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Pulmonary Rehabilitation for People With Persistent Symptoms After COVID-19 Peer-reviewed author version

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- 1 Pulmonary Rehabilitation for individuals with persistent symptoms following COVID-19
- 2 Keywords: Pulmonary Rehabilitation, COVID-19, exercise, long-COVID
- 3 Abbreviations

6MWD 6 Minute Walk Distance	PEM Post Exertional Malaise
BPAT Breathing Pattern Assessment Tool	PESE Post Exertional Symptom Exacerbation
BPD Breathing Pattern Disorder	PR Pulmonary Rehabilitation
COPD Chronic Obstructive Pulmonary Disease	

4

5 Abstract

- 6 Topic importance
- 7 COVID-19 can cause ongoing and persistent symptoms (such as breathlessness and fatigue) that lead
- 8 to reduced functional capacity. There are parallels in symptoms and functional limitations in adults
- 9 with post-COVID symptoms and adults with chronic respiratory diseases. Pulmonary Rehabilitation is
- a key treatment for adults with chronic respiratory diseases with the aims to improve symptom
- 11 management, increase functional capacity. Given the similarities in presentation and aims, a
- 12 Pulmonary Rehabilitation programme may be optimally placed to meet the needs of those with
- 13 ongoing symptoms following COVID-19.
- 14 Review findings
- 15 Aerobic and strength training has shown benefit for adults living with Long COVID though there is
- 16 little evidence on structured education in this population. Breathing pattern disorder is common in
- adults with Long COVID and considerations to treatment prior to rehabilitation, or alongside
- 18 rehabilitation are necessary. Considerations to Post Exertional Malaise is important in this
- 19 population and evidence from the Chronic Fatigue Syndrome literature supports the need for
- 20 individualisation of exercise programmes, and considerations for those that have an adverse
- 21 reaction to activity and/or exercise.
- 22 Summary
- 23 This narrative review summarises the current evidence of Pulmonary Rehabilitation programmes in a
- 24 long COVID population. Where the evidence is lacking in long COVID the supporting evidence of
- 25 these programmes in chronic respiratory diseases has highlighted the importance of aerobic and
- 26 strength training, considerations for fatigue, potential mechanism for immunology improvement and
- 27 management of breathing pattern disorders in these programmes.
- 28

29 Introduction

- 30 SARS-CoV-2 infection can lead to ongoing symptoms long after the initial infection. Symptoms
- 31 persisting greater than 12 weeks following the initial virus has been termed "long-COVID "or "post-
- 32 COVID-19 condition" as outlined by the World Health Organisation (WHO)¹ (herein after described as
- 33 long-COVID). Long-COVID reportedly effects upwards of 17 million people across the WHO European
- Region¹, and female sex, aged between 40-59, with two or more comorbidities have an increased
- 35 risk². The common symptoms include fatigue, breathlessness, pain, and, cognitive dysfunction,
- though there are approx. 200 recognised symptoms of Long-COVID, leading to complex
- 37 presentations due to multi-system involvement during COVID infection¹. In some instances, those
- 38 with long-COVID may also experience post Intensive Care Syndrome that may contribute to their
- 39 symptoms³. Individuals with long-COVID experience a reduction in quality of life, and physical
- 40 impairment due to limitations caused by their symptoms², and other factors such as period of
- 41 immobility, contribution of comorbidities and the presence of frailty⁴.
- 42 Pulmonary Rehabilitation (PR) is highly evidenced, effective and, cost effective intervention
- 43 developed for adults with chronic respiratory conditions. PR is a comprehensive programme of
- 44 aerobic and strength training, education, and supportive self-management strategies^{5,6}. The exercise
- 45 component is individually prescribed and adapted/progressed in line with individuals' symptoms and
- 46 improvements. Programmes can vary in duration and delivery but require the essential components
- 47 of individual comprehensive assessment, including an exercise test, subsequent exercise
- 48 prescription, and delivery by qualified healthcare professionals^{5,6}. Structured education is a desirable
- 49 component of PR and may provide important knowledge for managing respiratory symptoms. PR has
- 50 demonstrated significant improvements in symptoms, health-related quality of life, mental
- 51 wellbeing and functional capacity in multiple chronic respiratory diseases⁷. Those that attend PR
- 52 present similarly to adults with long- COVID including symptoms of breathlessness, fatigue, pain, and
- 53 cognitive dysfunction. An early consensus of experts identified the need for support of adults living
- with long-COVID and that PR may be an optimal setting to offer this support, particularly with the
 presence of respiratory symptoms⁸. Since then, guidance has supported that an adaptive PR model
- 55 presence of respiratory symptoms . Since then, guidance has supported that an adaptive
- 56 may be suitable for adults living with long-COVID^{9,10}.
- 57 Whilst there are some similarities between long-COVID and chronic respiratory conditions, long-
- 58 COVID is poorly understood with a wide range of phenotypes and symptoms, some of which may
- respond to rehabilitation, however there are some additional considerations in regards to these
- 60 interventions². There has been an increasing amount of evidence for the prevalence of breathing
- 61 pattern disorder and long-COVID, which appears higher than other disease areas¹¹. This cohort may
- 62 present with additional complications such as post-exertional symptom exacerbation or post
- 63 exertional malaise whereby individuals experience an extreme, adverse reaction to exercise
- 64 training/activity (PESE/PEM) that require consideration in relation to rehabilitation strategies.
- Additionally, there are individuals with long-COVID that present with frailty and related limitations as
- a direct result of their acute COVID event (which may include hospitalisation), where they may have
- 67 previously not been frail⁴.
- 68 The complexity and heterogeneity of long COVID highlights the importance of understanding the
- 69 literature in relation to PR for adults living with Long COVID therefore this review will aim to assess
- the current literature on COVID rehabilitation and where evidence is lacking, explore the evidence of
- PR that may provide relevance to this population. This will give particular attention to the evidence

- 72 on exercise training; and its subsequent effect on fatigue, breathing pattern disorder and frailty
- 73 (figure 1).

74 Literature search

- 75 Searches were conducted in February 2023 (and updated in November 2023) from database
- 76 inception and were performed on: PubMed (MEDLINE) and CINAHL. Combinations of the following
- terms were used in the searches: "COVID-19", "COVID", "SARS-CoV-2", "rehabilitation", "exercise"
- 78 "frailty", "dysfunctional breathing", and "disordered breathing". The abstracts of original
- 79 investigations and review articles and the references of selected studies were screened and included
- 80 based on relevance to the topics covered in this Series paper. Additional searches on
- 81 ClinicalTrials.gov for active and planned clinical trials of investigational exercise or rehabilitation
- 82 interventions in COVID-19 populations using the following terms: "COVID-19", "COVID", "pulmonary
- 83 fibrosis", "fibrotic", "fibrotic lung disease", and "post-COVID fibrosis".

84 COVID rehabilitation review of the literature

- 85 There has been increasing evidence to support rehabilitation strategies for adults living with long-
- 86 COVID symptoms. Several systematic reviews have demonstrated improvements in breathlessness
- 87 and anxiety following rehabilitation, however there is heterogeneity among the interventions
- 88 delivered¹². Reviews that include interventions outside the American Thoracic Society definition of
- 89 PR tend to have a diluted response in relation to exercise capacity and quality of life. These
- 90 systematic reviews demonstrate promise for COVID rehabilitation, and have been supported by
- 91 observational studies which include a form of exercise training, have shown significant
- 92 improvements in the six minute walking distance (6MWD) compared to no intervention¹³⁻¹⁵. There is
- 93 some evidence to suggest that rehabilitation with inspiratory muscle training and/or breathing
- 94 exercises can improve lung function compared to a control in adults with long-COVID, however data
- 95 are inconsistent and at odds with chronic respiratory disease data^{13,14}. Two reviews concluded that
- 96 PR has the potential to improve symptoms post-COVID and found moderate to large effects in
- 97 breathlessness, physical function and quality of life, though were not able to demonstrate
- 98 improvements in fatigue. This review includes a broad definition of PR and non-randomised
- 99 controlled trials and therefore the lack of control group may dilute the results¹⁶. The studies in the
- systematic review include a variety of interventions but differ from "traditional" pulmonary
- 101 rehabilitation models, and do not necessarily include the reported key components, but focus more
- 102 on breathing techniques and respiratory muscle training¹⁷.
- 103 Early data for COVID rehabilitation approximately four months after infection, that is based on a PR
- 104 model, has shown promise in improving symptoms, exercise capacity and quality of life however
- studies to date have lacked a control group and may be affected by government mandated
- 106 lockdown restrictions/shielding measures¹⁸. Similarly, a pilot study in North Africa has implemented
- a PR programme post-COVID-19 which shows improvements in quality of life, anxiety and
- 108 depression, and physical activity¹⁹.
- 109 The evidence for COVID rehabilitation is encouraging but further research of randomised controlled
- 110 trials comparing rehabilitation based on PR key components, compared to a control group is
- 111 required. There are several registered trials that will explore these models of care through face to

- face and digital modes²⁰ (trial registrations NCT05317975, NCT05244135, NCT04961333,
- 113 ISRCTN10980107, ISRCTN11466448).

114 Learning from Pulmonary Rehabilitation

115 Aerobic training

- 116 Aerobic exercise has long been recognized as an important part of PR and likely forms an integral
- 117 part of the management of long-COVID⁵. A systematic review of 433 participants with long-COVID
- 118 has demonstrated an improved lung capacity, cardiovascular health, and, reduced risk of
- 119 complications ²¹. Increasing aerobic capacity is associated with increasing muscle endurance and
- 120 strength as well as increasing immunity²².
- 121 Aerobic exercise targets the reduced exercise tolerance that is an important factor in the symptoms
- and functional limitations present in long COVID²³. Following an 8-week exercise rehabilitation
- 123 programme consisting of aerobic exercise training in conjunction with strength training, a study of
- 124 50 patients with long-COVID showed significant improvement in cardiorespiratory fitness. Exercise
- 125 capacity increased from 17.8 mL/kg/min to 20.5 mL/kg/min²⁴. A significant increase in exercise
- 126 capacity and lung function was found following a similar exercise programme¹⁴.
- 127 A systematic review of aerobic exercise training in long-COVID provided recommendations for
- 128 aerobic exercise in the form of cycling or walking for 20-60 minutes at an intensity of 55-80% VO2_{max}
- 129 or 60-80% of maximum heart rate, defined as 220 minus age, 2-3 times a week²⁵. This exercise
- 130 prescription is similar to the aerobic exercise component of PR, however this review does not report
- the pooled results of the included studies and does not consider the complexities of adults with
- 132 long-COVID (such as fatigue and breathing pattern disorder- discussed in later sections). Therefore it
- is vitally important that aerobic exercise prescription is tailored to individual needs and symptoms,
- 134 and progressed in line with these symptoms 23 .
- 135 Interval training, defined as alternating short bursts of high-intensity exercise with periods of rest or
- 136 lower-intensity exercise, could provide benefit in this population due to its ability to allow
- accumulation of volume whilst limiting breathlessness²⁶, and particularly ventilatory limitations such
- as those with breathing pattern disorder. The addition of resistance exercise alongside aerobic
- exercise helps improve overall fitness and in turn the ability to perform aerobic exercise, however
- 140 there is a lack of evidence within a long-COVID population²⁷.
- 141 In addition to improving respiratory and cardiovascular health, aerobic exercise can also have
- 142 positive effects on mental health and well-being, a common symptom of long-COVID. Studies have
- shown that regular exercise can reduce symptoms of anxiety and depression in individuals with a
- 144 respiratory condition and individuals with an immediate history of COVID-19^{5,25,28-30}.
- 145 Overall, aerobic exercise could provide benefit in improving exercise capacity in long COVID.
- 146

147 Resistance training

- 148 Resistance exercises provide a potent stimulus for ameliorating the musculoskeletal consequences
- of COVID-19 and/or hospitalisation, which are often compounded by high levels of sedentary
 behavious³¹.
- Data in long-COVID suggests that improvements in muscle strength and function can be expected in 151 this population³², largely attributable to the resistance training portion of interventions. These 152 153 effects are of great importance, as muscle strength is broadly associated with a reduced risk of disease and all-cause mortality in the general population³³. A 28-day resistance programme 154 combined with aerobic exercise in individuals recovering from COVID-19 improved skeletal muscle 155 156 mass regardless of baseline muscle mass ("normal" +10.7% or "low" +8.5%), demonstrating equitable benefits irrespective of body composition³⁴. Conversely a rehabilitation programme did 157 158 not demonstrate changes in muscle mass in males with long-COVID and sarcopenia despite 159 improvements in hand grip strength³⁵. In a larger trial, individuals with impaired exercise capacity 160 following hospitalisation with COVID-19 performed aerobic and resistance training for an 8-week 161 period²⁴. Resistance training was incorporated for both lower (leg extension/flexion, 162 abduction/adduction, leg press) and upper body (push-up/pull-down and abdomen and back 163 exercises) and was performed with relatively conservative loads (40% of subjects' 1-repetition-164 maximum; 2-3 sets; 12 repetitions). Following the intervention, muscle strength increased for all 165 major muscle groups ranging from 16% to 33%, although functional capacity and quality of life were 166 not reported. This heterogeneity amongst studies in relation to muscle mass is perhaps unsurprising; 167 as prescription of training load, frequency and volume differs substantially and will have a considerable impact on hypertrophic adaptations³⁶. The utility of resistance training following 168
- 169 COVID-19 infection seemingly lies in improving muscle strength and physical function, rather than
- 170 driving body re-composition.
- 171 It is worth noting that adverse events are seldom reported in studies of resistance training in PR³⁷.
- 172 This is supportive of previous data demonstrating similar changes in VO₂ and minute ventilation
- 173 between individuals with COPD and healthy controls during a resistance training session³⁸.
- 174 Additionally, when compared to whole-body aerobic exercise such as cycling, walking, and stair
- 175 climbing, resistance training may elicit a lower relative cardiopulmonary stress response according to
- 176 these metrics³⁹. Although the safety and efficacy of resistance training in long-COVID has not been
- 177 extensively explored; several trials have demonstrated clear improvements in both muscle strength
- and function utilising modified, multi-component PR programmes. Ultimately, these adaptations will
- 179 likely facilitate the rehabilitation of musculoskeletal sequelae resulting from COVID-19, leading to
- 180 potential improvements in daily functioning and quality of life. Further research should explore the
- 181 duration, frequency and intensity for optimisation of resistance training.

182 Education and self-management

- 183 Education (formal and informal) and self-management strategies are essential within PR
- 184 interventions. There is a lack of literature that explore the impact of formal education on the
- 185 management of long-COVID, and few studies include details of education sessions. One study
- describes the educational topics as: breathlessness, cough, fatigue, fear and anxiety, memory and
- 187 concentration, taste and smell, eating well, getting moving again, sleeping well, managing daily
- 188 activities and, returning to work; suggesting some adaptations to the educational component are
- 189 required¹⁸. However, education needs, and response to interventions are seldom explored, and

- 190 therefore their importance remains uncertain. Within PR, formal education is a requirement and
- 191 there has been evidence to support increased knowledge of disease within Chronic Respiratory
 102 Disease⁴⁰
- 192 Disease⁴⁰.

193 Rehabilitation and breathing pattern disorder

Breathing pattern disorder (BPD) or dysfunctional breathing is characterised by alterations in breathing mechanics that results in dyspnoea that is disproportionate to the level of activity, or occurring at rest. Several studies have highlighted the presence of irregularities in the breathing pattern of individuals with dyspnoea following COVID-19. BPD is a well-recognised cause of exertional dyspnoea in the general population and is a prevalent co-morbidity in individuals with airways disease^{41,42}. Respiratory symptoms arising from BPD impact quality of life and influence simple activities such as climbing a flight of stairs⁴³.

- 201 In individuals with breathlessness and long-COVID, Hylton and colleagues used a simple breathing
- 202 pattern assessment tool, the BPAT, to identify and report a 30% prevalence of BPD in individuals
- with long COVID^{44,11}. Utilising the Nijmegen Questionnaire, hyperventilation was identified in
- approximately 21% of individuals assessed at an ambulatory care visit for persistent symptoms
- following COVID in a further study⁴⁵. Studies utilising cardiopulmonary exercise testing to
- characterize physiological reasons for exertional limitation, such as deconditioning, have also
 identified a high prevalence of breathing pattern irregularities, with hyperventilation and erratic
- tidal volume patterns^{46,47}. The use of non-linear statistical methods has been employed to emphasise
- and characterize the chaos of breathing in this context⁴⁸. It thus seems apparent that in some
- 210 individuals, BPD is an important factor underpinning the seemingly 'unexplained' dyspnoea
- associated with COVID-19 recovery, though the diagnosis of BPD remains a challenge⁴¹. Moreover,
- there is a recognised association between BPD and autonomic dysfunction and thus a likely interplay
- 213 between these phenomena, in the context of long-COVID⁴⁹.
- 214 To date, there are no prospective studies reporting BPD-related outcomes following exercise or PR-
- 215 based intervention in long-COVID. As described in this review, most studies have focussed on
- exercise capacity and quality of life associated metrics⁵⁰. There is however a logical rationale for
- 217 exploring the benefit of PR in this context, given the relevance of this condition, as described above,
- and also the known benefit of this class of interventions in non-COVID-19 associated BPD.
- 219 Specifically, in individuals with airways disease and co-morbid BPD, several randomised control
- 220 studies have shown that a physiotherapy-based intervention is associated with improved quality of
- life and perceived dyspnoea^{51,52}. There are interventional studies on the use of inspiratory muscle
- training to improve breathlessness and respiratory muscle function in long-COVID and therefore may
- 223 be considered a useful adjunct to PR⁵³. PR includes strategies for the management of breathlessness
- within the educational component that may also add value to those with BPD. Future research
- should characterise BPD in this setting to evaluate the overlap with autonomic dysfunction and
- refine specific tools to address this issue when identified within a PR management plan.

227 Rehabilitation and fatigue

- Fatigue is a hallmark symptom of COVID-19, both in acute disease and in individuals with long
 COVID⁵⁴⁻⁵⁸. A meta-analysis including 25,268 individuals reported that fatigue was found in 32% of
- 230 individuals with COVID-19 at 12 weeks after the infection, though the diagnosis and reporting of

- fatigue can vary⁵⁹. In the long-COVID literature fatigue is reported subjectively and importantly, both
- physical and mental fatigue has been described. Fatigue has been reported through questionnaires
- 233 (e.g Functional Assessment of Chronic Illness Therapy- Fatigue Scale⁶⁰), or through subjective
- 234 description of the symptom. Further diagnosis for fatigue such as Chronic Fatigue Syndrome⁶¹ may
- also be sought following long COVID whereby diagnoses may be made through clinician interviews.
- Fatigue can also be attributed to deconditioning, particularly following hospital admission such as
- post ITU syndrome⁶². Additionally, fatigue as a symptom is common in other chronic respiratory
- conditions such as COPD⁶³, and is a complex and multifactorial symptom.
- 239

There has been improvements in fatigue following rehabilitation in adults with COPD⁶⁴. While the 240 241 underlying mechanisms have not yet been unravelled, fatigue has been associated with changes in the immune response such as: a cytokine storm, glial activation, T-cell exhaustion, mitochondrial 242 impairment, neuronal toxicity and reactivation of Epstein-Barr virus⁶⁵⁻⁶⁷. Long-lasting fatigue is a 243 244 common signature of long-COVID, yet favourable effects of regular physical activity on immune cell 245 functions and pro-inflammatory cytokine release are apparent even with low to moderate levels of activity in populations with limited physical capacity and symptoms of daily fatigue^{68,69}. Furthermore, 246 247 reducing time spent sedentary (sitting, reclining or lying down) is independently associated with 248 lower circulating concentrations of pro-inflammatory cytokines, even when adjusting for physical activity habits in large cohort of adults aged 60-64⁷⁰. An observational study examining lymphocyte 249 250 populations and inflammatory consequences in previously hospitalised COVID-19 individuals found 251 persistent perturbations in T cell function and phenotype at 6 months of convalescence⁷¹. In 252 particular, individuals exhibited elevated proportions of 'exhausted' terminally differentiated 253 effector memory (TEMRA) T cell subsets. These cells have reduced capacity to respond to future 254 antigen challenge, increasing the risk of more frequent and more severe infections, and reducing 255 responses to vaccines, which may in part explain the prevalence of fatigue within long COVID⁷¹. 256 Accordingly, a recent systematic review of 30 studies concluded that regular exercise limits the accumulation of exhausted CD8+ T cells⁷². The authors concluded that this effect seems likely related 257 258 to preferential mobilisation of exhausted T cells with each exercise session, subsequently promoting 259 their apoptosis in the peripheral blood compartment by other immune cells, creating 'immune 260 space' and stimulating the production of naïve T cells. The findings of these, and other exercise and 261 physical activity studies, even at lower intensities and volumes, may suggest some potential for 262 carefully directed activity within rehabilitation programmes to manage persistent immune perturbations within adults with long-COVID. 263

264 Many trials that have reported on the beneficial effects of rehabilitation in individuals with long-265 COVID – mostly including previously hospitalized individuals – did not include fatigue as an outcome. 266 Al-Chickanie et al reported an improvement of fatigue after PR in patient that survived respiratory failure due to COVID-19⁷³. In a cohort of 30 individuals (87% previously hospitalised), Daynes et al. 267 268 found a clinical important improvement in fatigue¹⁸. Importantly they also observed an improvement in fatigue and functional capacity in most individuals, with no individuals worsening in 269 270 both fatigue and functional capacity. Further studies have demonstrated functional improvements, 271 while fatigue remains indicating that individuals are able to do more before experiencing similar levels of fatigue^{74,75}. Two randomised controlled trials have demonstrated an improvement in fatigue 272

273 following tailored exercise or telerehabilitation^{76,77}.

- 274 It has been demonstrated that PR can improve fatigue in other disease areas such as COPD, which
- 275 can improve other important outcomes such as 5-year mortality⁷⁸. In patients with persisting
- 276 dyspnoea, Dalbosco-Salas observed an improvement of fatigue after a primary care tele-
- 277 rehabilitation programme⁷⁶. Strategies within PR programmes, such as pacing and prioritising
- 278 techniques are recommended for the management of long-COVID and there has been evidence in
- 279 individuals with COPD that pacing/energy conservation techniques are effective at reducing energy
- 280 consumption, and therefore would likely add value in the management of long-COVID fatigue⁷⁹.
- 281 While fatigue might be a treatable and transient symptom in a proportion of individuals, there may
- 282 be a proportion of individuals where exercise is not beneficial, particularly in the presence of PESE.
- 283 There has been guidance on the management of PESE and PEM for consideration in long-COVID,
- 284 drawing parallels from the myalgic encephalomyelitis and chronic fatigue syndrome literature. PEM
- 285 or PESE refer to a significant a debilitating worsening of symptoms despite minimal physical or 286 mental exertion, lasting several days or weeks. The prevalence of this phenomenon is not known,
- 287 largely due to challenges in diagnosing this phenomenon and there has been no research that has
- 288 explored the impact of rehabilitation strategies on the changes in PESE in adults with long-COVID.
- 289 Data from post viral diseases identified that the severity of the initial virus and recurrence of
- infection can lead to increased severity of PEM⁸⁰. Patient selection, individualisation and symptom 290
- titrated rehabilitation, alongside strategies such as pacing are crucial to ensure the correct 291
- management of this symptom⁸¹. Progression of exercise and activity should be based on the 292
- 293 symptom improvement and should be regularly reviewed. Rehabilitation services should ensure that
- 294 fatigue, PEM, and PESE are screened and monitored throughout the programme in order to guide
- 295 interventions, and where necessary other interventions should be explored.
- 296

297 Rehabilitation and physical frailty/skeletal muscle dysfunction

- 298 Among survivors of COVID-19 a significant burden of frailty has been seen with 7% of those
- 299 hospitalised being categorised as frail one year following discharge while a further 59% were found
- to be at risk of developing frailty⁴. PR, involving a combination of aerobic and resistance exercise, 300
- has well described impacts upon skeletal muscle⁸² and frailty⁸³ with measures of both improving 301
- 302 following the completion of PR among individuals living with COPD. Similarly, patients with
- 303 sarcopenia or frailty who participate in PR programmes have favourable outcomes despite those
- living with frailty being less likely to complete PR programmes^{82,83}. Furthermore, the two domains of 304 phenotypic frailty most frequently observed were low physical activity and reduced hand grip 305
- strength⁴, both areas may benefit from PR, particularly with strength training, and reassurance
- 306 around aerobic exercise and physical activity. Evidence for improved physical activity following PR is
- 307 308 conflicting, and exploration of how frailty status may impact physical activity remain unknown⁸⁴.
- 309 Skeletal muscle weakness and loss of muscle mass have both been noted among individuals 310 suffering long-COVID^{85,86} while a high prevalence of sarcopenia has been seen in some populations⁸⁷
- 311 with the extent of muscle deficit relating to the severity of the acute illness. This suggests that for
- 312 many survivors of COVID-19 with ongoing health impairments muscle changes may follow similar
- patterns to those seen following hospitalisation and critical care admission for other conditions 313
- where rehabilitation strategies implemented both during⁸⁸ and following the acute illness⁸² have 314
- 315 proven effects on ameliorating the loss of muscle function. Pharmacological interventions have yet

- to show clinically relevant benefits for patients suffering muscle loss or sarcopenia⁸⁹ further
- 317 highlighting the importance of rehabilitative interventions.

318 Adaptations and considerations for COVID Rehabilitation

319 In addition to exercise training, PR offers a multidisciplinary approach to support physical, 320 psychological and functional impairments. Whilst there are similarities between those with chronic 321 respiratory disease and long-COVID, there are differences that require consideration in COVID 322 rehabilitation. Return to work support through education, adjustments and signposting, is highly 323 relevant in this population, with 23.3% of 16-64 year olds reportedly off work with self-reported long 324 COVID⁹⁰. This may lead to challenges in progression of exercise/activity, whereby individuals may 325 increase activity rapidly and worsen symptoms. Therefore strategies for gradual return to activity/work and detailed symptom management in vital⁹⁰. Adults with long-COVID may have new 326 327 onset of oxygen requirements, particularly those with pre-existing comorbidities⁹¹. This can be 328 supported within PR, whereby healthcare professionals are experienced in supporting supplemental 329 oxygen. Additionally, there is a high prevalence of anxiety and depression; however this is 330 comparable to those living with a chronic respiratory disease, whereby PR has demonstrated improvements in mood disorders⁹². As a result, patient selection is vital in the success of PR for 331 332 adults living with long COVID, highlighted within the British Thoracic Society Clinical Statement⁹³. 333 Notably, PR should be offered to those with ongoing functional impairment \geq 3 months, with 334 considerations to complex symptoms as listed above. PR may be prioritised or stratified for those 335 phenotypes with a more severe functional impairment, where those with milder impairment may benefit from "lighter touch" interventions⁹⁴, as guided by the COVID-19 Functional Status Scale⁹⁵. 336

Considerations of the timing of intervention would be helpful, though there is little exploration of this in the literature. As some individuals will recover and not be classified as "long COVID" it would seem appropriate for rehabilitation to be offered after this stage. Though, those that have had a long stay in intensive care or signs of post intensive care syndrome, may be more appropriately treated early and in line with intensive care rehabilitation services⁹⁶. Generally, the population may be younger, and of working age, and therefore there is opportunity for digital rehabilitation to support individuals, though this has not been explored at length in this review.

344

345 Discussion

This review has explored the evidence for COVID rehabilitation, and where evidence is lacking, the 346 347 potential usefulness of PR evidence (figure 2). Adults living with long-COVID will experience a 348 plethora of symptoms including breathlessness and fatigue, which have long been addressed within 349 PR. The PR model of aerobic and resistance exercise, alongside symptom management shows 350 promise in improving symptoms associated with long-COVID. Evidence has demonstrated improvements in health-related quality of life, and functional capacity though particular 351 considerations may be required for the presence of BPD, frailty and severe fatigue. The anti-352 353 inflammatory benefits of exercise and promoting physical activity may begin to explain some 354 improvements in key symptoms such as fatigue among this population. Currently there is a lack of evidence for adapted PR programmes in the treatment of long-COVID that has a control group, 355 356 though there are several registered trials that aim to answers these unknowns.

357 Future prospects

- 358 Research is ongoing for PR in adults with Long COVID, and it is important for high quality, rigorous
- 359 studies with an appropriate control group in order to provide recommendations for PR, and there

360 are several studies ongoing, due to read out in the short-term. Further research on who benefits,

- and when would be beneficial, and exploration of potential mechanisms in adults with Long COVID.
- 362 Evidence for diagnosing and treating breathing pattern disorder and post-exertional malaise/post
- 363 exertional symptom exacerbation would be useful in recommending and identifying appropriate
- 364 participants.

365 Summary

366 PR programmes can provide benefit and support for adults living with long COVID. Considerations

367 for timing of the intervention, particularly in relation to Breathing Pattern Disorder, and paying

- 368 consideration to natural recovery is important. Fatigue is a prevalent symptom in Long COVID and
- 369 programmes need to ensure the delivery of individualised care.
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- 371 reviewed the final, submitted manuscript.

372 References

- 1. World Health Organisation (WHO). Coronavirus disease (COVID-19): Post COVID-19
- 374 condition. 2023. <u>https://www.who.int/news-room/questions-and-answers/item/coronavirus-</u>
 375 <u>disease-(covid-19)-post-covid-19-</u>
- 376 condition#:~:text=Post%20COVID%2D19%20condition%20is,falls%20ill%20with%20COVID%2D19
 377 (accessed 13/06/2023).
- Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of
 COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021; 9(11): 1275-87.
- 381 3. Rawal G, Yadav S, Kumar R. Post-intensive Care Syndrome: an Overview. *J Transl Int Med* 382 2017; **5**(2): 90-2.
- McAuley HJC, Evans RA, Bolton CE, et al. Prevalence of physical frailty, including risk factors,
 up to 1 year after hospitalisation for COVID-19 in the UK: a multicentre, longitudinal cohort study.
 EClinicalMedicine 2023; 57: 101896.
- 386 5. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European
- Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; **188**(8): e13-64.
- Bolton CE, Bevan-Smith EF, Blakey JD, et al. British Thoracic Society guideline on pulmonary
 rehabilitation in adults. *Thorax* 2013; 68 Suppl 2: ii1-30.
- McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation
 for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; **2015**(2): CD003793.
- Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: Interim Guidance
 on Rehabilitation in the Hospital and Post-Hospital Phase from a European Respiratory Society and
 American Thoracic Society-coordinated International Task Force. *Eur Respir J* 2020; 56(6).
- 3969.British Thoracic Society (BTS). Delivering rehabilitation to individuals surviving COVID-19

using an adapted pulmonary rehabilitation approach – BTS guidance. 2020. <u>https://www.brit-</u>
 <u>thoracic.org.uk/document-library/quality-improvement/covid-19/pulmonary-rehabilitation-for-</u>
 covid-19-patients/ (accessed 17/05/2023).

400 10. Evans R, Pick A, Lardner R, Masey V, Smith N, Greenhalgh T. Breathing difficulties after covid-401 19: a guide for primary care. *BMJ* 2023; **381**: e074937. Hylton H, Long A, Francis C, et al. Real-world use of the Breathing Pattern Assessment Tool in
assessment of breathlessness post-COVID-19. *Clin Med (Lond)* 2022; **22**(4): 376-9.

404 12. Fugazzaro S, Contri A, Esseroukh O, et al. Rehabilitation Interventions for Post-Acute COVID405 19 Syndrome: A Systematic Review. *Int J Environ Res Public Health* 2022; **19**(9).

406 13. Li J, Xia W, Zhan C, et al. A telerehabilitation programme in post-discharge COVID-19 patients
407 (TERECO): a randomised controlled trial. *Thorax* 2022; **77**(7): 697-706.

40814.Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients409with COVID-19: A randomized controlled study. Complement Ther Clin Pract 2020; **39**: 101166.

410 15. Nopp S, Moik F, Klok FA, et al. Outpatient Pulmonary Rehabilitation in Patients with Long
411 COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life.

412 *Respiration* 2022; **101**(6): 593-601.

413 16. Melendez-Oliva E, Martinez-Pozas O, Cuenca-Zaldivar JN, Villafane JH, Jimenez-Ortega L,
414 Sanchez-Romero EA. Efficacy of Pulmonary Rehabilitation in Post-COVID-19: A Systematic Review
415 and Meta-Analysis. *Biomedicines* 2023; **11**(8).

416 17. Holland AE, Cox NS, Houchen-Wolloff L, et al. Defining Modern Pulmonary Rehabilitation. An
417 Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc* 2021; **18**(5): e12-e29.

18. Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for
individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort
study. *Chron Respir Dis* 2021; **18**: 14799731211015691.

421 19. Benzarti W, Toulgui E, Ghram A, et al. Impact of a pulmonary rehabilitation program on
422 social disadvantage and physical activity data of postCOVID19 patients: A North-African pilot study
423 [version 1; peer review: 1 approved]. *F1000Research* 2022; **11:1226**.

20. Daynes E, Baldwin M, Greening NJ, et al. The effect of COVID rehabilitation for ongoing
symptoms Post HOSPitalisation with COVID-19 (PHOSP-R): protocol for a randomised parallel group
controlled trial on behalf of the PHOSP consortium. *Trials* 2023; **24**(1): 61.

427 21. Fernandez-Lazaro D, Santamaria G, Sanchez-Serrano N, Lantaron Caeiro E, Seco-Calvo J.
428 Efficacy of Therapeutic Exercise in Reversing Decreased Strength, Impaired Respiratory Function,
429 Decreased Physical Fitness, and Decreased Quality of Life Caused by the Post-COVID-19 Syndrome.

430 Viruses 2022; **14**(12).

431 22. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise Capacity and
432 Mortality among Men Referred for Exercise Testing. *New England Journal of Medicine* 2002; **346**(11):
433 793-801.

434 23. Singh SJ, Baldwin MM, Daynes E, et al. Respiratory sequelae of COVID-19: pulmonary and
435 extrapulmonary origins, and approaches to clinical care and rehabilitation. *The Lancet Respiratory*436 *Medicine* 2023.

437 24. Barbara C, Clavario P, De Marzo V, et al. Effects of exercise rehabilitation in patients with
438 long coronavirus disease 2019. *Eur J Prev Cardiol* 2022; **29**(7): e258-e60.

439 25. Alawna M, Amro M, Mohamed AA. Aerobic exercises recommendations and specifications
440 for patients with COVID-19: a systematic review. *Eur Rev Med Pharmacol Sci* 2020; **24**(24): 13049-55.

441 26. Kortianou EA, Nasis IG, Spetsioti ST, Daskalakis AM, Vogiatzis I. Effectiveness of interval

exercise training in patients with COPD. *Cardiopulmonary physical therapy journal* 2010; **21**(3): 12.
Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position

stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory,

445 musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing
446 exercise. *Med Sci Sports Exerc* 2011; **43**(7): 1334-59.

Ahmed I, Inam AB, Belli S, Ahmad J, Khalil W, Jafar MM. Effectiveness of aerobic exercise
training program on cardio-respiratory fitness and quality of life in patients recovered from COVID-*European Journal of Physiotherapy* 2022; **24**(6): 358-63.

450 29. Betschart M, Rezek S, Unger I, et al. Feasibility of an Outpatient Training Program after 451 COVID-19. Int J Environ Res Public Health 2021; **18**(8). 452 30. Hayden MC, Limbach M, Schuler M, et al. Effectiveness of a Three-Week Inpatient
453 Pulmonary Rehabilitation Program for Patients after COVID-19: A Prospective Observational Study.
454 Int J Environ Res Public Health 2021; 18(17).

455 31. Vorrink SN, Kort HS, Troosters T, Lammers JW. Level of daily physical activity in individuals 456 with COPD compared with healthy controls. *Respir Res* 2011; **12**(1): 33.

457 32. Ahmadi Hekmatikar AH, Ferreira Junior JB, Shahrbanian S, Suzuki K. Functional and 458 Psychological Changes after Exercise Training in Post-COVID-19 Patients Discharged from the 459 Hospital: A PRISMA-Compliant Systematic Review. *Int J Environ Res Public Health* 2022; **19**(4).

Celis-Morales CA, Welsh P, Lyall DM, et al. Associations of grip strength with cardiovascular,
 respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million
 UK Biobank participants. *BMJ* 2018; **361**: k1651.

463 34. Gobbi M, Bezzoli E, Ismelli F, et al. Skeletal Muscle Mass, Sarcopenia and Rehabilitation 464 Outcomes in Post-Acute COVID-19 Patients. *J Clin Med* 2021; **10**(23).

Abdelbasset WK, Alrawaili SM, et al. Comparative effectiveness study of low versus
high-intensity aerobic training with resistance training in community-dwelling older men with postCOVID 19 sarcopenia: A randomized controlled trial. *Clin Rehabil* 2022; **36**(1): 59-68.

468 36. McLeod JC, Currier BS, Lowisz CV, Phillips SM. The influence of resistance exercise training
469 prescription variables on skeletal muscle mass, strength, and physical function in healthy adults: An
470 umbrella review. *J Sport Health Sci* 2023.

471 37. Liao WH, Chen JW, Chen X, et al. Impact of Resistance Training in Subjects With COPD: A
472 Systematic Review and Meta-Analysis. *Respir Care* 2015; **60**(8): 1130-45.

473 38. Houchen-Wolloff L, Sandland CJ, Harrison SL, et al. Ventilatory requirements of quadriceps
474 resistance training in people with COPD and healthy controls. *Int J Chron Obstruct Pulmon Dis* 2014;
475 9: 589-95.

476 39. Probst VS, Troosters T, Pitta F, Decramer M, Gosselink R. Cardiopulmonary stress during
477 exercise training in patients with COPD. *Eur Respir J* 2006; **27**(6): 1110-8.

478 40. Lewis A, Dullaghan D, Townes H, Green A, Potts J, Quint JK. An observational cohort study of
479 exercise and education for people with chronic obstructive pulmonary disease not meeting criteria
480 for formal pulmonary rehabilitation programmes. *Chron Respir Dis* 2019; **16**: 1479973119838283.

481
41. Boulding R, Stacey R, Niven R, Fowler SJ. Dysfunctional breathing: a review of the literature
482 and proposal for classification. *Eur Respir Rev* 2016; **25**(141): 287-94.

483 42. Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients
484 treated for asthma in primary care: cross sectional survey. *BMJ* 2001; **322**(7294): 1098-100.

43. Siewers K, Walsted E, Manivannan B, Warren C, McCabe C, Hull JH. Heightened ventilatory
response during stair climbing in individuals with dysfunctional breathing. *ERJ Open Res* 2022; 8(4).
44. Todd S, Walsted ES, Grillo L, Livingston R, Menzies-Gow A, Hull JH. Novel assessment tool to
detect breathing pattern disorder in patients with refractory asthma. *Respirology* 2018; 23(3): 284-

489 90.

490
45. Writing Committee for the Comebac Study Group, Morin L, Savale L, et al. Four-Month
491
Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. *JAMA* 2021; **325**(15): 1525492
34.

46. Frizzelli A, Di Spigno F, Moderato L, et al. An Impairment in Resting and Exertional Breathing
Pattern May Occur in Long-COVID Patients with Normal Spirometry and Unexplained Dyspnoea. J

495 *Clin Med* 2022; **11**(24).

496 47. Fresard I, Genecand L, Altarelli M, et al. Dysfunctional breathing diagnosed by

497 cardiopulmonary exercise testing in 'long COVID' patients with persistent dyspnoea. *BMJ Open*498 *Respir Res* 2022; **9**(1).

499 48. Samaranayake CB, Warren C, Rhamie S, et al. Chaotic breathing in post COVID-19

500 breathlessness: a key feature of dysfunctional breathing can be characterized objectively by

approximate entropy. *ERJ Open Research* 2023: 00117-2023.

503 postural orthostatic tachycardia syndrome (POTS): The impact of a physiotherapy intervention. 504 Auton Neurosci 2020; 223: 102601. Soril LJJ, Damant RW, Lam GY, et al. The effectiveness of pulmonary rehabilitation for Post-505 50. 506 COVID symptoms: A rapid review of the literature. Respir Med 2022; 195: 106782. 507 51. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a 508 randomised controlled trial. Lancet Respir Med 2018; 6(1): 19-28. 509 52. Thomas M, McKinley RK, Mellor S, et al. Breathing exercises for asthma: a randomised 510 controlled trial. Thorax 2009; 64(1): 55-61. McNarry MA, Berg RMG, Shelley J, et al. Inspiratory muscle training enhances recovery post-511 53. 512 COVID-19: a randomised controlled trial. Eur Respir J 2022; 60(4). 513 Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 54. 514 months of symptoms and their impact. EClinicalMedicine 2021; 38: 101019. 515 55. Marjenberg Z, Leng S, Tascini C, et al. Risk of long COVID main symptoms after SARS-CoV-2 516 infection: a systematic review and meta-analysis. Sci Rep 2023; 13(1): 15332. 517 56. Nguyen NN, Hoang VT, Dao TL, Dudouet P, Eldin C, Gautret P. Clinical patterns of somatic 518 symptoms in patients suffering from post-acute long COVID: a systematic review. Eur J Clin Microbiol 519 Infect Dis 2022; 41(4): 515-45. 520 O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long 57. 521 Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. 522 EClinicalMedicine 2023; 55: 101762. 523 Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, 58. 524 and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of 525 COVID-19. PLoS Med 2021; 18(9): e1003773. 526 59. Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in Post-COVID-19 527 Syndrome: A systematic review and meta-analysis. Brain Behav Immun 2022; 101: 93-135. 528 60. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) 529 Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes 2003; 530 **1**: 79. 531 61. National Institute for Health and Care Excellence (NICE). Tiredness/fatigue in adults. 2021. 532 https://cks.nice.org.uk/topics/tiredness-fatigue-in-adults/diagnosis/diagnosis-of-cfs/ (accessed 533 13/12/2023. 534 62. Morel J, Infantino P, Gergele L, Lapole T, Souron R, Millet GY. Prevalence of self-reported 535 fatigue in intensive care unit survivors 6 months-5 years after discharge. Sci Rep 2022; 12(1): 5631. 536 63. Goërtz YMJ, Spruit MA, Van 't Hul AJ, et al. Fatigue is highly prevalent in patients with COPD 537 and correlates poorly with the degree of airflow limitation. Therapeutic Advances in Respiratory 538 Disease 2019; 13: 1753466619878128. 539 Van Herck M, Goertz YMJ, Houben-Wilke S, et al. Severe Fatigue in Long COVID: Web-Based 64. 540 Quantitative Follow-up Study in Members of Online Long COVID Support Groups. J Med Internet Res 541 2021; 23(9): e30274. 542 65. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and 543 recommendations. Nat Rev Microbiol 2023; 21(3): 133-46. 544 Gottschalk CG, Peterson D, Armstrong J, Knox K, Roy A. Potential molecular mechanisms of 66. 545 chronic fatigue in long haul COVID and other viral diseases. Infect Agent Cancer 2023; 18(1): 7. 546 67. Peluso MJ, Deveau TM, Munter SE, et al. Chronic viral coinfections differentially affect the 547 likelihood of developing long COVID. J Clin Invest 2023; 133(3). 548 Noz MP, Hartman YAW, Hopman MTE, et al. Sixteen-Week Physical Activity Intervention in 68. 549 Subjects With Increased Cardiometabolic Risk Shifts Innate Immune Function Towards a Less 550 Proinflammatory State. J Am Heart Assoc 2019; 8(21): e013764. 551 69. Viana JL, Kosmadakis GC, Watson EL, et al. Evidence for anti-inflammatory effects of exercise 552 in CKD. J Am Soc Nephrol 2014; 25(9): 2121-30.

Reilly CC, Floyd SV, Lee K, et al. Breathlessness and dysfunctional breathing in patients with

502

49.

553 70. Elhakeem A, Cooper R, Whincup P, Brage S, Kuh D, Hardy R. Physical Activity, Sedentary 554 Time, and Cardiovascular Disease Biomarkers at Age 60 to 64 Years. J Am Heart Assoc 2018; 7(16): 555 e007459. 556 Shuwa HA, Shaw TN, Knight SB, et al. Alterations in T and B cell function persist in 71. 557 convalescent COVID-19 patients. *Med* 2021; 2(6): 720-35 e4. 558 72. Donovan T, Bain AL, Tu W, Pyne DB, Rao S. Influence of Exercise on Exhausted and Senescent 559 T Cells: A Systematic Review. Front Physiol 2021; 12: 668327. 560 Al Chikhanie Y, Veale D, Schoeffler M, Pepin JL, Verges S, Herengt F. Effectiveness of 73. 561 pulmonary rehabilitation in COVID-19 respiratory failure patients post-ICU. Respir Physiol Neurobiol 562 2021; **287**: 103639. 563 74. Bouteleux B, Henrot P, Ernst R, et al. Respiratory rehabilitation for Covid-19 related 564 persistent dyspnoea: A one-year experience. Respir Med 2021; 189: 106648. 565 75. Gloeckl R, Leitl D, Jarosch I, et al. Benefits of pulmonary rehabilitation in COVID-19: a 566 prospective observational cohort study. ERJ Open Res 2021; 7(2). 567 76. Dalbosco-Salas M, Torres-Castro R, Rojas Leyton A, et al. Effectiveness of a Primary Care 568 Telerehabilitation Program for Post-COVID-19 Patients: A Feasibility Study. J Clin Med 2021; 10(19). 569 77. Jimeno-Almazan A, Franco-Lopez F, Buendia-Romero A, et al. Rehabilitation for post-COVID-570 19 condition through a supervised exercise intervention: A randomized controlled trial. Scand J Med 571 *Sci Sports* 2022; **32**(12): 1791-801. 572 Van Herck M, Antons J, Vercoulen JH, et al. Pulmonary Rehabilitation Reduces Subjective 78. 573 Fatigue in COPD: A Responder Analysis. J Clin Med 2019; 8(8). 574 Wingårdh ASL, Göransson C, Larsson S, Slinde F, Vanfleteren LE. Effectiveness of energy 79. 575 conservation techniques in patients with COPD. Respiration 2020; 99(5): 409-16. 576 Ghali A, Richa P, Lacout C, et al. Epidemiological and clinical factors associated with post-80. 577 exertional malaise severity in patients with myalgic encephalomyelitis/chronic fatigue syndrome. J 578 Transl Med 2020; 18(1): 246. 579 Parker M, Sawant HB, Flannery T, et al. Effect of using a structured pacing protocol on post-81. 580 exertional symptom exacerbation and health status in a longitudinal cohort with the post-COVID-19 581 syndrome. Journal of Medical Virology 2023; 95(1): e28373. 582 82. Jones SE, Maddocks M, Kon SS, et al. Sarcopenia in COPD: prevalence, clinical correlates and 583 response to pulmonary rehabilitation. *Thorax* 2015; **70**(3): 213-8. 584 Maddocks M, Kon SS, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in 83. 585 COPD: a prospective cohort study. Thorax 2016; 71(11): 988-95. 586 84. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD 587 more active after pulmonary rehabilitation? *Chest* 2008; **134**(2): 273-80. 588 Montes-Ibarra M, Oliveira CLP, Orsso CE, Landi F, Marzetti E, Prado CM. The Impact of Long 85. 589 COVID-19 on Muscle Health. Clin Geriatr Med 2022; 38(3): 545-57. 590 Ramirez-Velez R, Legarra-Gorgonon G, Oscoz-Ochandorena S, et al. Reduced muscle strength 86. 591 in patients with long-COVID-19 syndrome is mediated by limb muscle mass. J Appl Physiol (1985) 592 2023; 134(1): 50-8. 593 87. Martone AM, Tosato M, Ciciarello F, et al. Sarcopenia as potential biological substrate of 594 long COVID-19 syndrome: prevalence, clinical features, and risk factors. Journal of Cachexia, 595 Sarcopenia and Muscle 2022; 13(4): 1974-82. 596 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in 88. 597 mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; **373**(9678): 598 1874-82. 599 89. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia 600 in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and 601 IWGS). Age Ageing 2014; 43(6): 748-59. 602 90. Office for National Statistics. Self-reported long COVID and labour market outcomes, UK: 603 2022.

- 604 <u>https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseas</u>
 605 <u>es/bulletins/selfreportedlongcovidandlabourmarketoutcomesuk2022/selfreportedlongcovidandlabo</u>
- 606 urmarketoutcomesuk2022 (accessed 07/12/2023).
- 607 91. Serrano MN, Munoz OM, Rueda C, Arboleda AC, Botero JD, Bustos MM. Factors associated 608 with oxygen requirement and persistent symptoms 1 year after severe COVID-19 infection. *J Int Med*
- 609 *Res* 2023; **51**(5): 3000605231173317.
- 610 92. Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR. Effect of Pulmonary
- 611 Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-612 Analysis. *Chest* 2019; **156**(1): 80-91.
- 613 93. Man W, Chaplin E, Daynes E, et al. British Thoracic Society Clinical Statement on pulmonary 614 rehabilitation. *Thorax* 2023; **78**(Suppl 4): s2-s15.
- 615 94. Salman D, Vishnubala D, Le Feuvre P, et al. Returning to physical activity after covid-19. *BMJ* 616 2021; **372**: m4721.
- 617 95. Klok FA, Boon G, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure 618 functional status over time after COVID-19. *Eur Respir J* 2020; **56**(1).
- 619 96. National Institute for Health and Care Excellence (NICE). Rehabilitation after critical illness in
- 620 adults, Clinical guideline [CG83]. 2009. <u>https://www.nice.org.uk/guidance/CG83/chapter/1-</u>
- 621 <u>Guidance#23-months-after-discharge-from-critical-care</u> (accessed 07/12/2023).
- 622

623

624