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Review Article

Developing effective strategies to optimize physical activity and cardiorespiratory fitness in the long Covid population- The need for caution and objective assessment

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ABSTRACT

The Post Covid-19 Condition (commonly known as Long Covid) has been defined by the World Health Organisation as occurring in individuals with a history of probable or confirmed SARS CoV 2 infection, usually within 3 months from the onset of acute Covid-19 infection with symptoms that last for at least two months which cannot be explained by an alternative diagnosis. Long Covid is associated with over two hundred recognised symptoms and affects tens of millions of people worldwide. Widely reported reductions in quality of life(QoL) and functional status are caused by extremely sensitive and cyclical symptom profiles that are augmented following exposure to physical, emotional, orthostatic, and cognitive stimuli. This manifestation prevents millions of people from engaging in routine activities of daily living (ADLs) and has important health and well-being, social and economic impacts. Post-exertional symptom exacerbation (PESE) (also known as post-exertional malaise) is an exacerbation in the severity of fatigue and other symptoms following physical, emotional, orthostatic and cognitive tasks. Typically, this will occur 24–72 h after "over-exertion" and can persist for several days and even weeks. It is a hallmark symptom of Long Covid with a reported prevalence of 86%. The debilitating nature of PESE prevents patients from engaging in physical activity which impacts functional status and QoL. In this review, the authors present an update to the literature relating to PESE in Long Covid and make the case for evidence-based guidelines that support the design and implementation of safe rehabilitation approaches for people with Long Covid. This review also considers the role of objective monitoring to quantify a patient's response to external stimuli which can be used to support the safe management of Long Covid and inform decisions relating to engagement with any stimuli that could prompt an exacerbation of symptoms.

Abbreviations: ACE2, Angiotensin-converting enzyme; ANS, Autonomic nervous system; ARDS, acute respiratory distress syndrome; a-vO_2, Arteriovenous oxygen difference; CO_2, Carbon dioxide; COVID, Coronavirus disease; COVID-19, Coronavirus disease 2019; CPET, Cardiopulmonary exercise testing; CRF, Cardiorespiratory fitness; CVD, cardiovascular disease; EBV, Epstein-Barr Virus; eCRF, Estimated CRF; HR, Heart rate; HRV, Heart Rate Variability; HRQoL, Health-Related Quality of Life; ICU, Intensive Care Unit; ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome; NPI, non-pharmacological interventions; O2, Oxygen; PA, Physical activity; PEM, Post-exertional malaise; PESE, Post-exertional symptom exacerbation; Q, Cardiac; QoL, Quality of life; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V/Q, Ventilation-perfusion.

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Long Covid symptomology and the effects on functional status and quality of life (Qo L)

Defined as a persistent and episodic symptom profile that presents after a suspected or confirmed infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] Long Covid is a multi-system disorder associated with >200 different symptoms involving multi-bodily organs[2] and is estimated to affect ~150 million people worldwide.[3] The most widely reported impact is reduced quality of life and functional status[4,5] due to highly sensitive and cyclical symptoms that manifest and are augmented following exposure to physical, emotional, orthostatic, and cognitive stimuli, preventing millions from engaging in routine daily activities, including employment, social activities and even family roles.[6] As the understanding of Long Covid has progressed it has become clear that Long Covid is an umbrella term for a heterogeneous disease process with distinct clinical phenotypes. Long Covid is a virally triggered immune mediated inflammatory condition occurring in response to SARS CoV 2 infection where several host response pathways are triggered in a pathophysiological manner. Within Long Covid we see distinct phenotypes such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CSF), post-exertional symptom exacerbation (PESE), post Covid dysautonomia including but not limited to postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia, mast cell activation syndrome, neuro-inflammation and a vascular/coagulopathic phenotype comprising of thrombotic endothelitis, fibrin amyloid microclotting, thrombotic microangiopathy and impaired fibrinolysis. These distinct, yet somewhat overlapping, phenotypes are due to the fact several host response pathways are being triggered in Long Covid and it is common for patients to exhibit multiple phenotypes simultaneously. In addition to the well-recognised syndrome and phenotypes of "Long Covid" Sars-Cov-2 has also been clearly shown to be associated with new onset thrombotic disease, cardiovascular disease, neurological (both neurovascular and neurodegenerative) disease and diabetes which may occur weeks, months or even years after index infection.[7] Multi-organ impairment has been a concern for individuals recovering from SARS-CoV-2 infection, resulting from both the direct effects of the viral infection, as well as indirect effects of the body's significant inflammatory response.[8] Potential mechanisms include direct viral cytotoxicity, chronic inflammation, acute reactivation of other viruses, ischaemic injury, metabolic derangements, dysfunctional neurological signalling, as well as acute treatment effects (e.g., invasive ventilation).[9] A recent MRI study (C-MORE) of 249 hospitalised patients confirmed that nearly one in three patients exhibited multiorgan injury, with a significantly higher proportion of lung, brain, and renal MRI abnormalities in these patients, compared to non-infected hospitalised controls.[9]

The most widely reported impact of Long Covid is reduced QoL and functional status due to highly sensitive and cyclical symptoms that manifest and are augmented following exposure to physical, emotional, orthostatic, and cognitive stimuli, preventing millions from engaging in routine daily activities, including employment, social activities and even family roles.[6] In a series of qualitative studies, individuals with Long Covid have highlighted challenges of engaging in physical activity due to extended symptoms of Long Covid and highlighted the need for improved support to resume physical activities, as well as greater clarity and tailoring of physical-activity-related advice.[5,10] Exercise intolerance and post-exertional malaise (PEM) are hallmark symptoms of Long Covid, which can have a significant impact on the ability to perform everyday activities.[11] A recent meta-analysis of 38 studies reporting cardiopulmonary exercise test (CPET) data in 2160 individuals, found a modest but consistent reduction (4.9 $mL \bullet kg^{-1} \bullet min^{-1}$) in cardiorespiratory fitness in individuals with Long Covid, compared with individuals without symptoms of more than three months following infection.[12] The underlying mechanisms reported for exercise intolerance are wide-ranging and include deconditioning, dysfunctional breathing, chronotropic incompetence, and abnormal peripheral oxygen extraction and/or use. Current evidence shows a large discrepancy in findings, which may partly be attributed to variability in methodology and interpretation between studies. Nevertheless, given the heterogeneity of possible mechanisms, pathophysiological phenotyping of individuals with Long Covid may be beneficial for targeting treatment strategies.[13]

PESE in long Covid

PESE is an increase in fatigue that occurs after physical, emotional, orthostatic and cognitive tasks.[14,15] PESE is common among Long Covid patients,[16] with one study reporting as much as 86% of sufferers reporting 'minimum exercise makes you tired'.[17] Whilst symptoms are broad, common symptoms include reduced energy, an increase in muscle soreness, breathing difficulties, and feeling sick/nauseous which occur usually 24-72 h after patients exceed the thresholds of their reduced "energy envelope".[17] The occurrence of PESE is also reported to be episodic, with 'relapses' of symptoms, which can be problematic with diagnosis and treatment. It is common that whilst symptoms could be minimal in phases, a return to exercise or life events such as returning to work/employment cause symptoms to re-appear.[18] In some studies, these symptoms can persist even 40 weeks to 2 years after the initial COVID-19 infection.[16] Whilst mechanisms are still being investigated, these symptoms may exist due to skeletal muscle myopathy including exacerbated muscle damage and subsequent regeneration, the increased presence of amyloid deposits, ischaemic-reperfusion injury, impaired oxygen delivery to tissue, impaired oxygen extraction, reduced anaerobic metabolism threshold and impaired mitochondrial function with reduced adenosine triphosphate production.[19,20] Other wide-ranging mechanisms also exist including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling.[7,21] Regardless of the mechanisms, PESE can have debilitating effects on Long Covid patients, and these effects can be long-lasting.

Whilst exercise rehabilitation and physical activity (PA) have been popular methods to improve cardiorespiratory fitness (CRF) broadly across chronic disease research and was even listed as a priority area for research in the National Institute for Health and Care Excellence guidelines,[22] the risk and prevalence of PESE must be considered in Long Covid and the closely related condition of ME/CSF and supported with detailed diagnostic assessment and monitoring. For this reason, the World Health Organisation and World Physio Guidelines for Long Covid do not recommend graded exercise therapy for Long Covid patients with PESE due to the risk of potential harm. Many studies to date have reported positive findings following exercise rehabilitation strategies, however, have failed to measure PESE, and/or have conducted only short-term interventions (8–12 weeks typically).[23] Due to the 'relapsing' nature of PESE, this is a glaring omission from the literature to date, with many studies not initially screening for, monitoring, or including a follow-up within the study design. This is problematic as patients with PESE could unknowingly be recruited and therefore placed at risk of exacerbating symptoms, and two, there is a clear lack of empirical evidence derived from appropriate study designs to demonstrate if Long Covid patients with PESE could benefit from rehabilitation programs if this was done following treatment of the underlying pathophysiology of the disease process first with detailed and highly individualised monitoring. For example, careful and symptom limited CPET can differentiate between cardiovascular deconditioning and impaired peripheral oxygen extraction and lowered anaerobic thresholds. The former may benefit from a carefully monitored rehabilitation program, the latter may be at risk from harm with exercise rehabilitation programs. Detailed investigation of the Long Covid phenotype(s) by a Long Covid Physician, with treatment of the underlying conditions identified using a combination of non-pharmacological interventions (NPI) and pharmacological therapies followed by careful monitoring of treatment response (potential methods for monitoring treatment response might include monitoring of change in HRV, pSVO2, microclot burden, pro-inflammatory cytokines, vWF:ADAM-TS, PAI-1, pre and post exertional lactate monitoring as well as patient reported outcome measures (PROMS) and patient symptom diaries/daily step counts) might be useful in determining disease recovery, enabling further safe study looking at improvement in peripheral oxygen extraction and identifying a point in the patients recovery journey where it might be safe to re-introduce exercise in a carefully controlled and scientifically monitored way. Safe rehabilitation monitoring strategies might include pre-determining the patient's personal anaerobic threshold and designing a rehabilitation strategy that enables the patient to exercise within their energy envelope, without exceeding their anaerobic threshold. Lactate monitoring can be done using simple bedside monitoring equipment and might provide an easy-to-use surrogate marker for aerobic metabolism to guide safe rehabilitation approaches. This clearly requires further study.

Long Covid patients can have symptoms that persist for two years or more post-initial infection, and therefore previous shorter-term studies may fail to capture any potential issues through follow-up (such as 6- and 12-month post-intervention).[16] Furthermore, it has been widely reported that the drop-off rate could be up to 50% with exercise and PA rehabilitation approaches, which is due to exacerbation of chronic fatigue symptoms,[24] although this study was in ME/CFS, not Long Covid. Whilst research has identified similarities in the symptom presentation and reporting of ME/CFS and Long Covid patients,[25] can caution is needed until detailed investigations can pinpoint the extent of similarity in systemic and mechanistic processes that contribute to the complex and episodic symptom profile. Nonetheless, it is likely the studies reporting benefits from exercise and PA will only help a small proportion of Long Covid patients. These findings therefore must be treated with caution in terms of their value to patients with Long Covid and PESE.

Much of the exercise and PA prescription strategies in chronic conditions to date have occurred in cancer, chronic obstructive pulmonary disorder (COPD), and others.[17] This is worrying as studies have shown that energy/fatigue, physical functioning, and social and emotional functioning were significantly reduced in both Long Covid and ME/CSF compared to other conditions such as COPD, rheumatoid arthritis, and normative healthy individuals.[17] These types of approaches are too simplistic to account for the diverse nature of Long Covid symptoms. Instead, a contemporary approach has been to use the 'pacing' concept, which entails balancing rest and activities in daily life and has been used with ME/CFS patients previously.[26,27] These activities do not need to be exercise of PA as such but can be physical, cognitive, or social activities, and only completing an activity that is perceived to be available, often referred to as the 'energy envelope'.[28] This approach seems intuitive as it may reduce the risk of exacerbating symptoms. Using this approach ensures that Long Covid rehabilitation is personalised, has accurate expectations (including setbacks), psychologically safe and supportive, which are key factors recently highlighted by patient led Long Covid groups.[29]

One positive to date is that in many studies, exercise has been strictly supervised and prescribed. This is required for Long COVID rehabilitation approaches to capture patients' symptoms, and potential red flags, and support their rehabilitation. It is worth noting, however, that exercise rehabilitation is not the route to recovery for most Long Covid patients[17] and we must address the deep underlying mechanistic challenges that result in this episodic and disabling condition. Whilst the focus on increasing CRF is arguably required to restore pre-pandemic functional status,[30] patients must be carefully guided and supported to prevent PESE. In line with this, the pacing approach could be adopted, and this should initially focus on symptom stabilization and avoiding events that could exacerbate symptoms (e.g., exercise, work tasks, socially demanding events). It is important to still monitor PESE with these tasks, as symptoms can be caused by emotional and cognitive tasks. Finally, it is important that in any rehabilitation approach, a whole-system approach is taken including patient input to design and consistency across providers to care and support.[31]

Reduced thresholds of tolerance

The debilitating nature of PESE and its impact on functional status and quality of life is widely documented,[32,33] but the mechanistic properties that prompt an inability to engage with everyday tasks due to an exaggerated response to physical, mental and emotional stimuli remain equivocal. Whilst there is ambiguity and consensus in the aetiology of this condition, recent evidence depicts that it is most likely caused by a complex immunological and neurophysiological manifestation[7] which is linked to a broad and inconsistent symptom profile[4] with adverse downstream effects on mitochondrial function, the organelles involved in the production of cellular energy in the form of adenosine triphosphate. ME/CFS is a poorly understood disease that unfortunately, to the detriment of patients, has had a paucity of investment in biomedical research for decades[34] with no recognised successful treatment. The prevalence of Long Covid patients reporting ME/CFS-like symptoms (~58%)[35] has accelerated attempts to better understand the mechanistic processes causing the debilitation symptoms of these conditions to help inform the development of therapeutic approaches (pharmacological and non-pharmacological) to improve patient outcomes. Whilst research has identified similarities in the symptom presentation and reporting of ME/CFS and Long Covid patients,[25] caution is needed until detailed investigations can pinpoint the extent of similarity in systemic and mechanistic processes that contribute to the complex and episodic symptom profile. Prominent in Long Covid patients is the reporting of PESE after engaging in a variety of physical, mental, emotional, or orthostatic tasks. In a study by Twomey et al,[17] two hundred and thirteen Long Covid patients completed a cross-sectional observation study to determine the prevalence of PESE. The results demonstrate that 71.4% of patients were experiencing chronic fatigue and PESE 58.7% met the thresholds of PESE. What is clear is that a high proportion of patients living with Long Covid have a reduced tolerance to external and dynamic stimuli and the effect on quality of life and functional status can be disabling and patients have resorted to strict pacing approaches to manage their daily activities.[36] Research to test developed hypotheses and mechanistic understanding is ongoing and emergent theories point to persistent issues with the transport, delivery, and function of vital systems within the body,[37] which to date includes dysfunction/dysregulation or impaired pulmonary perfusion, endothelial function, blood clotting processes, inflammation and immune responses, autonomic function and oxidative phosphorylation via mitochondrial activity.[7,38] These mechanisms will likely interact in a complex manner, contributing to a lack of understanding but it is plausible in some cases that resolution might not be feasible. Of particular importance here is a need to restore functional status via effective interdisciplinary rehabilitation pathways.[39] It has been hypothesized that an increased dependence on anaerobic contributions to everyday activities extends beyond previously documented post-viral infection deconditioning and could be associated with impaired tissue oxygenation and substrate oxidation.[40] Therefore, the integrity of the cardiopulmonary system should be investigated due to its primary role of transport and delivery of oxygen (Fig. 1) in maintaining bodily functions and for regulating aerobic and anaerobic contributions to the provision of energy. It has been highlighted that people experiencing Long Covid exert a higher anaerobic contribution to energy provision, which is well documented as being time-limited and associated with broad perceptual responses and systemic responses.[41]

It is therefore plausible that patients with ME/CFS and Long Covid are working with a much smaller energy envelope compared to healthy controls and are likely to breach aerobic thresholds and work in an anaerobic state at markedly lower intensities.

The myth of deconditioning in long Covid

Initially, the deterioration of CRF was suggested to be caused by deconditioning, due to the reduction in habitual PA in patients with

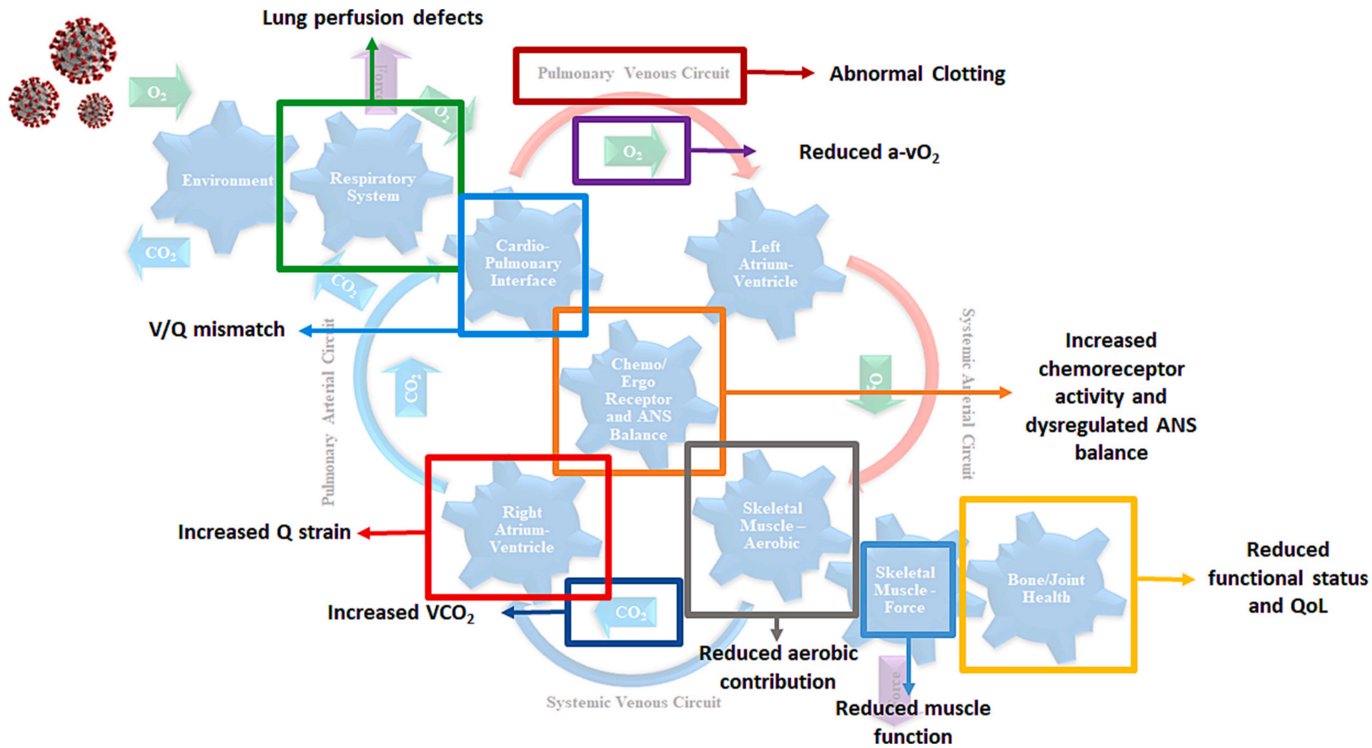

Fig. 1. Graphical narrative of the systems involved in oxygen consumption, carbon dioxide production and muscle force production adapted with permission from.[30,110] ANS, autonomic nervous system; a-vO_2, Arteriovenous oxygen difference; CO_2, carbon dioxide; O2, oxygen; QoL, Quality of life; V/Q, Ventilation-perfusion; Q, Cardiac.

COVID-19 and Long Covid. A recent paper declared 2021 as 'the year of reconditioning',[42] declaring it a second pandemic.[43] More recently, however, the deconditioning mechanism has been debated as to whether this is the mechanism to explain Long Covid symptoms and the reduction in VO_2max observed.[44] Whilst tests of CRF can play an important role in determining the integrity of CRF interface,[45] numerous studies have reported a reduction in CRF markers and associated this with the deconditioning from reduced physical activity following a COVID-19 infection, or Long Covid.[46] For example, Skjørten et al reported that participants only reached 84% of the predicted VO_2 max.kg BM-1 3 months following a COVID-19 infection, which was attributed to deconditioning.[47] However, the broad application of a deconditioning theory has been described as a reductionist view for many reasons. Firstly, the deconditioning effect does not explain the level of deconditioning observed within those who had asymptomatic/mild acute infection, many of whom required no hospitalisation or medical involvement.[44] Equally, there is no linear relationship that has been observed between the length of hospitalisation (or inactivity) and the reduction in VO_2max, which would be the case if it were only deconditioning.[48] In fact, in one study, the intensive care unit (ICU) versus non-ICU treated patients only reported an 8% reduction in percent predicted VO_2max for the ICU group.[47] Finally, some patients demonstrate preserved VO_2max, yet still have persistent symptoms of dyspnoea, fatigue and PEM/PESE, which has recently been linked to hyperventilation or acid-base balance disturbances rather than deconditioning.[49,50] In these patients, it makes little sense that conditioning would be required if VO_2max has been preserved and it points to more complex pathophysiological issues. Based on this evidence, Long Covid has far-reaching mechanisms beyond deconditioning alone, and this could include myopathy due to the viral injury following a COVID-19 infection such as organ damage, myocarditis, and endothelial cell or mitochondrial dysfunction.[51,52] In any of these latter scenarios, reconditioning or attempting to increase CRF will not address these issues. Considering the multi-faceted nature of Long Covid, a personalised approach is required to rehabilitation strategies, whilst further research is needed to determine the mechanisms for reduced CRF.[53]

Long-term impacts on patients/health systems and global health

Long Covid is impacting patients and health systems globally, with variable clinical outcomes, ranging from undiagnosed asymptomatic infection in mild upper respiratory infection to severe viral pneumonia resulting in respiratory failure and death[54]; whilst a reduction in diffusion capacity has been reported as one of the most common physiological impairments.[54,55] Deconditioning is associated with long-term impacts for patients with Long Covid, and it has been postulated as being a result of a direct effect of the viral load on the muscle tissue, with a resultant impaired oxygen extraction and use,[56] a reduction in CRF, muscle strength or aerobic capacity due to the inability to be mobile and restrictions in daily activities,[4,57] and is related to a prolonged hospital stay and post-hospitalisation syndrome.[48] Although reported as less common, hospitalised COVID-19 survivors have been found to have restrictive pulmonary physiology at three and six months,[58] similarly observed in historical acute respiratory distress syndrome (ARDS) survivors.[59] In a further observational cohort study of 1250 patients with COVID-19, from 38 United States hospitals, dyspnoea while walking up the stairs (22.9%), coughing (15.4%) and persistent loss of taste and/or smell (13.1%), were commonly reported.[60] Findings from a European study reported the persistence of symptoms in 87.4% of 143 patients at a mean follow-up of 60 days from the onset of symptoms, with fatigue (53.1%), dyspnoea (43.4%), joint pain (27.3%) and chest pain (21.7%), being the most reported symptoms, with 55% of patients experiencing three or more symptoms and a decline in quality of life reported by 44.1% of patients.[61]

The long-term complications experienced by Long Covid patients may be the result of direct viral invasion of tissues such as the lungs, heart, gastrointestinal mucosa, vascular endothelium, T lymphocytes, macrophages, and neurons.[62] Within these tissues the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor, and activates a cytokine storm, immune system damage, or a combination of the two,[63,64] culminating in pervasive tissue damage[65]; this damage can occur in each affected organ. The World Health Organisation (2020) recommended a recovery time of two weeks for individuals with mild disease and six weeks for those with severe disease. However, Sova *et al*[66] showed that many individuals who recovered from acute disease continued to suffer from long-term sequelae. Evidence suggests that although an increase in physical function and CRF is detected within the first 6 months post-COVID-19,[67,68] recovery is incomplete, and patients may experience alterations in physical function and CRF at one- or 2-years post-infection.[69] Therefore, targeted interventions to promote the physical recovery of patients are required. All these complications present a substantial long-term burden on the health care systems of many countries, due to the large numbers of people who have been diagnosed with COVID-19.

The literature suggests that patients who had greater severity of acute COVID-19 (required a high-flow nasal cannula and non-invasive/invasive mechanical ventilation) possessed a higher risk for long-term pulmonary complications, including persistent diffusion impairment and radiographic pulmonary abnormalities (e.g., pulmonary fibrosis).[70] Furthermore, pulmonary vascular micro- and macro-thrombosis has been identified in 20–30% of patients with COVID-19.[71,72] The severity of endothelial injury and thrombosis viewed on lung autopsies was notably greater than that seen in ARDS from influenza,[73] emphasising the problems for individuals and health care systems.[74] A recently conducted study assessed 268 participants who were mostly affected during the first COVID-19 wave in 2020, plasma factors, blood leukocytes and antibodies to SARS2 were examined and those with Long Covid presented with lower circulating cortisol, higher activated B and cytokine-secreting T cells, higher anti-Spike IgG, higher Epstein-Barr Virus (EBV) reactive antibodies and no significant differences in autoantibodies.[75] This study was exploratory yet provides important first steps towards identifying biomarkers which can be used for future COVID-19 testing. Further Long Covid complications are that it can cause catabolic muscle wasting, feeding difficulties and frailty,[76] and presents risk factors for bone demineralisation related to systemic inflammation, immobilisation, vitamin D insufficiency and interruption of antiresorptive or anabolic agents for osteoporosis,[77] all increasing the likelihood of poor outcomes impacting patients individually, but also health systems globally.

Overview of the current evidence on the effects of rehabilitation interventions on CRF and PA in long Covid?

As aforementioned, the multisystem manifestations of Long Covid can significantly impact the ability of individuals to carry out everyday activities, including household, work, and leisure activities.[6] Therefore, safe and effective rehabilitation strategies to improve long-term outcomes in patients with Long Covid-19 are needed.[78] Guidance issued by international medical associations emphasises the necessity for multidisciplinary rehabilitation in the clinical management of patients with persistent symptoms and disability following COVID-19.[79–81] Nevertheless, in the absence of evidence from dedicated studies to guide best practices for safe and effective rehabilitation, current rehabilitation guidelines are based on expert consensus, preliminary results, and previous evidence on the rehabilitation of patients surviving critical illnesses. Due to the clinical complexity and uncertainty of Long Covid, the publication of precise rehabilitation guidelines is challenging, however, to prevent harm to patients, leading health authorities should be encouraged to convene leading experts and researchers to reach consensus and develop guidelines for the development and implementation of safe and effective rehabilitation of Long Covid patients. A recent Delphi study in the UK highlighted the importance of detailed and ongoing interdisciplinary assessment that should be included as part of any Long Covid support mechanism.[82] It is important to note that the level of physical fitness, characteristics, type of training and individual's immunological characteristics must be considered in depth to allow for tailored immunological and anti-inflammatory responses,[39,83] as individuals respond very differently to PA. Any symptoms that could affect the safety of rehabilitation should be fully investigated before participation, to avoid deterioration or occurrence of an acute event.[79] Whilst the number of studies investigating the feasibility, safety, and efficacy of rehabilitation interventions for Long Covid is growing, the evidence remains limited to small, prospective, single-cohort studies. Several early studies have investigated the feasibility of existing rehabilitation programmes (e.g., pulmonary and cardiac rehabilitation) in post-COVID-19 patients,[84–86] based on the rationale that these programmes are effective for improving symptoms such as breathlessness and fatigue, reducing hospital admissions and improving Health-Related QoL (HRQoL) in other chronic conditions.[87] A rapid review of nine studies suggested that although pulmonary rehabilitation may lead to improvements in exercise capacity, HRQoL and/or pulmonary function in hospitalised patients with post-COVID symptoms, the evidence is limited and low quality due to smaller sample sizes, short follow-up, and/or non-randomised study designs.[88] Nevertheless, there were no adverse events reported in 309 participants across the included studies.

A challenge to understanding the benefits of rehabilitation post-COVID-19 is the limited knowledge of the long-term trajectory and to what extent natural recovery occurs. A recent study by Asimakos *et al*[84] compared supervised multidisciplinary rehabilitation consisting of supervised exercise training, education, breathing control, dietary advice and psychological support to patients receiving usual care only in the early stages of post-COVID recovery. Whilst natural recovery in functional capacity and pulmonary function was shown, outpatient rehabilitation elicited significantly greater improvements in measures of fatigue, respiratory symptoms, functional capacity, mental health and HRQoL. Importantly, there were no adverse effects reported throughout the exercise training programme. These results are promising for patients recovering from hospitalisation for COVID-19 generally, however, this study along with many previous observational studies cannot be generalised to individuals with Long Covid, who likely present with more complex needs.[11] That said, in non-hospitalised patients with Long Covid, Jimeno-Almazán et al. showed that an 8-week supervised, tailored multicomponent exercise programme at a low to moderate intensity significantly improved health markers for quality of life and fatigue, depression, cardiovascular fitness and muscle strength, compared to a control group receiving self-management recommendations only.[89]

Early rehabilitation programmes highlighted a need to include[90] and introduce respiratory muscle training to maximise the benefit for COVID-19 patients by increasing their respiratory muscle strength, and endurance and enhancing their respiratory function, helping to reduce the problems of COVID-19 sequelae.[91] Regular exercise of moderate intensity is recommended for COVID-19 patients with milder symptoms; moderate aerobic or resistance exercise is also prescribed for milder suffering patients to allow physical activity to reduce intracellular and extracellular oxidative stress.[92] It has been emphasised that programmes with aerobic and resistance training can improve physical function and CRF in the first 2 months after being discharged from hospital.[93] Patients with lower CRF at baseline have the greatest pronounced improvement from lower-intensity rehabilitation models.[94] Research has also recommended adding yoga and tai chi to rehabilitation programmes to improve the disease effectively.[92] Individuals with mild to moderate COVID-19 have been recommended to include elements of cardiopulmonary and neuromuscular rehabilitation, proprioceptive neuromuscular facilitation and exercise like yoga, tai-chi-chuan to their rehabilitation interventions, and for individuals with moderate-to-severe COVID-19 breath training, posture management, passive range of motion exercise and simple active-movements, as per the clinical-conditions and safety profile have been recommended.[95] Equally, research suggests, when possible, that PA should be introduced gradually to individuals with Long Covid to avoid physical disability and myopathy.[92] However, caution is required as physical activity could potentially aggravate certain COVID-19-associated cardiac and other complications, especially in symptomatic patients,[96] and this needs further exploration for individuals with Long Covid.

To improve the accessibility and scalability of rehabilitation for patients with Long Covid, some studies have also investigated the effectiveness of community and digital-based rehabilitation programmes.[97] In a randomised controlled trial involving 120 formerly hospitalised COVID-19 patients, a 6-week home-based tele-rehabilitation programme comprising breathing control and thoracic expansion, aerobic exercise and lower limb strength exercises, delivered via smartphone, and remotely monitored with heart rate telemetry, was found to be superior to no rehabilitation for improving exercise capacity, lower limb muscle strength and physical strength.[98] Similarly, in 601 adults with Long Covid, Smith *et al*[99] implemented a 12-week blended digital and community-based rehabilitation programme and reported significant and clinically meaningful improvements in dyspnoea, functional capacity and HRQoL, along with reductions in GP and hospital visits. However, this study was limited by a lack of a control group.

Overall, the evidence of rehabilitation for post-COVID-19 so far is promising, but highlights the importance of interdisciplinary assessment, individualisation, and careful management of symptoms such as PESE. Due to the global scale of this pandemic, the development of scalable healthcare models is a necessity for the improved physical health of survivors of COVID-19 in the long term.[100] Despite the growing evidence evaluating outpatient, community and telerehabilitation programmes for this population, more high-quality randomised controlled trials are required to establish the true safety and clinical effectiveness of these programmes. Recently published protocols should begin to address this gap.[101] Identifying and understanding possible recovery phenotypes of Long Covid-19 will also help to stratify rehabilitation strategies.[102]

Objective monitoring and assessment to inform clinical decision making

This review provides a brief insight into the complex pathophysiology of Long Covid which is entwined with detail relating to the broader health and wellbeing, social and economic impacts of the condition. What is clear is that the complexity of the condition must be represented in the design of empirical research, assessments and support strategies that attempt to address and improve the understanding of mechanistic hypotheses that have been established. The role of PA and rehabilitation approaches could form part of a detailed programme to improve patient outcomes, but this must be considered alongside detailed mechanistic insight to determine the safety and suitability for engaging in PA-related activities. This must include detailed assessment and monitoring tools that make the most of a continually evolving technological landscape that can be used to determine/profile changes in physiologic status and provide feedback to patients to help inform decisions about the time and intensity of everyday activities. Currently, this predominantly occurs via reactive approaches, which see patients experience a worsening of symptoms (often referred to as a crash) which can last for several days and even weeks[103] and tests are then run to determine the causes and effect. However, the complex physiology of exacerbations has been linked to transient changes in physiology over time which could be detected by observing patterns in key physiological variables, a notion that has been postulated in other chronic disease areas.[104] Combining objective data with advances in machine learning and artificial intelligence could provide an opportunity to increase the knowledge and awareness of an exacerbation (or crash) which with appropriate intervention could mitigate the outcomes for patients and healthcare systems. In the context of Long Covid, this could include monitoring of heart rate variability (HRV) which directly monitors variability in duration between consecutive heartbeats and is a marker of autonomic function and impaired HRV is associated with poor outcomes in various diseases.[105] HRV methods can be analysed to determine changes in time domain indices to include normal-to-normal intervals, the standard deviation of all normal R-R intervals, the root mean square of successive RR interval differences and the percentage of successive RR intervals.[105] Low and high-frequency domains are also commonly assessed in spectral analysis. High frequency outlines changes in parasympathetic activity, low frequency delineates both sympathetic and parasympathetic activity and the low-high frequency index represents sympathetic and parasympathetic balance.[106] A raft of technologies exist that can be used to support the monitoring of symptoms and physiological outcomes in Long Covid and more broadly chronic disease, we recommend that healthcare settings adopt work closely and in an interdisciplinary manner[107] to engrain these approaches into clinical pathways to inform decision making relating to diagnostic assessment and in the development of treatment plans and to monitor responses to prescribed medications/interventions.

Objective monitoring to support safe PA in long Covid

Whilst prevention is preferred to the management of chronic conditions,[108] for millions living with Long Covid this is not a reality due to sustained transmission and viral mutation. Whilst research strives to increase the understanding of the mechanistic basis of a complex pathology, tens of millions of people globally require support to undertake activities of daily life.[3] The role of PA in public health is established and has far-reaching impacts that extend into social and economic areas, but as described above the ability for patients with Long Covid to engage in such activities carries an inherent risk of PESE.[6] Recognising the role of technologies and objective monitoring approaches in clinical practice, these approaches could play a considerable role in the implementation and management of Long Covid patients engaging in functional and physical activities. As highlighted previously, it is widely acknowledged that Long Covid patients work with a reduced energy envelope and tolerance to physical and other external stimuli. This creates a compelling case to proactively and objectively monitor the volume and intensity of stimuli to ensure that people with Long Covid with PESE can safely stay within their threshold of tolerance and reduce the risk of an exacerbation/crash. To ensure success, detailed assessments of each patient's symptoms would be required. This information can then be combined with artificial intelligence and machine learning processes[109] to establish truly personalised, safe and effective methods that can improve patient outcomes and reduce the risk to patients. This creates an opportunity for researchers to investigate and develop effective approaches that can improve functional status and quality of life alongside physical and mental well-being in this space, must also be cognisant and demonstrate an awareness of previous approaches to recommend inappropriate, often dangerous and ineffective approaches that contain physical activity and messaging about 'exercising yourself better' which has and expectedly developed a hesitancy in some to engage with PA and exercise approaches.[29] The benefits of physical activity are widespread, but in Long Covid and arguably many chronic disease areas, including ME/CSF, there is a need for vigilance and caution which can be developed in consideration of the lived experience[6] and collaboration with established advocacy groups. These approaches could result in the development, testing and implementation of efficacious treatments and management strategies for Long Covid patients and ease the burden of a global health and well-being challenge.[74]

Conclusion

The role of PA in public health outcomes is well established but for patients with Long Covid engaging in these activities carries an inherent risk of PESE. Whilst understanding the mechanisms is at the forefront of an international research agenda, there remain millions of people worldwide who remain unable to engage with PA. The role of PA and rehabilitation approaches could form part of a detailed programme to improve patient outcomes, but this must be considered alongside detailed mechanistic investigation to determine the safety and suitability for engaging in PA-related activities, in addition to appropriate NPI and pharmacological treatment of the underlying pathophysiological processes causing the symptoms and organ dysfunction in Long Covid. Incorporating objective monitoring through various technologies coupled with advances in machine learning and artificial intelligence could provide an opportunity to increase the knowledge and prevent exacerbations, could mitigate the impact for patients and allow them to engage in structured, proactively managed and safe physical activity with broad benefits to patients, their families and healthcare systems.

CRediT authorship contribution statement

Mark A. Faghy: Supervision. **Rae Duncan:** Supervision. **Emily Hume:** Supervision. **Lewis Gough:** Supervision. **Clare Roscoe:** Supervision. **Deepika Laddu:** Supervision. **Ross Arena:** Supervision. **Ruth E. M. Asthon:** Supervision. **Caroline Dalton:** Supervision.

Declaration of competing interest

None.

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