THE IMPACT OF PULMONARY REHABILITATION ON INDIVIDUALS EXPERIENCING SYMPTOMS OF LONG COVID

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A dissertation submitted in fulfilment of the requirement for the master's degree (MRes) of Sports and Exercise Science

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September 2023

ABSTRACT

Purpose: The purpose of this study was to investigate the impact of a pulmonary rehabilitation (PR) programme on exercise capacity and reports of dyspnoea and well-being in patients with Long COVID symptoms and Interstitial lung disease. **Method:** 14 participants, with a gender split of 8 males to 6 females and with a mean age of 62 ± 11.4, took part in a 6-week, twice weekly pulmonary rehabilitation programme. Pre assessment consisted of a 6-minute walk test, a bicep curl one repetition maximum and questionnaires assessing anxiety, depression, and quality of life. These included the Chronic Respiratory Questionnaire, Generalised Anxiety Disorder 7, Patient Health Questionnaire 9, Medical research council questionnaire and the COPD assessment test. The pulmonary rehabilitation consisted of mainly cardiovascular exercises, such as walking, 5-minutes of stepping and seated cycling. There was various resistance exercises included as well, such as dumbbell upright row and bicep curls. The exercise sessions were followed up with educational talks, on different topics, relevant to the participants, providing them with education based on the conditions they are dealing with and ways in which they can aid their rehabilitation themselves, as well as taking part in the exercise. Following the 6-week intervention, the post assessment was completed, which consisted of the same tests and questionnaires as the pre assessments. Statistical analysis was conducted using a paired sample t-test using IBM SPSS statistics (SPSS Inc., Chicago, IL, USA) with statistical significance set at $P<0.05$. **Results:** Mean 6MWT score (m) improved significantly (*M=71.7m, P=0.01).* Improvements in participants CRQ scores were observed with fatigue (*M=4.17*, *P=0.03)* and emotional (*M=5.4, P=0.01,* however, dyspnoea (*M=8.5, P= 0.24)*, and mastery

(*M=3.43, P=0.13)* were not significantly different, both clinically and statistically. Improvements in PHQ-9 scores were also reported (*M=4.4, P=0.05)*, as well as improvements in anxiety levels, scored using the GAD-7 (*M=2.85, P=0.03).* Participants mean CAT scores (*M=2, P=0.47)* and the MRC questionnaire (*M=0.29, P=0.86)* were not significantly different. However, participants 1RM mean score decreased by a mean of 0.07KG (*P=0.02).* **Conclusion:** Evidently, improvements in participants functional capacity, physical and mental health were observed. This could be attributed to the long-term effects of exercise on aerobic capacity, as well as mood and functional capacity. However, more research is required on the sole impact that PR has on Long COVID symptoms using a control group. Additionally, further research is required on the effect of PR on severe/ critical symptoms in Long COVID patients.

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Chapter I: Introduction

What is COVID?

SARS-CoV-2 is a disease which is caused by severe acute respiratory syndrome coronavirus 2 (COVID-19) with the first known case originating in the Wuhan area of China, December 31st, 2019 (Yang et al., 2020). As of 6th September 2023, there has been 770,437,327 confirmed cases of COVID-19, including 6,956,900 deaths (WHO coronavirus (COVID-19) dashboard, 2023). COVID-19 effects multiple systems of the body with its pathophysiology mainly involving direct virus-mediated cell damage, endothelial and microvascular injury, and hyper inflammatory response (Longobardi et al.,2022). These acute mechanisms can lead to a wide range of clinical manifestations such as gas-exchange abnormalities to cardiovascular and mitochondrial dysfunction. The long-lasting effects of the disease often include symptoms such as muscle weakness, fatigue, and dyspnoea, as well as often developing exertional intolerance leading to a reduced exercise capacity (Longobardi et al., 2022).

COVID-19 is transmitted and spread primarily through airborne transmission, when an infected person speaks, breathes, coughs or sneezes. SARS-CoV-2 particles are then released which, when inhaled, or come in to contact with the nose, eyes or mouth of another person spread infection, hence the importance of face masks and social distancing (Lofti et al., 2020). Furthermore, indirect transmission is also possible when the SARS-CoV-2 particles contaminate other surfaces and then come in to contact with a person’s mouth, nose, or eyes (Lofti et al., 2020).

Although most COVID-19 patients suffer mild symptoms, some encounter further altercations and develop more severe symptoms such as pneumonia, severe symptoms of acute respiratory distress syndrome (ARDS) and multiple organ failure (Yang et al., 2020).

What is long COVID?

Long COVID, otherwise known as post COVID-19 condition and post-acute sequelae of COVID-19, is thought to affect more than one hundred and forty-five million people around the globe with long COVID affecting every person differently resulting in a wide variety of symptoms (DeMArs et al., 2022). The NHS described long COVID as unexplained, persisting signs or symptoms over twelve weeks, developed during or after the COVID-19 infection. Prolonged COVID-19 is commonly used to describe signs and symptoms that continue or develop after acute COVID-19 (Almazan et al., 2021). Long COVID also affects multiple systems of the body and requires a multidimensional approach to effectively manage the condition (Berenguera et al.,2021).

Symptoms of Long COVID

Long COVID can affect anyone, people that had severe COVID-19 infection, or mild infection, as well as affecting people in excellent health and good quality of life pre-Long COVID (Berenguera et al.,2021). The list of continuing and new symptoms described is broad, including a persistent cough, breathing difficulty and breathlessness, chest tightness, cognitive dysfunction, and extreme fatigue (Berenguera et al.,2021). It has been reported that some symptoms improve, while others worsen. Due to the symptoms endured, many individuals often suffer with mental health problems such as depression, anxiety, and insomnia due to the persistent symptoms, and decrease in quality of life.

In Spain, individuals with Long COVID reported that the common symptoms have affected the everyday life: seventy five percent find it difficult socialising, seventy two percent are unable to work in the office as normal and require to work from home and seventy percent report difficulty in attending family responsibilities (Berenguera et al.,2021).

A meta- analysis reported that eighty percent of COVID-19 survivors showed at least one Long COVID symptom, with fatigue (58%), headache (44%), attention disorders (27%), hair loss (25%) and dyspnoea (24%) being the most commonly reported (Lopez-Leon et al., 2021).A systematic review reports that more than 60 percent of COVID-19 survivors show at least one Long COVID symptom for more than thirty days after onset or hospitalisation, which were still the most commonly reported symptoms after sixty to ninety days after the onset or hospitalisation (Fernández-de-las-Peñas et al., 2021). Additionally, the most reported respiratory Long COVID symptoms were fatigue (52%), dyspnoea (37%), chest pain (16%) and persistent cough (14%) between three weeks and three months after hospital discharge (Cares-Marambio et al., 2021). Additionally, a study investigated the clinical course of hospitalised patients with COVID-19, found that dyspnoea was reported as high as ninety two percent in patients hospitalised in intensive care units compared to thirty seven percent in patients in non-intensive care (Huang et al., 2020). This data suggests that the more severe the infection, the greater chance of developing dyspnoea as a symptom of Long COVID.

Furthermore, a meta-analysis compiled a list of all the symptoms of Long COVID that were reported, with the percentage of people that reported these symptoms with the most common symptoms as shown below in figure 1.1 (Lopez- Leon et al., 2021). Figure 1.1 below shows all the Long COVID symptoms that have been reported, found within this meta-analysis (Lopez- Leon et al., 2021). This data shows that the most reported Long COVID symptoms are a persistent cough, fatigue, and dyspnoea.

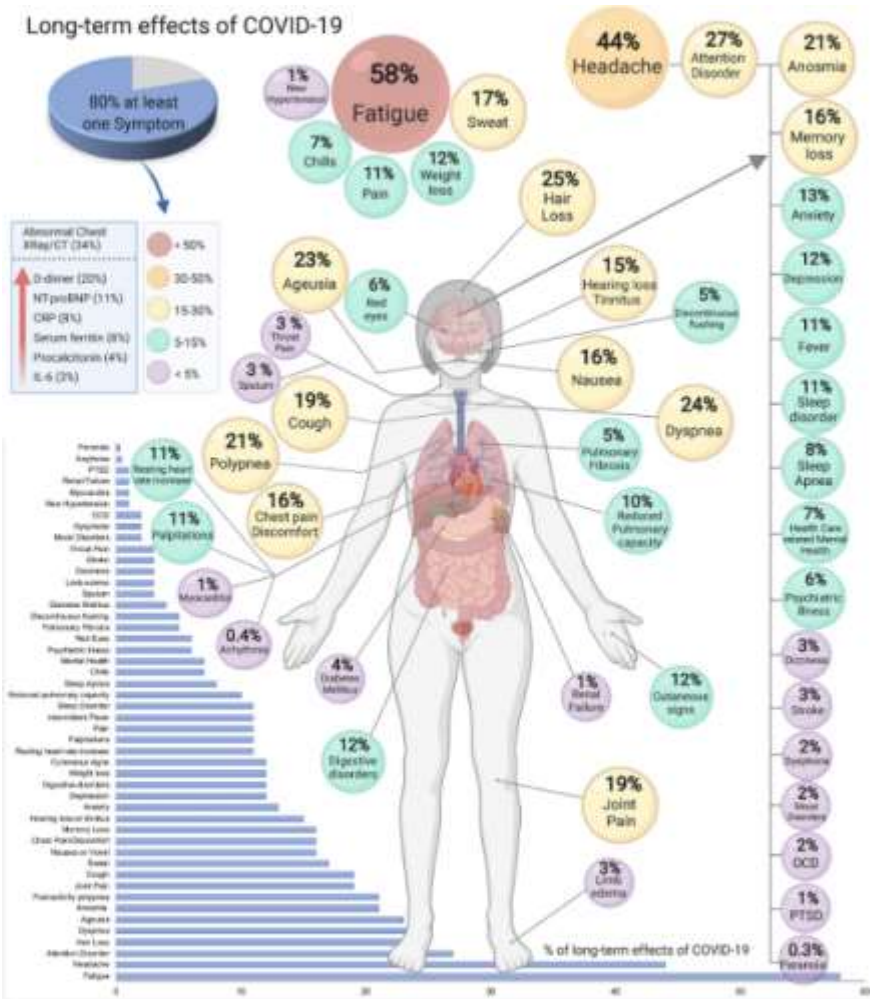

Figure 1.1- the long-lasting effects of COVID-19 (Lopez- Leon et al., 2021)

Breathlessness and Long covid

Breathing pattern disorders (BPDs) are a common cause of chronic breathlessness, including after acute respiratory illnesses such as COVID (Hylton et al., 2022). Breathlessness, otherwise known as dyspnoea, is a common symptom that is reported by almost forty percent of individuals suffering with Long COVID (Cares-Marambio et al., 2021). Dyspnoea has been described as a subjective experience of breathing discomfort, consisting of qualitatively distinct sensations that vary in intensity (Parshall et al., 2012). Dyspnoea is a subjectively experienced symptom, this can make measuring severity of dyspnoea challenging as everyone will be affected differently, just like pain and pain pressure thresholds vary for each individual (Hentsch et al., 2021). However, breathlessness is a sensation less frequently experienced compared to pain which may make recognising breathlessness more difficult (Hentsch et al., 2021). Additionally, there are many factors that affect the perception of breathlessness. Elderly people are more likely to report lower levels of breathlessness, this is down to ageing affecting peripheral structures and receptors as well as denervation (Hentsch et al., 2021).

Dyspnoea impacts individuals' life daily, often limiting daily activities in their life, affecting an individual's well-being and social life. Avoiding exercise to reduce dyspnoea begins a cycle, which can lead to deconditioning in general performance, as well as social isolation, reduced self-esteem, and anxiety (Janssen et al., 2015).

What is COVID Interstitial lung disease?

Interstitial lung diseases (ILD) are a highly disabling group of conditions including idiopathic pulmonary fibrosis (IPF), acute and chronic interstitial pneumonias, asbestosis and silicosis (Dowman et al., 2021). Individuals diagnosed with ILD often experience dyspnoea which leads to a decrease in quality of life due to inability to complete everyday tasks. Fatigue is also commonly reported in individuals diagnosed with ILD (Dowman et al., 2021). Treatment options for ILD are limited. Antifibrotic therapies are used to slow the progression of the disease and potentially improve survival in IPF (Dowman et al., 2021). However, pulmonary rehabilitation is often used as a treatment to improve symptoms of ILD, as well as improving health related quality of life and functional status (Dowman et al., 2021).

Reduced exercise capacity because of ILD comes from a series of mechanisms and alterations. Impairment of the gas exchange occurs due to the destruction of the capillary bed, resulting in ventilation-perfusion mismatch and oxygen diffusion limitations (Agusti et al., 1989). Peripheral muscle dysfunction can also play a major role in reduction of exercise capacity because of deconditioning and atrophy as patients who experience dyspnoea often reduce activity levels, which leads to a cycle of decrease in exercise capacity and an increase in symptoms (Dowman et al., 2021).

ILD's are often progressive and result in structural alterations. Lung fibrosis and decreased functional lung capacity severely affect an individual's quality of life and outcome of disease (Fesu et al., 2023). Lung viruses and intracellular pathogens can alter alveolar epithelial cells, this can affect the regeneration of alveoli. Irregular healing processes may also result in ILD’s. (Fesu et al., 2023). ILD patients with COVID-19 are at risk of developing epithelial changes and diffuse alveolar damage, as well as developing pneumonia, this again leads to the risk of developing fibrotic alterations or accelerations in development of fibrosis (John et al., 2021).

What is pulmonary rehabilitation?

Pulmonary rehabilitation includes an assessment of the patient to understand the symptoms they are experiencing as well as their exercise capabilities. It also involves regular participation in an exercise training programme which is followed by education and behavioural changes that could benefit the individual (Spruit et al., 2013). The exercise training makes up the bulk of the rehabilitation programme and includes a focus on aerobic training, often including walking and cycling. However, resistance training is also used to rebuild strength and muscle that may have been lost due to deconditioning, this will help improve the individual’s ability to complete everyday tasks, therefore improving overall quality of life (Dowman et al., 2021). The aim of pulmonary rehabilitation is to not only improve the patients physical and mental health and wellbeing, but also help the patient return to family and society more promptly (Yand and Yang, 2020).

Guidelines state that exercise and education should be provided in PR (Bolton et al., 2013). There is evidence-based recommendations around delivery of exercise, however there is a lack of research around the delivery and content of the educational aspect. In a randomised controlled trial, patients in an education-only intervention made no improvements in breathlessness or functional capacity, raising questions regarding the benefit and impact of the education provided (Ries, 1995). Additionally, there has been further research conducted where evidence has suggested that after a PR programme with education only, there were no improvements observed in breathlessness or exercise tolerance (Blackstock and Evans, 2019). This is also the case for comparing a PR program of just exercise to a program of exercise and education, where there were no significant differences observed between the two (Blackstock and Evans, 2019).

PR education typically consists of 25-50% of patient time taking part in knowledge based formal group activities, with informal teaching (Blackstock and Evans, 2019).Traditionally, education has been included in PR based on the idea that teaching patients about their condition would lead to better health, with health-care professionals choosing the topics (Blackstock and Evans, 2019). Health education within PR Is aimed to influence five areas: knowledge, perception of benefit, health beliefs, health behaviours and health outcomes. Knowledge and patient perception being positively influenced by education, with patients reporting a strong sense of learning that allowed them to acquire skills and knowledge to improve patient health and wellbeing (Blackstock and Evans, 2019).

With education being assessed as an addition to exercise training in PR, improvements have not been observed beyond the improvements observed with exercise training alone (Blackstock and Evans, 2019). However, although there are no improvements made directly from the educational aspect of PR, patients still find it beneficial to learn about the condition they are living with (de Sousa Pinto et al., 2013), which shows the education is still an important aspect of PR and should continue to be practiced.

Pulmonary rehabilitation is well established as a treatment option for other pulmonary diseases such as chronic obstructive pulmonary disease (COPD), at which there is evidence that the rehabilitation improves exercises capacity as well as reducing symptoms experienced (Spruit et al., 2013). Individuals with ILD often report similar symptoms (e.g., breathlessness (Dowman et al., 2021)) to those with COPD and other pulmonary diseases, given these similarities and that many symptoms can be seen to improve in COPD, its believed that pulmonary rehabilitation would have similar effects for individuals with COVID ILD (Dowman et al., 2021).

The mechanism as to which pulmonary rehabilitation might improve the symptoms of COVID ILD is not yet known. However, in individuals with other respiratory diseases, pulmonary rehabilitation is used to improve aerobic capacity and improve peripheral muscle strength and endurance, leading to an improvement in quality of life (Spruit et al., 2013). Guidelines for pulmonary rehabilitation have encouraged the inclusion of individuals diagnosed with ILD as there is more evidence to support the inclusion of these different patient groups (Spruit et al., 2013). Therefore, patients with ILD and Long COVID should be suitable for participation in pulmonary rehabilitation.

It has been suggested that the effects of pulmonary rehabilitation will not be as effective on individuals with COVID ILD (Dowman et al., 2021). This is because the elderly population are more likely to have underlying comorbidities, such as cardiovascular diseases and osteoporosis, which all negatively impact the performance capacity of individuals, meaning the PR programme may not be as effective (Butler et al., 2019).

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There is limited research and evidence to support the above statement regarding the effectiveness of PR on patients with COVID ILD. . A systematic review and meta-analysis (Reina-gutierrez et al., 2021) provided evidence supporting the effectiveness of PR in patients with ILD and COVID ILD. Improvements in lung function, exercise capacity and health related quality of life (HRQOL) were observed, suggesting that PR is an effective tool for patients with COVID ILD (Reina-gutierrez et al., 2021). A mean increase of 44.55m was observed in the 6MWT, which means a clinically significant increase was observed. A mean increase in forced vital capacity was also observed with an increase of 5.47%, which again is a clinically significant improvement, and although an improvement of a 3.9- point improvement was observed on HRQOL, this fell below the threshold for a clinically significant improvement (Reina-gutierrez et al., 2021). This data supports the claim that PR is an effective tool for improving functional capacity and quality of life in patients with COVID ILD.

How comorbidities could impact the outcome of pulmonary rehabilitation

Many patients admitted to PR programmes are often affected by multiple comorbidities, although the prevalence varies depending on how the comorbidities are reported (Butler et al., 2019). Self-reporting suggests a prevalence of at least one comorbidity in 50-60% of patients, whereas objectively diagnosed comorbidities has shown 97% of patients with COPD entering PR had at least one or more comorbidity, with 53.3% of patients having four or more comorbidities (Butler et al., 2019). Common comorbidities include, but are not limited to; cardiovascular disease, musculoskeletal disease, lung cancer, gastro-oesophageal reflux disease and diabetes. Risk factors of these common comorbidities include age, smoking, sedentary lifestyle and an unhealthy diet (Decramer et al., 2013).

It has been reported that younger patients with comorbidities responded better to exercise and were more likely to improve exercise capacity compared to older patients with comorbidities (Butler et al.,2019). Furthermore, it has been reported that both musculoskeletal and connective tissue diseases and circulatory system diseases negatively impact the ability to improve exercise capacity in a pulmonary rehabilitation programme (Butler et al., 2019). To maximise improvements for everyone in PR, it could be beneficial to individualise each programme to cater to the needs of the patient. This is often not available due to time and space constraints that are often placed upon the PR programmes. By personalising the programme for the patient, it will allow for greater improvements by tailoring the programme to suit the patient due to each patient having different requirements and comorbidities (Wouters et al., 2018). This will likely lead to a great improvement observed in exercise capacity, as it has been suggested that personalised programmes lead to greater improvement (Butler et al., 2019).

Guidelines for pulmonary rehabilitation for patients with COVID-19 in China have been issued to ensure the safety of participants is maintained, these guidelines are as follows:

1. The short-term goal of pulmonary rehabilitation is to alleviate symptoms of dyspnoea, anxiety and depression with the long-term goal to preserve the patients function to the maximum extent, improving quality of life and facilitate the return to society (Yang and Yang, 2020).
2. Before partaking in rehabilitation, assessments should be performed on the patient's clinical symptoms, vital signs and comorbidities, with questionnaires

used to assess quality of life daily activity endurance and psychological factors (Yang and Yang, 2020).

3. Rehabilitation should be carried out in a safe manner with Spo2 levels monitored throughout (<88% minimum threshold), also if symptoms are exacerbated or palpitations/ chest tightness etc are experienced then rehabilitation should be terminated immediately (Yang and Yang, 2020).
4. For mild and moderate cases of COVID-19, rehabilitation should be offered as early as possible. In contrast, in severe cases, life saving measures should be prioritised and rehabilitation should only be offered when patient is stabilised (Yang and Yang, 2020).
5. Operations that increase infectivity should be minimised with social distancing maintained where possible (Yang and Yang, 2020).
6. Evaluation and monitoring should be conducted throughout rehabilitation (Yang and Yang, 2020).

These guidelines are like the strategies applied by pulmonary rehabilitation currently in the UK (Bolton et al., 2013).

An observational study where participants with a mild to critical case of Long COVID took part in a 3-week pulmonary rehabilitation programme produced promising results for the effectiveness of pulmonary rehabilitation (Gloeckl et al., 2021). Following the 3-week pulmonary rehabilitation programme, improvements in 6MWD were observed, with a mean increase of 48m observed (Gloeckl et al., 2021), which is a clinically significant improvement, where an improvement of 30m-32m is considered clinically significant 30m-32m (Shoemaker et al., 2013). This shows that aerobic capacity improved in participants over a course of just 3 weeks, which shows pulmonary rehabilitation improves aerobic capacity of participants.

Summary of introduction

To summarise, COVID-19 is a disease which can have long lasting effects, on many different systems within the body, even after the infection has cleared, which is known as Long COVID **(**Longobardi et al., 2022). The resources available for patients with Long COVID are not widely accessible, with research taking place to look at the treatments for Long COVID. In particular, the impact of pulmonary rehabilitation on the effects of Long COVID symptoms and whether PR is suitable for Long COVID patients. The review of the literature which follows will look at the impact of Long COVID on the body and treatment for this, as well as the mechanisms of Long COVID which bring about these symptoms and complications.

Chapter II: Review of literature

This review of literature will highlight the impact that Long COVID has on the body and exercise, and the mechanisms that cause these changes within the body. Additionally, a focus will be on treatment for Long COVID and whether exercise is a suitable option to improve symptoms of Long COVID.

The effect of Long COVID on exercise

Muscular atrophy of the respiratory system

Patients' ability to exercise after contracting COVID-19 will be affected depending on the severity of the infection (Woods et al., 2020).

At the height of the COVID-19 pandemic in April 2020, in the UK there were 2849 patients placed on mechanical ventilators (National Audit Office, 2020). These patients developed respiratory failure and were required to be placed on a ventilator throughout the recovery period from COVID-19 infection to maintain adequate pulmonary gas exchange (Woods et al., 2020). Fifty four percent of patients hospitalised with COVID-19 suffered with respiratory failure with up to thirty percent of hospitalised patients requiring mechanical ventilation to breathe (Woods et al., 2020). Although the ventilator more often than not saved a patient's life, there were consequences of relying on ventilators to breathe, muscle atrophy occurred at the diaphragm and intercostal muscles, which are vital muscles for ensuring proper breathing with proper breathing techniques (Dres and Demoule, 2018). This muscular atrophy results in a weakness of the diaphragm and intercostal muscles, creating a vicious cycle where patients are taken off the ventilator but due to atrophy, breathing is still very difficult which then requires patients to be placed on a ventilator again (Vassilakopoulos and Petrof, 2004). This muscular atrophy within the respiratory system will negatively impact the individual's ability to take part in exercise. Due to the weakness of the diaphragm and intercostal muscles, the effectiveness of respiration will be reduced on the inhalation and exhalation (Vassilakopoulos and Petrof, 2004). Respiratory muscle weakness leads to a decrease in the tidal volume, therefore limiting the flow of gas during the expiratory phase (Lo Mauro and Aliverti, 2016). This occurs because of reduced chemosensor feedback in response to the rise in carbon dioxide partial pressure (Lo Mauro and Aliverti, 2016). Upper airway resistance also increases, as a result, a drop in oxygen saturation and an increase in carbon dioxide are observed (Lo Mauro and Aliverti, 2016).

The impact of COVID-19 infection on physical activity

A common symptom of COVID-19 is muscle aches, these muscle aches are a direct response to harm to the tissue because of infection in the tissue itself as well as the inflammatory response which causes excessive cytokine release (a cytokine storm) within the muscle tissue (Inciardi et al., 2020). These muscle aches are also present within the heart and the peripheral muscles with COVID-19 infection posing the potential risk of tissue damage within these areas. Muscle scarring induced by viral infection can lead to exertion related arrhythmias as well as myocarditis and heart failure (Inciardi et al., 2020). Furthermore, viral infections can lead to an inflammatory reaction that aggravates the lining of the coronary arteries, inflammation can lead to tears within artery tissue, which in turn can cause fatal arrhythmia or hypoxia and cardiac tissue dying due to lack of oxygen supply. This is a common cause of sudden cardiac arrest and death at rest and during exercise (Thompson and Dec, 2021).

Therefore, the patients that have recovered from COVID infection still face the risk of increased cardiac complications during and after exercise. Post-mortem analysis has revealed that exercising when infected with a viral infection places extra stress on the coronary artery walls due to an inflammatory reaction, this then places the patient at risk of sudden cardiac death during and after exercise (Inciardi et al., 2020). Additionally, myocardial scarring will leave patients at risk of sudden cardiac death for a lifetime (Inciardi et al., 2020). Non- steroidal anti-inflammatory drugs (NSAIDs) are often taken to relive muscle aches and pains during viral infection, such as COVID-19, however, this increases the risk of a patient suffering with cardiac events, so it is advised that NSAIDs are not taken to relive muscle aches and pains while fighting viral infections (Woods et al., 2020).

However, it has been found that patients infected with COVID-19 that take part in mild to moderate intensity aerobic exercise, benefitted from this as the effectiveness of the immune response was increased (Nieman and Wentz, 2019). Therefore, mild aerobic exercise during infection with COVID-19 may outweigh the risks of exercising whilst infected as it means the severity of the infection may be suppressed due to the benefits of the aerobic exercise on the immune response.

Benefits of an increased aerobic capacity to defend against infection

SARS-CoV1 is known to lead to lower respiratory tract infections and extra- pulmonary tuberculosis (Chan et al., 2015), this is a strain like that which caused the SARS-CoV2 (COVID-19) outbreak which means the properties of the disease may have similar effects on the body as SARS-CoV1. T-lymphocyte cells play a major role in fighting viral infections and pathogens. These T-cells increase the production of virus-specific antibodies and own properties that allow the cells to survive in the infected lungs and destroy the infection (Mohamed and Alawna, 2020). This underlines the importance of the role T-lymphocytes playing in controlling and fighting the COVID-19 infection.

Increasing the aerobic capacity leads to an immediate improvement in the action of T-cells and has shown that aerobic exercise can create immediate and long-term improvements in the immune response of leukocytes, T-lymphocytes, lymphocyte subpopulations, interleukins, and immunoglobulins (Gannon et al., 2001).

However, immune activity can be influenced by the mood of the host, with common symptoms of COVID-19 being anxiety and depression, this may also play a part in the effectiveness of the immune activity (Mohamed and Alawna, 2020). It has been found in other studies (Marshall, 2011 and Gaspersz et al., 2017) that mental health and decreased immune activity go hand in hand together, with stress leading to increased morbidity and mortality rates in immune based diseases like COVID-19 (Marshall, 2011). The relationship between mental health conditions and decreased immune activity is unclear, however it is believed that stress can decrease immunity by fluctuating the balance of T-cells, by increasing the level of serum corticosteroids, leading to a decrease in immune response (Marshall,2011).

This takes us back to the point of the benefit of increasing aerobic capacity, as it not only benefits physiologically, with the improvements in T-cells, but also psychologically due to the benefits that are observed in mood when people take part in aerobic exercise due to the effect aerobic exercise has on decreasing stress hormones which were mentioned above, serum corticosteroids (Mohamed and Alawna, 2020). It has been found that performing just ten to thirty minutes of light aerobic exercise is beneficial in improving mood (Reed and Buck, 2009).

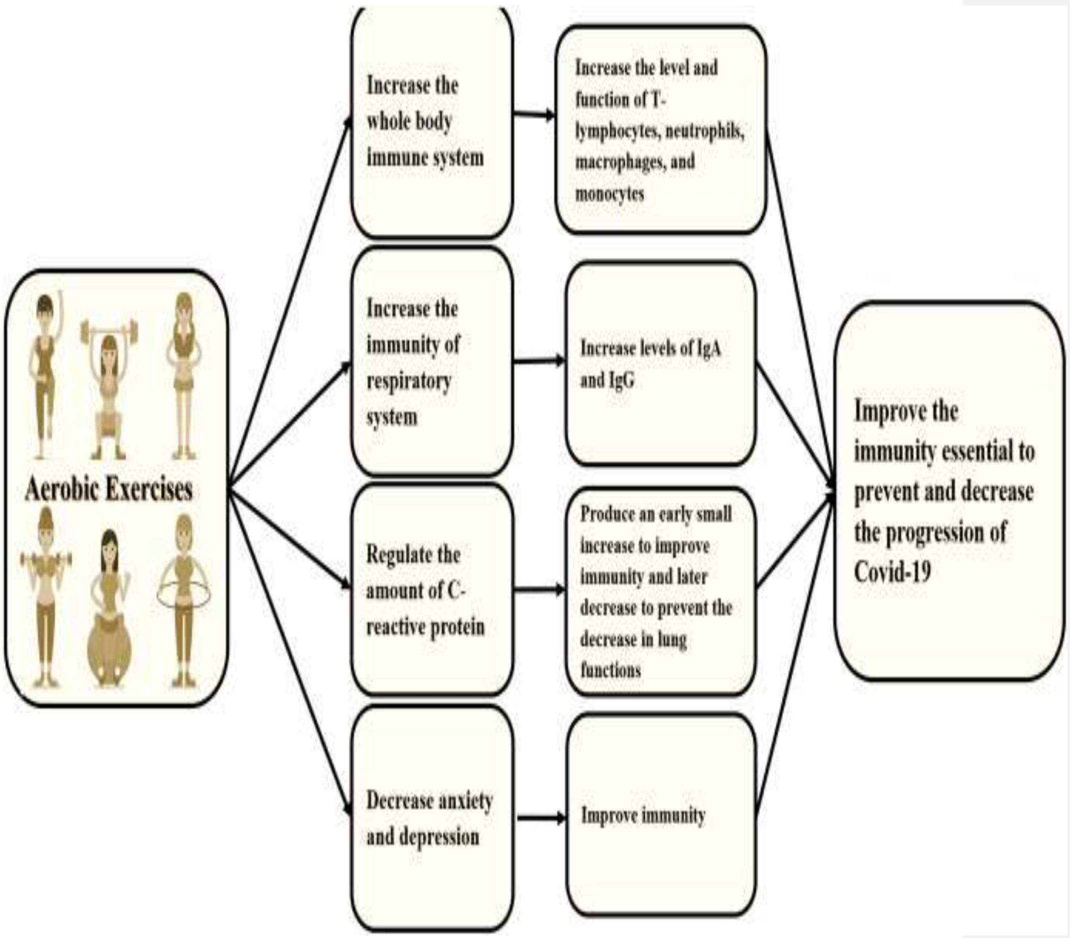

Figure 2.1 highlights how exercise improves the immune system, through different mechanisms (Mohamed and Alawna, 2020).

Aerobic exercise improves the immune response by increasing the levels of T-cells and other cells and elements in the body which fight against infection, increasing the levels of immunoglobulins, which in turn regulate C-reactive protein levels by producing a short-term increase to fight viruses in the lungs and prevent a drop in lung functions long term. Aerobic exercise also decreases the levels of anxiety and depression by rebalancing T-helper 1/ T-helper 2 cells which in turn improves immunity (Mohamed and Alawna, 2020).

COVID-19 mainly affects the respiratory system often causing pneumonia and ARDS (Mohamed and Alawna, 2020). It has been found that increasing the aerobic capacity can play a major role in preventing pneumonia as well as decreasing the severity of pneumonia (Baumann et al., 2012). It has been observed that walking is enough to reduce the risk of pneumonia, respiratory diseases, and pneumonia mortality (Williams, 2014). This occurs due to aerobic exercise producing a significant anti-inflammatory response which attenuates pulmonary inflammation (Olivo et al., 2014). An increased aerobic capacity has also shown to reduce the severity of ARDS as well as prevent it by reducing acute lung inflammation by decreasing cytokines and stress markers (Mohamed and Alawna, 2020).

Mechanisms of COVID-19

Pathophysiological mechanisms of COVID-19

The pathophysiology of COVID-19 is a complex system which consists of multiple mechanisms, although the pathophysiological mechanisms are not one hundred percent agreed on.

A well-regulated immune response to SARS-CoV-2 is essential for controlling the infection and minimising severity of infection, a hyperinflammatory innate immune response combined with an insufficient adaptive response may provoke extensive local and systemic tissue injury (Eijik et al.,2021).

The progressive nature of disease of COVID-19 is deemed to result from a complex interaction between multiple pathophysiological mechanisms. These mechanisms include direct cytopathic effects of SARS-CoV-2 on the cells, a dysregulated immune response featuring a cytokine storm- elevated levels of cytokine and immune- cell hyperactivation, disbalance and decreased inactivation of des-Arg^9-bradykinin and uncontrolled localised and/ or systemic immunothrombosis (physiological process based on the release of neutrophil extracellular traps to immobilise, contain and kill bacteria (Franchi et al., 2019) and auto immunity injury (Eijik et al.,2021).

Immunopathology mechanisms

The innate immune system is the first line of defence against COVID-19 infection. A key part of the innate immune response is the complement system, which acts as a rapid immune surveillance system against pathogens (Eijik et al.,2021). In individuals fighting a COVID-19 infection, the complement activation is vast which results in harmful acute and chronic inflammation, endothelial cell dysfunction and intravascular coagulation (Eijik et al.,2021). This complement activation has been observed in the systemic circulation as well as locally in various organs of individuals infected with COVID-19 (Eijik et al.,2021).

The innate immune system interacts with coagulation, in a process which is known as immunothrombosis (the process of containing and destroying pathogens) which is thought to be dysregulated in cases of severe COVID-19, which therefore leads to coagulopathy (condition in which the bloods' ability to clot is impaired) (Nakazawa and ishizu, 2020).

The adaptive immune system also plays a role in removal and destruction of the COVID-19 pathogen. This happens via activated cytotoxic T-cells that destroy infected cells and through the help of B-cells that produce antibodies which neutralise virus specific antigens (Eijik et al.,2021). Additionally, reinfection could be caused by a loss of germinal centre formation within the spleen and lymph nodes which provides potential for suboptimal humoral immunity (Tillett et al., 2021). Overall, a coordinated response to COVID-19 infection via the adaptive immune response is linked with a milder infection and are therefore vital for controlling viral infections.

Effect on respiratory system

COVID-19 primarily targets the respiratory system with viral entry in to the upper and lower respiratory epithelial cells, leading to influenza-like symptoms such as fever, cough, and dyspnoea (Sungnak et al., 2020). In the latter stages of the infection, hyperactivation of immune responses often leads to extensive hyperinflammation, followed by development of severe disease, including ARDS (acute respiratory distress syndrome). Additionally, DAD (Diffuse alveolar damage) with interstitial T-cell infiltration has been observed in individuals during histological examinations. Additionally in some cases more severe forms of DAD had been observed, these being acute fibrinoid and organising pneumonia (Kory and Kanne, 2020). An autopsy study learned that two distinct immunopathological reaction patterns in the lungs of deceased COVID-19 patients. There were two subgroups, the first, patients died early after being admitted to hospital with relatively limited pulmonary pathology, implying that there were other contributing factors to the death. The second group was made up of patients that had a longer disease course, yet also prominent DAD (Nienhold et al., 2020).

Another main finding from the autopsy study was that vascular alterations were observed, including the presence of intussusceptive angiogenesis (process of new blood vessels being created) and severe endothelial injury (Ackermann et al., 2020). This endothelial injury can allow for an increase in the formation of microthrombi due to local dysregulated immunothrombosis (Ackermann et al., 2020).

Effect on Cardiovascular system

Pre diagnosed cardiovascular diseases is correlated with poor prognosis of COVID-19, whereas COVID-19 itself can induce cardiovascular complications, these include acute heart failure, arrythmias, acute coronary syndrome and myocarditis (Shi et al., 2020). Myocardial inflammation has also often been reported after recovery of COVID-19. It's been suggested that myocarditis occurs as a result from direct cardiotoxic effects of COVID-19 or from triggering an auto immune response against cardiac components (Lindner et al., 2020). COVID-19 has also been detected in a variety of cells in myocardial tissue, this indicates that SARS-CoV-2 may directly infiltrate the heart via the bloodstream or also indirectly via immune cell transmigration (Lindner et al., 2020).

Cardiac inflammation has also been very commonly reported, a prospective autopsy cohort study analysing postmortems of the heart from twenty COVID-19 patients found that epicarditis and endocarditis were present in all twenty cases, whereas myocarditis was observed in 55% of patients (Schurink et al., 2020).

Host specific factors that can determine the severity of disease

Inter-individual differences are a suitable explanation as to why people suffer differently when infected with COVID-19 (Eijik et al.,2021). Ageing and disease control failure are often linked with uncoordinated responses of adaptive immunity. Immunosenescence is a condition which is linked to the age-related decline in immune function, this affects the pathogen recognition, alert signaling and clearance, 3 of the 4 stages of the immune system (Mueller et al., 2020). This therefore affects the innate and adaptive immune responses, reducing the impact of the immune response against fighting infection compared to that of a younger person (Mueller et al., 2020). Additionally, aging leads to a common immune system change of a chronic increase systemic inflammation called inflammaging, which is caused by an overactive but ineffective alert system (Mueller et al., 2020). These adaptive changes (Immunosenescence and inflammaging) that occur as age increases can explain why elderly people are at greater risk of COVID-19 infection compared to younger people.

Adults over the age of 65 account for eighty percent of hospitalisations and have a twenty- three times greater risk of death than those under the age of sixty-five (Mueller et al., 2020). Additionally, mortality rates in those over the age of eighty is eighteen-point eight percent, compared to just eight-point three percent in individuals aged over fifty. This is due to the prevalence of comorbidities such as hypertension, diabetes, and obesity (Niu et al., 2020).

Following on from this, it is not just age that has been shown to affect the severity of disease, male patients showed a healthier innate immune response with higher plasma cytokine levels, compared to female patients that had healthier T-cell activation (Takahashi et al., 2020). It was found that when males had a poor T-cell response, the disease was more severe compared to females who experienced a more severe disease when higher levels of cytokines were detected (Takahashi et al., 2020). This discovery could potentially mean that different treatments may be required for different genders. A multicentre study where 40 men and 40 women who were treated for severe COVID-19 in ICU and required mechanical ventilation were compared (Jirak et al., 2022). The study reported that males in ICU had longer intubation times, longer ICU stays and higher rates of catecholamine dependence. Male patients also displayed a higher disease severity, this was reflected in higher rates of vasopressors, duration of ICU stay and duration of intubation (Jirak et al., 2022). In comparison, there were no differences observed in mortality rates, organ replacement therapy and complications during the ICU stay (Jirak et al., 2022).

An analysis of COVID-19 related deaths reported that the male mortality rate was 1.77 times higher, compared to females, with this observed worldwide (Yanez et al., 2020). There are various explanations as to why the mortality rate is increased in males, molecularly, higher expressions of ACE-2 occur in males, which is a key factor for cell entrance of the virus (Hoffmann et al., 2020). Additionally, females generally exhibit more robust cell-mediated immune responses to antigenic challenges such as infection and vaccination compared to males, due to different types of oestrogens which can mediate many of the sex-based differences in immune responses (Fish, 2008). Women also have a higher CD4 T-cell count than men (Fish, 2008). One potential treatment method considered was to increase the ACE-2 activity in men as a therapeutic option for COVID-19 treatment as which was considered in the SARS outbreak of 2002/2003 (Kassiri et al., 2009). However, this was shown to increase the risk of organ failure in specific organs when infected with SARS in 2002/2003 (Yang et al., 2010).

A poor T-cell response, otherwise known as T-cell exhaustion, is a state of T-cell dysfunction that arises during many chronic infections and cancer. T-cell exhaustion is defined as a poor effector function and a sustained expression of inhibitory receptors (Wherry, 2011). T-cell exhaustion prevents optimal control of infection and tumours

(Wherry, 2011). For adults, a normal CD4 cell count, which is a type of T-cell, is anywhere between 500-1200 cells/mm^3 (Hocqueloux et al., 2013) Anything below this threshold is considered a low T-cell count, and possibly a sign of T-cell exhaustion. However, to test for T-cell exhaustion, is a very analytically robust process. Increased inhibitory receptor levels alone are not a sufficient measure to analyse the exhaustion of T-cells. Instead, it is the measurement of secreted cytokine levels after stimulation coupled with the inhibitory receptor levels that enables the ability to approximate exhaustion of a T-cell population (Schillebeeckx et al., 2022).

Figure 2.2 below highlights the many different reasons as to why everyone may be affected by COVID-19 disease differently.

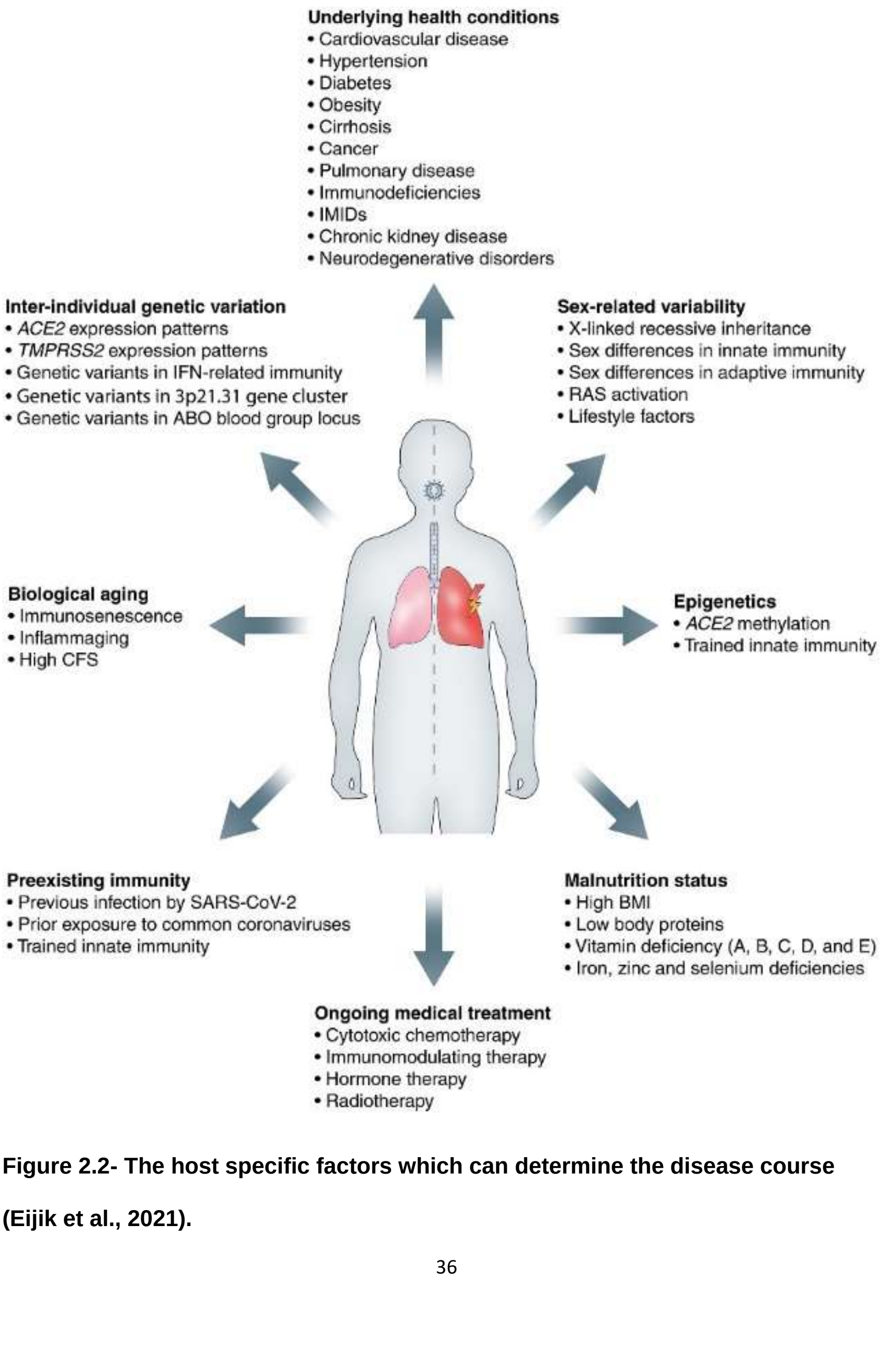

Figure 2.2- The host specific factors which can determine the disease course (Eijik et al., 2021).

Individuals with underlying morbidities and single severe diseases are at greater risk of developing severe cases of COVID-19, including those individuals with cardiovascular disease, hypertension, diabetes, pulmonary disease, immunodeficiencies and obesity to name a few (Williamson et al., 2020). A cross- sectional study carried out in the Netherlands (Van Der Voort et al., 2020) found that obese patients in ICU had increased activity of pulmonary leptin receptors, this led to increased local inflammation which further decrease the patient's ability to breathe due to the obese state already (Eijik et al., 2021).

An observational study found that ICU admission was higher in patients with comorbidities, as 35.8% of them required ICU admission, compared to 16.4% of those without any comorbidities (Khedr et al., 2022). Patients with comorbidities also required invasive mechanical ventilation more than those without comorbidities (31% vs 10.7%) (Khedr et al., 2022). The study was made up of 439 moderate to severe COVID-19 patients, with a mean age of 51.2. One factor that can attribute to this increase in comorbidity severity is that age is often linked with comorbidities, the more elderly a population, the more vulnerable they are to comorbidities as well as infection of COVID-19 (Khedr et al., 2022). A weakness of elderly patients is that the function of T and B-cells are often reduced, along with the excess production of type 2 cytokines, which can lead to an increased inflammatory response, leading to a higher chance of severe infection and mortality (Khedr et al., 2022). Additionally, the upregulation of ACE-2 expression in different parts of the body, like the heart and lungs, in patients with diabetes or CVD, increases the susceptibility to COVID-19 infection. This also increases the risk of disease aggravation as it has been identified as an important functional receptor for COVID-19 infection (Khedr et al., 2022).

The mechanisms of COVID specific to breathlessness

CT scans on patients infected with COVID-19 highlighted pneumonia and ground glass opacities because of inflammation within the respiratory system (Rothan et al., 2020).

The main mechanisms in which COVID-19 can cause dyspnoea are inflammation of the alveoli and lung tissue and thrombosis and associated micro clots (Hentsch et al., 2021).

Inflammation in the alveoli and lung tissue

Inflammation in the alveoli and lung tissue are responsible for the impaired gas diffusion capacity and intrapulmonary shunting, causing hypoxaemia with hypocapnia (Hentsch et al., 2021). Autopsy findings of patients with confirmed COVID-19 found there was significant alveolar damage as well as severe capillary congestion, oedema and alveolar haemorrhage (Menter., et al., 2020). Inflammation and oedema caused by COVID-19 increases the distance between the alveoli and capillaries, this can contribute to decreased diffusion, through which carbon dioxide continues to diffuse because of its higher diffusion coefficient, whereas oxygen diffusion diminishes (Hentsch et al., 2021). Additionally, because of pulmonary oedema and the following reduction in alveolar air space, intrapulmonary shunting occurs because of the persistence of arterial perfusion in non-aerated lung tissue (Hentsch et al., 2021). Finally, patients affected by mild to moderate COVID-19 have an increased ventilatory drive in response to hypoxaemia, maintaining low levels of carbon dioxide (Hentsch et al., 2021).

Thrombosis and micro clots

Thrombosis and micro clots are responsible for an increase in ventilation/ perfusion mismatch and physiological dead space. However, there is evidence that COVID-19 infection causes an activation of the coagulation cascade and subsequent endothelial damage resulting in a prothrombotic state. This has very commonly been observed within COVID-19 patients, with the coagulation activation and endothelial dysfunction recognised as predictors of further complications after infection and death (Lodigiani et al., 2020). It's believed these responses are an attempt to prevent DAD, however in reality they worsen respiratory failure through extensive formation and deposition of fibrin. Furthermore, multiple thrombi in pulmonary vessels can impair perfusion by increasing the functional dead space in the alveoli (Spiezia et al., 2020).

How does long COVID affect breathlessness and fatigue?

Although COVID-19 is described as a multi- organ infection, its primarily defined as a respiratory infection, which often creates a sustained restrictive lung function pattern after individuals have recovered from infection (Stockley et al., 2021).

A decrease in lung functions in patients that were admitted to ICU was observed with adult respiratory distress syndrome and barotrauma (caused due to high pressure ventilators used in ICU wards) often leading to pulmonary fibrosis in a systematic review carried out by Stockley et al., 2021. Furthermore, it was also observed that in 78.1% of patients, there was a slightly raised carbon monoxide transfer coefficient (K_{CO}) which is often more consistent with patients suffering with an extrapulmonary pathological infection (Stockley et al., 2021). This is an important finding as a raised K_{CO} figure can mean that the lungs are incapable of fully expanding to the predicted level (Hughes and Pride, 2012). Furthermore, a high K_{CO} figure indicates that pulmonary capillary volume is prioritised over alveolar ventilation due to incomplete alveolar expansion. This means that the lungs will not be receiving the required amount of oxygen needed for the body, as well as a reduced capacity at expelling carbon dioxide from the body (Bryan et al., 1964). This could explain the breathlessness which is observed by patients during and after COVID-19 infection.

Additionally, a three month follow up study of COVID-19 survivors showed that pulmonary radiological abnormalities and functional impairments were detected in seventy one percent and twenty five percent respectively, with ten percent developing severe pneumonia (Yong, 2021). Even up to six-months after symptom onset, lung radiological abnormalities associated with persistent symptoms were still present in approximately half of the COVID-19 survivors (Huang et al., 2021). It has also been found that pulmonary issues related to long COVID are often not detectable by standard CT scans, and further pulmonary complications may have been missed during diagnosis (Li et al., 2021). It was found that maximal aerobic capacity was reduced among young participants with symptomatic COVID-19, and it is believed that pulmonary scarring may be a common sequela, which is most likely responsible for the persistent dyspnoea and cough in long COVID (Swigris et al., 2014).

An autopsy study examined lungs obtained from patients who died from COVID-19 infection and found that there was severe endothelial injury and disrupted endothelial cell membranes (Ackermann et al., 2020). As a result of this, the blood vessel walls will begin to vasodilate leading to decreased blood flow to the heart through the coronary artery. Furthermore, it was observed that there was widespread vascular thrombosis with microangiopathy and obstruction of the alveolar capillaries, because of this, diffusion will be limited due to the blockages within the capillaries, therefore effecting the efficiency of breathing and the ability to expel carbon dioxide (Ackermann et al., 2020).

Mechanisms of breathlessness related to Long COVID

The perception of breathlessness begins in the lungs and lower respiratory tract, where unmyelinated C-fibres and small myelinated Aδ- fibres transmit chemical and mechanical signals to the nucleus of the tractus solitarius in the brain stem, through the afferent vagal nerves. These fibres are only activated when triggered by noxious stimuli and are considered nociceptive. After converging at the nucleus of the tractus solitarius, these fibres are relayed to the somatosensory cortex where the signal is interpreted, and in turn generating a perception of breathlessness (Gonzalez-Duarte et al., 2020). It has been found that negative emotions have a major impact on breathlessness perception, while positive emptions reduce the intensity of perception of breathlessness (Von Leupoldt et al., 2006). This could lead to individuals' perception of breathlessness being wrongly misinterpreted due to the negative emotions such as anxiety and depression that are often reported by individuals with Long COVID, therefore increasing the duration of the symptom of dyspnoea.

It has been hypothesised that the cause of dyspnoea can be related to a common central nervous system pathway due to other conditions causing the same sensation of dyspnoea, these conditions include lung disease, chronic heart failure and neurodegenerative disease (Parshall et al., 2012).

There are many hypotheses raised as to how and why dyspnoea occurs after infection. To begin with, it is suggested that the neuroinvasive potential of COVID-19 may be responsible for the variation in breathlessness perception due to its effect on the brainstem and the medullary cardiorespiratory centre of infected patients (Li et al., 2020). A decreased breathlessness perception may also be a reason for dyspnoea due to the adaptation of the peripheral structures such as the altered perception of muscle effort, decreased thoracic compliance or altered input from mechanoreceptors from the respiratory tract and chest wall (Dhont et al., 2020). Finally, it has also been hypothesised that COVID-19 directly impacts the vagal nerve, therefore affecting the chemical receptors on the nerve which are responsible for the exacerbation of dyspnoea (Das et al., 2020)

The impact of exercise as a treatment for long COVID

Throughout the pandemic, exercise choices were limited due to the closure of gyms, social distancing, and the fear of contracting COVID-19, this led to a decline in the amount of people exercising during the lockdowns which in turn, lead to exercise deterioration of many people, which as mentioned above, exercise played a major role in fighting the infection as well as preventing it.

Exercise can be used as a tool to manage the symptoms of patients with long COVID, as exercise has been shown to be beneficial in the recovery in multiple pathologies in which long COVID shares similarities in both symptoms and mechanisms (Almazan et al., 2021). For example, dyspnoea is a commonly reported symptom of Long COVID, however, one benefit of exercise is that oxygen uptake is increased, which is suggested as to one of the reasons as to how dyspnoea can improve after exercise (Almazan et al., 2021). See figure 2.3 below.

The common symptoms of long COVID are illustrated below in figure 2.3, along with the benefits of exercise and how this will help improve the symptoms experienced.

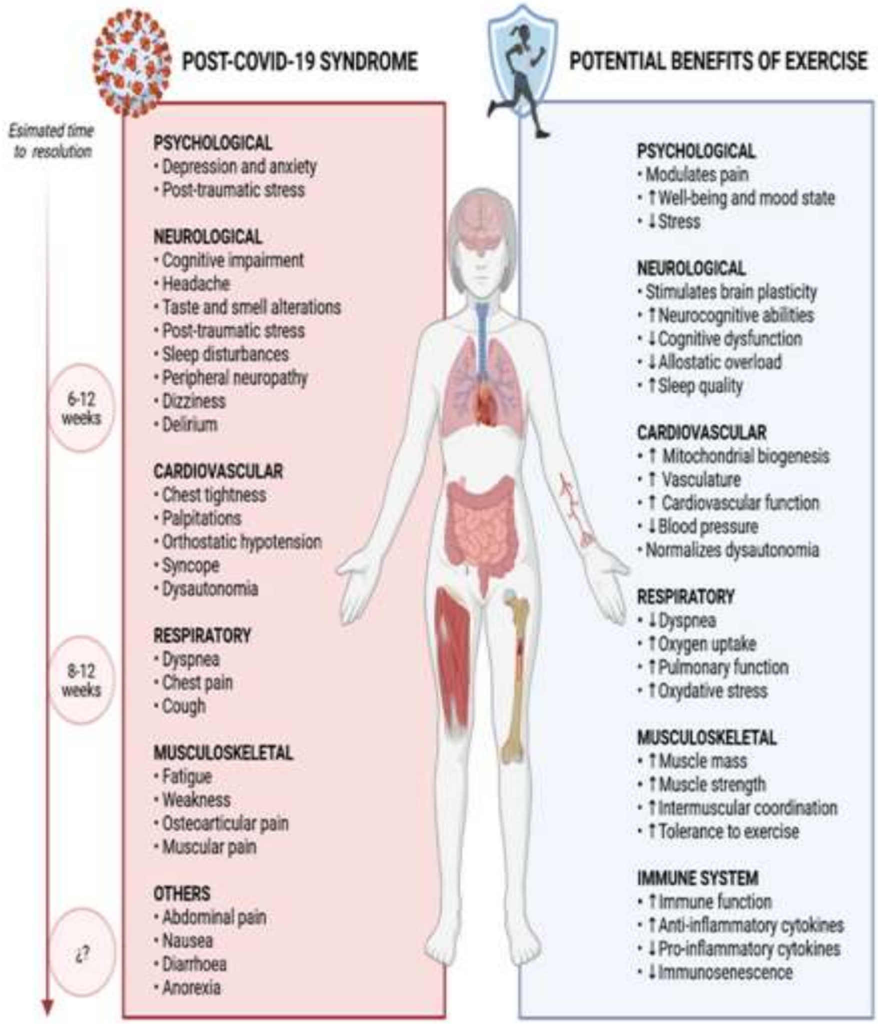

Figure 2.3 highlights the proposed common symptoms and complications experienced with long COVID and the benefits of exercise (Almazan et al., 2021)

The effect of exercise on musculoskeletal diseases that impair exercise

Exercise has been recommended as a non-pharmacologic strategy for treatment of musculoskeletal diseases, which entail symptoms such as chronic pain, muscle weakness, fatigue, and low tolerance to exercise, (Hilberdink et al., 2020) which are also symptoms of long COVID. Strength training has been shown to be beneficial in reversing frailty and muscle weakness in elderly and vulnerable people as well as restoring functional capacity in the short and long term (Asteasu et al., 2020). Furthermore, strength training provides multi-systemic benefits to the musculoskeletal system. These include neurological benefits such as improving intermuscular coordination and regulating the whole-body metabolism as well as increasing the synthesis of contractile assemblies of actin and myosin (Maestroni et al., 2020). These benefits that are observed will allow for improvements in quality of life due to the adaptations of actin and myosin which will make everyday tasks easier like lifting themselves out of a chair and housework, for people that suffer with muscle weakness and fatigue.

Recent studies (Van Zanten et al., 2021) have identified that strength training using low intensity and low volume produced significant improvements in maximal dynamic strength, power output and muscular hypertrophy whilst also preventing delayed onset of muscle soreness which is typically experienced when partaking in strength training (Vieira et al., 2021). This is relevant for long COVID patients since many patients suffer with fatigue, muscle weakness, deconditioning and low tolerance to exercise, which often makes long COVID patients reluctant to exercise.

It is key to start patients with long COVID symptoms at a low level of intensity to ensure patient retention is high, as any exercise is better than no exercise. If the exercise intensity begins too high, then it is likely that the patient will not complete an exercise programme due to not being able to tolerate the exercise because of the symptoms suffered.

Methods to assess breathlessness, anxiety and quality of life in respiratory patients

One of the aims of pulmonary rehabilitation is to relieve symptoms of respiratory diseases, such as breathlessness, anxiety, and quality of life. These symptoms are often managed and assessed using a variety of questionnaires. Quantifying these symptoms using scales and questionnaires is vital in order to describe the level of chronic disability and to assess the changes of symptoms after intervention (Crisafulli and Clini, 2010).

There are many questionnaires and scales that are used to assess breathlessness in patients with respiratory diseases in pulmonary rehabilitation. Breathlessness is often the main symptom present within PR patients; by using dyspnoea as an outcome measure, it allows for comparison of symptom changes after intervention and to assess the efficacy of the intervention for each individual patient (Crisafulli and Clini, 2010). There is a series of descriptors that are used to define dyspnoea in patients, these are chest tightness, increased effort of breathing, unsatisfied inspiratory effort, rapid or superficial breathing and breathlessness (Crisafulli and Clini, 2010). The difficulty in measuring and assessing a symptom involves being able to translate a subjective personal experience into a quantifiable figure (Crisafulli and Clini, 2010). Dyspnoea can only be assessed through direct assessment of the specific symptom and is impossible to evaluate the levels of dyspnoea through direct physical assessment, such as spirometry (Crisafulli and Clini, 2010). For this reason, questionnaires, and scales such as the chronic respiratory questionnaire and the Borg breathlessness scale are used to assess the levels of dyspnoea experienced by patients and to determine the efficacy of the intervention on the patient. Additionally, questionnaires and scales are often used to assess anxiety and quality of life by quantifying the symptom the patient experiences. and the GAD-7 is an example of a questionnaire used to assess anxiety changes.

The Chronic respiratory questionnaire is often used to assess quality of life in patients with COPD and is a self-reported questionnaire, with the questionnaire being split in to four categories; dyspnoea, fatigue, emotional and mastery (Wijkstra et al., 1994). However, due to the questionnaire being self- reported, there is room for inaccuracies and over and under estimations of symptom severity. It’s been suggested that the fatigue, emotional and mastery sections of the questionnaire are valid and reliable, however the dyspnoea section had lower validity and reliability of scores provided (Wijkstra et al., 1994). It has been recommended to score dyspnoea separately using a separate breathlessness scale for more valid and reliable results (Wijkstra et al., 1994).

The patient health questionnaire (PHQ-9) is a self-administered depression questionnaire, with the questionnaire assessing the presence and severity of depressive symptoms (Kroenke et al., 2001). Its been suggested that the PHQ-9 provides valid and reliable results of depression severity, as well as providing sensitive results, which makes it a useful tool in a clinical and research setting (Kroenke et al., 2001).

The generalised anxiety disorder (GAD-7) questionnaire is a seven-point self-report anxiety questionnaire which is used to assess patients' anxiety status within the last 2 weeks (Williams, 2014). The GAD-7 has been shown to be sensitive at determining change in anxiety status when used in a clinical setting, whilst also providing reliable results (Williams, 2014). This suggests that the GAD-7 is a reliable questionnaire to use for assessing anxiety change.

Additionally, the medical research council (MRC) questionnaire is a tool used to study respiratory epidemiology in communities and occupational groups. It reliably relates symptoms and lung functions (Cotes and Chinn, 2007). The MRC is self-administered questionnaire which allows participants to answer truthfully without feeling embarrassed by having to explain symptoms to a practitioner, however the questionnaire can also be answered in an interview type setting depending on the preference of the participant. The MRC has shown to be effective and reliable at identifying and categorising patients with respiratory diseases (Bestall et al., 1999).

The COPD assessment test (CAT) is a self-administered questionnaire that measures health related quality of life (Gupta et al., 2014). The CAT is based on 8 areas of symptoms experienced and is scored on a 0-5 scale, with 0 being no impairment and 5 being severe impairment. The CAT isn't used to diagnose patients with COPD, it is more of a tool to allow patients to be able to express how their symptoms are affecting them (Gupta et al., 2014). It has been suggested that the CAT is a reliable and valid tool for assessing patients with COPD, and is responsive to interventions (Gupta et al., 2014). This indicates that the CAT could be a useful tool for assessing patients with long covid symptoms due to similar symptoms experienced, as well as similar exercise programs prescribed.

There is evidence that both anxiety and quality of life are often improved after a PR programme, with both measures being assessed by various questionnaires that are available (Camp et al., 2000), with clinically significant changes observed in both measures. Additionally, another method of gathering data regarding the symptoms experienced by a patient is through personal interviews. By completing this interview, it allows for a more personalised and personal touch to the PR, allowing a rapport to be built from the get-go, it also allows the patient to elaborate on certain aspects if needs be compared to just answering what could be vague questions (Camp et al., 2000). There are suggestions that interview methods are often beneficial to identifying unique issues, which can be unique to each individual which may not be picked up by a questionnaire (Camp et al., 2000). However, due to the number of patients that pass-through PR, this will require a lot of resources and can prove very time consuming to complete for every individual, which is often why personal interviews are not often used within the NHS (Camp et al., 2000).

Treatment for long COVID

The literature for Long COVID treatment thus far is limited and is pointing towards rehabilitation as the best treatment overall for Long COVID.

Within the rehabilitation, patients are advised to complete light aerobic exercise at an intensity according to the individuals exercise capacity (Yong, 2021). The intensity is then gradually increased as exercise becomes easier and improvements in dyspnoea and fatigue are seen, usually this takes four to six weeks (Yong, 2021). As part of the rehabilitation, breathing exercises should also be included. These breathing exercises aim to control slow, deep breaths to strengthen the respiratory muscles, improving the efficiency, especially the diaphragm (Yong, 2021).

The literature is providing conclusions to these rehabilitation style treatments for Long COVID. An observational study of 23 discharged COVID-19 patients with Long COVID symptoms took part in a personalised rehabilitation programme involving breathing, mobilisation and psychological interventions saw an improvement in lung functions and physical capacity, although most participants lung functions did not heal entirely and neurological symptoms remained present (Puchner et al., 2021). Additionally, a randomised control trial of seventy-two elderly COVID-19 survivors found that a six-week rehabilitation programme, made up of breathing exercises, stretching and home exercises, improved lung function, exercise capacity, quality of life and anxiety, although no improvements were noticed in depression (Liu et al., 2020).

What is breathing pattern training and the different types?

The diaphragm plays an important role in the mechanism of breathing, with its movement helping with inhaling and exhaling, however, after viral infections and deconditioning, the breathing pattern is likely to be altered with less emphasis on diaphragmatic breathing and more reliance on accessory muscles such as the neck and shoulders (Greenhalgh et al., 2020). As a result of this, the tidal volume begins to reduce, with an increase in breathing frequency which results in higher energy expenditure to the action of ventilation, increasing fatigue and breathlessness due to shallow breathing (Greenhalgh et al., 2020). These effects of decreased tidal volume are also symptoms of long COVID, this means that breathing pattern training could have an impact on the severity of symptoms experienced by patients suffering with long COVID if they are educated on how to retrain their breathing pattern.

Types of breathing pattern training

There are many types of breathing pattern training aimed at helping individuals return to diaphragmatic breathing as opposed to shallow breathing.

One form of breathing pattern training is called the “breathing control” technique, this aims at normalising the breathing pattern to improve reliance on respiratory muscles such as the diaphragm and intercostal muscles, because of this, it should reduce the energy expenditure and reduce fatigue levels as well as breathlessness experienced by the patient (Greenhalgh et al., 2020). This can be completed by making sure the patient is sat upright against a chair and instructing them to inhale through the nose and exhale through the mouth ideally, whilst sitting with relaxed shoulders and chest, whilst allowing the stomach to rise. The inspiration to expiration ratio should aim to be 1:2, this technique is very simple to complete and can be completed multiple times throughout the day (Greenhalgh et al., 2020).

This is important for individuals suffering with long COVID as well due to the reduction in breathlessness and fatigue, which means that the severity of symptoms experienced can be helped just by altering the breathing pattern.

Another type of breathing pattern training is diaphragmatic breathing. This is slow, deep breathing that affects the brain and the cardiovascular, respiratory and gastrointestinal systems through the modulation of autonomic nervous functions (Hamasaki and Hidetaka, 2020). Diaphragmatic breathing seems to be beneficial when it comes to improving the exercise capacity and respiratory function in patients with chronic obstructive pulmonary disease (COPD), there are also signs that this breathing technique may also help in reducing stress and anxiety (Hamasaki and Hidetaka, 2020).

Diaphragmatic breathing could be beneficial for long COVID patients that suffer with stress and anxiety, due to COPD and long COVID patients often sharing similar symptoms, which may allow for a reduction in stress and anxiety in long COVID patients, due to the breathing pattern training, even if a short-term improvement is observed (Saha and Sharma, 2022).

Pursed lip breathing is another type of breathing pattern training that is used in patients with respiratory diseases (Fleig et al., 2018). Pursed lip breathing is described as nasal inspiration followed by prolonged expiration with the lips partly closed and is a ventilatory strategy frequently used by patients with COPD to relieve dyspnoea, with its practice often taught in pulmonary rehabilitation to increase exercise capacity (Fleig et al., 2018). This breathing technique could be useful for long COVID patients due to dyspnoea often affecting long COVID patients. This means that pursed lib breathing could be another effective breathing technique that can be used as a tool to reduce dyspnoea.

Summary of review of literature

To conclude, its widely agreed that exercise is a suitable treatment for Long COVID, with studies providing evidence of improvements in Long COVID patients after taking part in exercise programmes (Yong, 2021, Puchner et al., 2021, Liu et al., 2020, Romanet et al., 2023). However, more research is still required on this subject. It has also been found that there are multiple mechanisms of Long COVID which led to breathlessness and fatigue being experienced as a symptom, with pulmonary fibrosis often being developed throughout the recovery process of Long COVID, if patients were placed on ventilators (Stockley et al., 2021). Additionally, pneumonia has been seen to present in patients with Long COVID (Yong et al., 2021), with pulmonary scarring also present which is most likely responsible for breathlessness and the cough experienced with Long COVID (Swigris et al., 2014).

Finally, the symptoms of Long COVID, such as anxiety, depression and quality of life are often increased due to dyspnoea, fatigue, and reduced exercise capacity (berenguera et al., 2021). Therefore, it was important to analyse how anxiety, depression and quality of life are affected and how to improve these symptoms, with exercise also being proven to improve these symptoms (Gloeckl et al., 2021).

Research question

What is the impact of pulmonary rehabilitation (exercise and education) on exercise capacity, breathlessness, and quality of life in patients with symptoms of Long COVID and ILD?

Hypothesis

For this thesis, the hypothesis is that participants exercise capacity will increase which will be observed through the 6MWT score. After partaking in pulmonary rehabilitation, symptoms of Long COVID will also reduce in severity, with a reduction in dyspnoea, fatigue, anxiety and depression observed, along with improvements in wellbeing.

Chapter III: Method

The University of Kent School of Sport and Exercise Science Ethics Board granted ethical approval for this study. Additionally, Medway Community Healthcare approved our request to use their data, anonymously for this current study.

This observational study has been conducted following the STROBE guidelines for observational studies using the 22 point checklist (Cuschieri, 2019).

Participants

All participants that were part of this pulmonary rehabilitation were aged 18 and over, diagnosed with COVID ILD and experienced respiratory symptoms (e.g., breathlessness, fatigue, anxiety and depression, Dowman et al., 2021) at the time of rehabilitation. The mean age of participants was 62.0 ± 11.4 years old with a gender split of 8 males to 6 females.

Participants for this pulmonary rehabilitation were referred on to the Pulmonary rehabilitation team via either a respiratory consultant or were discharged from hospital and were then sent for a pre assessment if they met the inclusion criteria.

Inclusion criteria

Diagnosed with COVID ILD

Experiences symptoms of COVID ILD (Dowman et al., 2021):

Dyspnoea, fatigue, anxiety and depression

Oxygen saturation (Sp02) at rest greater than 92%

Heart rate less than 100bpm at rest

Blood pressure less than 180/ 100mmHg

Exclusion criteria

Cardiac health complications (e.g coronary heart disease, angina, peripheral artery disease)

Unmotivated and unwilling to take part in exercise consistently

Unable to travel to health centre where rehabilitation takes place

Any co-morbidities that severely restricts participants mobility e.g., wheelchair bound

Uncontrolled hypertension- above 140/ 100mmHg and not being treated or medication is ineffective

Unexplained haemoptysis (coughing up blood)

Not referred by a respiratory consultant or discharged from hospital

Pre assessment

If participants met the inclusion criteria, then they were invited to enrol for the 6-week pulmonary rehabilitation programme. Before participants could begin the 6-week programme, basic health measurements were required as well as an understanding of the participants' symptoms they suffer with, as well as the severity, (the pre assessment lasted roughly about an hour and a half). This was achieved through the use of multiple questionnaires.

The questionnaires used were as followed:

Chronic respiratory questionnaire (CRQ, (Guyatt et al., 1987)

Patient health questionnaire (PHQ-9, (Kroenke et al., 2001)

Generalised anxiety disorder (GAD-7, (Spitzer et al., 2006)

Medical research council (MRC, (Williams, 2017)

COPD assessment test (CAT, (Gupta et al., 2014)

These questionnaires focused on different aspects of symptoms that participants may have been experiencing, the CRQ provided an insight into the symptom experience of the participant, levels of anxiety, quality of life, fatigue, and the level of breathlessness experienced (Guyatt et al., 1987). The PHQ-9 was used to determine the levels of depression the participants were experiencing as well as the symptoms they experienced/ may have been experiencing due to depression (Kroenke et al., 2001). Additionally, the GAD-7 allowed participants to express the levels of anxiety they were experiencing prior to taking part in the pulmonary rehabilitation programme (Spitzer et al., 2006). On top of this, the MRC dyspnoea scale was used to assess the level of functional disability due to breathlessness experienced (Williams, 2017). Finally, the CAT was used to assess the symptoms of COPD and the effect these symptoms had on the participants everyday life and wellbeing (Gupta et al., 2014). These participants were not diagnosed with COPD, the questionnaire measures symptoms associated with lung health conditions and is used for other lung conditions, which is why it was used for this study.

Following the completion of the questionnaires, participants basic health data was collected, this data consisted of Sp02, Heart rate and blood pressure which was taken at rest as well as height, weight, and a resting BORG scale, the scale used was the Borg 1-10 breathlessness scale (Borg et al., 2010). Following the collection of this data, the participant could then move on to complete the 6-minute walk test.

6-minute walk test (6MWT)

The 6-minute walk test is a submaximal exercise test which is used to assess aerobic capacity and endurance. The distance covered over the duration of 6 minutes in metres is used as the outcome which is used to compare changes in functional capacity (Rikli and Jones, 1998). In addition, participants oxygen saturation and dyspnoea during exertion can also be collected throughout the duration of the test. The 6MWT became popular due to the ease and minimal equipment required to complete the test, along with increased safety for participants. The test also better reflects activities of everyday life compared to other aerobic capacity tests (Rikli and Jones, 1998).

Before the 6MWT could begin, the participants were instructed how the test works and what is expected of them within the test. The participants completed the test twice for the pre assessment. A familiarisation test was first completed to allow the participants to get used to the test, allowing the participants to practice pacing and with the aim to reduce variability (Hibbert et al., 2017).

The 6MWT was set up by marking a 10-metre stretch with cones at either end used as turning points for the participants, this is due to the hall not being large enough to be able to complete a 30m stretch. Chairs were also placed along either side of the walking stretch in case of exacerbation of symptoms of any participants, this allowed them to have a space to rest if needed. Once, the stretch is set up, the participants can begin the 6MWT. It was important to encourage and motivate the participants throughout the duration of the test as this extra motivation can lead to participants pushing themselves further, with it being shown that motivation and encouragement can increase 6MWD by up to 30% (Enright, 2003). It was also important that if participants carried an oxygen supply with them, that there was no assistance with this as this could have affected the individuals walking distance (Enright, 2003).

A lap counter was used to keep track of the distance travelled by the participants, and if a participant did not complete a full lap at the end of the 6-minute duration, then a trundle wheel was used to measure the distance covered in the uncompleted lap. Upon completion of the familiarisation test, participants were given 20 minutes to recover before then completing the pre assessment 6MWT with the set up the same. Once the participant completed the 6MWT, the Sp02, HR and Borg breathlessness was recorded of the participant as well as recording the distance covered in the test.

One- repetition maximum (1RM)

Following the completion of the 6MWT, a one rep max (1RM) was recorded. A 1RM is often considered as the 'gold-standard' exercise for assessing an individual's strength capacity. It's defined as the maximal weight an individual can lift for one repetition whilst maintaining correct technique (Brzycki, 1993).

For this exercise, a bicep curl on the participants dominant arm was completed. For this, the Brzycki formula was used to work out the participants 1RM. This formula states that

1RM= w/ (1.0278) – (0.0278 x r), with w representing weight in pounds, lifted for 10 successful repetitions, with the r representing the number of repetitions completed (Brzycki, 1993).

Intervention

Following the completion of the pre assessment, participants would then start the 6-week intervention at the next session possible. The programme was a rolling programme which meant that new people would join the existing participants for the 6-week duration, for 2 sessions a week with sessions lasting approximately 1 hour and 30 minutes. Participants were allowed to miss only 2 sessions throughout the whole 6-week programme, only for medical purposes were participants allowed to miss sessions, if a participant missed more than 2 sessions, then they were removed from the programme.

The data was recorded from 2 separate locations based in Kent, however, the personnel delivering the exercise was the same at both locations, along with the same equipment used at both locations. The personnel delivering the programme were fully qualified respiratory physiologists with experience of working with respiratory patients, and with immediate life support training.

When participants arrived, there resting HR and Sp02 were recorded along with a breathlessness score, using the BORG breathlessness scale.

Following the recording of the measurements mentioned above, the warmup started. This consisted of a basic cardiovascular warmup along with some static stretches. The warmup looked something as follows in table 3.1 below, with the stretches changing each week to add variety and to show the participants different stretches that they can use.

Table 3.1- Warm up used for the pulmonary rehabilitation programme

Exercise	Duration	Explanation
Walking (CV)	5 minutes	Brisk walk around the room with focus on swinging arms and picking knees up
Back stretch	10 seconds	Hands clasped Infront of body as though hugging a tree, round the shoulders with a stretch being felt along the top of the back
Chest stretch	10 seconds	Hands clasped behind the back, pull shoulder blades back with a stretch felt along the upper chest
Calf stretch	10 seconds each leg	Could be completed against a wall or freestanding. Step forward with one foot, ensuring both feet facing forwards, whilst keeping back leg straight until a stretch was felt in the calf of the straight leg. Hands were placed on the bent leg for support.

Table 3.1 explains the breakdown of the warmup, with the duration for each exercise completed as well as an explanation on how to complete each exercise.

Following the completion of the warmup, the main bout of exercise could start. Participants were advised to complete all cardiovascular exercises one after another, and all resistance exercises in a row, participants could choose in what order they wanted to complete this, whether they completed resistance exercises first or cardiovascular.

The main bout of the exercise programme was as follows below in table 3.2:

Table 3.2- The main exercise intervention programme which was completed

Exercise	Duration	Intensity	Progressions	Explanation
Walking (CV)	20 minutes	This was set depending on participants 6MWD from the pre assessment using an excel spreadsheet chart. For example, if a participant scored 400m in the 6MWT, then in the 20-minute walk, the participant should aim to complete 53.3 laps	Participants could increase duration up to 25 minutes and 30 minutes. Aim was to complete more laps than the previous session.	Participants walking end to end on a 10m track, keeping track of lengths completed using a step counter.
Step ups (CV)	5 minutes	Height of adjustable step could be altered to increase/ decrease intensity	Step height can be increased as progression, as well as trying to increase the number of steps completed compared to previous session.	Participants aim was to complete as many step ups as possible using the adjustable step. Participants recorded steps completed.
Seated cycling (CV)	5 minutes	Participants should be working at a Borg breathlessness score of 3-4	Cycle revolutions were recorded, and each session the participants aim was to	Cycle continuously for duration of exercise. Ensuring the cycling machine was wedged against a wall to prevent the machine from moving. Participants recorded cycle revolutions also.

			beat the cycle revolutions from the session before.	
Dumbbell upright row	3 sets of 10 reps	50%-60% of 1RM	Gradually increase the weight as participants progressed throughout the course of the programme	Exercise used to target deltoids and trapezius. Stand with feet shoulder width apart with dumbbells held at arm's length by the thigh palms facing towards the body. Slowly lift the dumbbells, with elbows driving the lift with elbows higher than the forearm throughout. Slowly lower dumbbells back to start position when they reach collarbone height.
Bicep curl	3 sets of 10 reps	50%-60% of 1RM	Gradually increase the weight as participants progressed throughout the course of the programme	Completed either seated or standing, one arm at a time, or both simultaneously. Started with dumbbells by the side of the body, palms facing out. Lifting weight by flexing elbow so dumbbell approaches shoulder. Keeping elbows tucked in, slowly lower weight back to the start position.
Chest press	3 sets of 10 reps	50%-60% of 1RM	Gradually increase the weight as participants progressed throughout the course of the programme	chest press was completed standing, which meant there was less chest activation throughout the exercise, with more muscle activation in the deltoids, as well as the stabilizer muscles such as the abdominals and erector spinae. feet shoulder width apart, with the dumbbells held at chest height in line with the pectorals in front of the body. The movement was started by extending the elbow, and keeping the shoulder blades pinned back, ensuring posture was strong, standing tall and engaging the abdominals to keep strong posture throughout the movement. Extend the elbow just before the elbow locks up, to keep tension on the pectoral muscles, squeezing the pectoral muscles at the end of the movement, followed by slowly flexing

				the elbow until the dumbbells return to start position in front of the chest.
Sit to stand	3 sets of 10 reps	50%-60% of 1RM	N/A	A test of muscular endurance within the legs. The participants begun standing in front of a chair that is firmly placed against a wall or hard object which stopped the chair from moving. The participants then begun the sit to stands whilst keeping arms crossed across the front of the body, this removed the ability to use momentum to aid the participant in standing up. One rep was completed when the participants back touched the back of the chair and then stood up straight with straight legs again.

Table 3.2 explains the layout of the exercise intervention which was used throughout the 6-week pulmonary rehabilitation programme, with reps and sets used, intensity used, progression methods and an explanation for each exercise.

Following the completion of the main bout of exercise, a cool down was completed, which was the same format as the warmup, refer to table 3.1.

Following the completion of the session, participants heart rate, Spo2 and Borg breathlessness score were recorded at the end of the session.

Post assessment

Following the completion of the 6-week programme, the participants were required to complete a post assessment. This post assessment which was completed was the same set up and contents included as in the pre assessment (the post assessment lasted roughly about an hour and a half also). The post assessment began with the completion of all the questionnaires (CRQ, PHQ-9, CAT, GAD-7, and MRC). Basic health measurements were then also recorded (Sp02, HR and blood pressure at rest, height, weight, and resting 6-20 BORG scale).

Following the completion of the questionnaires and data collection, the 6MWT was completed. However, this time no familiarisation test was completed, so the 6MWT was completed just once for the post assessment. The same set up was used for the test, with the same protocol also being used. Participants were informed of how the test worked in case they had forgot. Throughout the test, participants were motivated to push as hard as they can for the duration of the test, with each lap of the test being recorded. Upon completion, the trundle wheel was used to measure any uncompleted laps to record an accurate reading. Participants HR, Sp02 and Borg breathlessness score was recorded post-test, and this was used for data analysis.

Participants were given 20 minutes to recover before completing the 1RM test using the dominant arm for a bicep curl, which was again completed using the Brzycki formula, ensuring correct technique was maintained throughout.

Safety procedures

Due to working with participants that were at increased risk of health complications due to the disease and symptoms they were suffering with, there were some safety procedures and protocols that were also in place in case of exacerbation of symptoms or other complications experienced by participants.

Due to participants suffering with dyspnoea, Sp02 levels had to be monitored throughout the exercise class, at the pre and post assessments and pre and post 6MWT, to ensure the levels did not drop below 85%. If the Sp02 level dropped below

85%, then ambulatory oxygen therapy was considered based on the safety of oxygen, also if a participant was a nonsmoker. Ambulatory oxygen therapy refers to the provision of oxygen during exercise and day to day activities (Ameer, et al., 2014).

The gold standard for participants in this scenario who desaturated below 85% on the 6MWT or during the exercise programme would be to repeat the 6MWT at another date, with the use of ambulatory oxygen therapy until a minimum Sp02 of 90% was achieved, the level of oxygen would be adjusted until this Sp02 level was achieved (Leuschner and Behr, 2017).

For example, the participant would complete the 6MWT on an oxygen level of 3 Litres per minute, if at the end of the 6MWT, the Sp02 levels were still below the 90% threshold, then the 6MWT would be repeated at increased level of oxygen per minute until the 90% threshold was met post 6MWT. However, due to time and resourcing constraints when working with a clinical population, this is not always the case. Therefore, if a participant dropped below an Sp02 level of 85%, then the participants were then trialled on ambulatory oxygen and a decision was made as to the litres per minute they required based on the level of desaturation and the breathlessness the participants were experiencing at the time. The Sp02 levels were then continually monitored whilst on ambulatory oxygen therapy to ensure the level of oxygen was enough to restore the oxygen saturation.

In the event of a participant experiencing exacerbation of symptoms (increased dyspnoea, increased sputum load or change in colour of sputum, increased wheeze and increased coughing) (Leuschner and Behr, 2017), then the professional clinicians that were on hand at the exercise, if possible, they were able to prescribe antibiotics and or steroids, if the clinicians were not able to prescribe, then a prescription was requested from the participants general practitioner.

Data analysis

Before analysing the results, the data was inputted into IBM SPSS (SPSS Inc., Chicago, IL, USA) to test for normality within the data, using the Shapiro- Wilk test. The primary outcome measures were the 6MWT walking distance mean scores, pre and post assessment (mean distance walked by participants (m)). Secondary measures included the mean scores from the CRQ, PHQ-9, GAD-7, CAT, and MRC questionnaires. From the data collected, the key variables (6MWT scores, CRQ, PHQ-9, GAD-7, CAT, and MRC mean scores) which were collected from the pre and post assessments, were analysed using a paired t test, with the 6MWT mean score being the primary outcome. Statistical significance was assumed that $p<0.05$.

Chapter IV: Results

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The test for normality showed that all data sets were normally distributed, below the normal distribution average of 0.05.

An increase in 6MWD (6-minute walk distance) was observed where a mean of 71.7m difference was recorded between the pre assessment score *357.5m* ± *113.3* and post *429.2* ± *111.30* assessment 6MWT (P=0.01).

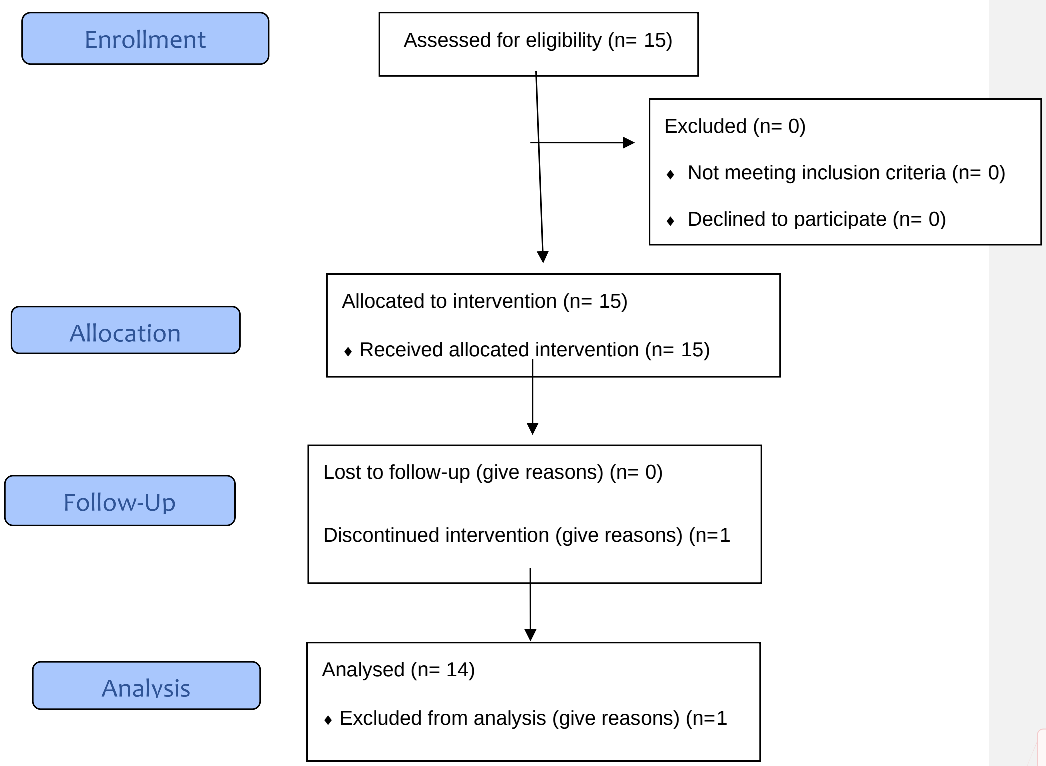

Figure 4.1- Consort flow diagram to highlight dropout rates of participants in the 6-week pulmonary rehabilitation programme

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An increase in 6MWT scores was observed between the pre assessment score of *357.5m* ± *113.3* and post assessments *429.2* ± *111.30* as shown below in figure 4.2. Furthermore, the data is also statistically significant, with a P value of 0.01. Out of the 14 participants, 9 of these were deemed clinically significant with improvements of 30m-32m observed (Shoemaker et al., 2013).

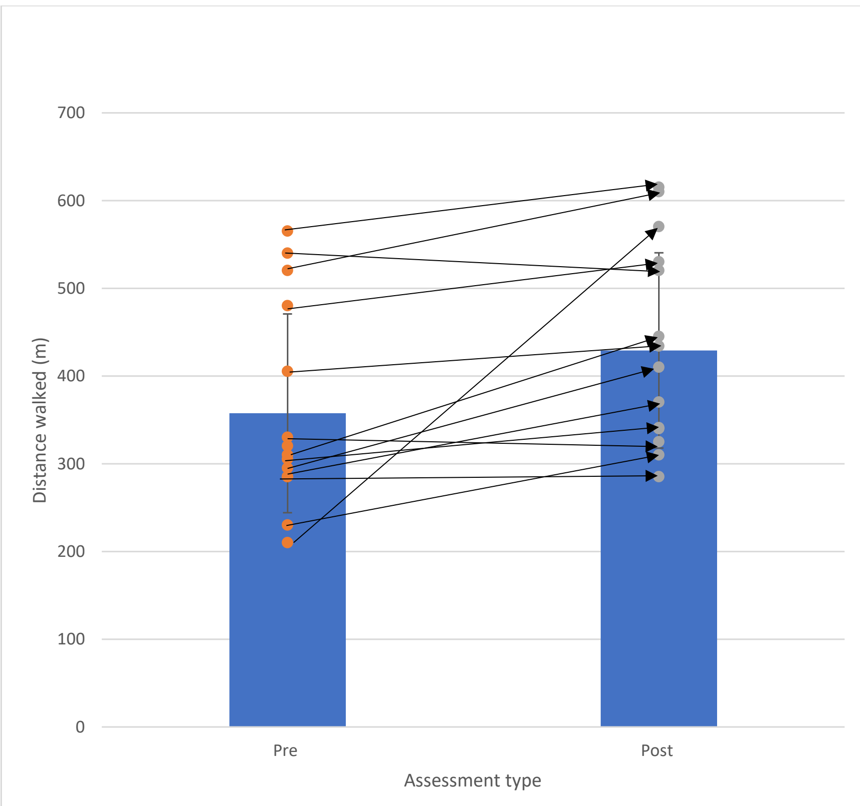

Figure 4.2- The mean 6MWT scores, pre and post assessment (m) collected as part of the 6-week pulmonary rehabilitation programme

Reports of dyspnoea did not significantly change from baseline (*15.0* ± *4.85)* to 6 weeks (*23.5* ± *7.1; P=0.24; figure 4.3).*

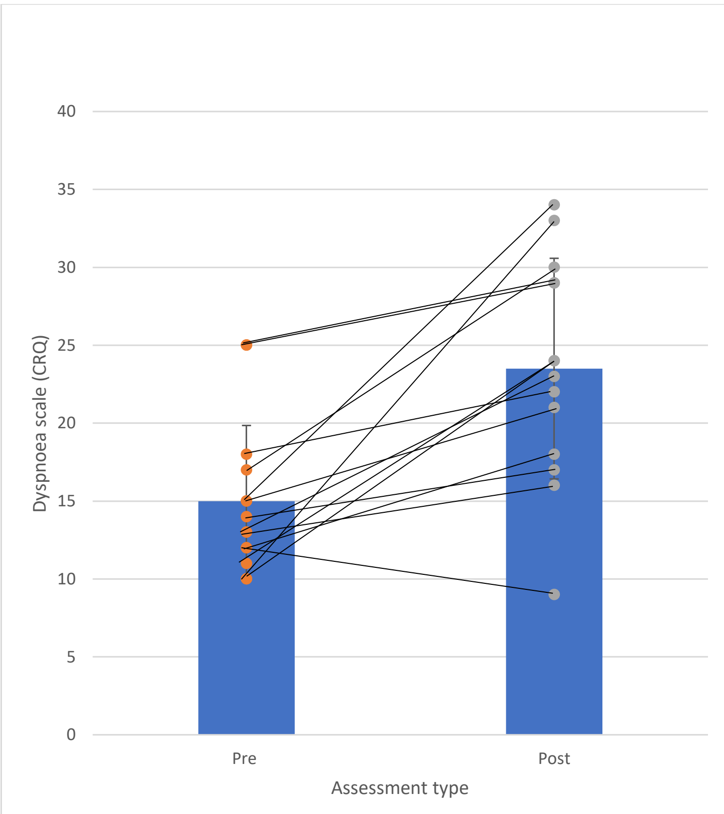

Figure 4.3- **The mean dyspnoea scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

Fatigue measured via the CRQ increased from *14.5* ± *6.3* to *18.7* ± *5.0 (P=0,03; figure 4.4).*

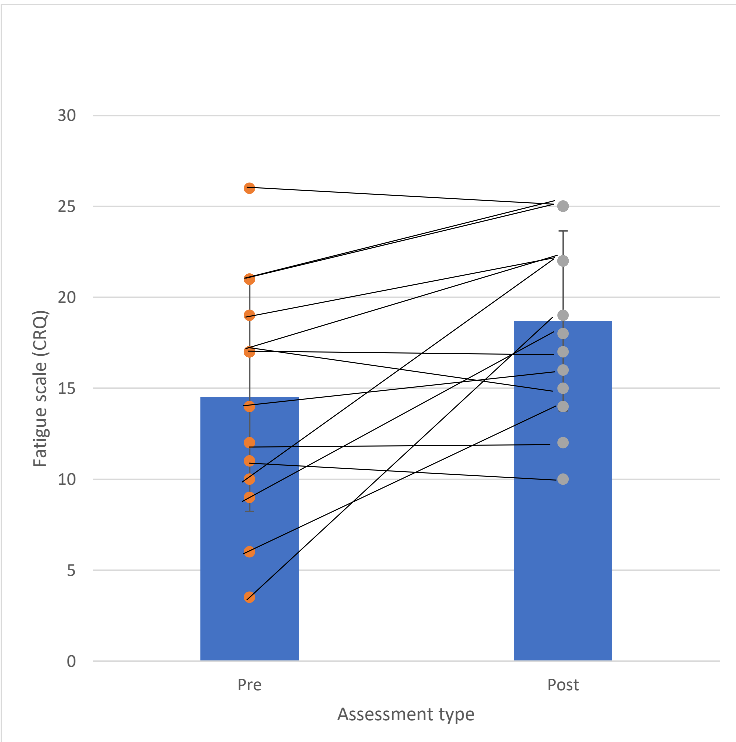

Figure 4.4- **The mean fatigue scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

Emotional scores measured using the CRQ increased from *32.5 ± 8.2* to *37.9 ± 8.4 (P<0.01; figure 4.5).*

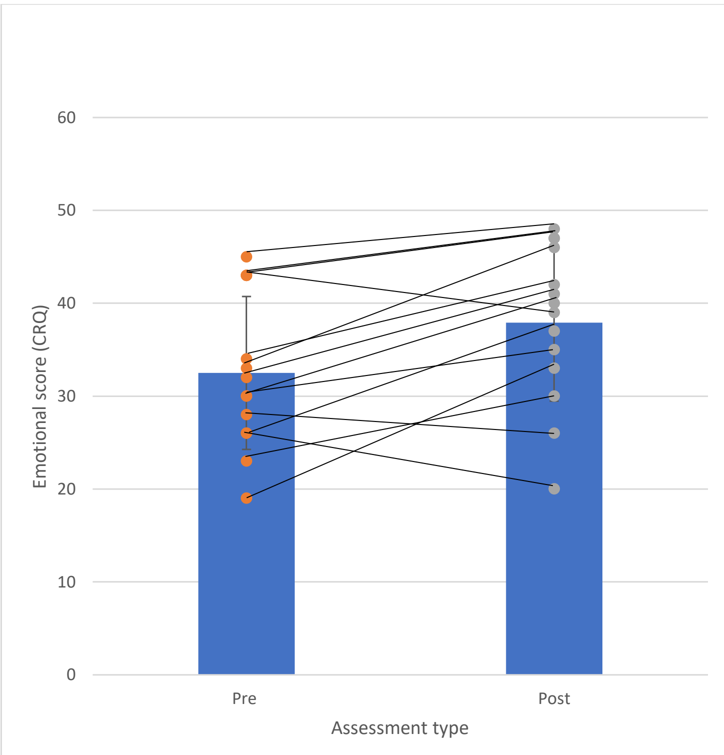

Figure 4.5- **The mean emotional scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

Mastery measured using the CRQ increased from *20.9* ± *4.7 to 24.3* ± *3.5 (P=0.13; figure 4.6).*

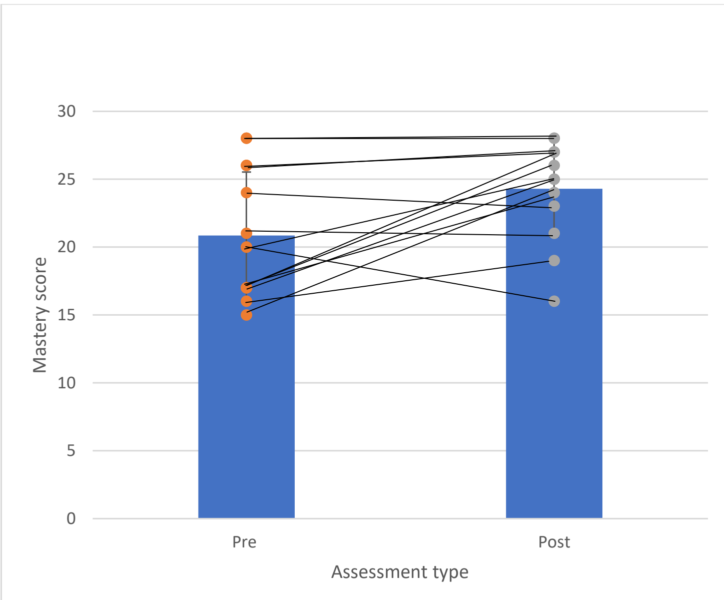

Figure 4.6- **The mean mastery scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

PHQ-9 scores decreased from *9.5 ± 6.4* to *5.1 ± 4.7 (P=0.05; figure 4.7)*

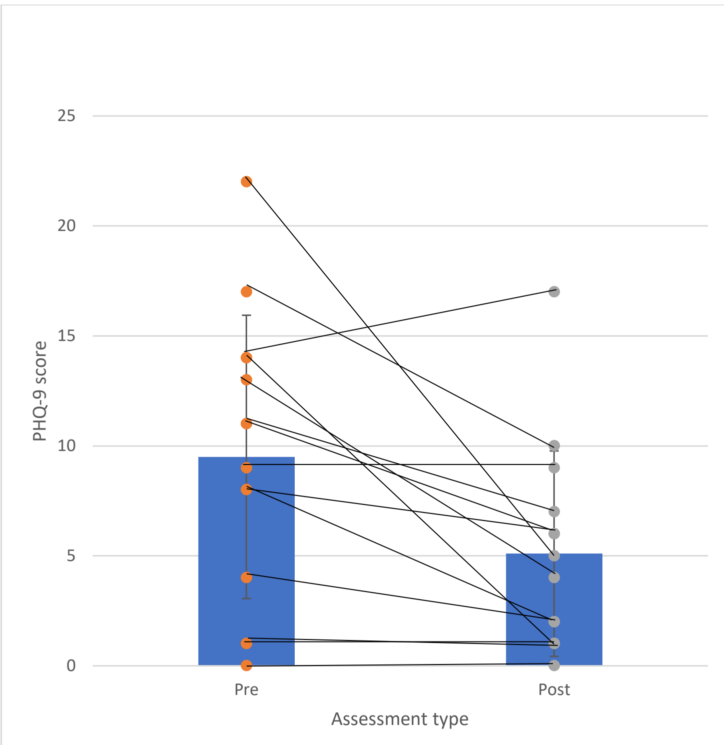

Figure 4.7- The mean PHQ-9 scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme

GAD-7 questionnaire scores decreased from *5.1 ± 4.1* to *2.3 ± 3.3 (P=0.03; figure 4,8).*

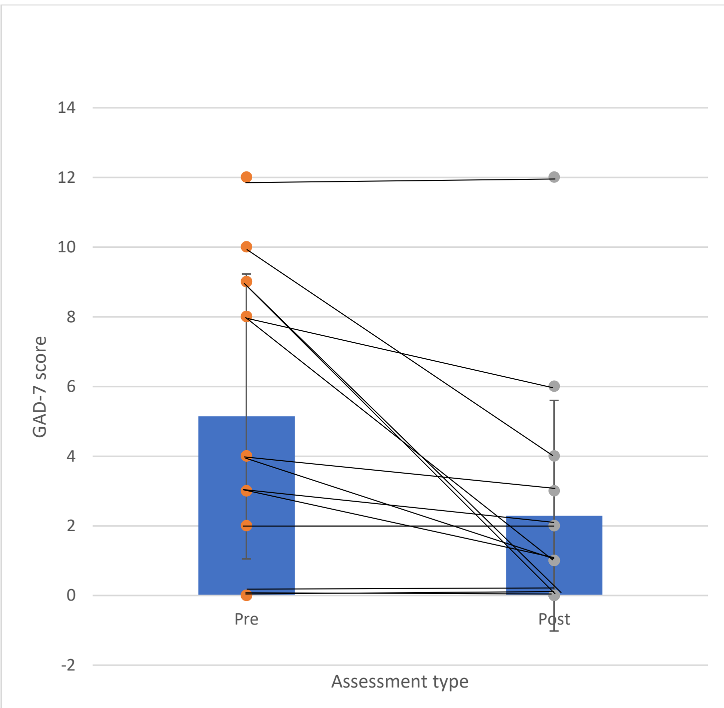

Figure 4.8- The mean GAD-7 scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme

A decrease in CAT scores were observed from *15.4 ± 6.3* to *11.4 ± 6.4 (P= 0.47; figure 4.9)*

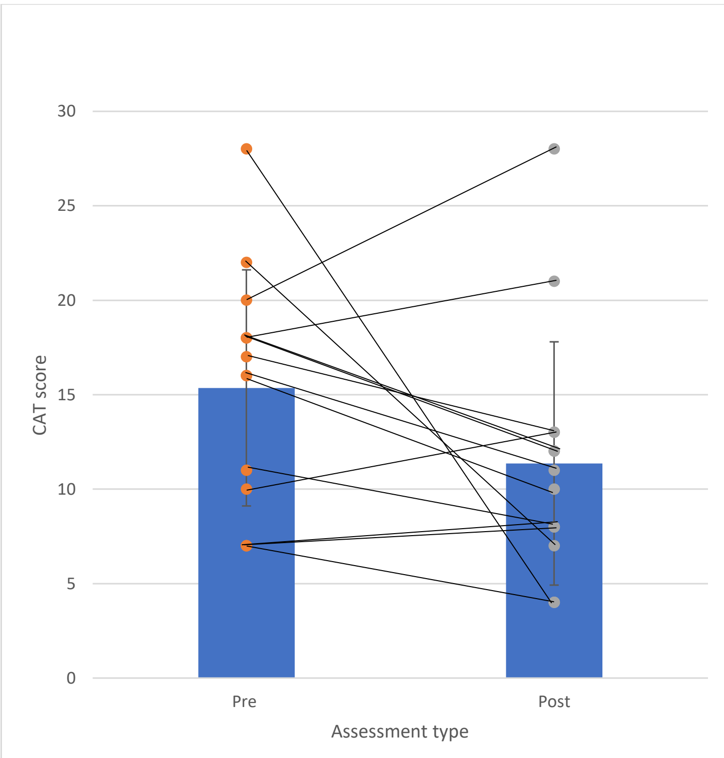

Figure 4.9- **The mean CAT scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

The MRC score decreased from *2.8 ± 0.8* to *2.5 ± 0.9 (P=0.86; figure 4.10)*

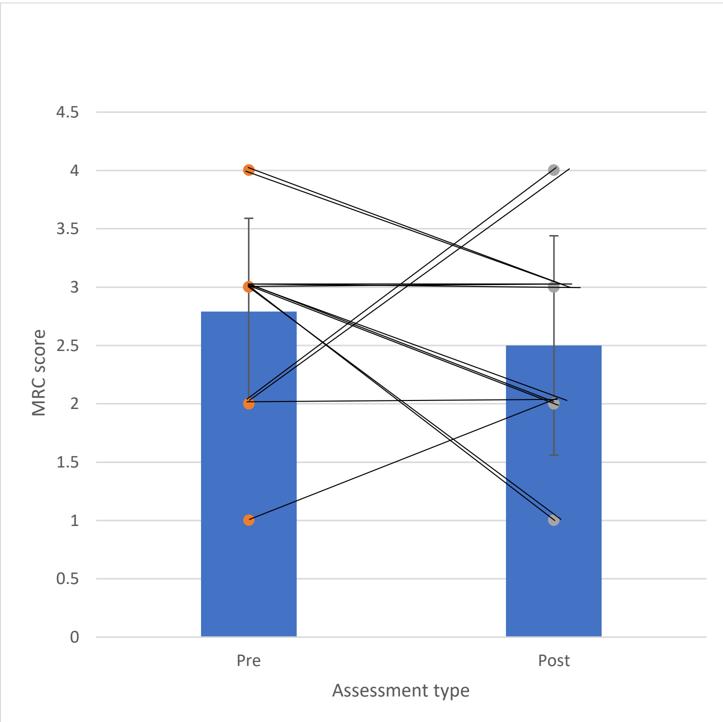

Figure 4.10- **The mean MRC scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

An increase in 1RM bicep curl was reported from *5.7 ± 2.1 to 5.6 ± 3.6 (P=0.02; figure 4.11).* There were also 2 participants that did not record a post assessment score.

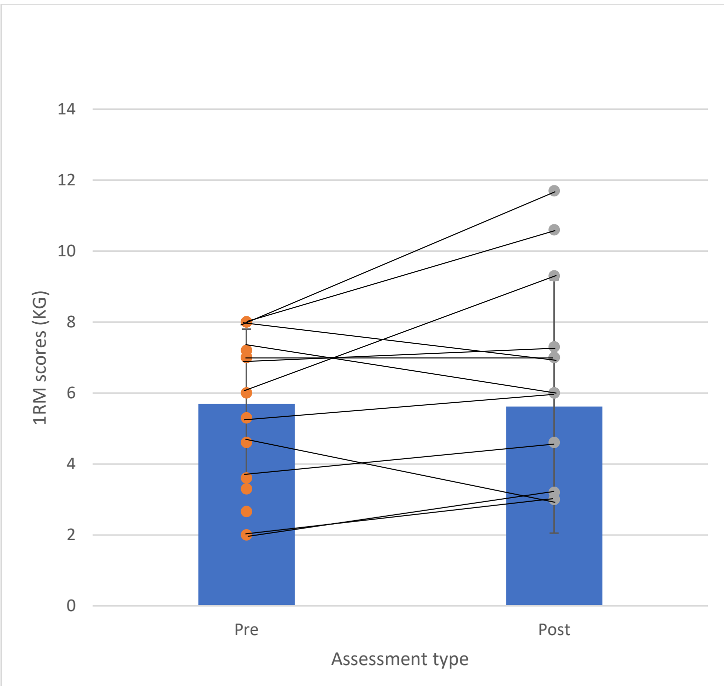

Figure 4.11- **The mean 1RM (kg) scores, pre and post assessment collected as part of the 6-week pulmonary rehabilitation programme**

Summary of data

Below in table 4.1, the data has been presented in a table to easily compare and analyse the data. The table is made up of the pre and post means for each variable, the difference between the means, standard deviation for pre and post assessments, the P value as well as whether each variable is statistically significant.

Table 4.1- Outcome measures from a 6-week pulmonary rehabilitation programme in patients with long COVID ILD.

Variable	Pre	Post	Mean difference	P value	Stat sig
Dyspnoea	15.0 +/- 4.9	23.5 +/- 7.1	8.5	0.24	N
Fatigue	14.5 +/- 6.3	18.7 +/- 5.0	4.2	0.03	Y
Emotional	32.5 +/- 8.2	37.9 +/- 8.4	5.4	<0.01	Y
Mastery	20.9 +/- 4.7	24.3 +/- 3.5	3.4	0.13	N
PHQ-9	9.5 +/- 6.4	5.1 +/- 4.7	-4.4	0.05	Y
Gad-7	5.1 +/- 4.1	2.3 +/- 3.3	-2.8	0.03	Y
CAT	15.4 +/- 6.3	11.4 +/- 6.4	-2.0	0.47	N
MRC	2.8 +/- 0.8	2.5 +/- 0.9	-0.3	0.86	N
6MWT	357.5M +/- 113.30m	429.2M +/- 111.30m	71.7M	0.01	Y
1RM	5.7 +/- 2.1	5.6 +/- 3.6	-0.1	0.02	Y

Chapter V: Discussion

This study suggests that pulmonary rehabilitation can be used as a resource for improving symptoms of Long COVID in individuals as improvements in exercise capacity, dyspnoea and quality of life were observed. The mean difference walked (m) in the 6MWT between the pre (357.5m) and post (429.2m) assessment was 71.7m. This mean difference of 71.7m (P=0.01) is a clinically significant change of 6MWT scores as an increase between 30m-32m (Shoemaker et al., 2013) is considered significant. Therefore, the results suggest that the change is clinically significant as there was over a 200% increase in 6MWT distance compared to the clinically significant change of 30-32m.

Impact of Pulmonary rehabilitation on exercise capacity

Long COVID is known to leave patients with multiple long-term symptoms after a COVID-19 infection (dyspnoea, fatigue, anxiety, and depression e.g. (Lopez-leon et al., 2021), these symptoms can negatively impair the pulmonary and cardiac function as well as exercise performance of individuals suffering with Long COVID (Huang et al., 2020). An increase in aerobic capacity, through an exercise programme like that which was completed in the pulmonary rehabilitation has positive effects on the symptoms experienced by participants (Rodriguez-Blanco et al., 2021). However, in the USA there are concerns over the use of exercise as a treatment for Long COVID symptoms, due to participants reporting post-exertional malaise (PEM), a worsening of symptoms after exercise, amid fears that exercise could cause more harm than good to participants (UNMC, 2023). However, in the current study, the participants reported no PEM as well as no adverse events or exacerbation of symptoms during or after exercise, which indicates that pulmonary rehabilitation is a safe and effective method of improving participants exercise capacity.

An increase in exercise capacity was observed by all 14 participants in the study, similarly, an increase in 6MWD was also observed in participants with COPD where a clinically significant increase was observed (Riario-Sforza et al., 2009). An increase of 54m was observed in 142 out of 222 participants compared to just 8 out of 62 participants in the control group, which were treated with just medication, reaching the same increase after the same time interval (Riario-Sforza et al., 2009). The layout of the pulmonary rehabilitation which the participants attended in the study by Riario-Sforza et al were similar to which was carried out in the methods stated in the current study, with 12 visits, twice weekly for 6 weeks. The focus was similarly on improving cardiovascular fitness, through the use of cycling or treadmill work with additional upper limb and trunk exercise training (Riario-Sforza et al., 2009). The main difference of the methods was that Riario-Sforza et al, used respiratory muscle training by using low pressure peak expiratory pressure (PEP), which could have led to improvements in participants exercise capacity. To my knowledge, there is no other studies that have reported a negative impact, where improvements haven't been made in exercise capacity in Long COVID patients.

One factor that led to an increase in exercise capacity could be that the participants that took part were often inactive due to the symptoms experienced, which can often lead to an increase in weight gain (Kazmi et al., 2022). However, after taking part in regular exercise, the body weight of participants would most likely have decreased, as low levels of inactivity are linked with weight gain, and an increase in energy expenditure combats this (Jebb and Moore, 1999).

Although taking part in exercise is useful for weight loss, it is often used as the secondary means of weight loss behind diet control (Volek et al., 2005), which therefore exercise alone most likely wouldn't have had an impact on the exercise capacity which was observed. For future research, it could be useful to keep dietary logs and track caloric intake to analyse the effect of exercise and dietary control on weight loss during the PR programme, although significant weight loss during the 6-week PR programme is likely to be small.

Exercise training also stimulates vascular adaptations in several tissues, this protects against vascular stress and reduces the likelihood of a cardiac event (Pinckard et al., 2019), which are often reported after a COVID-19 infection. Additionally, an increase in exercise capacity also positively impacts dyspnoea, improving the levels of dyspnoea experienced (Casaburi et al., 1991).

Although an increase in aerobic capacity was highlighted, there were no improvements made in participants muscular strength. This was assessed using a bicep curl 1RM, where the mean pre assessment (5.7) score was slightly higher than the post assessment (5.6), with a mean decrease of 0.07kg ($P=0.01$) reported. This highlights the fact that strength may have decreased throughout the PR programme.

Although the 1RM is an effective way to measure an individual's strength in pulmonary rehabilitation, the best exercise may not have been chosen for this, this choice of exercise however was down to ease and lack of resources available. A better test of

1RM strength may have been by using a leg exercise, similar to which was completed in a PR programme on patients with COPD (Oliveira et al., 2021). The 1RM test was used using a leg extension, this may be a better test of strength due to the main focus of the PR programme being on aerobic capacity, which involves a lot of leg work and repetition of leg movements, therefore a leg exercise may be a better test to determine if any strength changes have been observed. Oliveira et al., 2021 found that there was a mean increase of 7.5kg in the quadriceps after taking part in the PR programme, which was a significant change, with the significant change having to be above a 5.7kg increase (Oliveira et al., 2021). It has been reported that exercise protocols that include aerobic and resistance training improve the 1RM strength above the minimal clinically significant value (Kozu et al., 2011). In comparison to resistance training only PR programmes where the improvements are just below the threshold of clinical significance (O'shea et al., 2007). A correlation between improved 6MWT distances and improved 1RM scores for the quadriceps were observed (Oliveira et al., 2021), which again backs up the point that more appropriate exercises could have been chosen for the 1RM test in the current study, such as a 1RM seated leg extension.

Impact of Pulmonary rehabilitation on dyspnoea and fatigue

Although an increase of 8.5 (P= 0.24) in mean score between the pre and post assessments for dyspnoea were observed, the data was statistically insignificant. A clinically significant change, as the minimum clinical change to be deemed significant is an increase of 0.5, with a change of 1.5 on the scale reporting a large increase (Jaeschke et al., 1989). A similar study where COVID-19 participants took part in an aerobic exercise training programme, 3 times a week for 5-weeks, also reported a decrease of 33% in dyspnoea symptoms post assessment (Ahmed et al., 2022). The sessions were made up of 20-60 minutes of aerobic training along with 10 minutes of breathing pattern training per session, with a 6MWT used at pre and post assessment. This backs up the hypothesis of the current study that pulmonary rehabilitation is effective at relieving symptoms of Long COVID. However, a study where mild/ moderate Long COVID patients were compared to severe/ critical Long COVID patients during a 3-week pulmonary rehabilitation programme. However, 73%% of the severe/ critical group reported symptoms of dyspnoea at discharge (Gloeckl et al., 2021). This could be down to the fact that the pulmonary rehabilitation was only for 3-weeks. Additionally, this could be because the participants involved in the group were part of the severe/ critical symptom group. This could lead to further research and expansion of the current study, to test whether a shorter pulmonary rehabilitation will still have the same effect, and test more severe Long COVID patients to see whether the programme improves more severe symptoms, and what can be done to aid the symptoms of more severe Long COVID patients.

Long term effects of exercise influence dyspnoea positively, reducing the effects through many factors e.g., cardiovascular improvements, decreased ventilatory demand, decreased impedance to ventilatory muscle action and non-physiological factors (Stendardi et al., 2007). One of the main factors which is hypothesised which led to the decrease in dyspnoea is that exercise training reduces the inspiratory effort, end expiratory lung volume and respiratory rate (Stendardi et al., 2007). This leads to a decrease in the neuromuscular coupling e.g., the ratio of respiratory effort to concurrent flow (Stendardi et al., 2007). However, due to dyspnoea being a subjective selfassessed measure, and fairly difficult to objectively assess, due to breathlessness being experienced less often, with a lack of previous exposure (Hentsch et al., 2021), it's possible that participants could build a tolerance to the perception of pain experienced with dyspnoea after taking part in exercise over a period of time, which means participants could report a much lower level of dyspnoea than they are actually experiencing. Alternatively, they could also overestimate the level of dyspnoea that they are experiencing.

A reduction in dyspnoea experienced is a positive, not just for the participant, but also for the people around the participant as dyspnoea also effects the quality of life of patients, limiting the everyday tasks and activities that they can complete (Janssen et al., 2015). Up to 70% of individuals suffering with Long COVID reported that the symptoms, including dyspnoea, ~~has~~ stopped the individual from completing everyday tasks, going to work, and socialising (Berenguera et al., 2021). By reducing the level of dyspnoea experienced, it will allow individuals to get back to a more normal way of living sooner by taking part in pulmonary rehabilitation, with social and intimate relationships often improving (Jones et al., 2018). This will also have an economic impact, as individuals will be able to work to full capacity without needing time off, which helps the company. Also, the individual will be able to go back to socialising and completing everyday tasks without the worry of feeling embarrassed about the dyspnoea, which leads to an improvement in quality of life. This can be a measure that can be implemented into further studies, to assess the impact of pulmonary rehabilitation on how quickly it allowed participants to get back to completing normal activities, such as work and everyday tasks.

The fatigue levels reported after completion of the pulmonary rehabilitation also led to an increase in quality of life. Between the pre (14.5) and post (18.7) assessment of fatigue using the CRQ, an increase of 4.2 (P=0.03) was reported. Again, this is a clinically significant change, as an increase of 0.5 is considered clinically significant on the CRQ (Jaeschke et al., 1989), which indicates that pulmonary rehabilitation was effective at reducing symptoms of fatigue. Exercise has been shown to improve symptoms of fatigue (Wender et al., 2022). It's believed that exercise reduces feeling of fatigue through several mechanisms. One being that long term exercise stimulates an increase in the number of mitochondria, meaning the energy supply over time will be improved. Additionally, the oxygen circulation within the body will be improved, leading to an increased efficiency of energy production and usage **(**Ament and Verkerke, 2009) Additionally, exercise promotes better sleep which improves the symptoms of acute fatigue **(**Ament and Verkerke, 2009). However, mild/ moderate Long COVID patients were compared to severe/ critical Long COVID patients during a 3-week pulmonary rehabilitation programme indicate that 58% of the participants within the severe/ critical symptom group still reported symptoms of fatigue at the discharge of the pulmonary rehabilitation (Gloeckl et al., 2021). These results could be down to the fact that the participant group were experiencing severe/ critical symptoms, as well as the fact that the pulmonary rehabilitation programme lasted only 3 weeks.

Again, an improvement in fatigue levels means that the individual will experience an improvement in quality of life, individuals will be able to complete everyday tasks without the feeling of fatigue after completing the task, or even not being able to take part in the task entirely due to fatigue.

Impact of Pulmonary rehabilitation on anxiety and depression

The pulmonary rehabilitation programme also led to an improvement in quality of life, which were reported by multiple questionnaires. Increases in mean emotional scores on the emotional section of the CRQ were observed (5.4, P= 0.00). However, mastery (3.4, P= 0.13) was deemed statistically insignificant. Emotional results were deemed clinically significant as an increase of 0.5 on the CRQ is deemed clinically significant, with an increase of 1.5 deemed a large increase (Jaeschke et al., 1989). This suggests that the hypothesis is correct, that pulmonary rehabilitation is effective at improving quality of life in Long COVID patients.

Furthermore, depression levels of participants were decreased using the PHQ-9. A decrease of 4.4 (P=0.05) was observed between the pre (9.5) and post (5.1) assessment means. This decrease in the PHQ-9 score indicates that participants mental health improved, with the pre assessment mean of 9.5 in the upper threshold of mild depression, with the post assessment score of 5.1, in the lower threshold of mild depression, with mild depression being categorised within the range of 5-9 on the scale (Kroenke et al., 2012). However, this is just below the clinically significant threshold of a 5-point change (Kroenke et al., 2012), although it is still a positive change.

Anxiety levels of the participants were decreased, this was observed by the GAD-7 questionnaire. The pre assessment (5.1) and post (2.3) assessment means resulted in a difference of 2.9 (P=0.03). The pre assessment mean score of 5.1 is categorized as mild anxiety levels, compared to the mean post assessment score of 2.3 which is categorized as no anxiety (Lee et al., 2022). This is deemed clinically insignificant as a

4-point change is the minimum threshold for clinically significant improvements (Lee et al., 2022).

Aerobic exercise has been proven to reduce anxiety and depression (Sharma, 2006). These improvements in mood are proposed to be caused by exercise-induced increase in blood circulation to the brain and by an influence on the hypothalamic-pituitary-adrenal (HPA) axis, which in turn affects the physiologic reactivity to stress (Guszkowska, 2004). The monoamine hypothesis is proposed to be the most promising physiological mechanism. The hypothesis states that exercise leads to an increase in availability of brain neurotransmitters (serotonin, dopamine, and norepinephrine) that are reduced with depression. These neurotransmitters increase in plasma and urine following exercise (Craft and Perna, 2004).

Other hypotheses include the distraction hypothesis where exercise serves as a distraction from worrying and depressing thoughts (Craft and Perna, 2004), self-efficacy, and social interaction (Peluso and Andrade, 2005). Pulmonary rehabilitation is often completed in a group setting which allows for social interaction between participants that are suffering with the same symptoms. This social interaction between others can lead to a decrease in anxiety and depression through communicating with others and having a support network available to them.

Further proving the hypothesis, Gloeckl et al., 2021 found that there were improvements in participants mental health after just 3 weeks of pulmonary rehabilitation in severe/ critical Long COVID patients. A mean improvement of 14.4 was observed on the mental component of the 36-item short form survey (SF-36). Gloeckl et al were wary of the fact that the improvement in mood could have been from remission, however the symptoms of depression were present 2 months before the pulmonary rehabilitation began, with the improvements in depression being mainly down to the exercise programme (Gloeckl et al., 2021).

In comparison, the anxiety scores of participants increased slightly, but also significantly, using the GAD-7 questionnaire (Gloeckl et al., 2021). Gloeckl et al hypothesised that these increases in anxiety levels observed were due to the participants only beginning to reflect on daily life challenges after starting PR. Specifically, the focus on day to day functioning along with participants awareness of the persistent symptoms and impairments (Gloeckl et al., 2021). Compare this to another study, Liu et al., 2021, where PR and group psychological intervention was used to treat anxiety in mild COVID-19 patients, where a decrease in anxiety levels were also observed. The state anxiety inventory was used to assess anxiety levels. There was a mean difference of 15.9% between the trial group and the control group, which was a significant decrease (Liu et al., 2021). These findings support this hypothesis that pulmonary rehabilitation is a suitable programme for improving symptoms of anxiety and depression within Long COVID patients. There is also an argument that these improvements could be down to the education that was provided as part of the PR, although more research would be required to conclude if this is the case. Its possible that the information and education the participants received regarding the symptoms and the way they were feeling reassured them and improved the self-confidence and the participants overall mentality.

Impact of Pulmonary rehabilitation on day-to-day functionality

The participants day to day functionality and experience with symptoms daily were assessed using the CAT and MRC questionnaires. Improvements were observed in both questionnaires.

There was a 2.0 (P=0.47) decrease between the mean pre assessment (15.4) and post (11.4) scores, however, this data sets were deemed statistically insignificant. A change in 2 points is deemed clinically significant (Kon et al., 2014). Slight improvements in the MRC questionnaire were reported, with a 0.3-point (P=0.86) change observed, however, this was also statistically insignificant, which means these results cannot be deemed clinically significant. The pre assessment (2.8) score decreased to 2.5 post assessment. Grade 2 on the MRC scale highlights a mild dyspnoea response which stayed consistent between the pre and post assessments, leading to a clinically insignificant change (Bestall et al., 1999).

Additionally, no improvement in mMRC scores were observed in another study assessing COPD patients throughout PR (Rubi et al., 2010). Although no significant changes were found in the mMRC questionnaire, improvements were observed in breathlessness through other questionnaires in Rubi et al 2010., study. It has been suggested that the scale is not sensitive enough to detect changes in patients with advanced COPD and high functionality disability (Rubi et al., 2010). This could explain why no changes were observed in the mMRC questionnaire results in the current study, due to the functional disability which was observed in participants in the study.

Limitations

Due to the lack of resources and research around Long COVID rehabilitation, there are some limitations to this study.

The first limitation of this study was that there was no control group involved, and the intervention wasn't randomised for the study. Without the use of a control group, we have no data to determine whether the PR programme improved the symptoms experienced compared to another group, or the symptoms improved over time, which is very unlikely in such a short space of time. However, there is differing opinions on this matter, with evidence to suggest that symptoms improved on their own throughout the course of a year, with improvements observed in fatigue levels, PEM, brain fog, irritable bowel syndrome and feeling unsteady (Oliveira et al., 2023). On the other hand, it has been reported that over the course of a year, neurocognitive symptoms increased in severity, with improvements observed in most other areas (Jason Leonard et al., 2021). Both studies were carried out over a year long period, which allows for much more time for improvements compared to this observational study. However, in future studies, it would be beneficial to have a control group for this same study to be able to fully determine the impact the PR programme alone has on the symptoms experienced by participants. A way to go about this could be to have an intervention group and a control group, with the control group not taking part in the exercise, until the intervention group has completed the intervention This way we would be able to compare the pre and post assessment data from both groups and analyse the changes and impacts of both groups, and whether the control group experienced any changes in symptoms compared to the intervention.

Another limitation of the study was that participants maximal cardiorespiratory functional capacities were not assessed. Again, this was down to a lack of resources and time. This meant that participants VO_2max was not measured which meant that we were unaware of the capabilities of each participant aerobic endurance capabilities and the effectiveness of the respiratory system., i.e., the participants ability to use oxygen effectively. By assessing the participants VO_2max, it would allow us to set individual intensities based on the participants fitness levels, tailoring the PR programme to be more specific to each participants needs and capabilities. For a future study, participants VO_2max can be assessed using a cardiopulmonary exercise test (CPET). The CPET is known as the gold standard for assessing VO_2max and is under-utilized in assessing patients with symptoms of dyspnoea and exercise limitations (Stringer, 2010). The gas exchange information acquired from a CPET is helpful in identification of a more precise diagnosis, assessing severity of impairments, determination of response to treatment and mortality predictor (Stringer, 2010). With a CPET completed at both pre and post assessment, it will enable an analysis of the impact of the PR programme on the effectiveness of the programme at improving cardiovascular fitness and its effectiveness, measured by increase in VO_2max, carbon dioxide and ventilatory measurements (Albouaini et al., 2007).

A further limitation of the study was that during the 1RM which was used pre and post assessment, the participant had to complete multiple reps at different weights until a 1RM was found, this could have led to a buildup of fatigue within the bicep, pointing to one of the reasons as to why an increase in 1RM was not observed. This may impact the results, as an increase in muscular strength may have occurred, but due to the buildup of fatigue in the bicep, along with other symptoms such as dyspnoea, the participant may not have been able to give a true reading of 1RM. For this population, a muscular endurance test may have benefited the participants more. For example, a 1-minute sit to stand test could have been used either as well as or instead of the 1RM. As muscular endurance provides cardiovascular benefits in addition to strength benefits (Hughes et al., 2018). This may have been more beneficial as PR focus is on cardiovascular improvements, rather than improvements in strength, although it shouldn't be neglected. There is a positive correlation between 6MWD, and the reps completed on the 1-minute sit to stand test on patients in pulmonary rehabilitation with COPD (Fernandes et al., 2021). Therefore, this could be a suitable assessment for Long COVID patients during PR due to the similarity in some symptoms.

Due to this study taking place in a group community setting, resources, space and time were limited which meant a pragmatic approach was required. This meant that a realistic time limit had to be set on the rest period between the familiarisation 6MWT and the pre assessment 6MWT. The rest period was set at 20 minutes between each 6MWT to allow enough time for the rest of the pre assessment testing to be completed within the limited amount of time which was available. However, if a participant was not ready to complete the pre assessment 6MWT after the 20-minute rest, then they were made to wait until the participants heart rate had returned to a normal heart rate (within 10 beats per minute of resting HR) for that individual, and when this had happened, they could then complete the pre assessment 6MWT. Due to this limited amount of rest between each 6MWT, fatigue could've impacted the pre assessment 6MWT results, however the panel fatigue effect was not recorded.

(Mador and Acevedo, 1991). It has been suggested that inspiratory muscle fatigue can take effect after just 6-15 inspiratory efforts, which means there was a possibility that participants could've suffered from inspiratory muscle fatigue (Romer et al., 2006) Due to the participants potentially suffering with respiratory complications already due to the symptoms (e.g. dyspnoea and chest pain) experienced from long COVID ILD, this could have potentially increased the fatigue effect on the respiratory system, leading to a decrease in performance during the pre-assessment 6MWT. It's been suggested that dyspnoea can impact the level of inspiratory muscle fatigue due to the increased level of metabolic carbon dioxide which is produced from weak or poorly conditioned respiratory muscles, paired with hyperinflation that increase symptom intensity (Calverley, 2006). These mechanisms mentioned above could have potentially had an impact on the participants 6MWT scores as hyperinflation often increases during exercise, increasing the levels of dyspnoea to distressing or intolerable levels (Thomas et al., 2013). For future research, it could be beneficial to complete the familiarisation test the day before to allow for plenty of time for recovery to combat any fatigue effects during data recording. Additionally, it could be beneficial to include inspiratory muscle training as part of the pulmonary rehabilitation as it has been shown that inspiratory muscle training has positive effects on dyspnoea by reducing the severity of dyspnoea experienced during exercise (Ramsook et al., 2017), although the physiology behind this is still poorly understood.

Although there were no exacerbation of symptoms or post exercise malaise reported, it was also not recorded so it is uncertain whether it occurred during the programme or not. A way to record this, to be certain that participants are not suffering with PEM is to complete a questionnaire such as the Short Form 36 Health Survey (Stussman et al., 2023) to record any worsening of symptoms, severity and duration of the symptoms. By doing this it would allow for an analysis of the symptoms that were increased, but also to assess any improvements in quality of life throughout the programme, as PEM has the capability to be severe enough to be disabling and stop individuals completing everyday tasks, which can also affect the quality-of-life results from the study (Vollestad and Mengshoel, 2023).

Application of results

These results back up the limited literature that is already available, that pulmonary rehabilitation is a good programme at relieving symptoms of Long COVID in participants. These results can be used by general practitioners, exercise physiologists and anyone other healthcare professional that may have to deal with Long COVID patients. It shows that a structured exercise programme will help relieve the symptoms of Long COVID as well as improving the quality of life, if participants stay consistent throughout the PR programme. The next steps are to make pulmonary rehabilitation more readily available for individuals suffering with Long COVID, as there is a current lack of resources available to help people overcome these symptoms and get back to a normal way of living; enjoying their life with no struggles like they were before the symptoms of Long COVID arrived. This will then take the strain off other NHS resources like mental health support for example, as PR has been shown to improve mental wellbeing as well as physical health, which will reduce the chance of individuals with Long COVID requiring mental health support. Additionally, there is a case to be made that even though some symptoms may not improve significantly, there is still huge benefits to participants. By taking part in the PR, it is preventing further deconditioning and worsening of symptoms by ensuring the participants are moving and active, when without the PR they may not be active.

Chapter VI: Conclusion

In conclusion, this study provided evidence for the effectiveness of pulmonary rehabilitation as a method at relieving symptoms of Long COVID ILD in individuals after a COVID-19 infection. This is highlighted by the mean increase in 6MWD between the pre and post assessments, where a mean increase of 71.7m was observed, as well as the changes in questionnaire answers which were used. This increase is likely down to an increase in cardiorespiratory fitness (VO_2) by increasing the mitochondrial content and desaturation of myoglobin in skeletal tissue, leading to an increase in the oxidative capacity of the muscle tissue (Pinckard et al., 2019). Fatigue saw clinically significant reductions with a 4.17 difference observed on the CRQ. It's hypothesised that exercise training reduces the inspiratory effort, end expiratory lung volume and respiratory rate. This leads to a decrease in the neuromuscular coupling e.g., the ratio of respiratory effort to concurrent flow (Stendardi et al., 2007). This study has also shown that anxiety, depression, and quality of life are improved after partaking in a PR programme, with a decrease in levels of anxiety, depression, and quality of life within the participants. These findings suggests that pulmonary rehabilitation (exercise and education) improves exercise capacity, anxiety and depression, fatigue, and quality of life in patients with symptoms of Long COVID and ILD and is an effective resource for relieving Long COVID symptoms.

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