Balancing the value and risk of exercise-based therapy post-COVID-19: a narrative review

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Those with ongoing COVID-19 symptoms could benefit from a symptom-titrated exercise training programme, provided considerations are given to complex cardiorespiratory pathologies, skeletal muscle dysfunction and fatigue. https://bit.ly/3Qk8MrI

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Abstract
Coronavirus disease 2019 (COVID-19) can lead to ongoing symptoms such as breathlessness, fatigue and muscle pain, which can have a substantial impact on an individual. Exercise-based rehabilitation programmes have proven beneficial in many long-term conditions that share similar symptoms. These programmes have favourably influenced breathlessness, fatigue and pain, while also increasing functional capacity. Exercise-based rehabilitation may benefit those with ongoing symptoms following COVID-19. However, some precautions may be necessary prior to embarking on an exercise programme. Areas of concern include ongoing complex lung pathologies, such as fibrosis, cardiovascular abnormalities and fatigue, and concerns regarding post-exertional symptom exacerbation. This article addresses these concerns and proposes that an individually prescribed, symptom-titrated exercise-based intervention may be of value to individuals following infection with severe acute respiratory syndrome coronavirus 2.

Background
Coronavirus disease 2019 (COVID-19) caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global health emergency and was identified as a global pandemic by the World Health Organization in February 2020. COVID-19 can lead to a number of persisting and disabling symptoms. Significant symptoms include breathlessness, fatigue and muscle pain, reducing an individual's ability to engage in activities of daily living for months and often beyond a year [1, 2]. This post-COVID-19 condition is most frequently referred to as "long COVID" and can present as a complex cluster of symptoms that can fluctuate in number and severity over time [3]. Long COVID is a heterogeneous condition that can have a significant impact on an individual and which potentially extends to their family. It can disrupt overall wellbeing, with consequences for returning to work, as well as social and family life [4].

It is estimated there are upwards of 1.3 million people living with long COVID in the UK alone [2]. Interventions, including rehabilitation programmes, are necessary to support people in regaining their physical health [2, 4]. Importantly, the burden of the persistent symptoms associated with COVID-19 does not appear to be limited to those with severe acute disease [5]. Early in the pandemic, a European Respiratory Society and American Thoracic Society taskforce identified the need for a comprehensive rehabilitation programme for COVID-19 patients post-hospitalisation. This programme would include a formal assessment, aimed at understanding physical and emotional functioning, in order to determine rehabilitation requirements [6].

In previous similar viral pandemics, the value of exercise-based rehabilitation has been reported in small-scale observational cohorts [7]. COVID-19 survivors present with a large number and variety of symptoms; therefore, multi-dimensional rehabilitation programmes should be developed that have an exercise component to accommodate and address the complexity of long COVID [6]. Early data from the COVID-19 pandemic suggests that rehabilitation with an exercise component may be beneficial for people post-hospitalisation with persisting symptoms [8–13]. The timing of any intervention has yet to be defined and optimised. Given that the World Health Organization definition identifies a 3-month threshold for the diagnosis of long COVID, it would seem reasonable to offer interventions after this time point, allowing for natural recovery, the completion of other diagnostic tests to exclude other causes for the symptoms experienced and to ensure that exercise is safe [14].

There have been safety concerns regarding exercise and rehabilitation following COVID-19, in particular around worsening or exacerbating symptoms such as fatigue, post-exertional malaise [15], exercise desaturation [16] and cardiac abnormalities [17]. However, these concerns need to be balanced against the potential benefits of exercise, as a low exercise capacity has been associated with the most severe health impairments post-hospitalisation for COVID-19 [4, 18].

The importance of rehabilitation was identified in the Post-hospitalisation COVID-19 (PHOSP-COVID) study (https://phosp.org/), where a collaborative effort between clinicians and patients was made to establish research priorities. These priorities were aimed at identifying key research questions related to the long-term sequelae of COVID-19 [19]. This process identified two key questions relevant to this review:

1) What are the problems within the muscles associated with symptoms limiting activity/function/exercise? If so, what can be done to help?
2) What medications, dietary changes, supplements, rehabilitation and therapies aid recovery?

This review aims to evaluate the current literature on COVID-19 in relation to long-term consequences (where relevant/present) in order to:

- Provide an expert opinion on COVID-19 in relation to long-term consequences with respect to the safety of exercise.
- Understand the potential effects of exercise in the long-COVID population.
- Propose red flags regarding contraindications for exercise-based therapy.
- Provide clinicians with a rationale to provide individualised comprehensive rehabilitation programmes for long COVID.

There is overwhelming evidence supporting the benefit of symptom-titrated exercise for a large number of long-term conditions (LTCs). A systematic review has highlighted the benefit of exercise-based interventions for LTCs across five categories: cardiorespiratory, metabolic, neurological, mental health and musculoskeletal problems [20]. The broad range of symptoms described in long COVID overlap with many of those reported in many of the LTCs included in this review.

Fatigue, breathlessness and pain (including chest pain) are commonly reported symptoms associated with long COVID [2]. Therefore, this review will consider the current literature pertaining to the impact of COVID-19 on the cardiorespiratory system and peripheral skeletal muscle, examining the potential benefit and concerns associated with exercise-based rehabilitation. A specific review of data on mental health and cognition post-COVID is out of scope for this article, but we acknowledge the close interplay between physical and mental health [4].

Search terms

References for this review were identified through searches of PubMed for articles published from January 2020 to October 2022, by use of the terms "COVID-19", "COVID", "exacerbation", "SARS-CoV-2", "long COVID", "breathlessness", "cardiovascular disease", "heart disease", "respiratory disease", "breathlessness", "shortness of breath", "muscle-skeletal", "exercise", "rehabilitation", "physical therapy", "frailty", "dysfunctional breathing" and "disordered breathing". Relevant articles published between 2018 and 2020 were identified through searches of the authors' personal files, in Google Scholar and the Springer Online Archives Collection. The search dates reflect the inception of the first known case of COVID-19 (officially documented in humans in December 2019) and ensures the inclusion of all relevant articles. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English, French and German were included. Searches of Google Scholar were performed for any other references that were not identified through other searches. Reference lists for included studies were also searched.

Long COVID and the respiratory system

Breathlessness and to a lesser degree cough are among the most commonly reported symptoms in individuals with long COVID, although cough is becoming less of a concern through later mutations [4, 21, 22]. They are more prevalent in patients who were treated for moderate and severe forms of acute COVID-19 illness, *i.e.* those who were hospitalised, treated with supplementary oxygen or required ventilatory support [4]. Although acute COVID-19 affects multiple organs, the acute lung injury and parenchymal inflammation raise major concerns about the long-term pulmonary sequelae of COVID-19, namely permanent pulmonary damage manifested as lung fibrosis [23]. Currently, concrete data about the prevalence and severity of lung fibrosis post-COVID-19 is not available. A follow-up cohort study from China showed that nearly half of those who underwent high-resolution computed tomography (CT) scanning (n=353) have at least one abnormal CT scan finding at 5 months post-discharge [24]. This is largely replicated in other follow-up studies. The most commonly identified abnormality on CT scans is ground glass opacity [25].

Pulmonary function tests post-hospital discharge demonstrated abnormalities in more than 40% of COVID-19 survivors at 3 months [26]. The most common abnormality was impaired diffusion capacity, which was seen predominantly in those who required ventilatory support [1, 4]. A smaller proportion was found to have a restrictive pattern on their follow-up pulmonary function tests [1, 4], which mimics the results from acute respiratory distress syndrome caused by other acute illnesses [21].

Based on the available studies of COVID-19 survivors and building on evidence from previous viral respiratory pandemics, there is likely to be a large number of COVID-19 survivors with a significant burden of respiratory symptoms with or without persistent radiological and physiological evidence of pulmonary fibrosis and to some extent small airway disease [4, 5, 8]. Considering the global number of the likely affected population, this burden will put further significant strain on already overwhelmed healthcare systems. The impact of the wide use of approved therapies during acute COVID-19 illness, namely corticosteroids and anti-interleukin therapies, on the development of long-lasting pulmonary damage is unknown.

Rehabilitation and the respiratory system

The role of pulmonary rehabilitation (PR) in improving the quality of life and survival of patients with underlying interstitial lung diseases has emerged over the last decade as a topic of great interest to clinicians and patients [27]. A recent Cochrane review found that PR in patients with pulmonary fibrosis improved exercise capacity (measured using the 6-min walk test), reduced dyspnoea and improved health-related quality of life (HRQoL) (assessed using the Chronic Respiratory Disease Questionnaire and the St George's Respiratory Questionnaire) [28]. These effects were mainly observed 6–12 months after completion of the programme. Overall, the review of 21 studies concluded that the effect of PR on the long-term survival of patients with pulmonary fibrosis was uncertain but had a good safety profile with no reported adverse events. The few reported deaths during the studies were all considered to be unrelated to the intervention. The National Institute for Health and Care Excellence guidelines for idiopathic pulmonary fibrosis (IPF) in adults concluded that PR was highly likely to be cost-effective as a tool to improve the quality of life of patients with IPF [29]. These recommendations could potentially be extrapolated to COVID-19 survivors with features of pulmonary fibrosis. The outstanding conundrum in the management of this group of patients revolves around exercise-induced desaturation and the need for supplemental oxygen. The effectiveness of incorporating supplemental oxygen into exercise training is inconclusive regarding routine clinical care prior to the pandemic. However, it is notable that exercise-induced hypoxaemia is not a contraindication to exercise. The termination of exercise is only recommended when associated with complications such as myocardial ischaemia or arrhythmia [30].

Long COVID and the cardiovascular system

The bidirectional relationship between cardiac diseases and COVID-19 severity was recognised in the early months of the pandemic. Patients with cardiovascular co-morbidities were at greatest risk of severe infections, while cardiac injury was more common in those with severe infections and linked to a worse prognosis [31].

During the acute phase of infection, myocardial damage may be mediated by either direct or indirect mechanisms. SARS-CoV-2-mediated cytotoxicity [32, 33], cytokine release storm [21], a dysregulated renin–angiotensin–aldosterone system [21], endothelial dysfunction [34], ischaemic or hypoxic injury [35] and catecholamine-induced injury have been proposed to contribute to cardiac injury. In the post-acute phase, autoimmunity [36], cytokine-mediated vascular and myocardial injury, platelet hyperactivation [37], and chronic thromboembolism may contribute to chronic sequelae. A recent study of electronic health record data from the veterans' healthcare database in the United States confirms an increased risk of cardiovascular disease (CVD), including ischaemic heart disease, arrhythmias, heart failure and myocarditis, by at least two- to threefold up to a year after COVID-19 [38]. In addition to the rising diagnoses of CVD, cardiopulmonary symptoms (chest pain, dyspnoea, palpitations) [1, 4] are also commonly experienced by convalescing patients.

The relative frequency of cardiac complications varies based on published reports and reflects the variable population characteristics. These include symptom and hospitalisation status, timing of assessment, and the methodologies used for the diagnosis of myocardial injury [17]. In general, hospitalised patients have a higher reported burden of chronic cardiovascular sequelae, whereas those with mild infection infrequently present with new-onset cardiac dysfunction [39]. Follow-up echocardiography studies of post-hospitalised patients [40–42] have reported that up to 14% of patients have evidence of either left or right ventricular systolic dysfunction at a median interval of 3 months from infection. Diastolic dysfunction may be more common in patients [42], although the extent to which this is due to co-morbid conditions is unclear in the absence of comparative pre-infection imaging. The prevalence of myocardial inflammation on cardiac magnetic resonance scans has varied based on the patient characteristics, ranging from 0% to 60% of patients being affected [43–45]. Among patients with biomarker evidence of myocardial injury, myocarditis and ischaemia/infarction were observed in nearly half the patients at a median of 68 days from infection, affecting 26% and 23% of patients, respectively [46]. A further 6% demonstrated evidence of both myocarditis and infarction.

Rehabilitation and the cardiovascular system

Current guidelines endorse exercise-based cardiac rehabilitation as a class 1A recommendation for patients with selected cardiovascular disorders, including heart failure and coronary artery disease [47–51]. Several studies have noted that a combination of multidisciplinary education and exercise training tailored to individuals is associated with significantly fewer hospitalisations and improved cardiovascular and all-cause mortality. Recently the American College of Cardiology extrapolated these findings to the post-COVID population, with some exceptions, notably patients with suspected myopericarditis and significant post-exertional malaise [52]. From a pathophysiological perspective, the beneficial effects of exercise training (moderate-to-severe exercise, interval training and high-intensity exercise) on endothelial function (*via* an increased nitric oxide bioavailability) are well described [53–55], with benefits on thromboembolic risks anticipated. This is particularly relevant for young patients who were previously assumed to be at low cardiovascular risk, but current evidence highlights the presence of endothelial dysfunction following COVID-19 [56]. Similarly, an increased expression of antioxidants and anti-inflammatory cytokines associated with exercise-based interventions is expected to favourably modify patient-perceived recovery, given the potential for inflammation to mediate ongoing physical and mental health impairments [4]. The only situation where exercise-based rehabilitation may not be suitable is in patients with suspected active myocarditis. It is worth noting that the incidence of probable or definite myocarditis post-acute COVID-19 as per the European Society of Cardiology task force criteria [57] is modest, affecting up to 13% of hospitalised patients in one study [58]. Nevertheless, an expert consensus statement in the *Journal of the American College of Cardiology* [52] recommend a minimum duration of 3–6 months of rest following a diagnosis of myocarditis, with a gradual return to exercise thereafter – a recommendation also echoed by UK and European experts [17, 59].

Autonomic manifestations such as postural orthostatic tachycardia syndrome (POTS) and orthostatic intolerance are frequent, affecting up to 30% of patients [60–64]. POTS is defined by a sustained increase in heart rate by >30 beats·min^{-1} or above 120 beats·min^{-1} within 10 min of active standing or head tilt. The nonpharmacological treatment of POTS centres around the correction of reversible causes such as dehydration (*e.g.* liberal salt and water intake), hypovolaemia (*e.g.* correction of anaemia and fever), venous pooling (*e.g.* using compression stockings [65]) and physical reconditioning with an exercise programme (*e.g.* recumbent exercise such as cycling and rowing is typically preferred with a graduate transition to upright exercise) [66–70]. Pharmacological measures may also be necessary in specific circumstances and typically include therapies such as ivabradine, β blockers, midodrine and fludrocortisone.

Long COVID and the skeletal muscles

Acute admission to hospital, including to a nonintensive care setting, is known to have a rapid and deleterious effect on muscle mass, with over 8% loss in quadriceps muscle seen during a median 5-day admission (the equivalent to several months of resistance training) among patients with chronic respiratory disease [71]. This is akin to the experience of critical care survivors, who showed an acute loss of 18% of pre-admission body weight, recovering to a 6% loss by 6 months. This likely represents persistent muscle wasting [72], including that of respiratory muscles [73]. Persistent and new functional limitations have been noted in hospitalised patients, with older age a risk of failure to recover [74]. It is notable that, in the UK at least, a minority of individuals who suffered symptoms of COVID-19 required hospital admission. However, a proportion of those managed in the community would have similarly been confined to bed for at least the period of their acute illness, with the potential for a similar loss in muscle mass to those individuals who were admitted to hospital. A confounding factor in the UK and many other countries may also be the imposition of home quarantine of 10–14 days or longer following developing symptoms later confirmed to be COVID-19 with a positive test combined with significant periods of "lockdown" generally reducing physical activity, muscle size and function, cardiovascular fitness, and inhibiting self-directed recovery for some individuals [75].

Although changes in skeletal muscle following COVID-19 are yet to be fully investigated, there is evidence of immune-mediated myopathy in COVID-19 autopsy samples [76], suggesting a possible mechanism for post-infectious muscle pain and weakness in at least some patients warranting further investigation. Whether this represents myositis is unclear [77, 78]. Given the factors discussed above, it is likely that the majority of skeletal muscle changes following COVID-19 will result from a combination of deconditioning and disuse, as seen in patients admitted to hospital or an intensive care unit (ICU) with other medical conditions. Consequently, it is likely that recovery will follow a similar pattern and respond to similar interventions. In addition, other mechanisms of skeletal muscle dysfunction beyond disuse have been noted in the intensive care setting and may be relevant in the acute and post-acute hospitalised COVID-19 population, particularly as patients in intensive care had a longer than average length of stay. Notably, increases in intramuscular inflammation and hypoxia in muscle have been noted [79]. In the longer term, reduced satellite cell content and muscle regeneration capacity have been noted in the post-ICU population [80], which could potentially impair muscle recovery in the short and medium term. In addition, injury to the peripheral nervous system, resulting in polyneuropathy and neuromuscular junction degradation, may compound and contribute to reduced skeletal muscle function [81].

Skeletal muscle and fatigue

Regarding the specific concerns raised about the safety and tolerability of training and rehabilitation in long COVID, it is important to note that scientific reports of adverse events are limited and under-investigated. Delayed-onset muscle soreness (DOMS) and muscle fatigue are physiological responses to effective muscle training. In the short term, these cause acute muscle inflammation as part of the overload principle [82], but in the long term result in adaptation and training effects. DOMS and muscle fatigue are uncomfortable and may discourage further exercise or training without education, particularly if these effects have not been explained. Interventions to target improved mitochondrial density and increased muscle buffer capacity are likely to be beneficial [83]. The skeletal muscle remains plastic and adaptable across all age ranges, with previous interventional studies showing that clinically and functionally important strength improvements can be obtained using resistance training across all age groups [84]. Similarly, it is likely that physical activity, exercise and strength training, increased gradually from an appropriate starting point, will be both tolerable and effective for patients suffering symptoms of weakness following COVID-19.

The most likely mechanism and explanation for muscle fatigue with or without hospitalisation is deconditioning related to a period of significantly reduced physical activity, although a post-viral myopathy may be present in a subset of individuals [85]. Muscle fatigue during and post-exercise, including DOMS and post-exertional malaise, which are distinct entities, and the impact of post-exertional symptom exacerbation (PESE) and exercise is discussed below. Fatigue is one of the most common symptoms following COVID-19, even after adjusting for observed confounders [86]. Among hospitalised survivors of COVID-19, prevalence rates vary, with a recent review suggesting that fatigue persisted in 13–33% of individuals within the cohorts at 16–20 weeks [87]. Fatigue is a normal physiological response during the acute phase of an infection when the immune system releases cytokines to promote inflammation. These cytokines are also associated with physical and mental fatigue. It is thought that this stage functions as an evolutionary adaption, with the body signalling the individual to rest and thereby promoting a behavioural response to enhance the role of fever in combating infection [88].

Persistent fatigue in those who have been hospitalised has been associated with time spent in an ICU [89] and hospital length of stay, although this relationship is not consistent across studies [90]. In addition, reduced exercise capacity as a result of critical illness hospitalisation is thought to contribute to reduced

HRQoL and fatigue outcomes in recovered patients [91]. In a review examining predictors of fatigue, there was an inconsistent relationship between exercise capacity and fatigue outcomes in those who had more severe disease, with some studies finding a decrease in HRQoL despite improved exercise capacity [92]. A variety of common mental health outcomes, including post-traumatic stress disorder, anxiety and depression, were associated with fatigue 1 year post hospitalisation, although the pre-morbid burden of these was unknown.

Deconstructing fatigue and associations with physiological, behavioural, affective and perceptual processes are key to informing the development of targeted interventions. While pharmacological treatments aimed at reducing inflammation have been proposed to alleviate fatigue, evidence of their effectiveness is lacking. Treatments likely to hold the most promise are rehabilitative in nature and have an established moderate evidence base for effectiveness [93].

Rehabilitation, skeletal muscle and fatigue

Exercise-based interventions resulting in improvement of fatigue have been reported in other LTCs [94, 95]. In chronic lung disease, for example, the burden of fatigue is commonly reported as a component of HRQoL scores, but has recently been examined in some detail, including its response to exercise [96]. The symptom of fatigue may be compounded by the presence of PESE commonly reported in myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) and treatment in these conditions remains controversial.

Graded-exercise therapy (GET) has been examined as a potential modality for managing the symptoms of fatigue in the absence of other LTCs [97], although this intervention has been met with the concern that it may cause harm and not be suitable for individuals with PESE/fatigue. Unlike symptom-titrated exercise, GET implements exercise training involving large increments of progression. A recent meta-analysis of the safety of GET for CFS, including two randomised controlled trials, found that it did not cause harm and was as effective for those with post-exertional malaise [98]. An individualised, negotiated approach with symptom-titrated exercise is key to its success and should be guided by a healthcare professional trained in such approaches. This symptom-titrated approach, with established practice in both PR and cardiac rehabilitation, proposes to calibrate the "dose" of exercise against baseline exercise performance and the symptom burden. It is recommended that pre-programme levels of fatigue be evaluated using standardised questionnaires [99, 100].

PESE has been associated with long COVID; however, to date, there are no studies quantifying its prevalence or burden in this population. As a precaution, a screening questionnaire has been proposed to evaluate symptoms of CFS and ME prior to any exercise-based therapy. However, its use has not yet been widely reported in long COVID populations [15, 101].

There is evidence from other LTCs to suggest that exercise-based therapy may be beneficial for long COVID sufferers with fatigue, though direct evidence is lacking [96, 102, 103]. Vigilance for safety and harm is paramount, with the American College of Sports Medicine describing a comprehensive list of contraindications, most of which are unlikely to be relevant in sufferers of long COVID [30]. It is crucial that exercise programmes are individualised and titrated to the symptoms of the individual presenting with long COVID, particularly as long COVID is heterogeneous in nature. Notably, individuals with profound fatigue and PESE associated with minimal exertion are unlikely to be referred for exercise-based rehabilitation programmes but instead may be referred to services specialising in managing individuals with disabling fatigue.

Cardiopulmonary exercise testing (CPET)

CPET is widely acknowledged as a valuable tool for the assessment and prognostic stratification in health and cardiopulmonary diseases. In patients recovering from COVID-19, studies have identified the contribution of deconditioning and/or muscular impairment to exercise intolerance on CPET [104]. Longitudinal studies have further demonstrated that exercise limitation (due to skeletal muscle impairment) may persist in some patients, despite an interval improvement of cardiopulmonary abnormalities [105–108]. CPET has demonstrated benefits in distinguishing causes of breathlessness and, in particular, highlighted the presence and increased prevalence of breathing pattern disorder within COVID-19. A systematic review of the use of CPET post-COVID-19 has reported a lower peak oxygen uptake in those with breathlessness compared to those who report a full recovery. Deconditioning was the primary cause of breathlessness, although breathing pattern disorder was also commonly reported [109].

Delivering an exercise-based rehabilitation programme – service considerations

There is a juxtaposition between the pressing clinical need to establish therapeutic interventions and at the same time gaining evidence for optimal regimes. Among individuals with persisting symptoms, evaluations of both the safety and the effectiveness of interventions must be made. Many individuals with persisting symptoms were well prior to COVID-19 infection or undiagnosed; however, they may have been physically inactive and now suffering the effects of multi-organ damage (figure 1). The heterogeneous nature of long COVID therefore requires a thorough assessment and adaptive approach to treatment, highlighting the need for an individualised approach.

As individuals with persistent symptoms are likely to have different pre-COVID-19 levels of physical capacity and varying severity of disease presentation, expectation management and discussing the role and likely extent of deconditioning in causing their symptoms is key. When negotiating a rehabilitation programme (table 1), assessments of an individual's pre-morbid function and performance, their illness severity, and their current level of fitness and activity are imperative. This may be particularly relevant for individuals who previously engaged in high-level sport where their ambition to return to baseline may have unrealistic timescales. Activities and exercise should be built up slowly with realistic goals negotiated.

Obtaining information regarding pre-COVID-19 comorbidities and any new diagnoses or complications resulting from their acute illness is vital. This should include those that may have manifested at the time of acute infection (*e.g.* myocarditis or pulmonary emboli) or since (*e.g.* pulmonary fibrosis or diabetes mellitus). Further to this, an accurate current medication record will help guide the safety of activities and assist in ensuring correct adherence to medications that are taken on an as-needed basis. This is relevant for recently initiated bronchodilators, which often benefit from education on technique and may be useful for alleviating symptoms during activities. An awareness of resting oxygen state and possible oxygen desaturation are key safety aspects that should be assessed.

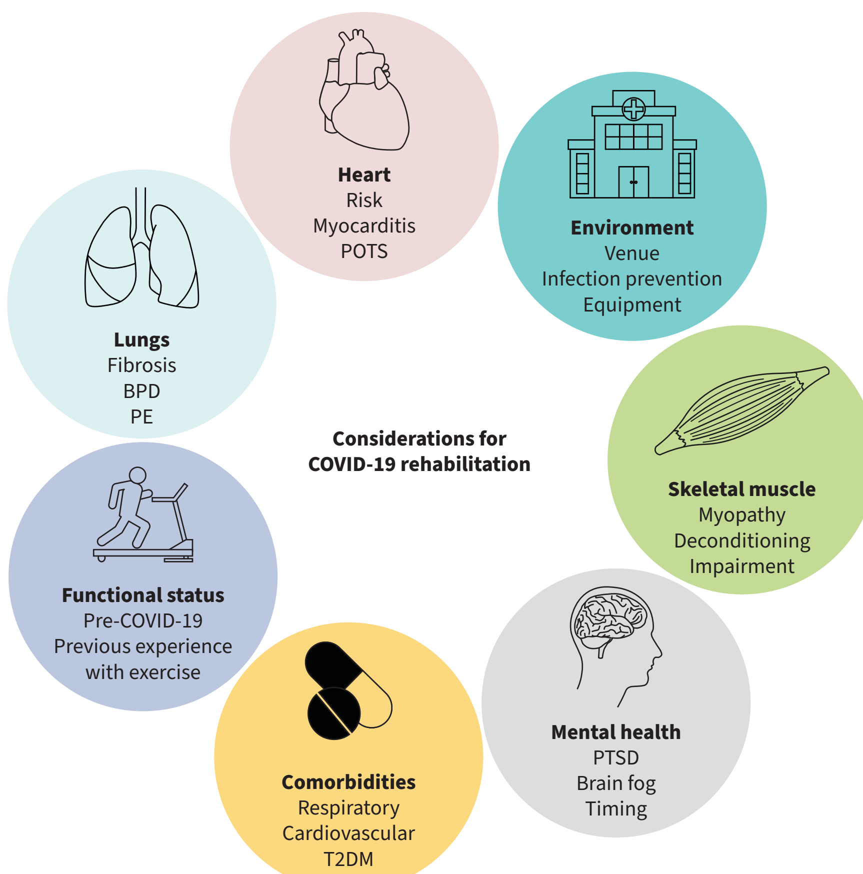

FIGURE 1 Considerations for long COVID exercise-based rehabilitation. BPD: bronchopulmonary dysplasia; COVID-19: coronavirus disease 2019; PE: pulmonary embolism; POTS: postural orthostatic tachycardia syndrome; PTSD: post-traumatic stress disorder; T2DM: Type 2 diabetes mellitus.

TABLE 1 Considerations for rehabilitation

Stage	Aspects needing consideration for rehabilitation programme
Set-up	Ensure a robust infection prevention and control protocol to minimise the risk of reinfection for all individuals. Infection prevention measures should be monitored and modified frequently in line with organisational policy. Access to a multidisciplinary team with expertise in the symptom areas of long COVID. This may include experts from pulmonary rehabilitation, cardiac rehabilitation, chronic fatigue programmes and mental health professionals.
Pre-assessment	Ensure that the core symptoms pertaining to the referral do not need further diagnostic investigation. Consider investigations for severe breathlessness and fatigue. Verify that the other symptoms do not warrant further investigation, for example, palpitations, dizziness. Address known pre-COVID-19 comorbid conditions that might have an impact on an exercise rehabilitation programme and could be affected by COVID-19; for example, diabetes, musculoskeletal concerns, respiratory and cardiac comorbidities. Address more recent established diagnoses made at or since acute COVID-19 infection such as postural tachycardia syndrome.
Assessment	Detailed history regarding the former functional status of the patient to indicate realistic goals and expectations from rehabilitation. Assessment of work commitments, social circumstances, degree of mobility and feasibility of attending a face-to-face appointment. Consideration of psychological wellbeing, particularly following admission to intensive care, and its impact on the timing of exercise intervention. Comprehensive assessment of functional status and symptoms, which include measures of exercise capacity (*i.e.* field walking test), common symptoms (breathless and fatigue), mental health, employment status, *etc.*
Rehabilitation intervention	Ensure trained staff, competent in exercise prescription and delivery, are in place to guarantee individualised symptom titration and rehabilitation. Offer a self-management support programme that includes disease management, symptom management (breathlessness and fatigue), return to work, mental health support and support for family/carers.
Discharge	Comprehensive discharge assessment to repeat previous measures and refer to other services for ongoing support (including multidisciplinary team).

COVID-19: coronavirus disease 2019.

For many, persisting breathlessness or fatigue will be the prompt for referral. While both symptoms can be attributable to multiple causes, they are also terms often used to "clump" multiple discrete symptoms together. For example, fatigue may refer to overwhelming tiredness from a disturbed sleep pattern, muscle limb fatigue, cognitive fatigue, post-exertional malaise or a systemic fatigue stemming from a primary cardiac or respiratory cause [86]. Meanwhile, underlying hyperglycaemia or side-effects of new medications given to assist mood, sleep or other medical diagnoses may also contribute [87]. Breathlessness may result from deconditioning, dysregulated breathing (or breathing pattern disorder), bronchial hyper-reactivity, pulmonary fibrosis or a cardiac disease. A brief review of more recent symptoms, even if not the primary cause for referral, is worthwhile, especially those most common following COVID-19 including palpitations/tachycardia, chest pain, light-headedness and breathlessness [86]. Whilst these in themselves are unlikely to prohibit an exercise programme, they may guide adaptations and/or trigger further investigations.

Given the evidence of mental health deterioration and its association with ongoing symptoms following COVID-19 [4], a suitable assessment is paramount. Many patients have experienced traumatic events associated with their acute COVID-19 illness. Similarly, in many patients with protracted symptoms, their mental health may have deteriorated. Addressing mental health alongside exercise programmes may help manage symptoms [109]. The evidence for exercise to improve mood is substantial and may support motivation during an exercise programme [110, 111].

Lastly, an individual's social circumstances including their current employment should be considered, particularly when planning an acceptable rehabilitation regime.

Evidence to date for exercise-based interventions in long COVID

To date, there is limited evidence for the deployment of exercise-based therapies for long COVID. A systematic review has demonstrated improvements in long COVID to improve breathlessness, anxiety and functional status, therefore lessening disability. However, these findings are on small sample sizes and few of the included studies are randomised controlled trials [20]. There is strong evidence for the benefits of exercise in multiple LTCs that may have similar features [9]. A limited number of randomised controlled

FIGURE 2 Risk and benefits of exercise-based rehabilitation.

trials have reported the effects of exercise interventions post-COVID-19, mainly utilising technology-based solutions such as an app, despite there being an increased appetite for these interventions in response to the pandemic [20, 112, 113]. Observational studies have also reported encouraging improvements in exercise capacity, HRQoL and psychological wellbeing with no adverse events. However, they are generally uncontrolled studies or matched with controls that are unmatched in respect to their baseline abilities [114, 115]. An early observational study monitoring fatigue reported a reduction in overall symptom burden, including fatigue and an improved exercise capacity [8]. A systematic review and meta-analysis exploring "pulmonary rehabilitation" interventions demonstrated improvements in breathlessness, physical function and HRQoL, but there is high heterogeneity across the included studies. The studies included in this review use the term "pulmonary rehabilitation", but includes a range of interventions from breathing exercises alone for 2 days to intensive aerobic and resistance training delivered for up to 20 weeks, which may dilute the benefits of exercised-based rehabilitation and make generalisability difficult [116]. A number of funded research trials are in progress (ISRCTN10980107, ISRCTN11466448) exploring various forms of exercise-based therapies that will improve this evidence base in the future.

Summary

Long COVID is a highly disruptive, burdensome syndrome with a negative impact on HRQoL, occupation, social life and family (figure 2). Whilst awaiting results of current ongoing rehabilitation trials, existing evidence for exercise-based rehabilitation in other LTCs with similar symptomatology and organ impairment provides a rationale for individualised, exercise-based therapy in long COVID. There are specific challenges for some individuals with long COVID who experience PESE. However, the most concerning legacy from the COVID-19 pandemic would be leaving millions of adults not only with ongoing symptoms and reduced quality of life, but also with physical inactivity – the largest risk factor for future long-term conditions and premature mortality [116]. This review recommends thorough assessment and screening in order for safe patient selection for rehabilitation interventions. Access to a multidisciplinary team and optimisation of pre-morbid conditions and the investigation of unexplained symptoms such as palpitations and dizziness is vital for safe care. Detailed history and assessment of functional status, social circumstances and psychological wellbeing will ensure individualised and feasible care. Rehabilitation should be delivered by trained healthcare professionals competent in exercise prescription and delivery and should include individualised symptom management techniques.

Points for clinical practice

- Ongoing symptoms of COVID-19 could benefit from individually prescribed, symptom-titrated exercise training.
- Considerations should be given to those who present with complex respiratory and cardiovascular pathologies.
- Adaptations to training should incorporate the needs of the individual, with assessments of skeletal muscle dysfunction and fatigue.

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