot{V}O_2$)

was calculated from participant-measured heart rate and ratings of perceived exertion at the end of each stage.

To assess changes in daily function, habitual physical activity and sleep, a non-dominant wrist-worn GT9X accelerometer was used (ActiGraph, Pensacola, FL, USA), measuring at 30 Hz for seven consecutive days. Physical activity, sedentary time and sleep analyses were performed in R (http://cran.r-project.org) using the GGIR package (version 2.3-0). To be included in the analyses, a minimum of 12-hours/day of wake wear-time on three week and one weekend day [22] and daily sleep time of $\geq$ 160-minutes/night with >90% estimated wear-time [23] were required, resulting in 132 and 113 pre- and post-intervention participants, respectively, in the analyses. To provide insights into the full 24-hour activity profile, average acceleration, intensity gradient and the acceleration associated with each participant's most active 30 and 60 minutes were obtained, and, time spent in each activity intensity, according to age- and accelerometer-specific raw-acceleration cut-points [24].

Mental health and wellbeing were assessed using validated questionnaires underpinned by self-determination theory [25] that measured treatment self-regulation, perceived competence, and needs satisfaction in relation to IMT [26-28]. The 15-item treatment self-regulation questionnaire assessed reasons for completing IMT regularly via different forms of motivation. Responses to each subscale were averaged to provide a reflection of each form of motivation. The Perceived Competence Scale includes four-items with a seven-point Likert scale to assess participants' context-specific competence perceptions. A total score was calculated, with a higher score representing higher perceived competence. The 21-item Basic Needs Satisfaction Scale assessed the degree to which participants felt their basic psychological needs for autonomy, competence and relatedness were satisfied [26, 29].

Sample size considerations
A target sample size of 250 participants was calculated to detect a post-intervention between-group MCID of five in KBILD total score. A 1:1 allocation ratio and alpha of 0.05 yields a power of 0.90. However, to allow more participants to receive the intervention, an allocation ratio of 4:1 was chosen, resulting in a power of 0.75. We deemed this acceptable because i) the study was conducted during an ongoing pandemic with no available rehabilitation strategies; ii) the intervention included implementation of an entirely new technology in

home-based rehabilitation; and iii) a higher drop-out rate was expected in the intervention group, thus enhancing the power of the *per-protocol*-based analysis [30].

Statistical analysis

Following confirmation of a normal distribution, linear mixed models with a random intercept at the individual level were used to determine the influence of time, group and their interaction, along with time post-acute COVID-19 infection and the number of IMT sessions completed. Planned contrasts were used to explore significant interaction effects. All analyses were conducted according to an intention-to-treat (ITT; last one carried forward) and *per-protocol* approach, for which participants were required to adhere to the IMT intervention by completing at least 16 sessions (equivalent to two sessions/week for eight weeks). All analyses were conducted in Stata (V13; StataCorp LP, College Station, TX, USA) and significance accepted as *P*<0.05.

RESULTS

148 (IMT: *n*=111; controls: *n*=37; **Figure 1**) participants completed the post-intervention testing and were included in the ITT analysis. Withdrawal between recruitment and enrolment (*n*=57) was predominately associated with enrolment delays due to COVID-19-related IMT-device manufacture issues. On average, participants completed two IMT sessions/week, with 87 participants meeting the adherence criterion and thus being included in the *per-protocol* analysis, along with 37 controls.

KBILD

There was no between-group difference post-intervention for KBILD total score in the ITT population, even though the time main effect was significant (**Figure 2**), with a significant improvement in the IMT group. In the *per-protocol* population, a higher total KBILD score was present in the IMT than control group post-intervention (**Table 2**). Furthermore, significant improvements were found in only the intervention group for the KBILD subdomains "Breathlessness and Activities" and "Psychological", whilst both groups demonstrated improvements in the "Chest Symptoms" domain in both the ITT (**Figure 1**) and *per-protocol* (**Table 2**) populations. The improvements in the total and subdomain scores of the KBILD were positively associated with adherence in the ITT population (β=0.33–0.49; *P*=<0.001–0.03). Increased time since COVID-19 was associated with poorer psychological quality of life (β=-0.80(-1.38– -0.22); *P*=0.007).

BDI and TDI

Whilst there were no differences between groups pre-intervention in dyspnoea (BDI: 5.60±2.54 vs. 5.65±2.89), IMT was associated with a greater reduction in dyspnoea post-intervention in the ITT (TDI: 2.0±2.0 vs. 0.9±1.7; *P*=0.005; **Figure 2**) and *per-protocol* populations (TDI: 2.1±0.2 vs. 0.9±0.3; *P*=0.005).

Inspiratory muscle strength

IMT significantly improved inspiratory muscle strength, with MIP, SMIP and FIT significantly increased post-intervention in the IMT group only, both in the ITT and *per-protocol* populations (**Tables 2-3**). Furthermore, in the *per-protocol* population, a greater time since COVID-19 acute-infection was associated with lower MIP (β=-1.7 (-3.3- -0.07); *P*=0.04).

Physical fitness and functional capacity

IMT led to improvements in functional capacity, with increased estimated $\dot{V}O_{2max}$ and time spent in moderate physical activity in the *per-protocol* population only (**Tables 2-3**). Furthermore, IMT elicited a significantly less steep intensity gradient (greater distribution of activity intensities) and increased physical activity during the most active 30- and 60-minutes post-intervention in the *per-protocol* population only. These changes in physical activity were accompanied by less sedentary time post-intervention in the IMT group compared to the control group. Functional capacity was not affected by time since acute COVID-19 infection.

Perceived competence and satisfaction

Neither perceived competence nor the domains of the Basic Needs Satisfaction Scale or Treatment Self-Regulation Scale were influenced by IMT, with perceived competence improving over eight weeks in both groups, and populations (ITT and *per-protocol*; **Tables 2-3**). However, perceived competence and autonomous motivation were both associated with time since COVID-19 infection, with greater time periods associated with a lower perceived competence (β=-0.37 (-0.62– -0.11); *P*=0.005) and greater autonomous motivation (β=0.23 (0.04–0.43); *P*=0.020). Time since COVID-19 infection was also associated with decreased amotivation in the *per-protocol* population (β= -0.12 (-0.23– -0.02); *P*=0.02).

Withdrawals

In general, no reason was provided for subsequent withdrawals following enrolment (**Figure 1**). Those who withdrew following the pre-intervention testing were significantly younger (42.1±13.0 vs. 48.4±11.4 years; *P*<0.001) and had a higher MIP (86.2±40.2 vs. 74.3±31.8 cmH$_2$0; *P*=0.02), introjected regulation (8.0±3.2 vs. 7.1±3.4; *P*<0.05) and autonomous motivation (37.0±35.4; *P*=0.04). There was a similar distribution of males (14%) and females (11%) and time since COVID (8.5±5.2 vs. 9.3±3.5 months), irrespective of attrition status. Whilst not significant, those who withdrew were more active (moderate physical activity: 85.1±39.2 vs. 75.5±39.1 minutes; *P*=0.09), less sedentary (732.7±84.7 vs. 749.9±108.5 minutes; *P*=0.16) and had a higher SMIP (474.2±254.6 vs. 438.7±196.5 PTUs; *P*=0.14) and FIT (21.3±21.3 vs. 19.2±14.0; *P*=0.20).

DISCUSSION

In this first RCT focusing on a home-based, unsupervised rehabilitation strategy for people recovering from COVID-19, the impact of eight-weeks IMT on health-related quality of life, breathlessness, respiratory muscle strength and functional capacity was investigated. Whilst there was no clinically meaningful effect of IMT compared to standard care on the primary outcome, KBILD total score, in the ITT population, such an effect was evident in the *per-protocol* analyses for those that adhered to the prescribed intervention. Importantly, IMT elicited significant and clinically meaningful improvements in markers of breathlessness (KBILD subdomain and TDI) in both the ITT and *per-protocol* populations, along with concomitant benefits in estimated aerobic fitness and physical activity levels. However, IMT was not associated with significant changes in habitual physical activity or mental health and wellbeing.

The discrepancy in the effect of IMT on the primary outcome in the ITT and *per-protocol* populations likely reflects the lower, albeit not significantly, total score pre-intervention in those randomly allocated to the IMT arm; the total score significantly and clinically meaningfully increased from pre- to post-intervention in the IMT arm but did not increase significantly above that of the control arm. However, the relatively high withdrawal rate from the study and the non-adherence to the protocol reducing the power associated with our ITT analyses, must be noted. Caution is therefore required in interpreting the results although they are suggestive that IMT is an efficacious home-based rehabilitation strategy when used as prescribed in the recovery after COVID-19.

In accord with the clinical effects of IMT reported here, a recent meta-analysis of the effect of IMT in COPD concluded that IMT was associated with reductions in breathlessness and improvements in quality of life, exercise capacity and MIP [13]. A recent systematic scoping review suggested that IMT exerted largely similar effects in interstitial lung disease [31]. These beneficial effects may be elicited through reductions in the neural respiratory drive and improvements in breathing patterns, which equalise previous imbalances between respiratory muscle loading and capacity [32]. Furthermore, improved respiratory muscle strength and dyspnoea have been associated with reduced diaphragm activation during maximal exercise, compatible with a decreased motor-unit recruitment to generate a given force as a result of respiratory muscle hypertrophy [33]. Neural drive impairment and respiratory muscle weakness reported in patients with COVID-19 [34] are supported by the present novel finding of MIP percentage-predicted values of 81% pre-intervention. Although the

mechanisms underpinning the improvements observed in the current study are hard to conclusively elucidate, given the remote and indirect measures available during COVID-19 lockdowns, the ability of eight -weeks IMT to elicit improvements in breathlessness indices that are of at least minimal clinically important magnitude, is significant on individual and public health levels.

Current estimates suggest over 1.2 million people in the UK are living with long COVID [4], presenting an unprecedented and, as of yet, unmet, need for rehabilitation. Following numerous reports of the most persistent symptoms of breathlessness and respiratory muscle weakness [35], pulmonary rehabilitation has been advocated as a rehabilitation strategy [36]. Whilst pulmonary rehabilitation is highly effective in a range of chronic respiratory conditions [37] including COVID-19 [9, 10], pulmonary rehabilitation provision does not, and cannot, meet the COVID-19-related demand due to the time- and resource-burden it places on an overstretched healthcare system. There is therefore an urgent need to identify home-based, self-guided rehabilitation strategies. Our findings suggest that IMT represents such a strategy that has a notable impact on several critical aspects of long COVID. Furthermore, the remote nature of IMT, requiring minimal supervision or monitoring, meets the recommendations of the Stanford Hall Consensus Statement [36].

Whilst the present study is highly novel and impactful, it has limitations. Many of the participants did not have a confirmed SARS-COV2 coronavirus according to PCR/lateral flow due to lack of available testing when many experienced COVID-19 symptoms. However, in the current definitions of long COVID a microbiological confirmation is not always required. We believe our population is representative of the target population describing long COVID. Our higher proportion of females also reflects the suggested distribution of long COVID in the general population [38], but it precludes gender comparisons. Whilst we had an eight-week waitlist control group, a learning effect may have been evident in the IMT group as no sham IMT protocol was utilised, converse to other ongoing trials [39]. It is, however, pertinent to note that even low-intensity IMT may elicit a beneficial response, thereby confounding interpretation of the intervention effect. Finally, we were unable to contact many of those who withdrew from the study to ascertain why. This limits our interpretation as to the generalisability of IMT as we cannot preclude the possibility of completion or self-selection bias (including, but not limited to, technological competency, high treatment self-regulation, participant choice) in our findings. Whilst the withdrawal rate from this study may be higher than typically reported in interventions prior to

the pandemic, the unique situation in which this intervention was remotely delivered (i.e. national lockdown, rapidly evolving disease and understanding of its aetiology, treatment and recovery) preclude comparisons to pre-pandemic interventions. Furthermore, we sought to minimise the impact of such withdrawals on the statistical power of the study by using a 4:1 allocation ratio, but the findings must nonetheless be interpreted with caution, notably in the ITT population. Despite the withdrawals, the sample size of the present study remains considerably larger than previous IMT trials.

In conclusion, in the first RCT investigating the effects of an entirely home-based rehabilitation strategy for those recovering from COVID-19, despite the absence of an effect of IMT on KBILD-based health-related quality of life, IMT elicited clinically meaningful reductions in the severity of dyspnoea and chest-related symptoms, as well as improved respiratory muscle strength and aerobic fitness. Our findings thus indicate IMT may be an efficacious home-based rehabilitation strategy during recovery from COVID-19.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Table 1. Participant characteristics

	Control (*n* = 37)	IMT (*n* =111)	P-value
Age (years)	46.13 ± 12.73	46.76 ± 12.03	0.765
BMI (kg·m^{-2})	27.81 ± 5.83	27.64 ± 6.80	0.881
Sex (% Male/Female)	5/95	14/86	-
Time since COVID-19 (months)	9.00 ± 3.67	9.04 ± 4.29	0.791
King's Brief Interstitial Lung Disease Questionnaire			
Breathlessness	59.7 ± 15.8	55.0 ± 12.6	0.081
Psychological	40.6 ± 23.3	36.8 ± 14.9	0.302
Chest	56.9 ± 18.7	57.8 ± 17.2	0.479
Total score	56.6 ± 13.5	53.2 ± 8.9	0.105

Mean ± SD. *n,* sample size; BMI, body mass index

Table 2. Pre- and post-intervention respiratory muscle strength, estimated physical fitness, physical activity, sleep levels, and mental health and wellbeing in the intention-to-treat population (N= 148).

	Pre-Intervention		Post-Intervention	
	Control (n = 37)	IMT (n = 111)	Control (n = 37)	IMT (n = 111)
Respiratory muscle strength				
MIP (cm H$_2$0)	82.8 ± 38.5	76.6 ± 33.9	90.5 ± 42.1	**104.0 ± 52.8**[*]
MIP (%)	84.2 ± 41.6	92.3 ± 46.6	79.8 ± 37.2	**108.9 ± 60.0**[*]
FIT (au)	20.5 ± 13.7	19.7 ± 17.2	22.3 ± 25.9	**23.0 ± 17.3**[*]
SMIP (PTUs)	475.1 ± 218.3	442.7 ± 215.3	478.0 ± 225.0	**539.1 ± 251.7**[*]
Physical fitness				
Estimated $\dot{V}O_{2max}$	37.9 ± 12.4	38.3 ± 15.1	36.8 ± 4.8	**42.0 ± 16.4**[*]
Device-based physical activity				
Sedentary time (mins)	757.8 ± 105.0	737.5 ± 95.4	774.6 ± 72.9	**734.3 ± 94.8**[#]
LPA (mins)	125.2 ± 62.05	122.8 ± 48.8	120.2 ± 44.7	122.3 ± 41.7
MPA (mins)	64.8 ± 36.6	83.7 ± 39.2	69.8 ± 32.3	**86.8 ± 41.4**[#]
VPA (mins)	2.6 ± 5.40	1.9 ± 3.2	2.5 ± 6.3	2.5 ± 5.3
Most Active 60 mins (*mg*)	107.8 ± 60.3	111.1 ± 30.4	107.1 ± 42.5	114.5 ± 33.0
Most Active 30 mins (*mg*)	150.8 ± 90.7	153.3 ± 55.0	156.2 ± 105.5	159.1 ± 63.3
Intensity Gradient	-3.2 ± 0.4	-3.4 ± 0.4	-3.3 ± 0.4	**-3.3 ± 0.4**[*]
Device-based sleep				
Sleep duration (mins)	413.3 ± 81.6	422.1 ± 73.3	399.8 ± 62.5	419.9 ± 77.7
Sleep Efficiency (%)	85 ± 11	86 ± 9	85 ± 9	85 ± 11
Perceived Competence	14.1 ± 9.3	14.3 ± 8.0	**16.7 ± 8.9**[*]	**15.4 ± 8.2**[*]
Basic Needs Satisfaction				
Autonomy	4.6 ± 0.9	4.6 ± 0.8	4.8 ± 0.7	4.6 ± 0.8
Competence	4.8 ± 1.0	4.8 ± 1.0	4.9 ± 0.9	4.9 ± 1.0
Relatedness	5.8 ± 0.8	5.7 ± 0.9	5.8 ± 0.7	5.7 ± 0.9
Treatment Self-Regulation				
Amotivation	5.4 ± 3.0	5.3 ± 2.5	5.4 ± 2.2	5.6 ± 2.8
External Regulation	7.4 ± 3.5	8.4 ± 4.7	8.0 ± 3.8	8.7 ± 4.3
Introjected Regulation	7.4 ± 3.1	7.4 ± 3.4	6.9 ± 3.7	7.3 ± 3.3
Autonomous Motivation	36.6 ± 6.2	35.7 ± 6.1	36.6 ± 5.2	35.3 ± 6.3

Mean ± SD. IMT, Inspiratory Muscle Training; KBILD, King's Brief Interstitial Lung Disease Questionnaire; MIP, Maximal Inspiratory Pressure; FIT, Fatigue Index Test; SMIP, Sustained Maximal Inspiratory Pressure. $\dot{V}O_{2max}$, maximal oxygen uptake estimated from the Chester Step Test; LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity. [*]Significant (P<0.05) difference between time-points within group. [#] Significant difference between groups within time-point.

Table 3. Pre- and post-intervention health-related quality of life, respiratory muscle strength, estimated physical fitness, physical activity, sleep levels, and mental health and wellbeing in the *per-protocol* population (N= 124).

	Pre-Intervention		Post-Intervention	
	Control (n = 37)	**IMT (n = 87)**	**Control (n = 37)**	**IMT (n = 37)**
KBILD				
Total	59.7 ± 15.8	56.8 ± 12.4	59.8 ± 12.6	**67.8 ± 14.4**[*#]
Breathlessness	40.6 ± 23.3	36.7 ± 13.1	41.9 ± 20.7	**49.7 ± 19.5**[*]
Psychological	56.9 ± 18.7	60.4 ± 17.4	**59.2 ± 18.7**[*]	**70.1 ± 16.9**[*#]
Chest	56.6 ± 13.5	54.0 ± 7.8	59.5 ± 12.4	**60.7 ± 10.8**[*]
Respiratory muscle strength				
MIP (cm H_2O)	82.8 ± 38.5	73.3 ± 28.7	90.5 ± 42.1	**112.6 ± 42.9**[*#]
FIT (au)	20.5 ± 13.7	19.7 ± 14.7	22.0 ± 27.6	**24.9 ± 14.0**[*]
SMIP (PTUs)	475.1± 218.3	445.3 ± 183.9	464.2 ± 226.8	**587.7 ± 215.0**[*#]
Physical fitness				
Estimated $\dot{V}O_{2max}$	37.9 ± 12.4	37.5 ± 15.6	36.8 ± 4.8	**43.4 ± 17.5**[*]
Device-based physical activity				
Sedentary time (mins)				
LPA (mins)	757.8 ± 105.0	766.2 ± 89.9	774.6 ± 72.9	742.8 ± 95.5
MPA (mins)	125.2 ± 62.05	117.7 ± 58.9	120.2 ± 44.7	124.2 ± 42.3
VPA (mins)	64.8 ± 36.6	70.9 ± 36.2	69.8 ± 32.3	**87.0 ± 40.0**[*]
Most Active 60 mins (*mg*)	107.8 ± 60.3	99.6 ± 29.6	107.1 ± 42.5	**115.6 ± 33.7**[*]
Most Active 30 mins (*mg*)	150.8 ± 90.7	132.8 ± 37.3	156.2 ± 105.5	**158.1 ± 59.4**[*]
Intensity Gradient	-3.2 ± 0.4	-3.4 ± 0.4	-3.3 ± 0.4	-3.3 ± 0.4
Device-based sleep				
Sleep duration (mins)	413.3 ± 81.6	398.3 ± 84.9	399.8 ± 62.5	412.5 ± 73.9
Sleep Efficiency (%)	85 ± 11	84 ± 14	85 ± 9	85 ± 10
Perceived Competence	14.1 ± 9.3	15.1 ± 7.7	**16.7 ± 8.9**[*]	16.5 ± 7.8
Basic Needs Satisfaction				
Autonomy	4.6 ± 0.9	4.6 ± 0.9	4.8 ± 0.7	4.7 ± 0.8
Competence	4.8 ± 1.0	4.9 ± 1.1	4.9 ± 0.9	5.0 ± 1.0
Relatedness	5.8 ± 0.8	5.7 ± 0.9	5.8 ± 0.7	5.7 ± 1.0
Treatment Self-Regulation				
Amotivation	5.4 ± 3.0	5.1 ± 2.2	5.4 ± 2.2	5.7 ± 2.6
External Regulation	7.4 ± 3.5	8.0 ± 4.5	8.0 ± 3.8	8.2 ± 3.7
Introjected Regulation	7.4 ± 3.1	7.0 ± 3.5	6.9 ± 3.7	6.9 ± 3.3

Autonomous Motivation	36.6 ± 6.2	35.2 ± 6.6	36.6 ± 5.2	33.8 ± 6.9

Mean $\pm$ SD. IMT, Inspiratory Muscle Training; KBILD, King's Brief Interstitial Lung Disease Questionnaire; MIP, Maximal Inspiratory Pressure; FIT, Fatigue Index Test; SMIP, Sustained Maximal Inspiratory Pressure. $\dot{V}O_{2max}$, maximal oxygen uptake estimated from the Chester Step Test; LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity. *Significant (P<0.05) difference between time-points within group. # Significant difference between groups within time-point.

REFERENCES

1.   World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. 2021 [cited 31/01/2022]; Available from: https://covid19.who.int/

2.   Jimeno-Almazán A, Pallarés JG, Buendía-Romero Á, Martínez-Cava A, Franco-López F, Sánchez-Alcaraz Martínez BJ, Bernal-Morel E, Courel-Ibáñez J. Post-COVID-19 Syndrome and the Potential Benefits of Exercise. *Int J Env Res Public Health* 2021: 18(10): 5329.

3.   Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ* 2021: 372: n136.

4.   Ayoubkhani D, Pawelek P, Bosworth M. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 4 November 2021: Office for National Statistics; 2021 4th November 2021.

5.   Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Redfield S, Austin JP, Akrami A. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021: 38.

6.   Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martinez AF, Paniz-Mondolfi A, Lagos-Grisales GJ, Ramírez-Vallejo E, Suárez JA, Zambrano LI, Villamil-Gómez WE, Balbin-Ramon GJ, Rabaan AA, Harapan H, Dhama K, Nishiura H, Kataoka H, Ahmad T, Sah R. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis* 2020: 34: 101623.

7.   Hutchinson A, Barclay-Klingle N, Galvin K, Johnson MJ. Living with breathlessness: a systematic literature review and qualitative synthesis. *Eur Respir J* 2018: 51(2): 1701477.

8.   Booth S, Johnson MJ. Improving the quality of life of people with advanced respiratory disease and severe breathlessness. *Breathe (Sheff)* 2019: 15(3): 198-215.

9.   Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complement Ther Clin Pract* 2020: 39: 101166.

10.   Zampogna E, Paneroni M, Belli S, Aliani M, Gandolfo A, Visca D, Bellanti MT, Ambrosino N, Vitacca M. Pulmonary Rehabilitation in Patients Recovering from COVID-19. *Respiration* 2021: 100(5): 416-422.

11.   Desveaux L, Janaudis-Ferreira T, Goldstein R, Brooks D. An International Comparison of Pulmonary Rehabilitation: A Systematic Review. *COPD* 2015: 12(2): 144-153.

12.   Enright SJ, Unnithan VB, Heward C, Withnall L, Davies DH. Effect of high-intensity inspiratory muscle training on lung volumes, diaphragm thickness, and exercise capacity in subjects who are healthy. *Phys Ther* 2006: 86(3): 345-354.

13.   Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *Clin Resp J* 2018: 12(7): 2178-2188.

14.   McCreery JL, Mackintosh KA, Mills-Bennett R, McNarry MA. The Effect of a High-Intensity PrO2Fit Inspiratory Muscle Training Intervention on Physiological and Psychological Health in Adults with Bronchiectasis: A Mixed-Methods Study. *Int J Environ Res Public Health* 2021: 18(6).

15.   Severin R, Arena R, Lavie CJ, Bond S, Phillips SA. Respiratory Muscle Performance Screening for Infectious Disease Management Following COVID-19: A Highly Pressurized Situation. *Am J Med* 2020.

16.   McCreery JL, Mackintosh KA, Mills-Bennett R, McNarry MA. The Effect of a High-Intensity PrO2Fit Inspiratory Muscle Training Intervention on Physiological and Psychological Health in Adults with Bronchiectasis: A Mixed-Methods Study. *Int J Environ Res Public Health* 2021: 18(6): 3051.

17.   Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR, Maher TM, Renzoni EA, Wells AU, Higginson IJ, Birring SS. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. *Thorax* 2012: 67(9): 804-810.

18.   Sinha A, Patel AS, Siegert RJ, Bajwah S, Maher TM, Renzoni EA, Wells AU, Higginson IJ, Birring SS. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. *BMJ Open Respir Res* 2019: 6(1): e000363.

19.   Mahler DA, Tomlinson D, Olmstead EM, Tosteson AN, O'Connor GT. Changes in dyspnea, health status, and lung function in chronic airway disease. *Am J Respir Crit Care Med* 1995: 151(1): 61-65.

20.   Witek TJ, Jr., Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003: 21(2): 267-272.

21.   Bennett H, Parfitt G, Davison K, Eston R. Validity of Submaximal Step Tests to Estimate Maximal Oxygen Uptake in Healthy Adults. *Sports Med* 2016: 46(5): 737-750.

22.   Ricardo LIC, Wendt A, Galliano LM, de Andrade Muller W, Niño Cruz GI, Wehrmeister F, Brage S, Ekelund U, Crochemore M. Silva I. Number of days required to estimate physical activity constructs objectively measured in different age groups: Findings from three Brazilian (Pelotas) population-based birth cohorts. *PLoS One* 2020: 15(1): e0216017.

23.   Lin Y, Tremblay MS, Katzmarzyk PT, Fogelholm M, Hu G, Lambert EV, Maher C, Maia J, Olds T, Sarmiento OL, Standage M, Tudor-Locke C, Chaput J-P. Temporal and bi-

directional associations between sleep duration and physical activity/sedentary time in children: An international comparison. *Prev Med* 2018: 111(June): 436-441.

24.   Hildebrand M, VT VANH, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. *Med Sci Sports Exerc* 2014: 46(9): 1816-1824.

25.   Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *AmP* 2000: 55(1): 68-78.

26.   Deci EL, Ryan RM. The "What" and "Why" of Goal Pursuits: Human Needs and the Self-Determination of Behavior. *Psychol Inq* 2000: 11(4): 227-268.

27.   Williams GC, Deci EL. Internalization of biopsychosocial values by medical students: a test of self-determination theory. *J Pers Soc Psychol* 1996: 70(4): 767-779.

28.   Ryan RM, Connell JP. Perceived locus of causality and internalization: examining reasons for acting in two domains. *J Pers Soc Psychol* 1989: 57(5): 749-761.

29.   Gagné M. The Role of Autonomy Support and Autonomy Orientation in Prosocial Behavior Engagement. *Motiv Emotion* 2003: 27(3): 199-223.

30.   Dumville JC, Hahn S, Miles JNV, Torgerson DJ. The use of unequal randomisation ratios in clinical trials: A review. *Contemp Clin Trials* 2006: 27(1): 1-12.

31.   Hoffman M. Inspiratory muscle training in interstitial lung disease: a systematic scoping review. *J Bras Pneumol* 2021: 47(4): e20210089.

32.   Charususin N, Dacha S, Gosselink R, Decramer M, Von Leupoldt A, Reijnders T, Louvaris Z, Langer D. Respiratory muscle function and exercise limitation in patients with chronic obstructive pulmonary disease: a review. *Expert Rev Respir Med* 2018: 12(1): 67-79.

33.   Langer D, Ciavaglia C, Faisal A, Webb KA, Neder JA, Gosselink R, Dacha S, Topalovic M, Ivanova A, O'Donnell DE. Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD. *JAPh* 2018: 125(2): 381-392.

34.   Anastasio F, Barbuto S, Scarnecchia E, Cosma P, Fugagnoli A, Rossi G, Parravicini M, Parravicini P. Medium-term impact of COVID-19 on pulmonary function, functional capacity and quality of life. *Eur Respir J* 2021: 58(3): 2004015.

35.   Carfi A, Bernabei R, Landi F, Group ftGAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 2020: 324(6): 603-605.

36.   Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, Ellis H, Goodall D, Gough M, Lewis S, Norman J, Papadopoulou T, Roscoe D, Sherwood D, Turner P, Walker T, Mistlin A, Phillip R, Nicol AM, Bennett AN, Bahadur S. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med* 2020: 54(16): 949-959.

37.   McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015(2).

38.   Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, Pujol JC, Klaser K, Antonelli M, Canas LS, Molteni E, Modat M, Jorge Cardoso M, May A, Ganesh S, Davies R, Nguyen LH, Drew DA, Astley CM, Joshi AD, Merino J, Tsereteli N, Fall T, Gomez MF, Duncan EL, Menni C, Williams FMK, Franks PW, Chan AT, Wolf J, Ourselin S, Spector T, Steves CJ. Attributes and predictors of long COVID. *Nat Med* 2021: 27(4): 626-631.

39.   Maldaner V, Coutinho J, Santana A, Cipriano GFB, Oliveira MC, Carrijo MM, Lino MEM, Cahalin LP, Lima AG, Borges R, Santos DB, Silva IO, Oliveira LVF, Cipriano G, Jr. Adjunctive inspiratory muscle training for patients with COVID-19 (COVIDIMT): protocol for randomised controlled double-blind trial. *BMJ Open* 2021: 11(9): e049545.

Figure 1. CONSORT flow diagram

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

Enrollment

Expression of Interest (n= 424)

Withdrawals – did not respond following initial expression of interest (n= 140)

Randomized (n= 281)

Allocation

Allocated to intervention (n= 224)
- Received allocated intervention (n= 176)
- Did not receive allocated intervention (n= 48)
  - Did not respond/no reason provided (n= 40)
  - Improved health since expressing interest (n= 6)
  - Unable to post equipment internationally (n= 1)
  - Change in personal circumstance (n= 1)

Allocated to control (n= 57)
- Received allocated intervention (n= 48)
- Withdrew on allocation (n= 9)
  - Did not respond/no reason provided (n= 8)
  - Waited too long for allocation (n= 1)

Follow-Up

Lost to follow-up (n= 65)
- Did not respond/no reason provided (n= 42)
- Fear of exacerbation (n= 8)
- Unwell (n= 5)
- Technical issues with IMT device (n= 4)
- Burden (n= 5)
- Unrelated surgery min-intervention (n= 1)

Lost to follow-up (give reasons) (n= 11)
- Did not respond/no reason provided (n= 8)
- Didn't attend baseline (no reason) (n= 2)
- Unwell (n= 1)

Analysis

Analysed (n= 111)
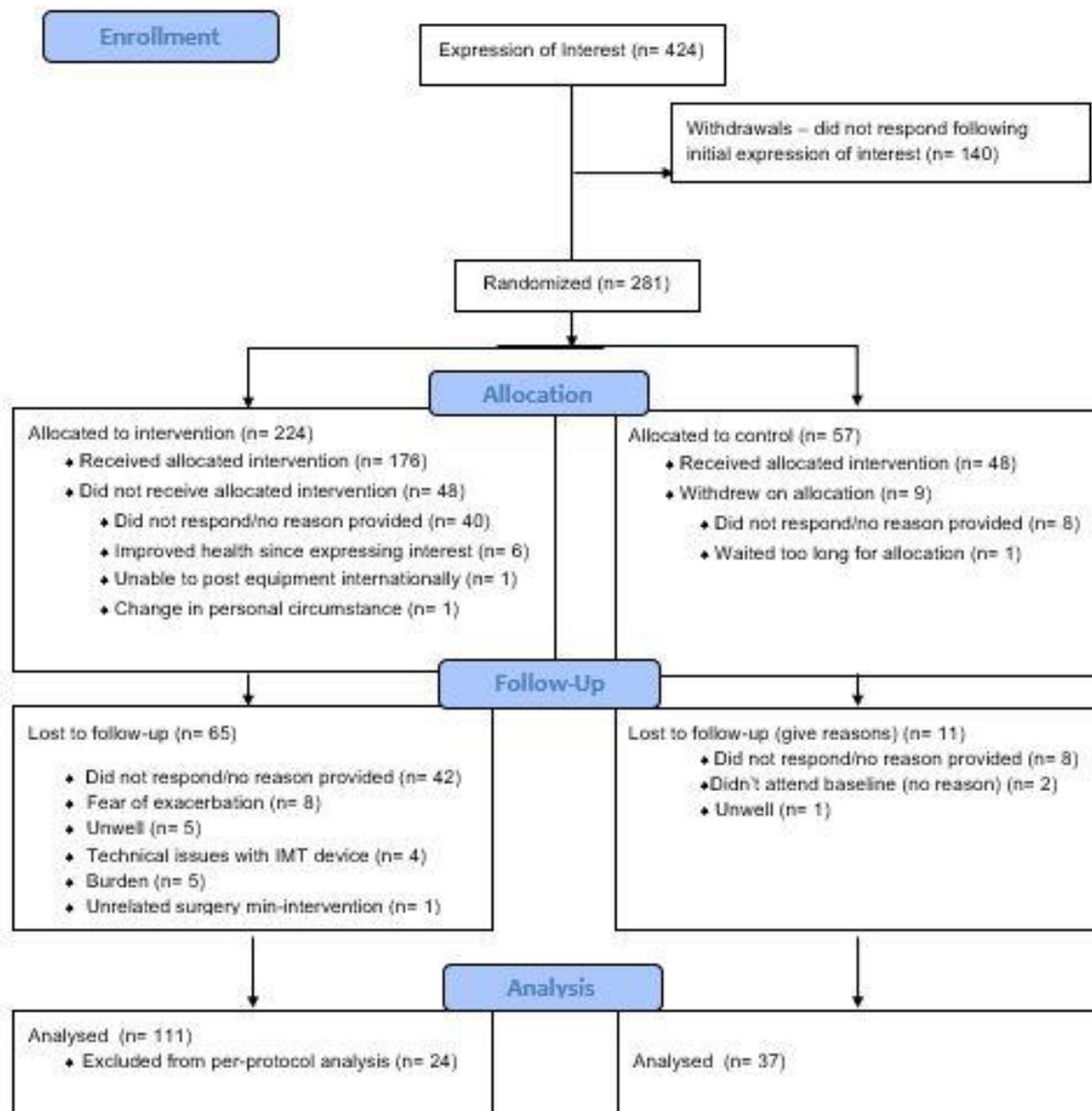- Excluded from per-protocol analysis (n= 24)

Analysed (n= 37)

Figure 2. Pre and post-intervention self-reported health and breathlessnesss according to a) the King's Brief Interstitial Lung Disease Questionnaire and b) the Baseline and Transition Dyspnea Index (* P < 0.05; ** P < 0.01)