Nutritional Supplementation during Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease

A thesis submitted for the degree of Doctor of Philosophy

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Candidate

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Declaration

I Abdulelah Aldhahir confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date:

Abstract

Introduction: Pulmonary rehabilitation (PR) is a cost-effective management strategy in chronic obstructive pulmonary disease (COPD) patients which improves exercise performance and health-related quality of life. However, adherence to PR is common issue and this may be compounded by reduced muscle mass and/or malnutrition. The use of nutritional supplementation to overcome malnutrition and enhance outcomes for COPD patients during PR has been limited by the absence of rigorous evidence.

Aim: To investigate relationships between malnutrition, nutritional supplementation, and PR in COPD. Specifically, to investigate the effect of protein-supplementation (Fortisip Compact Protein, FCP) during a COPD PR program on exercise capacity, peripheral muscle strength, anthropometrics measurements, anxiety and depression, health related quality of life, and physical activity. To assess whether any changes in exercise capacity, peripheral muscle strength, anthropometrics measurements, anxiety and depression, health related quality of life, and physical activity associated with nutritional supplementation are maintained at six weeks following PR.

Methods: A systematic review was conducted to summarise the current evidence for using nutritional supplementation during PR in stable COPD to enhance PR outcomes. The systematic review facilitated the development of the research questions and main hypothesis. To identify the prevalence of malnutrition in our population, we conducted a study in a COPD population referred to PR, examining relationships between nutrition and disease severity. We then conducted a double-blind randomised controlled trial using FCP as an intervention and preOp (a carbohydrate supplement) as control in COPD

patient who participated in a six-week PR programme. Participants were required to consume the intervention twice a day and attended PR sessions two hours long, twice each week for six weeks, with complete pre- and post-measures, including incremental shuttle walk test (ISWT) as the primary outcome. We conducted a follow-up study to identify if changes in exercise capacity and other outcomes were maintained six-week following completion of PR. Finally, participants' experience using both products was assessed in a survey.

Results: It was impossible to draw definitive conclusions in the systematic review due to heterogeneity, but nutritional supplements may enhance the benefit of PR with a need for further well-designed and rigorous research to address this area. In our PR population, the prevalence of malnutrition was 17% and lower BMI was significantly associated with lower FEV_1, FEV_1% and FEV_1/FVC. There were no statistically significant differences between intervention and control groups in exercise capacity measured by ISWT at the end of the PR, however, there was a clinically meaningful difference favouring the intervention group (intervention: 342 m ±149 vs. control: 305 m ±148, $p > 0.05$). Individuals who reached that improvement had larger mid-thigh circumference (responder: 62 cm ±4.5 vs. non-responder: 55 cm ±6.2; $p < 0.05$). Appetite did not change and the majority of participants were satisfied with product

Conclusion:

Malnutrition is common in stable COPD patients referred for PR and lower BMI is associated with lower lung function (FEV_1). Using a high protein nutritional supplementation in individuals with COPD who were enrolled in PR resulted in

a clinically meaningful difference favouring the intervention in exercise capacity measured by ISWT, and that improvement was maintained least six weeks later. A larger study would be necessary to demonstrate statistical significance. Individuals who reached that improvement had larger mid-thigh circumference. Nutritional supplements are acceptable to patients.

Impact statement

The key findings of my thesis are 1) there remains insufficient evidence on using nutritional supplements to improve outcomes during PR in COPD patients; 2) malnutrition is common in COPD patients referred to PR and lower BMI is associated with greater COPD severity of airflow obstruction; 3) a clinically meaningful difference in exercise capacity favouring the protein-supplementation group was seen in COPD patients during PR but a larger trial would be needed to demonstrate this definitively, and 4) participants accepted nutritional supplementation. Our results have potentially important implications for clinical practice. First, nutritional assessment should be integrated as part of PR assessments and should be performed routinely before, during, and after PR with a validated screening tool given that malnutrition is common and associated with poor outcomes in COPD. Second, our study suggests that nutritional assessment should account for BMI, unintentional weight loss, and body composition as some patients had abnormal muscle mass with stable or normal BMI. Lastly, nutritional supplementation should be further studied in adequately powered trials as part of PR research, as it appears to have a positive effect on exercise capacity in some COPD patients. Findings from this PhD highlighted the need for appropriately powered double-blind RCT studies with larger sample size to investigate the effect of using high energy/high protein nutritional supplement in enhancing PR outcomes in COPD, and longer-term clinical outcomes, especially those who are at high-risk of malnutrition. This would support recommendations to incorporate nutritional intervention in PR management. The findings have been and/or will be

disseminated through scientific journals, conferences, and social media to maximise the reach of our research.

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First, I would like to express my gratitude and appreciation to my ever-patient and supportive first supervisor Prof. John Hurst and my second supervisor Dr. Swapna Mandal for their continuous support and valuable contributions. Their guidance, advice, motivation, and immense knowledge have been crucial to the success of this thesis. Besides my supervisors, I would like to thank everyone who shared knowledge, work, and wisdom with me, which made my progress possible:

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Abbreviations

6MWT: Six Minute Walk Test

AAT: Alpha1-Antitrypsin

AATD: Alpha-1 Antitrypsin Deficiency

ACE: Angiotensin-Converting-Enzyme

ACOS : Asthma-COPD Overlap Syndrome

ACS: Acute Coronary Syndrome

AECOPD: Acute Exacerbations of COPD

AMED: Allied and Complementary Medicine Database

ATS: American Thoracic Society

BIA: Bio-impendence analysis

BiPAP: Bi-level Positive Airway Pressure

BLF: British Lung FoundationBMI: Body Mass Index

BTS: British Thoracic Society

CAT: COPD Assessment Test

CINAHL: Cumulative Index of Nursing and Allied Health Literature

CNWL: Central and North West London

COPD: Chronic Obstructive Pulmonary Disease

CV: Cardiovascular

CVD: Cardiovascular Disease

DEXA: Dual energy X-ray Absorptiometry

Embase: Excerpta Medical Database

ERS: European Respiratory Society

EWGSOP: European Working Group on Sarcopenia in Older People

FCP: Fortisip Compact Protein

FEV_1: Forced Expiratory Volume in 1 second

FFM: Fat Free Mass

FFMI: Fat Free Mass Index

FM: Fat Mass

FVC: Forced Vital Capacity

GBP: British Pound sterling

GCP: Good Clinical Practice

GDPR: General Data Protection Regulation

GINA: The Global Initiative for Asthma

GOLD : Global initiative for Obstructive Lung Disease

HADS: Hospital Anxiety and Depression Score

HF: Heart Failure

HIV: Human Immunodeficiency Virus

HRA: Health Research Authority

ICS: Inhaled Corticosteroids

IHD: Ischemic heart disease

IL: Interleukin

IQR: Interquartile Range

ISWT: Incremental Shuttle Walking Test

kPa: Kilopascal

LABA: Long-Acting Beta$_2$ Agonist

LAMA: Long-Acting Antimuscarinic

LVRS : Lung Volume Reduction Surgery

MCID: Minimum Clinically Important Difference

Medline: Medical Literature Analysis and Retrieval System Online

MEP: Maximal Expiratory Pressure

MIP: Maximum Inspiratory Pressure

mMRC: modified Medical Research Council

MRC: Medical Research Council

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NIV: Non-Invasive Ventilation

ONS: Oral Nutritional Supplement

PA: Physical Activity

PAD: Peripheral Artery Disease

PaO_2: Partial Pressure of oxygen

PCV13: Pneumococcal Conjugate vaccine

PDE4: Phosphodiesterase-4 inhibitors

PPSV23: Pneumococcal Polysaccharide Vaccine

PR: Pulmonary Rehabilitation

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PVD: Peripheral Vascular Disease

QALY: Quality adjusted life year

REE: Resting Energy Expenditure

RF_{CSA}: Rectus femoris cross-sectional area

SABA: Short-Acting $Beta_2$ Agonist

SAMA: Short-Acting Antimuscarinic

SD: Standard Deviation

SPSS: Statistical Package for the Social Sciences

TB: Tuberculosis

TNF: Tumor Necrosis Factor

TUAG: Timed-Up-and-Go Test

UCL: University College London

UK: United Kingdom

US: United States

1. Introduction

The scope of this introduction is to discuss the essential aspects or background areas investigated in this Ph.D. thesis, considering Chronic Obstructive Pulmonary Disease, Pulmonary Rehabilitation and nutritional supplementation.

1.1 Chronic Obstructive Pulmonary Disease (COPD)

In simple terms, COPD is a lung condition in which it is difficult to empty air out of the lungs because of narrowed airways, making it difficult to breathe. COPD is a common cause of morbidity and mortality worldwide (1); in fact it was the fourth leading cause of mortality in 2015 (1). Without any further action, COPD is expected to be the third leading cause of death by 2030 worldwide (2). It has significant implications both on quality of life and financially, both for individuals with the disease and healthcare organisations.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD is "a common, preventable, and treatable disease that is characterised by persistent respiratory symptoms and irreversible airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."(3)

COPD often coexists with emphysema and chronic bronchitis. Emphysema is pathologically defined as a permanent enlargement of the air spaces by destruction of the alveolar wall (Figure 1) (4). As a consequence of this destruction, pulmonary capillaries can be damaged, causing a significant reduction in the effective gas exchange surface area of the lungs. Unlike emphysema, chronic bronchitis is defined based on major clinical manifestations. It is an inflammatory process that causes chronic productive

cough for three or more months in two or more consecutive years (5). As a result of this chronic inflammation, the bronchial airways narrow due to both congestion and mucosal oedema. Patients with chronic bronchitis usually have an excessive amount of secretions. Both emphysema and chronic bronchitis can develop together. In order to confirm the existence of COPD, pulmonary function testing (spirometry) is required, as discussed further below.

Patients with COPD tend to have daily symptoms such as dyspnoea, cough with or without sputum production, wheeze, and chest tightness. They also have reduced exercise capacity, and susceptibility to frequent chest infections or worsening of their symptoms, which are referred to as ‘exacerbations’ all of which lead to impaired health related quality of life (6, 7).

COPD develops over many years after exposure to a causative factor, and usually becomes more prevalent after the age of 40. Smoking is the most common risk factor, although it can also be caused by indoor and/or outdoor air pollution, and/or occupational dust, or biomass fuel exposure (1, 3).

Individuals with COPD are commonly diagnosed at a later stage, after the lungs have already undergone significant damage (8). They rarely seek medical care until more severe stages, when symptoms such as coughing, breathlessness or decreasing physical activity are present, because people with COPD often consider these symptoms to be normal changes due to smoking and the ageing process (8).

Figure 1: A, normal alveoli. B, alveoli with emphysema, which show collapsed airway and damaged alveoli with loss of elasticity (9).

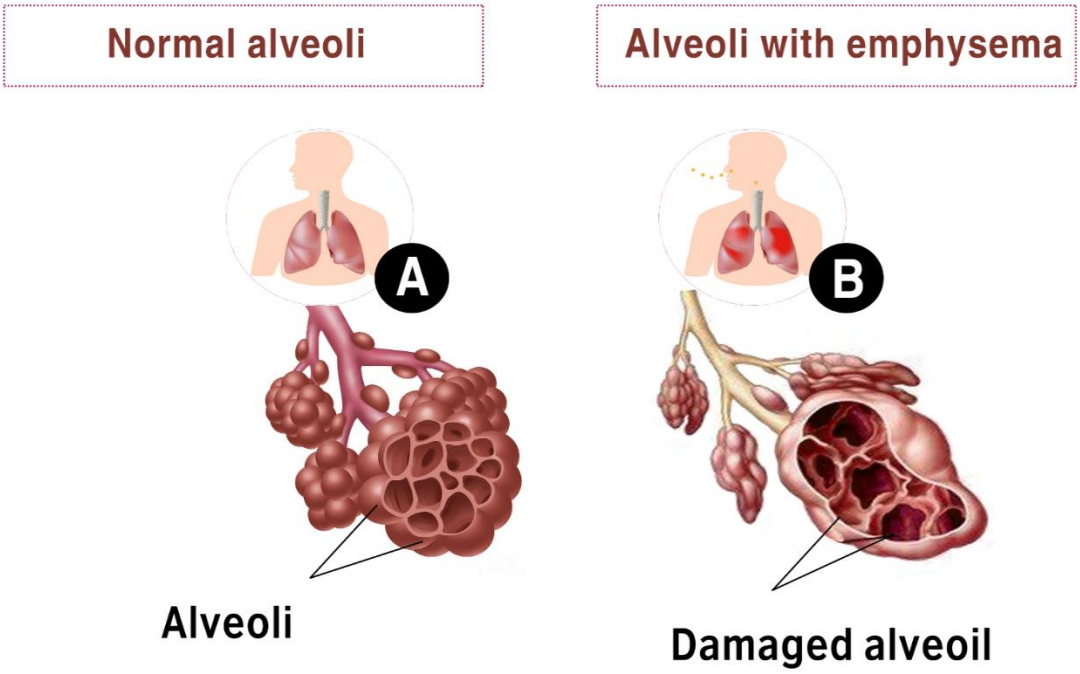
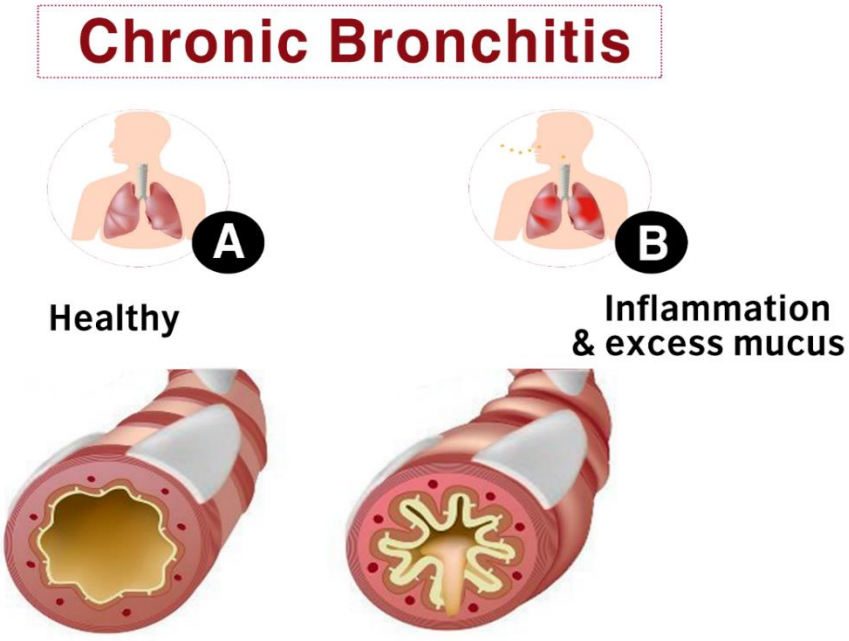


Figure 2: A, healthy airway. B, airway with chronic bronchitis, showing inflammation of epithelium & mucous accumulation (10).



1.1.1 Epidemiology

COPD is a common cause of morbidity and mortality worldwide (1). According to the World Health Organization (WHO) report, COPD is the fourth leading cause of mortality worldwide, and was responsible for the death of 3.2 million worldwide in 2015 (11). In 2016, around 251 million cases were reported globally (11). The prevalence of COPD was estimated to be 7.6% globally, especially in adult males who are 40 years old and above (12). COPD is expected to be the third leading cause of death by 2030 with 4.5 million deaths annually (13, 14).

The total economic cost of COPD in 2015 was 1.75 trillion GBP globally, which has a negative economic impact on the health care systems, and it is expected to increase by 2030 to 4 trillion GBP (15).

According to the British Lung Foundation (BLF), around 1.2 million people in the UK are diagnosed with COPD, making it the second-most common lung disease in the country. Around 4.5% of adults over 40 live with COPD, and two-third of people with COPD are still undiagnosed (16).

In the past, COPD in males was higher than in females but recent evidence has reported almost equal prevalence (3). In 2012, the mortality rate was around 30,000 deaths, 5% of total number of deaths in the UK, and 26% of those with lung disease (16). COPD is the third leading cause of pulmonary death in the UK (16, 17).

Annually, COPD costs the National Health Service (NHS) in the UK around 1.9 Billion GBP, with 140,000 emergency admissions, and more than one million bed days (15).

COPD has become a serious burden on health care systems globally, and further research to mitigate this is a must.

1.1.2 Aetiology

Individuals who either regularly smoke tobacco or are exposed to indoor and/or outdoor air pollution, and/or occupational dust, or biomass fuel, are at risk of developing COPD (1, 3). All possible COPD risk factors are explained in detail below (Table 1).

Table 1: Risk factors for Chronic Obstructive Pulmonary Disease (18).

Genetic factors (e.g. α -antitrypsin deficiency)	Smoking
Age and sex	Occupational dust and chemicals
Airway hyper-reactivity and asthma	Indoor and outdoor air pollution
Chronic bronchitis	Recurrent bronchopulmonary infections
Diet	Lung growth

1.1.2.1 Smoking

Globally, tobacco smoking has been and remains the most common risk factor for COPD (18, 19). According to the WHO, smoking is responsible for 73% and 40% of COPD mortality in high-income countries and low- to middle-income countries, respectively (18). Eight in nine cases are caused by smoking, which indicates a higher risk of developing COPD for those who smoke, and means the more one smokes, the more likely one is to develop COPD; however, some smokers never develop COPD. There is also genetic predisposition (e.g. alpha-1 antitrypsin deficiency) in those who have never

smoked (18). Some smokers are more susceptible to respiratory symptoms such as shortness of breath and chest tightness, and have a greater decline in forced expiratory volume in one second (FEV_1), which is a disease marker in COPD patients, higher mortality and morbidity rate, and have higher risk for lung cancer than non-smokers (3, 18). The harm of smoking cigarettes not only affects those who smoke (active smokers), but also affects people who have been exposed to others' cigarette smoke (passive smokers) (18).

1.1.2.2 Genes

Besides alpha-1 antitrypsin, other genetic variation such as in alpha-nicotinic acetylcholine receptor and hedge-hog interacting protein genes, might be considered as a risk factor for developing COPD (20). McCloskey et al. found that people who smoke and have a family history of COPD are at higher risk of airflow limitation development (21). Alpha1-antitrypsin (AAT), a proteinase inhibitor, is a protein that belongs to the SERPINA1 gene and protects lung tissue by inhibiting neutrophil elastase (19, 22). When a mutation takes place, a reduction of alpha1-antitrypsin (AAT) concentration in the blood occurs, which predisposes to emphysema. Alpha-1 antitrypsin deficiency (AATD) or Alpha-1 proteinase inhibitor deficiency is an autosomal codominant genetic disorder induced by a deficiency or variation of alpha-1 antitrypsin levels which leads to persistent tissue breakdown. AATD is considered a risk factor that accelerates lung function reduction and COPD (22). Individuals with AATD may live normally without developing COPD, but exposure to risk factors such as smoking cigarettes, occupational dust and chemicals, or indoor and outdoor air pollution increase the risk of having the disease. To confirm a diagnosis, a blood test is conducted to measure the alpha-1-antitrypsin concentration in the

blood and if diagnosis is confirmed, a further testing is performed to identify phenotype and or genotype.

1.1.2.3 Occupational exposure

Working as a sculptor, gardener or in a warehouse, amongst many other occupations, might expose workers to fumes, chemical agents, organic and inorganic dust which promote mucus hypersecretion. It has been estimated by the American Thoracic Society (ATS) that 10% to 20% of COPD cases develop due to occupational exposure such as dust, fumes or chemicals linked with lung function decline or disease symptoms (23). According to Hnizdo et al., 19.2% of cases of COPD in the United States were due to occupational exposure (24). Several longitudinal studies have reported a relationship between occupational dust exposure, a significant decline in FEV_1 and a higher mortality rate (18, 25, 26). Also, Paulin et al. studied the effect of occupational exposure on 1,075 COPD and healthy smoker participants and found decreased quality of life and exacerbation were associated with occupational exposure (27).

1.1.2.4 Indoor and outdoor pollution

Globally, around 33.3% of humans are exposed to indoor or outdoor factors such as industrial pollution or indoor air pollution (28). People use animal dung, biomass fuel such as wood and coal, crop residues such as sticks, twigs, grass, straw, dried leaves, and charcoal as sources for heating and cooking (28, 29). Air pollution may significantly reduce lung function and increase the risk of developing COPD, lung cancer and other lung conditions (29, 30). Rural women are three times more likely than urban women to develop COPD due

to higher exposure (31). In the last 20 years, the prevalence of COPD and the mortality rate has accelerated at a faster rate for women than for men in the world (32). To minimise the risk of COPD occurrence and to reduce lung function deterioration, researchers have suggested using biogas as an alternative to biomass for cooking, and enhancing household ventilation (30, 33).

1.1.2.5 Age and sex

Age is usually considered a risk factor for COPD occurrence. According to Mercado et al., some of the physiological changes in airway and lung parenchyma in healthy older individuals are similar to changes in COPD patients (34). In the past, researchers have reported that the COPD prevalence is higher in men than in women; however, recent studies have identified that the prevalence of COPD is equal or even higher in women than in men due to the later increase in smoking among women (35). Other scientists have found that both males and females have an equal chance of developing COPD, based on changes in their respective smoking habits (19, 36).

1.1.2.6 Chronic bronchitis

Chronic bronchitis is considered a risk factor for developing COPD. In the past, researchers did not find any relationship between the reduction in lung function or FEV_1 and chronic bronchitis (37). Subsequently, Allinson did find that there was an association between continuous FEV_1 decline and chronic bronchitis (38). Furthermore, chronic bronchitis increases the incidence of airflow limitation, which leads to a higher mortality rate in adult smokers who are under

the age of 50 (39). Additionally, individuals with chronic bronchitis tend to have a higher number of and more severe exacerbations (40).

1.1.2.7 Asthma

Individuals with asthma have increased frequency of COPD. The existing literature concludes that patients with asthma have a 12-fold higher risk of developing COPD over time, compared with those who were non-asthmatic (41). A longitudinal study was carried out by Vonk et al. (2003) which followed 228 asthma patients for 33 years to identify risk factors of developing irreversible airway obstruction (42). They found that irreversible airflow limitation developed in almost 20% of these asthma patients (42). People who reported with asthma had significantly higher FEV_1 reduction than those who did not (43). A meta-analysis conducted in 2018 by Boaheng et al. concluded that people with a prior history of asthma in childhood or adulthood had seven times higher risk of developing COPD at a later age (44). Exacerbations, lung function decline, and low quality of life are seen in patients with both asthma and COPD (45, 46). According to the Global Initiative for Asthma (GINA), asthma is a disease of heterogeneity described by chronic airway inflammation and a history of wheezing, chest tightness, shortness of breath and cough, and expiratory airflow limitation which all vary in intensity over time (47). The Asthma - COPD overlap (ACO) has not yet been precisely defined by GINA due to variation in clinical phenotypes, but it can be described as persistent airflow limitation, with several features associated with both asthma and COPD (47). Individuals with ACO usually experience symptoms of both asthma and COPD.

1.1.2.8 Recurrent bronchopulmonary infections

According to Mercado et al., severe respiratory tract infections that occurred during childhood play a major role in the development of COPD during adulthood (34). The literature reports that patients with Tuberculosis (TB), Human Immunodeficiency Virus (HIV), and other infectious diseases are also associated with COPD. Byrne et al.'s systematic review found that TB and COPD during adulthood had a strong association with COPD (48).

1.1.2.9 Lung growth

Lung development may be affected by pre term birth, exposure to noxious agents during childhood and adolescence. According to GOLD, infants born prematurely are at risk of developing airway obstruction (3). Barker et al. followed up 5,718 men to examine whether weight at birth and infancy, and childhood respiratory infections, were associated with lung function and death from COPD during adulthood (49). They found that low birth weight, bronchitis, whooping cough, and pneumonia during infancy are associated with worsening lung function during adulthood, and that mortality rate correlated with low birth weight and weight at infancy (49).

1.1.2.10 Diet

Only one study so far has linked chronic bronchitis with diet. It found that there was a correlation between lung function and consuming fresh fruit (18). According to the National Health and Nutrition Examination Survey, Vitamin C deficiency is related to the diagnosis of chronic bronchitis.

In summary, smoking remains the most common risk factor for COPD in high-income countries so smoking cessation is crucial to reduce the chance of

COPD occurrence. It is also important to reduce exposure to risk factors early in the life.

1.1.3 Diagnosis of COPD

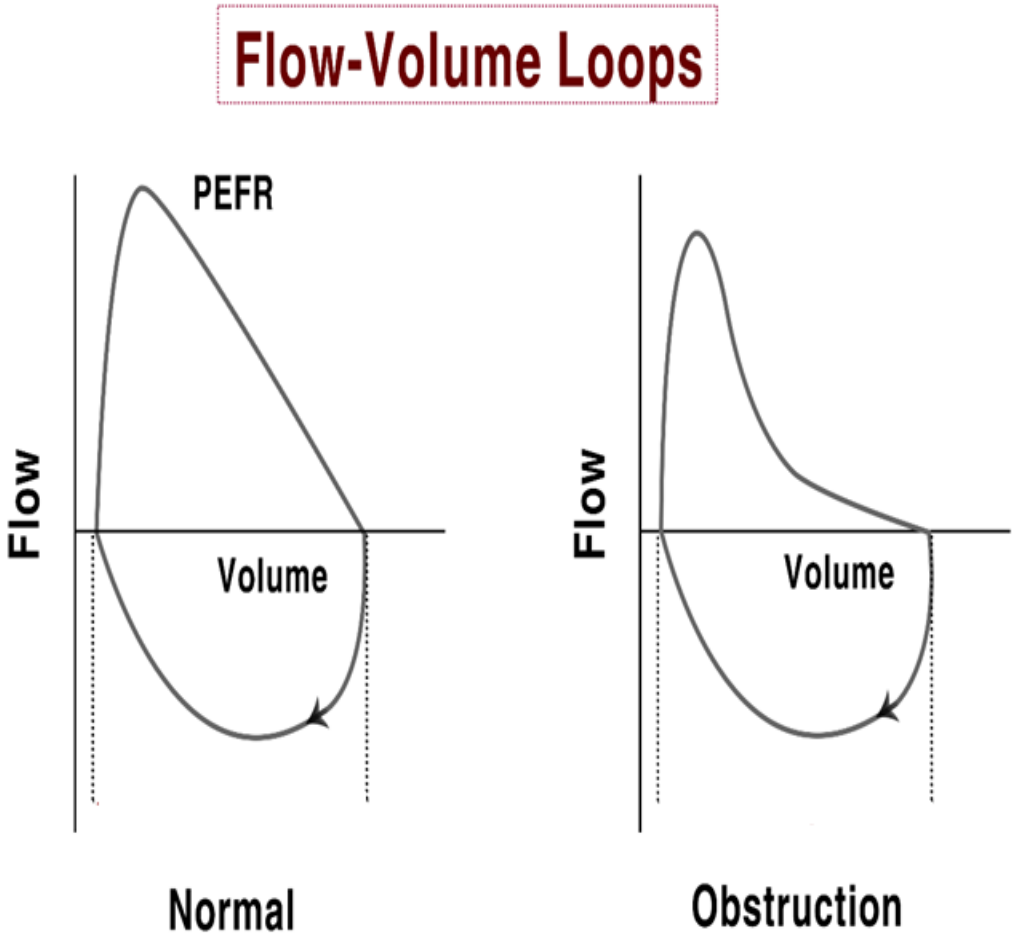
To confirm the diagnosis of COPD, post-bronchodilator pulmonary function testing using spirometry is required, together with a history of risk factor exposure (50).

This test is usually considered when the following respiratory symptoms are present: dyspnoea, chronic cough, sputum production, wheezing, history of frequent lower respiratory tract infection, and there is a history of risk factors such as smoking cigarettes, biomass fuel exposure, or any other risk factors. Pulmonary function testing (spirometry) is the only objective diagnostic test used to confirm the presence of airflow limitation due to COPD (3). In individuals with COPD, spirometry measures the exhaled volume of air in the first second (FEV_1), the exhaled volume of air starting from maximal inspiration (FVC), and the ratio of FEV_1/FVC ratio is calculated to confirm the diagnosis. To confirm someone has COPD, the ratio of FEV_1/FVC must be less than 70% after bronchodilator administration with an appropriate clinical context (3), or below the lower limit of normal. The FEV_1 percentage is used to define the severity (grade) of airflow obstruction, which is based on the value of a matched healthy subject for the same height, sex, age, and ethnicity (Table 2). Based on GOLD recommendation, spirometry measurements must be repeated three times for quality assurance, with no difference in FEV_1 of more than 150 ml or 5%. Figure 3 shows a normal spirometry flow- volume loop versus COPD flow- volume loop.

Table 2: Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1) (3).

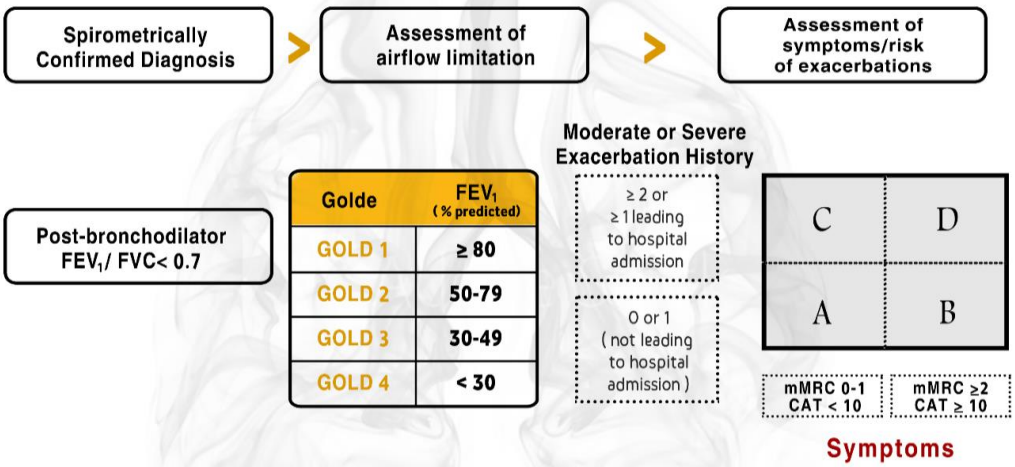
GOLD grade	Severity	FEV_1% predicted
GOLD 1	Mild	FEV1 ≥80% predicted
GOLD 2	Moderate	50%≤ FEV_1 <80% predicted
GOLD 3	Severe	30≤ FEV_1 <50% predicted
GOLD 4	Very Severe	FEV_1≤30% predicted

Figure 3: Normal spirometry flow loop vs COPD flow loop: note the curve 'scoped out' during expiration which represent airflow obstruction (51).



There are four GOLD stages in COPD based on the published ABCD assessment tool. The level of severity is determined by degree of breathlessness by using the Medical Research Council (MRC) dyspnoea scale, or quality of life using the COPD Assessment Test questionnaire (CAT), and the number of previous exacerbations and hospitalisation. According to GOLD, the first stage or mild COPD is characterised as a mild airflow obstruction and may have symptoms of chronic cough and sputum production (5). Moderate COPD, or the second stage, quite often has symptoms of dyspnoea, cough, and sputum production. At the second stage, patients often start seeking health care due to their respiratory distress. Stage III, or severe COPD, is characterised by worsening airflow limitation. Patients with severe COPD often have symptoms of shortness of breath, fatigue, and often repeated exacerbations, which affect the patient's quality of life. The last stage, or very severe COPD, has the characteristics of very severe airflow obstruction, and symptoms of dyspnoea, chronic cough, sputum production, and perhaps chronic respiratory failure (Figure 4).

Figure 4: The refined ABCD assessment tool for COPD (3).

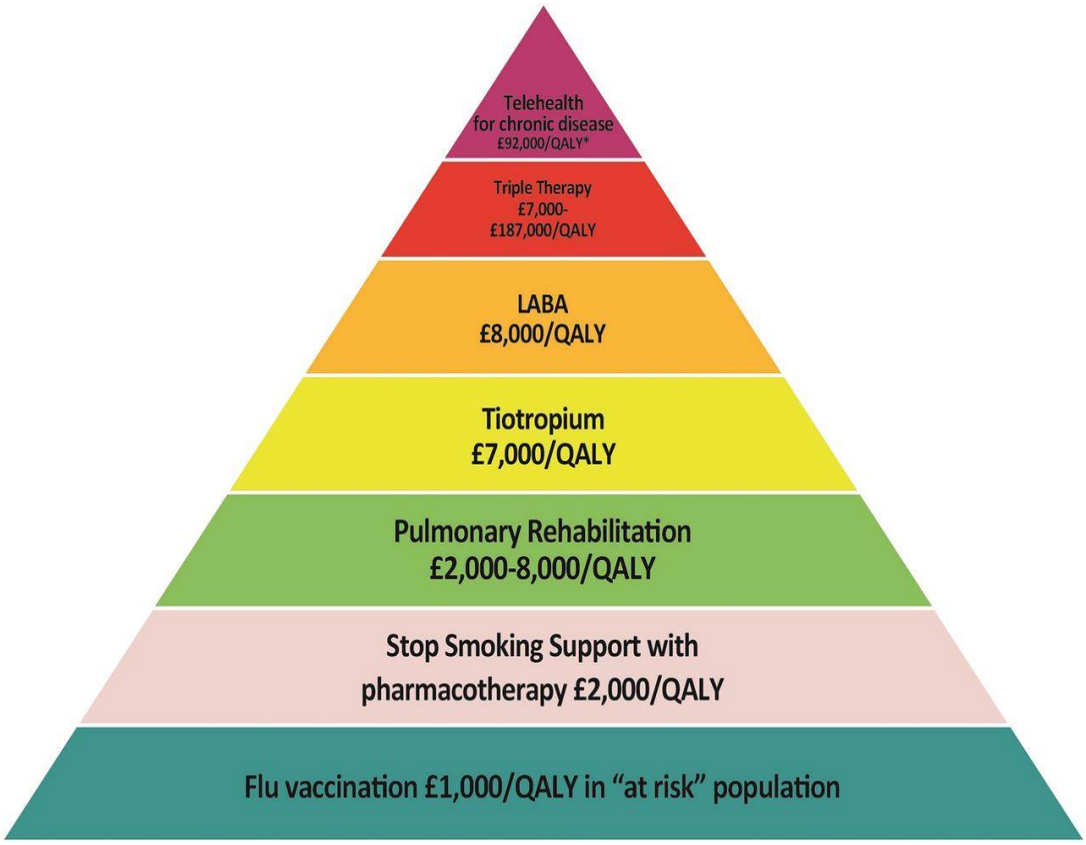


1.1.3 Management of stable COPD

Several studies have shown that COPD is a treatable disease, and its outcomes can be improved with careful management. The WHO recommends that effective COPD management should aim to prevent disease progression, relieve symptoms, improve exercise tolerance and health status, prevent and treat complications and exacerbations, and reduce mortality rate with the lowest risk possible (52). Cost-effective treatment approaches for stable COPD, assessed using the cost per quality adjusted life year (QALY), a method used to assess value of interventions in relation to cost, and as , described in the London Respiratory 'Value Pyramid', include: smoking cessation, influenza vaccination, and pulmonary rehabilitation, then medications such as long acting muscarinic antagonists (LAMA), long acting beta agonist (LABA), triple therapy (LABA+LAMA and inhaled corticosteroids),

(53) (Figure 5). As part of the management an individual with the disease should understand its nature and causes of deterioration. It is also important to reduce exposure to risk factors such as smoking or indoor and outdoor air pollution. Management should be tailored to each COPD individual and based on symptom level and exacerbation risk. GOLD guidelines support lifelong re-evaluation for the effectiveness and possible side effects of specific treatment, lung function, and smoking status, level of symptoms, frequency of exacerbation, comorbidities, and the need for oxygen therapy, ventilator support, and lung volume reduction surgery.

Figure 5: The COPD value pyramid (53).

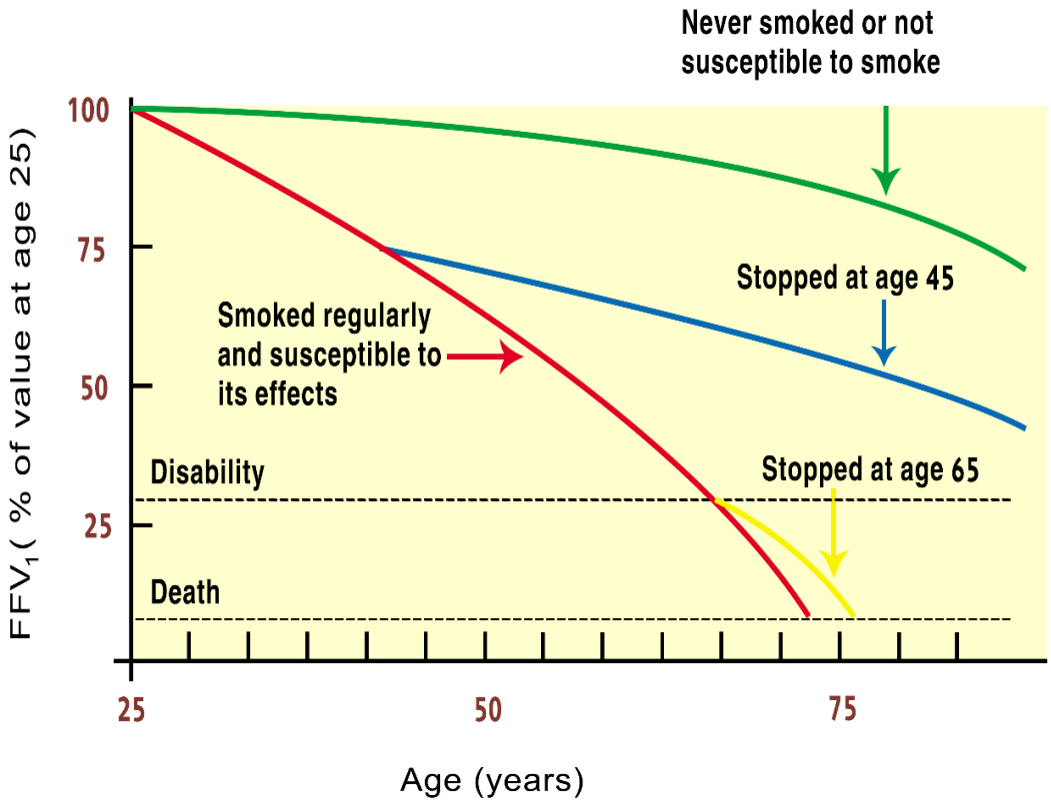


Abbreviation: QALY, quality adjusted life year.

1.1.3.1 Smoking cessation

Many studies have established that tobacco smoking has been and remains the most common cause of COPD worldwide; consequently, smoking cessation is an essential element of COPD management (19, 54). Fletcher and Peto indicated that smoking accelerates FEV_1 decline, and quitting smoking could not recover lost lung function; however, it would return the average rate of decline to normal in FEV_1, confirming the importance of smoking cessation (37) (Figure 5). Smoking cessation remains the most efficient intervention to reduce FEV_1 annual decline rate (55). Smoking cessation demonstrably improves respiratory symptoms in COPD patients (56).

Figure 6: The difference in FEV1% decline between non-smoker, ex-smoker and susceptible smokers (37).



Josephs et al. performed an observational cohort study to investigate the relationship of smoking status on mortality and hospitalisation in the UK (n = 16,479) COPD patients (57). Around 1.9 % had never smoked, ex-smokers accounted for 54.3% (n = 8,941), and current smokers were 35.1% (n = 5,787). They concluded that quitting smoking significantly reduced the risk of mortality, the chance of hospitalisation, and emergency department presence (57). Another randomised clinical trial was carried out by Anthonisen et al. in ten centres across the U.S and Canada. Male and female smokers (n = 5,887) were randomised to an intensive smoking cessation programme with bronchodilator, smoking cessation with placebo, and control groups. Smoking cessation significantly reduced the accelerated decline in FEV_1 when compared with the control group (58). The European Respiratory Society (ERS) recommends an integrated approached consisting of counselling and pharmacotherapy as the most effective approach for active smokers with COPD (55). Counselling sessions should include but not be limited to the effect of smoking on COPD, the effect of smoking on bronchodilators treatment, the benefits of quitting such as improved symptoms, and patient motivation. Pharmacotherapy includes nicotine gum, nicotine sublingual tablets, bupropion, nortriptyline, and varenicline (55). A strategy was introduced by GOLD to help healthcare providers to support patients who are interested in quitting smoking (Table 3).

Table 3: The five A's of smoking cessation (3).

BRIEF STRATEGIES TO HELP THE PATIENT WILLING TO QUIT	
• **ASK:**	Systematically identify all tobacco users at every visit. *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.*
• **ADVISE:**	Strongly urge all tobacco users to quit. *In a clear, strong, and personalized manner, urge every tobacco user to quit.*
• **ASSESS:**	Determine willingness and rationale of patient's desire to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).*
• **ASSIST:**	Aid the patient in quitting. *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.*
• **ARRANGE:**	Schedule follow-up contact. *Schedule follow-up contact, either in person or via telephone.*

TABLE 3.1

1.1.3.2 Vaccination

Respiratory infections in individuals with COPD might lead to COPD exacerbations or "chest infection"; therefore, it is crucial to identify effective ways to minimise current infection or stop future infections. Viral infection such as that caused by the influenza virus might be responsible for 33% of COPD exacerbation; therefore, influenza vaccination is highly recommended in COPD patients. Influenza vaccination is highly effective and cost saving in preventing or reducing respiratory infection that is caused by the influenza virus, with fewer hospitalisation and exacerbation frequency compared with people who did not get vaccinated, and a lower mortality rate in COPD patients (59-61). Seasonal vaccination is recommended by Bekkat-Berkani et al. after

a systematic review which evaluated the seasonal influenza vaccination in COPD patients (62).

Pneumococcal vaccinations such as Pneumococcal Conjugate vaccine (PCV13) and Pneumococcal Polysaccharide Vaccine (PPSV23) are recommended by GOLD for individuals with COPD, especially those aged 65 years old and above (3). The GOLD guidelines also recommend using PPSV23 for younger adults who have COPD with significant lung diseases or chronic heart conditions. According to Walters et al.'s systematic review of the efficacy of pneumococcal vaccination for preventing pneumonia in COPD, the risk of COPD exacerbation was significantly reduced for vaccinated individuals with COPD (63). Furthermore, they found that polyvalent pneumococcal vaccination and PPSV23 significantly reduced the risk of developing community-acquired pneumonia in COPD patients; COPD exacerbation did not happen in one out of every eight COPD patients who received vaccinations (63, 64). Bonten et al. confirmed that PCV13 reduced the incidence of pneumonia in COPD patients (65).

1.1.3.3 Pulmonary Rehabilitation (PR)

Pulmonary Rehabilitation (PR) is a multi-disciplinary programme that offers patient assessment, exercise training, and education, e.g. on COPD, nutritional counselling, and psychological counselling, to improve quality of life and exercise performance in patients with chronic respiratory disease (66-69). Models vary but the duration typically lasts between 4 and 12 weeks, and patients attend two or three times per week as out-patients (70). Multiple high-quality randomised controlled trials and meta-analysis have demonstrated that PR is an effective management strategy in COPD patients which improves

exercise performance, reduces dyspnoea, reduces the risk of exacerbation, and improves health-related quality of life (66-69, 71, 72). More details about PR are provided below in Part 1.2.

1.1.3.4 Pharmacological Therapy

The main goals of pharmacological therapy in stable COPD are to improve symptoms, lower the frequency and minimise the severity of exacerbations, improve exercise capacity and improve quality of life (3). Each treatment regime should be tailored to each individual and based on the severity of symptoms, airflow limitations, exacerbations, and more recently by considering biomarkers such as blood eosinophils (3). The pharmacological therapy in stable COPD includes: bronchodilators, corticosteroids, methylxanthines, phosphodiesterase-4 inhibitors, antibiotics, and mucolytic agents.

Bronchodilators are considered the cornerstone and the first- line of pharmacological therapy in COPD management. Bronchodilators include *beta$_2$ agonists*, both short-acting beta$_2$ agonists (SABA) and long-acting beta$_2$ agonists (LABA), and *antimuscarinics* including short-acting antimuscarinics (SAMA) and long-acting antimuscarinics (LAMA). Beta$_2$ agonist drugs work by targeting the beta$_2$ adrenergic receptors to relax the airway smooth muscles. The duration of action remains for 4 to 6 hours for SABA, or 12 to 24 hours for LABA. SABAs are fenoterol, levalbuterol, Salbutamol, and Terbutaline while LABAs are arformeterol, formeterol, indacaterol, olodaterol, and salmeterol (3). Antimuscarinic drugs work by blocking the muscarinic receptors to prevent bronchoconstriction effect; as a consequence, they relax the airway smooth muscles. The duration of action remains for 6 to 9 hours for SAMA, or 12 to 24 hours for LAMA. SAMAs include ipratropium bromide and oxitropium bromide,

while LAMAs include aclidinium bromide, glycopyrronium bromide, tiotropium, umeclidinium, and glycopyrrolate (3).

According to Sestini et al., in a systematic review assessing the clinical effectiveness of SABA in stable COPD which included thirteen RCTs, SABA alone improved lung function and symptoms (73). Also, a systematic review by Kew et al., assessed effectiveness of LABA in stable COPD which included 26 RCTs, and found that LABA significantly improved quality of life and reduced future COPD exacerbations related to hospitalisation (74).

Appleton et al. performed a systematic review of seven RCTs, with a sample size of 2,652 to compare the effectiveness of ipratropium bromide versus SABA, and found that ipratropium bromide alone improved disease symptoms and exercise endurance, when compared with SABA alone in stable COPD patients (75). Several studies and reviews have compared tiotropium bromide to placebo or other bronchodilators, and found that tiotropium bromide protected and reduced the risk of exacerbation, prevented moderate and severe exacerbation occurrence, and improved the quality of life (76-78). In the context of PR, tiotropium bromide improved the duration of activity, dyspnoea, health status, and exercise tolerance (79, 80).

Over the last decade, researchers have studied the efficiency of combining bronchodilators which have different durations and mechanisms of action to optimise a COPD management plan. Several studies have investigated the effect of combination therapy and concluded that combining bronchodilators from different classes resulted in significant improvement of lung function, quality of life measured by St. George's Respiratory Questionnaire (SGRQ), respiratory symptoms, and lower the risk of COPD exacerbations (81-84).

Methylxanthines include theophylline (most commonly) and aminophylline. The exact mechanism of xanthines is not fully understood and remains controversial. A double- blind RCT by ZuWallack et al., including 803 stable COPD patients concluded that a combination of beta$_2$ agonists such as salmeterol and theophylline significantly improved FEV_1, disease symptoms, dyspnoea, and reduced exacerbation when compared to salmeterol or theophylline alone (85, 86).

Anti-inflammatory agents such as *inhaled corticosteroids (ICS)* may have beneficial effect when used alone. However, a combination therapy (LABA+ ICS) appeared to be more effective than using ICS alone. ICS include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, and mometasone. In a systematic review of COPD patients to compare the efficacy of ICS and LABA combined, against LABA alone, Nannini et al. concluded that a combination therapy (ICS and LABA) reduced exacerbation and improved quality of life measured by SGRQ, dyspnoea, respiratory symptoms, FEV_1 (87, 88). Researchers have also investigated the effect of using triple therapy (LAMA+LABA+ICS) on lung function and exacerbation. Lipson et al. conducted an RCT to examine the benefits of triple therapy (ICS+LAMA+LABA) as compared with dual therapy (either ICS–LABA or LAMA–LABA) for 10,355 COPD patients. They found that triple therapy significantly reduced COPD exacerbations and hospitalisation due to exacerbations when compared with dual therapy (89). Halpin et al. explored the effect of triple therapy in 1,810 COPD patients and concluded that triple therapy improved lung function (FEV_1), health-related quality of life measured by SGRQ, and reduced annual COPD exacerbations (90). However, researchers noticed an increased risk of pneumonia, especially in moderate

and severe COPD patients. Therefore, GOLD recommends using ICS as an additional therapy to bronchodilators. To evaluate and predict the benefit of using ICS, researchers have linked eosinophil levels in the bloodstream with ICS effects (91).

Phosphodiesterase-4 inhibitors (PDE4) work to reduce inflammation by preventing the breakdown of adenosine monophosphate AMP. Roflumilast is the most common drug used with COPD patients to reduce COPD exacerbations and hospitalisation with severe COPD patients despite using ICS and LABA/LAMA in combination therapy (92).

Antibiotic therapy used as prophylactic treatment had previously shown no benefit in reducing COPD exacerbations; however, recent studies have proven the opposite. Ni W et al. conducted a systematic review and meta-analysis, including nine RCTs with 1,666 COPD patients, to evaluate the effect of prophylactic use of erythromycin or azithromycin treatment. They showed that using azithromycin or erythromycin as a prophylactic treatment reduced the number of COPD exacerbations (93). Herath et al. found in a systematic review that using prophylactic antibiotic for three days a week with moderate to severe COPD resulted in COPD exacerbation reduction and health related quality of life improvement, which may reduce healthcare system cost, mortality rate, and conserve lung functions (94).

Mucolytic agents are commonly used to help loosen sputum and make it easy to cough up (95). Common drugs include, but are not limited to, acetylcysteine, carbocisteine, and erdosteine.

1.1.3.5 Oxygen therapy and ventilatory support

When breathlessness occurs during exercise, especially in severe COPD, **oxygen therapy** is needed to relieve oxygen desaturation, momentarily improve exercise tolerance, and reduce disability. Cranston et al. performed a systematic review including six RCTs and 567 COPD patients, and concluded that continuous oxygen therapy significantly reduced mortality rate after two years, when compared with overnight oxygen therapy in COPD patients with acute exacerbation and mild hypoxaemia. They also discovered that domiciliary oxygen therapy for more than 15 hours per day significantly lowered mortality rate over five years when compared with the no oxygen therapy group (96). Based on NIEC and British Thoracic Society guidelines, long term oxygen therapy should be considered for stable COPD patients when resting PaO_2 ≤7.3 kPa or PaO_2 ≤8 kPa with signs of peripheral oedema, or with confirmed polycythaemia or pulmonary hypertension (97).

Ventilatory support such as non-invasive (NIV)/ bi-level positive airway pressure (BiPAP) ventilation has been used during hypercapnic respiratory failure with COPD patients, and showed significant reduction in hospital admission and higher survival rate (11). Using domiciliary ventilatory support has its benefit for individuals with COPD. According to Murphy et al.'s RCT to investigate the effect of using home NIV plus oxygen on readmission and death rate in 116 patients (59 used home oxygen only; 57 patients used NIV and oxygen) with persistent hypercapnia after a severe COPD exacerbation, NIV significantly postponed the readmission rate in the NIV plus oxygen group when compared with the oxygen group only. At the 12-month period, the mortality rate was reduced in the NIV plus oxygen group (16 deaths) versus

the oxygen only group (19 died) (98). A retrospective study in 2018 conducted by Melloni et al. concluded that the ten year- survival rate for COPD patients who received NIV with or without long-term oxygen therapy was much better (32.3% vs 11.8%) compared with COPD patients who received long-term oxygen therapy only (99). Other researchers have reported that NIV improved lung function, quality of life, and exercise tolerance in comparison with control groups.

1.1.3.6 Surgical Interventions

Lung volume reduction surgery (LVRS) is an invasive surgical procedure performed by resecting the over-inflated lung tissue to reduce hyperinflation, improve elastic recoil, and allow the remaining lung tissue to function well (100). LVRS showed other benefits such as improved peak expiratory flow, health status, exercise capacity, survival rate, and reduced exacerbations. Washko et al. conducted an RCT involving 1,218 COPD patients to investigate the efficacy, safety, and cost-effectiveness of LVRS, and concluded that LVRS significantly improved FEV_1 and elastic recoil. Lung function improvement consequently increased expiratory air flow, exercise capacity, and secretions clearance compared to participants who received standard treatment (101). Nevertheless, other researchers reported that LVRS increased mortality rate and some COPD individuals were unlikely to benefit from the procedure (102).

Bullectomy is an invasive surgical procedure performed to remove dilated air space called bulla to allow for a better gas exchange, improve respiratory symptoms, lung function, and exercise capacity in highly selected COPD patients (103). Several complications have been reported by researchers such as pulmonary hypertension and weight loss.

Lung transplantation improves overall health status and exercise tolerance in highly selected severe COPD cases (103). Due to the lack of organ donors, lung transplantation is very limited. Common complications after surgery include but are not limited to acute and chronic rejection, and infections (104).

1.1.3.7 Bronchoscopic interventions

Several less invasive bronchoscopic approaches such as endobronchial valve placement have been proposed and examined by researchers to minimise mortality rate that is associated with LVRS, improved lung function and respiratory muscle mechanics. Endobronchial valve placement significantly improves lung function, six minute walk test (6MWT), and reduces COPD exacerbation (3). Pneumothorax is one of the most serious complications of endobronchial valve placement, and further research is needed to identify the most appropriate bronchoscopic procedure with fewer complications.

1.1.4 COPD comorbidities

COPD frequently co-exists with other diseases, or 'comorbidities' that might significantly influence a patients' condition. Overall, the management of COPD must include a treatment plan for the comorbid diseases.

1.1.4.1 Lung cancer

Individuals with COPD are at three to four-fold higher risk of lung cancer than the healthy population who smoke and was associated with higher mortality rate, especially the severe cases (105). Turner et al. followed 448,600 COPD non-smokers for 20 years in an observational study and concluded that lung cancer was predominant in COPD individuals (106). According to Butler et al.'s systematic review and meta-analysis of 21 studies, the pooled prevalence of

lung cancer in COPD patients was 2.79%. Although this percentage is very low, it is higher than the prevalence of lung cancer in the general population (107).

Smoking cessation along with other considerations such as chemotherapy, radiation therapy and lung resection surgery are considered during lung cancer management.

1.1.4.2 Cardiovascular comorbidities

Hypertension is a common comorbid disease in COPD patients. In the general population, the prevalence of high blood pressure in adults is 13.1%, with a higher figure in COPD individuals, which might be due to shared similar risk factors, especially smoking and age (108-112). Usually, high blood pressure is an asymptomatic condition; however, it might lead to cardiovascular disease (CVD) by damaging the artery walls, causing more plaque to build- up (113, 114). Early management of hypertension is crucial and should be based on current guidelines.

The relationship between **ischemic heart disease (IHD)** and COPD is an interesting area for many researchers due to common shared risk factors such as smoking, and high morbidity and mortality rate (115, 116). COPD patients are at a higher risk of developing IHD, especially acute coronary syndrome (ACS), compared to the general population (116). Soriano et al. studied 450 participants with IHD and reported that 60% of CVD patients had airflow limitation; of these, 87% had coronary artery disease (117). It is challenging to detect IHD such as ACS in COPD patients because of shared common symptoms such as dyspnoea instead of chest pain occurrence. Pulmonary evaluation and cardiovascular (CV) risk profile should be checked, and an

integrated treatment approach should be considered for patients with COPD and IHD such as exercise training, smoking cessation, or medication.

Heart failure (HF) which is often the result of IHD frequently coexists with COPD because both conditions share similar risk factors such as smoking. The prevalence of heart failure among stable COPD individuals ranges between 3.8% to 16% (118). According to Jackson et al, almost nine out of ten HF cases resulted from either hypertension or IHD (119). A retrospective cohort study conducted by Sidney et al, included 45,000 COPD patients in order to investigate hospitalisation and cardiovascular mortality rates; they concluded that HF was the leading cause of hospital admission and death, compared to non COPD, and these findings were stronger for individuals < 65 years old (120). Beta- Blockers are the usual treatment choice for COPD patients with HF along with other treatment options, such as angiotensin-converting-enzyme (ACE) inhibitors and the guidelines do not suggest an alternative approach (121).

Stroke is a serious condition which can affect everyone including COPD patients (122). The relationship between stroke occurrence and COPD including COPD treatment approach and the reduction of stroke occurrence, has not been fully established. Kim et al. carried out a systematic review and meta-analysis which included eight studies, and concluded that COPD independently was associated with a higher risk of developing stroke or other similar risk factors for CVD, but more studies are urgently needed to further explore the nature of this relationship and identify efficient preventive approach (122).

Peripheral vascular disease (PVD) in simple terms is a circulatory disorder outside the heart and brain, where blood vessels, either veins or most commonly arteries, become narrowed, blocked, or spasm. Smoking is considered the most common risk factor for developing PVD. Smoking leads to a build-up of fatty deposits on artery walls which might restrict the blood flow to the legs by narrowing the arteries (atherosclerosis). Houben-Wilke et al., in a longitudinal study to determine the prevalence of peripheral artery disease (PAD) and its association with functional capacity and health status in >2,000 COPD patients, reported that 8.8% of COPD patients were diagnosed with PAD (123). COPD patients with PAD health status and exercise function were significantly worse compared to COPD without PAD; therefore, it is crucial for healthcare professions to understand PVD and quantify the damage that might be caused by PVD (123).

1.1.4.3 Osteoporosis

Osteoporosis is a disease characterised by reduced or weakened skeletal resistance causing lowered bone mass. Due to its nature, osteoporosis is usually diagnosed at a later stage when fractures occur. In COPD population, several risk factors play a major role in developing osteoporosis, including but not limited to ageing, being inactive, smoking, malnutrition, sarcopenia, use of steroids (118, 124). Osteoporosis with multiple fractures lead to frequent hospitalisation, higher mortality rate, and worsening quality of life (125). A systematic review and meta-analysis of 64 studies were conducted by Chen et al. to identify the prevalence of osteoporosis. They reported that 38% of COPD patients were diagnosed with osteoporosis (125). Health care providers must screen COPD patients for osteoporosis and provide an evidence-based

management approach such as smoking cessation, vitamin D and calcium supplementation, and PR.

1.1.4.4 Psychological disturbances

Anxiety is an emotional status characterised by an unpleasant state of feeling insecure, and worrying thoughts usually associated with nervous behaviour. Anxiety affects between 10% and 19% of the COPD population, and this percentage rises in those who are oxygen dependent. It has been reported that anxiety in COPD is under diagnosed and treated due to shared common symptoms. Researchers have reported the effect of being anxious in moderate to severe COPD individuals resulted in deterioration of SOB, health status and exercise capacity (126).

Depression is “mental disorder characterised by persistent sadness and a lack of interest or pleasure in previously rewarding or enjoyable activities” (127). It was reported that depression exists in 42% to 60% of COPD patients (126). It usually coexists with anxiety, and it is hard to differentiate between the two conditions. The exact mechanisms of anxiety and depression are not fully understood, and researchers have speculated that several factors such as smoking and systemic inflammation might increase the risk of occurrence. Both conditions are independently responsible for a significant reduction quality of life (126). A retrospective study by Abrams et al. included over 26,000 COPD patients to explore the relationship between COPD and anxiety with depression; it reported that the mortality rate and readmission rate were significantly higher for COPD patients who are anxious and depressed (128). Additionally, Sampaio et al. (2019) discovered in a systematic review that COPD patients were 1.9 times more likely to commit suicide than non COPD

(129). Hospital anxiety and depression scale (HADS) is a recommended, validated, easy to use, and self-administered questionnaire used to identify people who are at risk of anxiety and depression. Anxiety and depression should be treated as per guidelines, for example antidepressants and comprehensive PR (3). Franssen and Rochester reported that PR which included educational sessions for psychosocial support had a significant positive short term effect in reducing anxiety and depression (126).

1.1.4.5 Metabolic syndrome and diabetes

Diabetes mellitus is a chronic disease characterised by insufficient secretion of insulin, or in which the body becomes resistant to insulin. Both metabolic syndrome and diabetes type 2 are common in COPD populations, and the exact mechanism is not fully understood. According to Lipovec et al., a systematic review including 19 studies with 4,208 COPD patients reported that the prevalence of diabetes type 2 was 34%. Diabetes type 2 was significantly more common in COPD than the non-COPD population, and in smokers versus non-smokers, especially in COPD stage 3 and 4 (130, 131). Diabetes with COPD disease was associated with a higher risk of hospital admission and five-year-mortality rate than COPD disease alone (132). Metabolic syndrome and diabetes should be managed based on the usual guidelines for both conditions.

1.1.4.6 Peripheral Muscle dysfunction

In general, the function of body muscles in humans is to allow body movement; therefore, any disruptions to those muscles might lead to abnormality. Peripheral muscle dysfunction is a common issue reported with multiple

chronic diseases such as COPD. Muscle dysfunction is caused by reduced muscle mass, altered muscle metabolism or muscle fiber structure (133). Muscle dysfunction is more prominent in lower extremities than upper extremities, and more common in emphysematous patients than chronic bronchitis patients (134). COPD patients may lose skeletal muscle mass, which leads to muscle weakness and dysfunction or muscle disuse, thus negatively affecting activity, mobility, gait speed, quality of life, overall strength and fertility (133, 135). Muscle disuse is caused by a prolonged sedentary lifestyle and voluntary immobilisation which leads to muscle deconditioning; hence, reduced muscle strength and endurance (135). COPD is associated with myopathy, which is driven by systemic inflammation, hypoxia, smoking, corticosteroids usage, energy imbalance, and malnutrition (133, 136). At a cellular level, several pathophysiological factors such as protein imbalance due to more breakdown than synthesis, apoptosis, and mitochondria and oxidative stress dysfunction lead to muscle dysfunction (133).

Muscle wasting is associated with worsening outcomes such as hospitalisation and mortality rate in COPD (137). Two studies have demonstrated that rectus femoris cross-sectional area (RF_{CSA}) was reduced by 17% and 25% respectively, in patients with COPD compared to healthy subjects (138, 139). RF_{CSA} and quadriceps strength are positively correlated in COPD patients, thus RF_{CSA} is a good surrogate marker of muscle strength which correlates with mortality and morbidity (140, 141). Swallow et al. found that the mortality risk was increased in those individuals with COPD and reduced quadriceps strength (140). Therefore maintaining muscle mass is of the utmost importance.

In 1988, the term sarcopenia was introduced by Professor Irwin H. Rosenberg and defined as a loss of muscle mass or function due to disease or the normal aging process (142). According to The European Working Group on Sarcopenia in Older People (EWGSOP) (143) sarcopenia is an acute or chronic condition defined as "a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes." A systematic review and meta-analysis conducted by Benz et al. included ten articles with 2,565 COPD patients to determine the prevalence of sarcopenia and its association with pulmonary function, exercise capacity, and prognosis. They concluded that the average prevalence of sarcopenia was 21.6% with a higher percentage in older malnourished COPD patients who were more severely ill and had limited physical activity, exercise endurance and functional performance (144).

To confirm the diagnosis of sarcopenia in COPD, muscle mass should be measured by Dual energy X-ray absorptiometry (DEXA) or Bio-impendence analysis (BIA), muscle strength by handheld dynamometer or five-times sit-to-stand, and physical performance by gait speed or Timed-up-and-go test (TUAG) should be measured (145). Each measurement has a cut-off score based on the technique used to confirm the presence or absence and the severity of sarcopenia. Management approaches with sarcopenia should be based on EWGSOP recommendations. Nutritional supplements might be considered to optimise the recommended level of protein intake (1.2 to 1.5 g protein/kg body weight/day) for sarcopenic COPD patients (146). PR is an effective management approach which was confirmed by Jones et al. in a study to identify the relationship between PR and sarcopenia in 622 stable COPD patients; they reported that sarcopenia did not affect the response to

PR, moreover, participants who completed PR reversed muscle dysfunction sarcopenia (147). PR will be discussed further in the next section.

1.2 Pulmonary rehabilitation (PR)

1.2.1 History and definition

In 1895, the concepts of physical activity and healthy diet were introduced for the first time by Dr Denison, Professor of Diseases of the Chest and of Climatology at the University of Denver, in his book titled *Exercise and Food for Pulmonary Invalids* (148). Dr. Denison emphasised how important and beneficial exercise training and healthy diet are for those with lung disease, in terms of well-being.

In the middle of the 20th century, Barach et al. conducted a study which involved patients with pulmonary emphysema to investigate how to reduce dyspnoea (149). They discovered that using oxygen therapy alone in two patients reduced their dyspnoea during daily activities. When an exercise programme was initiated for these two patients, a remarkable improvement in dyspnoea and exercise capacity, as measured by daily steps, were observed. In addition, Barach and his colleagues noticed a substantial improvement without oxygen use in walking and minimal dyspnoea. Ten year later, Barach and his colleagues recommended exercise training be integrated into the management of patients with chronic lung diseases, based on their findings. Physical therapy and breathing retraining were reported to be beneficial for patients with pulmonary emphysema, and these are considered fundamental components of PR today (149).

Thomas Petty was the first to describe exercise programme short-term and long-term benefits for individuals with chronic airway obstruction (150). Petty et al. described the components of the exercise programme, starting with an initial evaluation of patients followed by daily instruction lasting one hour, for bronchial hygiene and breathing techniques, with tailored exercises and home visits. At the end of the programme and one year later, Petty evaluated the programme and reported that there was an improvement in daily symptoms, exercise capacity, hospitalisation, and length of hospital stay.

In the past, the benefits of PR were not fully understood by patients with reduced lung volume and limited exercise abilities, who usually believed their physical functions were irreversible; therefore, it was hard to persuade those patients to exercise. However, a report published in 1992 showed that PR was a beneficial management approach for individuals with COPD (151). According to the ERS taskforce, PR aims to: '1) decrease of physical and psychological impairment due to the disease, 2) increase in physical and mental fitness and performance, and 3) maximise social reintegration of the patient to lower the handicap.'

PR consists of exercise and education, where the exercise component is aerobic exercise for both lower and upper extremities. The beneficial effects of PR can be acquired regardless of the patient's smoking status, age, gender, or lung abnormality. Based on the evidence supporting PR utilisation, several guidelines and organisations recommended that every COPD patient should be referred to a PR programme. In 1981, the first official definition of PR was published by ATS, in which PR (152) was defined as 'an art of medical practice wherein an individually tailored, multidisciplinary programme is formulated

which through accurate diagnosis, therapy, emotional support and education, stabilises or reverses both the physio- and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible capacity allowed by his pulmonary handicap and overall life situation'. Recently, PR has been defined by the ERS and ATS as 'an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities' (153).

1.2.2 Aims and effectiveness of PR

PR is recognised as an effective non-pharmacological management approach for reducing hospitalisation, unscheduled hospital visits, symptoms of dyspnoea, leg discomfort, anxiety and depression, and healthcare costs (154). According to the ATS statement in 2013, PR intervention significantly improves exercise capacity, muscle strength and endurance, emotional function, health-related quality of life, exercise capacity, disease self-management, nutritional status and likelihood of improving physical activities in COPD individuals (153, 155-157).Handgrip strength is a valid measurement of peripheral muscle strength, and can be measured using a handgrip dynamometer, A reduction in muscle strength, measured by handgrip, is associated with longer length of stay in hospital, poorer quality of life, and higher morbidity and mortality rates in COPD patients (158, 159).

The exercise component of PR may improve FFM in COPD patients with low muscle mass by stimulating protein synthesis (68). Increased protein synthesis is a normal reaction to exercise. It has been reported that individuals with COPD may lose weight and skeletal muscle mass (FFM) which leads to muscle weakness. Franssen et al, reported a study that included 50 COPD

patients who participated in 8 week PR, and showed that weight and FFM significantly increased after PR (160).

The main goal of PR is to enhance exercise capacity, which is usually limited by shortness of breath, especially in individuals with chronic respiratory diseases, and to promote self-dependency in relation to activities of daily living (161). It is essential to differentiate between exercise capacity and physical activity, as they are related but must not be confused. The WHO has defined physical activity as ‘any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits’, whereas exercise capacity is the capability of someone to tolerate exercise, which usually consists of multiple physical activities to improve physical fitness (162, 163).

It is important to measure physical activity due to its benefits on health, and the negative consequences of not being active (164). Being inactive is considered one of the leading contributors to premature death worldwide, and is associated with increased risk of diabetes and ischaemic heart disease (162). In COPD, low physical activity is associated with higher risk of exacerbation, hospitalization due to COPD exacerbation, and mortality (165). It has been shown that physical activity reduces the incidence of high blood pressure, coronary heart disease, type 2 diabetes, stroke, and the metabolic syndrome. Several methods have been proposed to measure physical activity, such as pedometers. A pedometer is a device used to objectively measure physical activity (steps only), using motion-sensor technology.

The BTS describes PR as a comprehensive management approach whose components should improve exercise capacity, breathing retraining, disease education, pharmacological usage, and psychological and nutritional support (166). Thus, a PR programme is administered by a multidisciplinary team that includes but is not limited to doctors, nurses, physiotherapists, psychologists, occupational therapists, dietitians or nutritionists, psychologists and social workers.

To assess the effectiveness of PR intervention, exercise capacity evaluation is usually performed before starting and at the end of a programme (167). The incremental shuttle walk test (ISWT) and 6MWT are the most common field tests for evaluating exercise capacity and overall performance (168). The ISWT is a maximum exercise test, with 20 minutes as the maximum duration, where the patient walks between two cones ten meters apart and an audio recording plays the test instructions. The test starts once three bleeps are heard, and the person should gradually increase their speed of walking to synchronise with the bleeps (169). By contrast, the 6MWT is a submaximal exercise test to measure the patient's ability to walk back and forth on a marked 30-meter hallway for six minutes, and rest is allowed if needed (167). To identify the impact of ISWT or 6MWT, oxygen saturation, heart rate, level of dyspnoea are measured before and after both field walking tests. ISWT and 6MWT field tests are both valid and reliable for measuring exercise capacity function and the effectiveness of a PR intervention in patients with chronic lung disease (169).

Individuals with COPD have shown an improvement in self-dependence level and confidence by modifying these behaviours in the safe multidisciplinary

environment of a PR class (163). Troosters et al. reported in a review article (2010) that high-intensity exercise training during PR reduces oxygen requirement and reverses peripheral muscle abnormalities (170). PR changed the COPD individuals' perception of shortness of breath, improved levels of confidence and lowered fear, showing that PR has a favourable impact on patients' quality of life (171). COPD patients are advised to increase their physical activities, as this would further enhance their daily walk and independence level with regard to working, playing, carrying out household chores, travelling, and engaging in recreational pursuits. During PR, COPD patients become better at managing their symptoms and conditions due to sharing their experience and knowledge with other patients with the same condition and their healthcare practitioner (172, 173). PR improves functional outcomes such as walking and quality of life by reducing the unfavourable adverse psychological effects of the disease (156).

COPD patients with ventilatory disturbances and muscle dysfunction showed a significant benefit after attending the PR programme (156). The benefits of PR might not be maintained as the effect might differ for each patient, but those patients who do benefit from being in PR are more likely to continue exercising after the end of the PR programme PR and would be the most likely persons to favour future PR follow-up (174, 175). COPD patients who have been referred to PR more than once are more likely to maintain the benefits of PR for three months up to a year (176).

To conclude, PR benefits may vary based on various factors; therefore BTS guidelines recommend offering PR in addition to other management approaches to further enhance patients' quality of life (177).

1.2.3 Structure and content of PR

Globally, regular PR attendance depends on accessible locations (156, 178). The content of PR programmes varies between sites, based on geographical area, with regards to capacity, intensity of exercise, length, and number of sessions (179). According to the National PR audit report in 2019 there were remarkable differences around the UK between programmes in location, care process, referral criteria, PR healthcare teams, and patients' attendance (179). For instance, referral processes and criteria mentioned in the report vary, as some PR services accept self-referral, re-referral, or auto-referral after being hospitalised, while other PR services do not. The majority of PR services have multidisciplinary teams including physiotherapists, nurses, dieticians, and occupational therapists to administer PR. However, respiratory physicians and psychologists are restricted in some PR services and their availability based on the area where the PR services are held (180). PR service locations may vary, with some programmes taking place at convenience or community centres, practice surgeries, or hospitals (179). The National PR audit reported variations in the services being provided and the acceptability criteria for enrolment on PR programmes in the UK. For instance, only 8% of PR programmes in the UK accept patients who are in the late stage of their disease process and have an MRC grade of 5. BTS guidelines recommend that COPD patients who are admitted to hospitals with acute exacerbations of COPD (AECOPD) should be referred to PR at discharge (166). According to the National PR audit report, only 71% of PR services accept early post-hospital discharge referral, while 29% of PR services offer this one month after hospital discharge. Therefore, the group of experts who carried out the PR audit recommended that PR service providers and leaders should establish

clear and standard referral criteria. Furthermore, they recommend offering PR service to patients with an MRC score of 2 – 5, despite their exercise capacity status and disease severity (179).

The BTS guidelines summarised the essential components of an effective PR programme. Effective PR should consist of exercise, self-management, and education, nutritional and psychological support. Bolton et al. recommended that PR duration should be minimally twice a week for 6 to 12 weeks of supervised sessions, because this increases the chance of patient improvement (166). The guidelines also recommend that patients with mild to severe COPD who are admitted to hospital due to AECOPD should be offered PR following discharge. Man et al. (2015) recommend that COPD patients should participate in a PR programme following exacerbation of COPD, as exacerbation has an undesirable psychological and physical impact on patients (181).

1.2.4 Patient suitability for PR

The National Institute for Health and Care Excellence (NICE) guidelines recommend a PR programme for patients who have mobility disability and scored 3 to 5 on the MRC. NICE also advised referral to PR programmes for individuals with a stable condition and limited exercise ability due to breathlessness. The BTS supported the NICE guidelines and highlighted the importance of referral following discharge and within four weeks, especially for patients who were hospitalised with COPD (166). Hence, the time and location of a PR programme should be organised based on the individual's convenience to maximise their chance of attendance. The MRC breathlessness scale is considered one of the most common scales used for referring individuals to PR. However, the healthcare provider should not only

rely on the MRC breathlessness scale as it cannot detect improvement or deterioration, such as exercise capacity during PR. BTS recommended that healthcare providers should have a sufficient knowledge about PR and its benefit before referral to educate, motivate, and encourage patients to start PR (166).

1.3 COPD and Malnutrition

1.3.1 Malnutrition definition and background

Malnutrition can be considered to be both over- nutrition, where someone is in overweight or obese, or under- nutrition, where someone is underweight or losing weight. According to the European Society for Parenteral and Enteral Nutrition, malnutrition or “undernutrition” is defined as ‘a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease’ (182). In simple terms malnutrition is defined as an abnormal balance of protein, energy or other nutrients that leads to negative effects on body function, size, shape, or its composition. In COPD patients, malnutrition co-exists with higher protein, energy, other nutrient requirements, a reduction in food intake, and unintentional weight loss (183). The exact relationship between COPD and malnutrition is not fully understood, but malnutrition could be a cause and/or consequence of COPD. Ezzell and Jensen reported that COPD individuals with malnutrition, especially emphysema phenotype, were found to have higher air trapping, lower exercise capacity and diffuse capacity compared to patients of normal weight with same the condition (184). De Blasio et al. compared COPD symptoms, nutritional variables and inflammatory

parameters among COPD patients with and without malnutrition, and reported that malnutrition in COPD patients was associated with worsening gas exchange, functional status measured by 6MWD, and symptoms measured by COPD assessment test (CAT) tool (185). Sun et al. (2019) carried out a systematic review and meta-analysis which included five RCTs to identify the relationship between Body mass index (BMI) and FEV_1 decline. They concluded that being underweight was a risk factor for accelerating lung function decline in COPD patients (186). Marco et al. conducted a cohort study including 118 patients with COPD to predict hospitalisations and mortality in a two-year follow-up period (187). They reported that COPD patients who were malnourished were at almost four times higher risk of mortality in a two-year period, and those with a low fat free mass index FFMI (which will be described further below) were 17 times more likely to die. Being underweight was associated with a higher risk of hospitalisation (187).

In the UK the cost of treating an individual with malnutrition is three to four times higher than non-malnourished patients (188). It was estimated that the annual cost of malnutrition in the UK is equal to £19.6 billion, with 15% higher spending on healthcare (188).

1.3.2 Prevalence

In COPD patients, malnutrition may progress rapidly following COPD exacerbation, or develop gradually over years. Several studies have reported the prevalence of malnutrition in COPD patients, which usually varies based on disease severity, patient settings, and the diagnostic method (189). According to Steer et al. in a prospective study conducted in the UK which included 608 COPD patients who were hospitalised due to COPD

exacerbation, the prevalence of malnutrition was 33% (190). In UK, Ng and colleagues reported in 2013 the overall prevalence of malnutrition for 778 COPD patients who were referred to PR was 11%; 6% were at medium risk and 5% were at high risk (191). Collins et al. reported that the prevalence of malnutrition in 425 outpatients with COPD who were screened with the Malnutrition Universal Screening Tool 'MUST' was 21% (192). Malnutrition Pathway, who are a group of experts, concluded that around one in three hospitalised COPD patients or one in five outpatients, are malnourished or at risk of being malnourished (188).

1.3.3 Causes and consequences

COPD is recognised not only as a disease of lung alone, but also a systemic inflammatory disorder that is characterised by higher production of inflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-8, interleukin IL-6, IL-8, and chemokines (193, 194). A higher production of inflammatory cytokines might negatively prompt the hypermetabolism noticed in individuals with COPD. Several studies have been conducted on COPD patients to identify the relationship between TNF-a and weight loss. They found that TNF- levels were ten times higher in underweight than normal weight groups, and the increase in TNF-alpha production is the likely cause of weight loss associated with malnourished COPD patients (193, 195, 196). Individuals with COPD might have a lack of appetite or anorexia due to breathlessness or other factors which further contribute to weight loss. Koehler et al. have linked a lack of appetite with an IL-6 inflammatory cytokine, which higher production of the IL-6 was associated with anorexia (197) (Table 4).

Elevated energy requirements, especially resting energy expenditure (REE), have been observed in COPD patients and are considered a cause of their malnutrition. Schols et al. conducted a study to measure REE in 68 stable COPD patients and 34 healthy controls with stable weight, and they concluded that REE was significantly higher in undernourished COPD patients when compared with COPD patients with normal weight and control (198). Similarly, Wilson et al. supported the same conclusion when they discovered REE was significantly higher in undernourished COPD patients (199). Work of breathing is higher in COPD due to breathlessness; therefore, the increase in REE in COPD patients who are undernourished may be due to the higher cost of oxygen breathing; however; the higher work of breathing is not the only cause of undernutrition in COPD patients.

The use of corticosteroids medication by COPD individuals may indirectly lead to malnutrition by inhibiting protein synthesis and promoting catabolism. The type of steroid, dose, and the duration of use have a major impact on the unfavourable effect on muscle; therefore, a higher dose of corticosteroids might lead to respiratory muscle weakness, which further leads to muscle mass abnormality and malnutrition (200). As a consequence of malnutrition, researchers have reported that the number of hospital admissions doubled, and six- month mortality rate increased three times when compared with normal weight COPD patients (201).

Table 4: Causes and Consequences of malnutrition in COPD (188).

Causes of malnutrition	Consequences of malnutrition
Disease effects, e.g. breathlessness, anorexia, inflammation	Increased mortality
Psychological factors, e.g. motivation, apathy, depression	Increased healthcare costs
Social factors, e.g. social isolation, death of a partner, lack of practical support	Longer hospital stays
Environmental factors, e.g. living conditions, access to shops	More frequent readmissions
Increased nutritional requirements, e.g. energy, protein	Reduced muscle strength
Medication: - inhaled therapy and oxygen therapy, e.g. taste changes, dry mouth - frequent or prolonged use of corticosteroids adversely affecting bone density and muscle mass	Reduced respiratory muscle function

Collins et al. calculated the total healthcare cost over a one-year period for 424 COPD patients. They found the cost of healthcare for underweight COPD patients was two to three-fold higher than for normal weight and obese COPD patients (202). Other consequences are listed in Table 4.

1.3.4 Body composition

Body composition abnormalities are common in COPD patients, especially those who are moderate or severe and referred to PR. As previously discussed, the body starts to lose fat as the energy expenditure exceeds the available energy and when food intake is reduced, whereas muscle mass is affected by an imbalance of protein synthesis and breakdown. Body weight and height are usually measured to calculate BMI. BMI is a value calculated from someone's 'weight in kilograms divided by the height in meters squared'.

BMI is categorised into: underweight less than 21 kg/m^2, normal weight from 21 to 25 kg/m^2, overweight from 25–30 kg/m^2, and obese more than 30 kg/m^2. Several studies have linked BMI abnormalities with COPD outcomes. Marti et al. conducted a retrospective study to examine the association between body weight and respiratory mortality in 128 COPD patients. They found that low BMI was a predictor for respiratory mortality (203). Additionally, Park et al. compared the effect of BMI on the development of COPD using data from a cohort data of 437, 584 Korean participants. They discovered that low BMI is a risk factor for developing COPD (204). The measurement of BMI is easy and common; however, it does not accurately indicate the true changes in body composition especially COPD patients. Fat mass (FM) and fat free mass (FFM), which are considered the main components of body mass, are a more detailed indicator of body composition, and usually reflect the true changes if measured by validated techniques. Bioelectrical impedance is a validated technique that measures body composition based on the different electrical properties of FFM and FM by sending electrical current through the body. Slinde et al. examined whether body composition measured by bioelectrical impedance predicted mortality rate over one year in 86 stable COPD patients. They reported that body composition measured by bioelectrical impedance was an independent predictor of mortality in COPD patients enrolled in a PR programme (205).

For many years, measuring FFM accurately has been a concern for many researchers due to its association with COPD outcomes. Hopkinson et al. examined the association between body composition, disease severity, and exacerbation frequency over one year in 46 stable COPD patients. They reported that a reduction in FFM in COPD patients was associated with a

reduction in lung function (206). Additionally, Rutten et al. stated that continued decline of FFM in COPD patients was associated with more frequent exacerbations (207). It is well established that COPD individuals with a low or “depleted” FFM had impaired exercise capacity as measured by a 12-minute walk distance, and lower quality of life as measured by the St George's Respiratory Questionnaire (SGRQ), when compared with COPD patients who had preserved or “not depleted” FFM (208, 209).

In the last 30 years, several studies have measured and defined the normal range of FFM by calculating FFMI, which is equal to FFM divided by height squared (68). FFMI less than 16 kg/m^2 for men and less than 15 kg/m^2 for women are considered abnormal with COPD patients (210). FFMI is very important in COPD patients since it correlates well with exercise function, breathlessness, respiratory muscle function, and FEV_1, so it might be a useful predictor of COPD severity (211). Vestbo et al., in the Copenhagen City Heart Study which included almost 2,000 COPD patients, and reported that low FFMI was associated with mortality rate even in COPD patients with normal BMI (212). A lower quality of life was also detected in COPD patients with low FFMI who were in a PR programme (213). Therefore, it is very important to measure body composition with COPD patients to reveal any abnormality such as muscle depletion or malnutrition.

1.3.6 Screening for Malnutrition

It is of interest for many healthcare providers to detect and manage malnutrition in the whole population, and especially those with an existing medical condition such as COPD that might lead to malnutrition. Early recognition and management of malnutrition in COPD might be beneficial in

reversing malnutrition, improving clinical relevant outcomes, and reducing healthcare utilisation (214, 215).

Several tools such as the Malnutrition Screening Tool (MST), Mini Nutritional Assessment (MNA), and MUST have been introduced and validated across several healthcare settings. MUST is the most common, easy to use and recommended screening tool that has been used to identify COPD adults at risk of malnutrition in different healthcare settings. It is a five-step tool that assesses BMI, recent unintentional weight loss and the presence of illness (188). MUST has been useful in predicting the risk of mortality rates in hospitals and early readmission with COPD patients (190).

The NICE has advised healthcare providers to calculate BMI in all COPD patients and pay attention to unintended weight loss, especially in older adults (216). They also recommend that healthcare providers should routinely screen for malnutrition risk with a valid screening tool in all COPD patients, and attention should be paid to the percentage of unplanned weight loss in older people (216).

1.3.7 Management

Once malnutrition has been identified, a specific management approach should be started and should be based on the level of risk (low, medium, or high risk). With stable COPD individuals, one should aim for an increase in muscle mass and body weight; usually two kilograms is a recommended threshold. Healthcare facilities should offer a variety of management approaches such as but not limited to: dietary instruction or advice to increase the intake of all nutrients, modified diet plans, and oral nutritional supplements (ONS) (188).

There are many different types of ONS available for patients with COPD. Nutritional supplements may be classified as either caloric or non-caloric, and can be obtained as powder, liquid or tablet forms. High fat and high carbohydrate caloric supplements are used to increase body weight, especially in malnourished COPD patients who have a higher REE (217). They likely work by protein supplementation has been used in COPD patients due to positive effect in promoting exercise performance and protein synthesis (218). By promoting protein synthesis, body mass and muscle mass is increased . Non caloric supplements may also include micro-nutrients. For example, vitamin B12 is essential since it has a crucial role in homocysteine, hematopoietic and muscle metabolism (219). Vitamin D is crucial to maintain strong bones since COPD patients are susceptible to osteoporosis. Vitamin D has also been shown to reduce the risk and rate of exacerbations in COPD patients (220, 221).

1.4 Nutritional supplementation during pulmonary rehabilitation in COPD

Nutritional supplements have been used to overcome malnutrition in patients with COPD. Nutritional support, integrated with exercise training, may improve exercise activity, decrease the risk of mortality, and improve muscle strength in undernourished COPD patients (222, 223). A meta-analysis of nutritional supplementation for stable COPD published by Ferreira et al. in 2012 included 17 randomised clinical trials, which indicated that nutritional supplements increased muscle mass and body weight, improved respiratory function and exercise tolerance in COPD patients who were poorly nourished (224). Additionally, Collins et al. demonstrated in their meta-analysis of nutritional

support and functional capacity in COPD that nutritional supplements improved weight and handgrip strength in COPD patients (225). Both reviews included randomised clinical trials only, and participants did not need to be engaged in a PR programme.

An integrated approach of exercise training and nutritional support may offer the greatest potential benefit and might be the best way to seek functional improvements with COPD patients; however, this question remain unanswered. Therefore, we conducted and published a systematic review (226) to investigate the additional effect of using ONS during PR to enhance PR outcomes. Our main hypothesis is that nutritional supplementation taken by COPD patients during PR will enhance PR outcomes.

2. Hypothesis and aims

This thesis examines relationships between malnutrition, nutritional supplementation, and PR in COPD. We hypothesised that nutritional supplementation over a six week period of PR will enhance exercise capacity, muscle strength, health related quality of life and result in improvements in physical activity of stable COPD patients.

Aims of project

- To report and summarise the current evidence for using nutritional supplementation during PR in stable COPD patients to enhance PR outcomes.
- To investigate the effect of a nutritional supplement (FCP) during a pulmonary rehabilitation program when compared with control group (preOp) at PR discharge and six weeks post discharge on:
    I. Exercise capacity.
    II. Peripheral muscle strength.
    III. Anthropometrics measurements (body weight, BMI, FM, FFM, and FFMI, waist, hip, and mid-thigh circumference).
    IV. Level of anxiety and depression.
    V. Health related quality of life.
    VI. Physical activity.
        - To evaluate the level of agreement between the (Yamax Digi-walker SW-200) and Fitbit Alta HR (Fitbit Inc, USA) on counting steps.
- To investigate participants acceptability and experience of the using the products.

3. Methods

3.1 Ethical approval

Ethical approval was obtained from Central Research Ethics Committee and Health Research Authority (HRA) (reference 18/LO/1842) Appendix 1. Written informed consent was obtained for each participant before participating in the study. The study was registered at ClinicalTrials.gov (227).

3.2 Study setting

Subjects were recruited from Central and North West London (CNWL) NHS Foundation Trust the Peckwater Centre and St. Pancras Hospital pulmonary rehabilitation classes in (London, UK). To gain an access, an honorary contract was obtained from CNWL on 1012/2018 (appendix 2).

3.3 Eligibility criteria

- **Inclusion criteria**
  - Confirmed COPD (post-bronchodilator FEV_1: FVC ratio <0.7)
  - > 10 smoking pack year history.
  - Enrolling on a PR programme.
  - Age of 18 and above.

- **Exclusion criteria**
  - Patients with any physical or mental health disorders preventing compliance with trial protocol.
  - Unable to communicate in English.
  - Malabsorption syndrome.
  - Unable to perform the Incremental Shuttle Walk Test.

- Patients already using other types of oral dietary supplement, under the care of a dietitian.
- Galactosaemia (contraindication).
- Known cow's milk protein allergy or lactose intolerance.
- BMI >30kg/m^2 without recent weight loss of >5%.

3.4 Randomisation method and intervention

Participants were randomised using a web-based service called ‘sealed envelope’ to an interventional group or control group. To ensure BMI was similar between groups, randomisation was stratified based on BMI < and ≥ 20 kg/m^2. The intervention and control products were used from the starting date until the completion date of PR. Each participant would either receive twice a day supplement of Fortisip Compact Protein (Nutricia, B.V. *Zoetermeer, Netherlands*) (125 ml bottle has 300 kcal, 24% protein; 41% carbohydrate; 35% fat), or the control twice a day of PreOp (Nutricia, B.V. *Zoetermeer*, *Netherlands*) (200 ml bottle has 100 Kcal, 100% carbohydrate). We could not provide a placebo identical to the intervention – this would have required a separate production run which Nutricia were unable to supply - so we had to select an alternative, available zero-protein supplement (preOp).

Figure 7: Fortisip Compact protein.

Figure 8: PreOp.

.

3.5 Sealed envelope

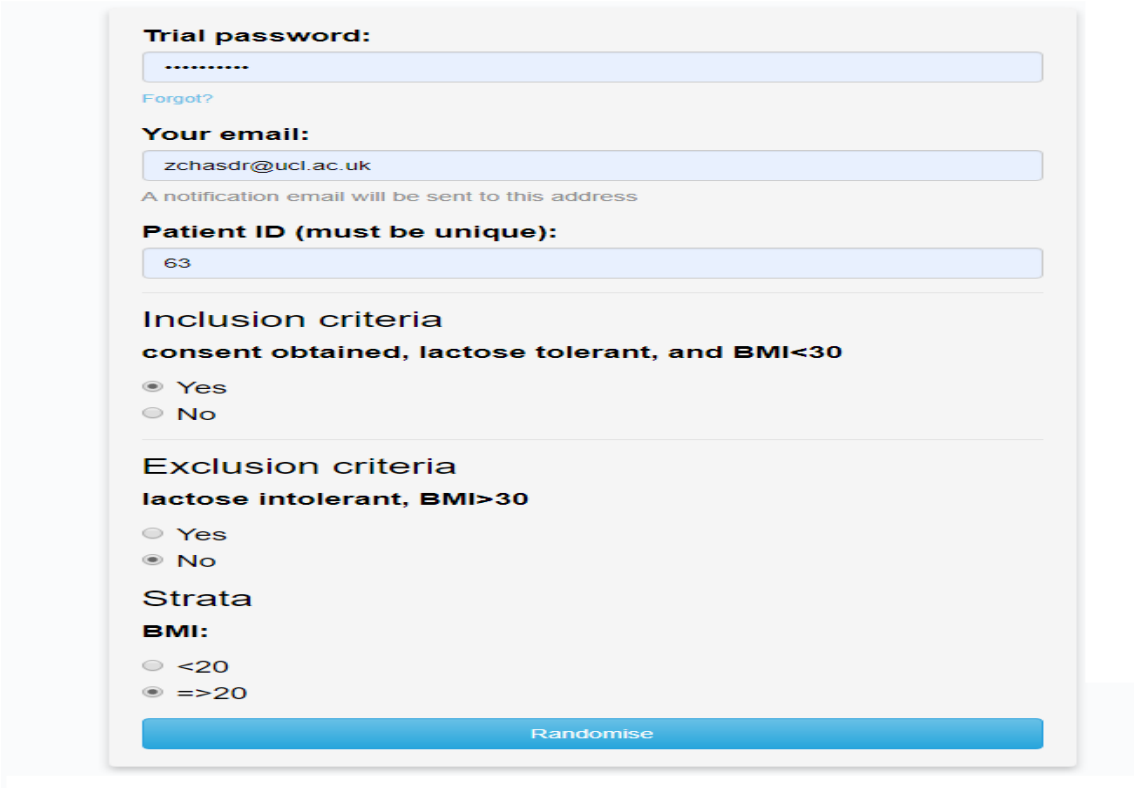
The sealed envelope service is an online service for randomisation. Participants' study number and BMI were required to run the randomisation process which was conducted by a member of our team not involved in the

study (Figure 9). For each participant, sealed envelope generated a random unique reference number (code). Then an email with the code was sent to the trial email address. This code was matched with a pre-existing list of codes, and subjects were allocated either to the intervention group or to the control group.

3.6 Method of sampling

Consecutive sampling approach was used in this research.

Figure 9: Sealed envelope randomisation page.



3.7 Recruitment of participants

In this study, the initial approach was made by clinicians running the PR programme and any patient who expressed an interest in taking part was provided with a written information leaflet (appendix 3). Patients expressing willingness to take part were introduced to the research team and a recruitment visit was scheduled. The recruitment visit started by giving a clear verbal description about the research including the purpose and potential benefits of participating in this study. Also, there was time for any questions that needed to be clarified by the researcher; furthermore, the participant was provided with the researcher's contact details for any further information. At this stage, any interested COPD patient who agreed to participate was asked to sign a consent form (appendix 4).

3.8 Study Design

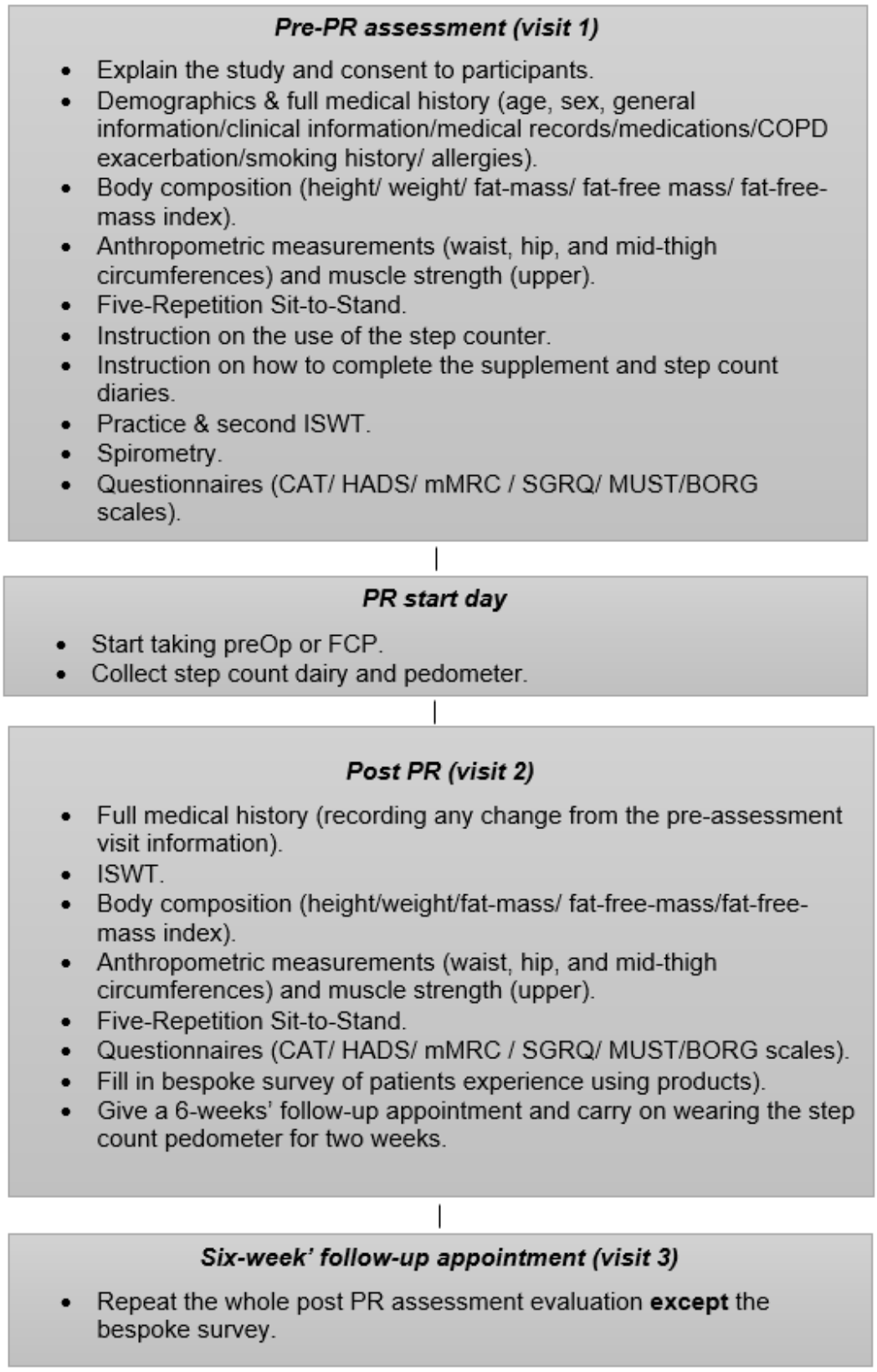
This was a double-blind randomised control trial. Both products were unlabelled and directly delivered to the participants' residential address with both researcher and participants being blinded. The following diagram 10 describes and summarise the study design.

3.9 Pulmonary rehabilitation programme

PR is a comprehensive out-patient rehabilitation programme consisting of one hour of exercise training and one hour of education which participants attend twice a week for a total of 12 sessions. The PR programme is supervised by respiratory physiotherapists and follows the BTS guidelines (228). The exercise training portion starts with a warm-up and is followed by low intensity of aerobic exercises such as cycling, treadmill walking and level walking, and

resistance exercise, such as progressive resistance of upper and lower body with free weights, step up, thigh muscle training with or without weight cuffs and sit to stand. Participants were encouraged during exercise by the respiratory physiotherapists to reach a score of 3 or 4 on the modified Borg scale but the intensity of exercises were depends upon the tolerance of each individual. The education part includes but is not limited to: stress management, signs of chest infection: early recognition, dyspnoea and symptom management, nutrition and healthy food, techniques using inhalers and nebulizers, energy conservation, smoking cessation and chest clearance techniques. All education topics were delivered by doctors, physiotherapists, nurses, psychologists, occupational therapists, and dietitians.

Figure 10: Study design.



3.10 Study Procedure

The following procedure describes the way that the data were collected in the consented patients. The researcher collected demographic data and distributed questionnaires to subjects who met the eligibility criteria: CAT to identify the impact of COPD on health-related quality of life, HADS to identify the levels of anxiety and depression, MRC and BORG scales to measure dyspnoea on exertion, SGRQ to assess health related quality of life, and MUST to identify subjects who at high risk of malnutrition. Number of chest infections and hospital admissions due to COPD exacerbation in the past 12 months were gathered. At the assessment date, the researcher measured the ISWT with Sit to Stand– Five Test (STS5) and baseline characteristics height and weight. Post-bronchodilator spirometry was done by hand-held spirometry using Micro 1 (CareFusion, Basingstoke, UK) to confirm the diagnosis of COPD. The researcher recorded waist, hip, and mid-thigh circumferences. Body composition was assessed using BMI, bio-electrical impedance to measure FM, and FFMI were assessed by a device called BodyStat (Bodystat, Douglas, Isle of Man). Handgrip strength was measured by handgrip Dynamometer. All measurements were recorded in a data collection sheet (appendix 5). Participants were given a simple step-counter (pedometer) and asked to record daily steps at the time of consent for 14 consecutive days before the start date (appendix 6). Also, Participants were also given drink diary to record daily intake of the products (appendix 7).

At the date of completion, all the measures described above were repeated. Participants were given a simple step-counter (pedometer) and asked to record daily steps post PR for 14 consecutive days (appendix 8), except showering and sleeping time. At the end of the study, the acceptance of the

intervention was assessed by using a bespoken survey (appendix 9). Six weeks after the completion of PR, participants were assessed at a final visit and repeated all the measurements.

- **Spirometry (FEV_1, FVC and FEV_1/FVC ratio)**

Post-bronchodilator hand-held spirometry were performed using a Micro 1 Handheld Spirometer (CareFusion, *Basingstoke*, UK) to confirm a diagnosis of COPD. The Micro 1 device is accurate, rechargeable, portable and works in accordance with the ATS/ERS standards of lung function (229). Participant were seated in upright position with head slightly elevated and during the test. Your patient needs to place his/her mouth around mouthpiece, and take a deep breath in as big as possible and blows out as hard and fast as possible until no air left in the lungs. Test were repeated three times to conform the published quality-assurance criteria (230).

Figure 11: Micro 1 Handheld Spirometer.

3.10.1 Questionnaires

Five validated questionnaires were used: 1: CAT, 2: HADS, 3: SGRQ, 4: MUST, 5: MRC

- **COPD Assessment Test (CAT)**

CAT is an 8- item questionnaire used to identify the impact of COPD, it has a score range of 0-40. The eight items used assess COPD symptoms (cough, sputum, dyspnoea, chest tightness, and one question assess the impact of sleep) (Appendix 10). Several studies have demonstrated that CAT is a valid and reliable tool to identify the impact of COPD on health-related quality of life (231, 232). The minimal clinically important difference is 2 points (233). Each participant was asked to fill the questionnaire at the assessment date, after the PR completion, and 6 weeks post PR.

- **Hospital Anxiety and Depression Score (HADS)**

HADS is used to measure both anxiety and depression. It consists of seven items for anxiety and seven items for depression, each item has a score from 0-3 (234). This means that a person can score between 0 and 21. Scores of seven and less in each domain is consider to be normal. Scores between eight and eleven in each domain indicate mild anxiety and/or depression; 11 to 14 suggests moderate anxiety and/or depression and 14 to 21 suggests severe anxiety and/or depression, respectively (234). The minimal clinically important difference of the HADS is 1.4 points (235). Each participant were asked to fill the questionnaire at the assessment date, after the PR completion, and 6 weeks post PR. (Appendix 11)

- **Modified Medical Research Council (mMRC)**

MRC breathlessness scale is used to classify the level of disability associated with breathlessness (236). MRC is a valid and simple tool to classify COPD according to disability level (236). Each subject was asked to fill the questionnaire pre and post PR after explaining the importance and the purpose of it. (Appendix 12)

Table 5: Medical research council grading of dyspnoea and description.

Grade of MRC	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

- **St. George's Respiratory Questionnaire**

SGRQ is an instrument design to measure the impact of obstructive airway disease on health, daily life, and wellbeing. It consists of 50 questions divided between symptoms, daily activities limited by breathlessness, and impact components which include psychological disturbances and social functioning (Appendix 13). Scoring range from 0 to 100 where 100 indicates more limitation (237). The minimal clinically important difference of the total score is

4 units (238). Each participant was asked to fill the questionnaire at the assessment date, after the PR completion, and 6 weeks post PR.

- **Malnutrition Universal Screening Tool (MUST)**

MUST has been created to identify adult subjects who are malnourished or at risk of becoming malnourished. It consists of five steps: 1) is to calculate BMI, 2) weight loss, 3) acute disease effect, and 4) (overall risk of malnutrition) is a sum of all scores from the previous three steps to identify step five (management guidelines). It has been used and validated with different adult population (239). (Appendix 14)

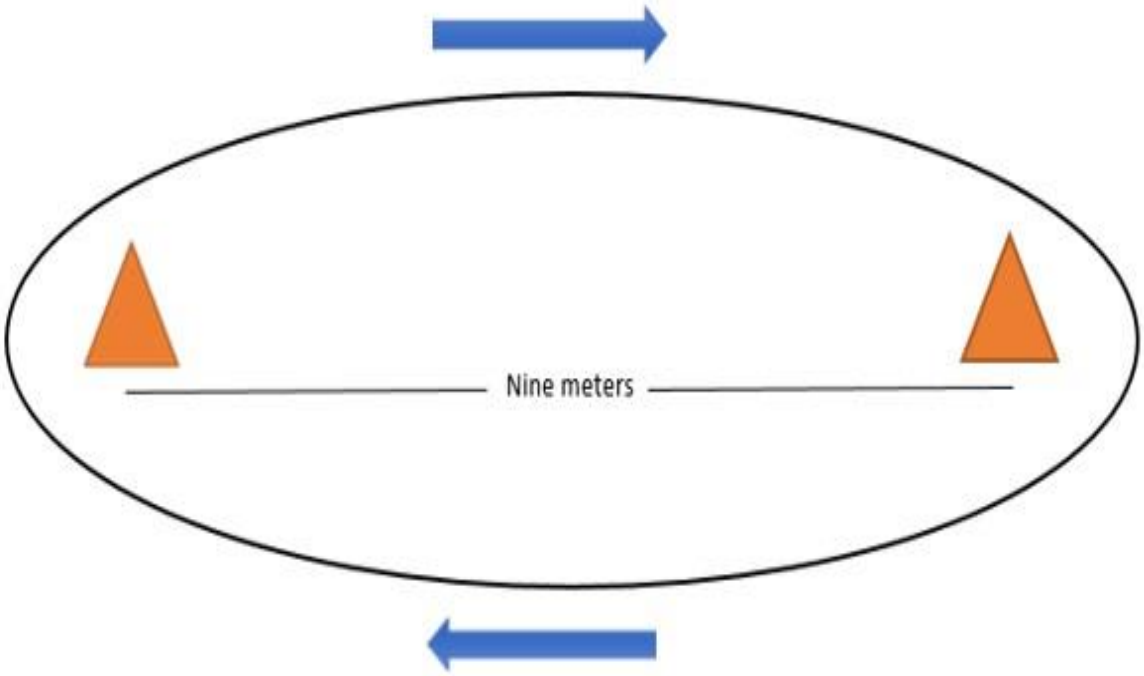
3.10.2 Functional Outcomes

- **The Incremental Shuttle Walk Test (ISWT)**

The test was conducted based on the ERS/ATS recommendations (169). Two cones were placed a distance of 9 m apart. The course is nine m in length and the cones are placed with an inset of 0.5 m from either end (Figure 12). An audio recording has the test instructions played to avoid any variation in the test. Once the recording is finished, the researcher confirmed that the patient understood the test. The research recorded heart rate, blood pressure, level of dyspnoea using modified Borg scale, and oxygen saturation before the test starts. The modified Borg scale is used to rate breathlessness, starting at 0 where breathing is not difficult at all and progressing to 10 where breathing is maximally difficult (240). The patient is positioned next to one of the cones, and the test is started once three bleeps are heard. Once the researcher hears triple bleeps, the patient was instructed to increase the speed of walking by saying ‘‘you need to increase your speed to keep up with the test.’’ Each

participant did the ISWT before enrolling in the PR twice, after the PR completion, and 6 weeks post PR to measure the change of exercise capacity with the effect of protein supplement. The minimal clinically important difference of the ISWT between 35.0 and 36.1 m (241).

Figure 12: Incremental Shuttle Walk Test. The arrows demonstrate the direction of patient walks.



- **Physical Activity Monitoring**

This is an important aspect due to its benefits for health and consequences of not being active (164). Participants were asked to wear a step counter pedometer (Yamax Digi-walker SW-200) on the left side of waist on the waist belt or waistband as per manufacturer manual and other studies (242, 243). Participants were required to record all daily steps for 14 days, except when showering and sleeping, before starting PR program. Again, each participant was asked to wear the pedometer for 14 days after PR completion. A diary

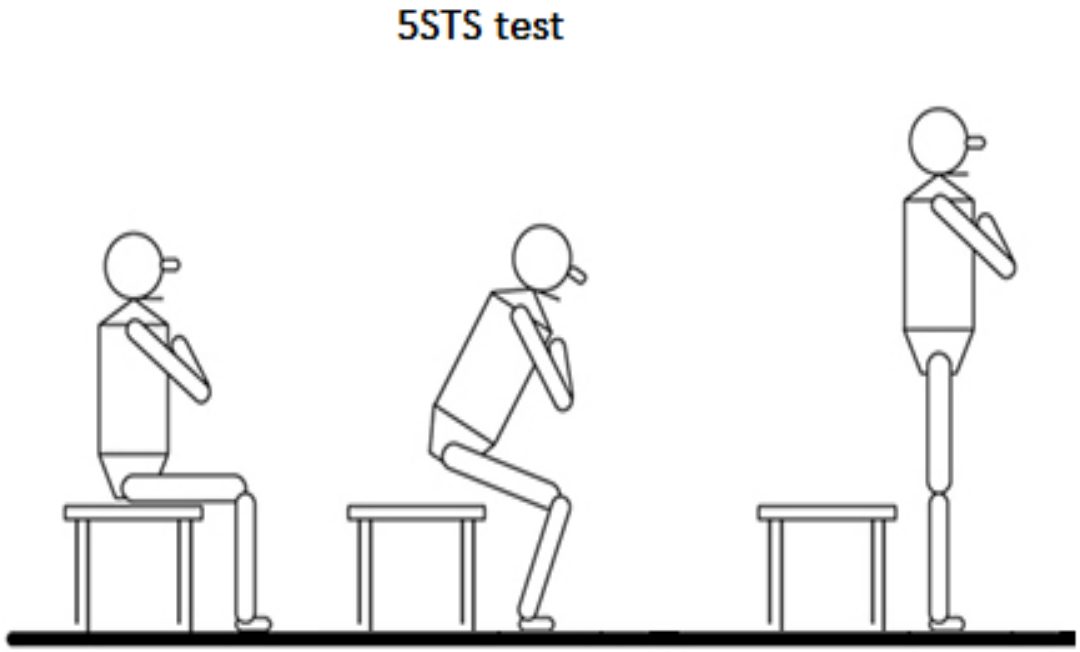
card was provided each period (Appendix 6 and 8). Participants were contacted once to make sure they are using the pedometer and to minimise confusion. (Figure 13)

Figure 13: Yamax Digi-Walker SW-200 pedometer device and instructions.

- **Sit to Stand – Five Test (STS5)**

STS5 is a functional outcome measure used commonly with COPD patients. It is simple and reliable tool which indicates exercise capacity and lower limb strength (244). It also correlates well with health related quality of life (244). Participants were instructed to sit on a straight-backed chair without arms with feet flat on the floor and hands folded across the chest, and asked to stand up and sit down without using arms support as fast as possible five times (Figure 14). For those who cannot do the manoeuvre, the test was terminated. The researcher used a stop-watch to count the time (245). It has been validated for participants with COPD and the MCID is 1.7 second (244, 245). The measurement was taken at the assessment date, after the PR completion, and 6 weeks post PR.

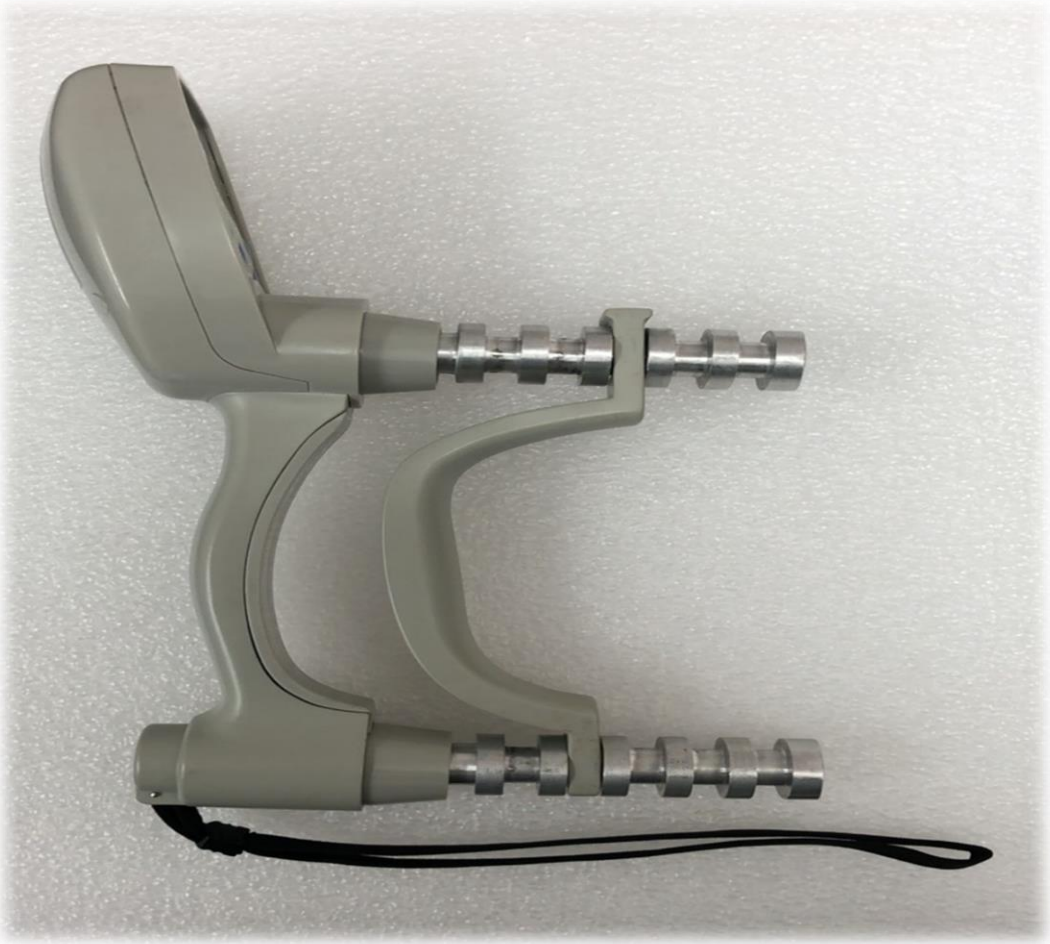
Figure 14: Sit to stand five test steps (246).



- **Handgrip strength**

The Jamar smart handheld dynamometer (Patterson Medical Ltd, *Warrenville*, Illinois, USA) (Figure 15) was used to measure the highest isometric strength of forearm muscles and the hand. The researcher asked participants to hold the device by one hand each time in order to measure both hands strength following specific guidelines during the procedure (247). The research used the best three measurements. It has been validated as a suitable method for monitoring change in muscle strength with COPD patients (247). The measurement was taken at the assessment date, after the PR completion, and 6 weeks post PR.

Figure 15: Jamar smart handheld dynamometer.



- **Body weight and height**

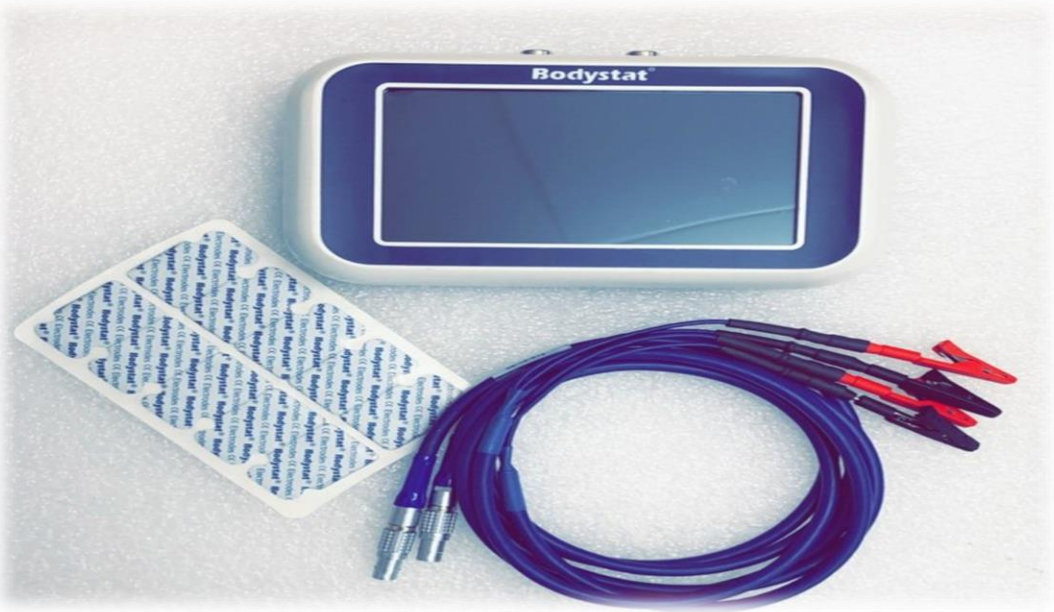
Body weight was measured in light clothing using a digital scale (EB4074C, *Anaheim*, US) while height was measured one time using a wall-mounted stadiometer and without shoes.

3.10.3 Body mass measurements

- **Bioelectrical impedance analysis (BIA)**

This is a safe non-invasive method used to determine body composition. Body composition means the percentages of bone, muscles, and water in human bodies. Participants were instructed to be in supine position. Bodystat Touch 1500 (Bodystat Ltd, Douglas UK) (Figure 16) was used to measure body composition. Two electrodes were placed on the anterior surface right hand and right ankle. Participants were requited to rest at supine position for three to four minutes. It has been validated with COPD patients by Schols et al.(248). The measurement was taken at the assessment date, after the PR completion, and 6 weeks post PR.

Figure 16: BodyStat Touch 1500.



- **Waist, Hip, and Mid-Thigh circumference**

Waist circumference

Participants were asked to wear light clothes. The researcher asked the participants to stand up with feet closed together, both hands close to the body, and relaxed. A stretch- resistant tape was placed top of the iliac crest and the lower margin of the least palpable rib with the measurement taken at the end of normal exhalation. The researcher repeated the measurement twice, and the mean was calculated with both measurements within 1 cm difference (249). The measurement was taken at the assessment date, after the PR completion, and 6 weeks post PR.

Hip circumference

Participants were asked to wear light clothes and stand up with feet closed together, both hands close to the body, and relaxed. A stretch- resistant tape was used horizontally to measure the widest portion of the buttocks with the measurement taken at the end of normal exhalation. The researcher repeated the measurement twice, and the mean was calculated with both measurements within 1 cm difference (249). The measurement was taken at the assessment date, after the PR completion, and 6 weeks post PR.

Mid-thigh circumference

Measurements were recorded for both legs. The participants were told to wear light clothes and stand on both legs. Measurement was made directly under gluteal fold with tape horizontally to the floor. Two measurements were made and the mean was calculated. The measurement was taken at the assessment date, after the PR completion, and 6 weeks post PR.

3.11 Power (sample size) calculation

The outcome variable of interest is the ISWT. The power calculation for the Steiner paper was adapted to calculate the sample size (250). Mean and standard deviation increases in ISWT performance from our own rehabilitation programme are 47 ±66 m. The clinical significance of further increases in performance resulting from treatment adjunctive to rehabilitation is unknown but we judged that an additional increase of 35 m as used in the Steiner paper would be of functional benefit to patients. The sample size was calculated with 90% power at 5% significant level and standard deviation of 53 m (the difference in a change between pre and post in ISWT from Steiner paper) to ensure we would detect this additional increase in ISWT performance in the intervention group, assuming a 29% dropout rate from rehabilitation. To achieve this we need to recruit 138 COPD patients, with 98 completing the study.

3.12 Statistical consideration

1. Primary outcome

The difference in change in ISWT distance (in meters) pre and post PR between intervention and control groups.

2. Secondary outcomes

A. The difference in change between intervention and control groups of the following measurements:

1. Peripheral muscle strength measured by Jamar Handgrip Dynamometer.

2. Body composition values (BMI, weight, FM, FFM, FFMI measured by BodyStat- bioelectrical impedance.

3. Waist, hip, and mid-thigh circumferences measured by a tape

4. Daily physical activity level by using step counter pedometer.

5. The impact of in health-related quality of life by recording CAT and SGRQ.

6. Levels of anxiety and depression by Hospital anxiety and depression Scale (HADS).

7. Malnutrition risk measured by MUST

8. In any re-assessed evaluation six-week post PR programme.

B. Participant's feedback and experience using nutritional supplementation.

3.13 Statistical analysis

Two end points were used for statistical analysis: 1) a per protocol analysis which include all participants who take 80% of the supplements and attend 75% of PR program within a maximum 10 weeks period and did not miss two or more consecutive weeks of PR, 2) intention- to- treat analysis which include all participants. Baseline characteristics of each group (interventional group vs. control group) were reported using mean and standard deviation/ median and interquartile range and percentage as appropriate. For the main outcome ISWT Between-group differences were compared by ANCOVA considering pre-ISWT value as covariate. Pre and post PR measurements for each group (intervention group vs. control group) were compared by using paired t-test analysis for normally distributed data and Wilcoxon signed-rank test if not normally distributed. Independent t-tests were used to compare the difference between both groups. Interim analysis and ANOVA to analyse results allowing for variation in baseline were proposed when we reach half of the calculated sample size but due to the COVID-19 pandemic we had to stop the recruitment. Data were assessed for normally by

visual inspection of the histogram, and the Kolmogorov-Smirnov test. Subjects were also stratified into depleted (Body mass index ≤21 kg/m^2 and/or FFMI ≤15 kg/m^2 for women or 16 kg/m^2 for men) vs. non-depleted patients to compare the effect of intervention in these subset (251). The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse our data.

Confidentiality

Participant's data was kept confidential. A study code number was assigned for storing confidential information. In the study, original paper questionnaires ، assessment forms and participants' contacts were collected from patients in accordance with the patient consent form and patient information sheet. The participants' data (original paper questionnaires ،assessment forms and participants' contacts) were appropriately kept within locked space at UCL Respiratory, London, NW3 2QG. University College London acted as the data controller for the study. Mr. Abdulelah Aldhahir (primary researcher), University College London processed and stored original paper questionnaires ، assessment forms and participants' contacts in accordance with all applicable legal and regulatory requirements, including the GDPR and any amendments thereto. Mr. Abdulelah Aldhahir (primary researcher), University College London will dispose of original paper questionnaires, assessment forms and participants' contacts in accordance with all applicable legal and regulatory requirements, including the GDPR and any amendments thereto. This project is covered by the UCL Data Protection Registration, reference No Z6364106/2018/06/10 health research.

All identification data such as name, address, file number, and phone number were saved in a password protected file on a UCL computer and kept separately from research data, with patients identified using study number only the researcher, chief investigator, and the research assistant in the respiratory medicine department as necessary.

Quality assurance

This study was performed in accordance with Good Clinical Practice (GCP).

Method Development

I wanted to use an inexpensive (Yamax) pedometer to measure physical activity. Because this has not previously been validated, I needed to complete some development work to compare the Yamax device against a 'Fitbit' which has been validated to measure step counts. This development work is the subject of the next section of my thesis.

3.14 Validation study:

Study 1: To evaluate the level of agreement between the (Yamax Digi-walker SW-200) and Fitbit Alta HR (Fitbit Inc, USA) on counting steps.

3.14.1 Comparison between Yamax Pedometer and Fitbit Alta Hr.

Introduction

Physical activity is defined by the WHO as “any bodily movement produced by skeletal muscles that requires energy”(162). Being inactive, is considered one of the leading contributors to premature death worldwide, associated with diabetes and ischaemic heart disease (162). It has been shown that physical activity reduces the incidence of high blood pressure, coronary heart disease, type 2 diabetes, stroke, and metabolic syndrome.

It is an important aspect of research to monitor physical activity due to its benefits and the negative consequences of not being active (164). Several methods have been introduced to measure physical activity, such as pedometers and accelerometers. A pedometer is a device used to measure physical activity (steps only) objectively using motion-sensor technology. An accelerometer is a piece of advanced technology used to measure the intensity and frequency of physical activity to estimate energy expenditure (252). Researchers have examined the accuracy and validity of several types of accelerometers and pedometers in certain populations. Fitbit One, Flex, Force, Zip, and Charge HR wristbands have been shown to be accurate when measuring steps in different populations (253). Fitbit works by collecting body movements in 3-dimensional space using three microelectronic axis accelerometer. The patterns of these movements were analysed to count steps taken. Noah et al. compared a Fitbit tracker with an indirect calorimetry in 23 subjects. The Fitbit was found to be a reliable and a valid device in measuring steps (254). Additionally, Storm et al. found that the Fitbit was one of the most accurate devices when steps were counted when compared to seven activity monitors. However, the device requires charging, needs a

smartphone connection, is relatively expensive, and can cause a rash. Alahmari et al. have suggested that the pedometer (Yamax Digi-walker SW-200) correlated well with steps during 6MWT in COPD patients (255). However, there is no published data compared a pedometer (Yamax Digi-walker SW-200) and the Fitbit Alta HR (Fitbit Inc, USA) wristband together. I wanted to use the pedometer (Yamax Digi-walker SW-200) because it is inexpensive, simple to use and unobtrusive. Therefore, I want to assess its accuracy against the Fitbit Alta HR which is part of the Fitbit generation.

Aim

To evaluate the level of agreement between the (Yamax Digi-walker SW-200) and Fitbit Alta HR (Fitbit Inc, USA) on counting steps when worn by healthy subjects.

Hypothesis

We hypothesise that there will be no significant difference in steps counted between the (Yamax Digi-walker SW-200) and Fitbit Alta HR (Fitbit Inc, USA).

Methods

Study subject:

Eleven healthy subjects (7 males; 4 females) verbally consented and participated in this study.

Measurement protocol:

Participants were asked to attach the pedometer (Yamax Digi-walker SW-200) to their beltless trousers, skirts, training suit or belt on the left side at all times, except when sleeping or showering, for five consecutive days. All participants

were instructed on how to use the device. It required a manual setup prior to use involving pressing the yellow button to reset it as shown in Figure 18. To record their daily steps for each day, participants were issued with a diary card. The participants were required to reset the pedometer each new day.

At the same time, participants were asked to wear the Fitbit Alta HR (Fitbit Inc, USA) wristband for five consecutive days. Each Fitbit watch was connected to a smartphone in order to record steps each day. Figure 18

Variable

To assess how similar the pedometer (Yamax Digi-walker SW-200) is in comparison to the Fitbit Alta HR (Fitbit Inc, USA) in detecting steps prior to use in future research.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse our data. To examine if our data were normally distributed, the Kolmogorov-Smirnov test was used. To identify the level of agreement between the pedometer (Yamax Digi-walker SW-200) and the Fitbit Alta HR (Fitbit Inc, USA), the Intraclass correlation coefficient (ICC) was used. An ICC of (0-0.20) indicates slight agreement; (0.21-0.40) indicates fair agreement; (0.41-0.60) indicates moderate agreement; (0.61-0.80) indicates substantial agreement; and > 0.81 indicates almost perfect agreement (256, 257). Bland Altman analysis was used to test the strength of the relationship of the two devices.

Results

Seven male and four female subjects with a mean age of (32 ±5) years participated. There was an excellent agreement between the pedometer (Yamax Digi-walker SW-200) and the Fitbit Alta HR (Fitbit Inc, USA) with an Intraclass correlation coefficient (ICC) = 0.98, 95% CI 0.93 to 0.99.. Figure 17 represent Bland-Altman plots with mean difference and SD of 273 ±955 steps/day for all participants, and the majority of values were within 95% confidence interval (CI: -1598.21 to 2144.21).

Figure 17: Bland-Altman plot demonstrating agreement between Yamax Digi-walker SW-200 and Fitbit Alta HR.

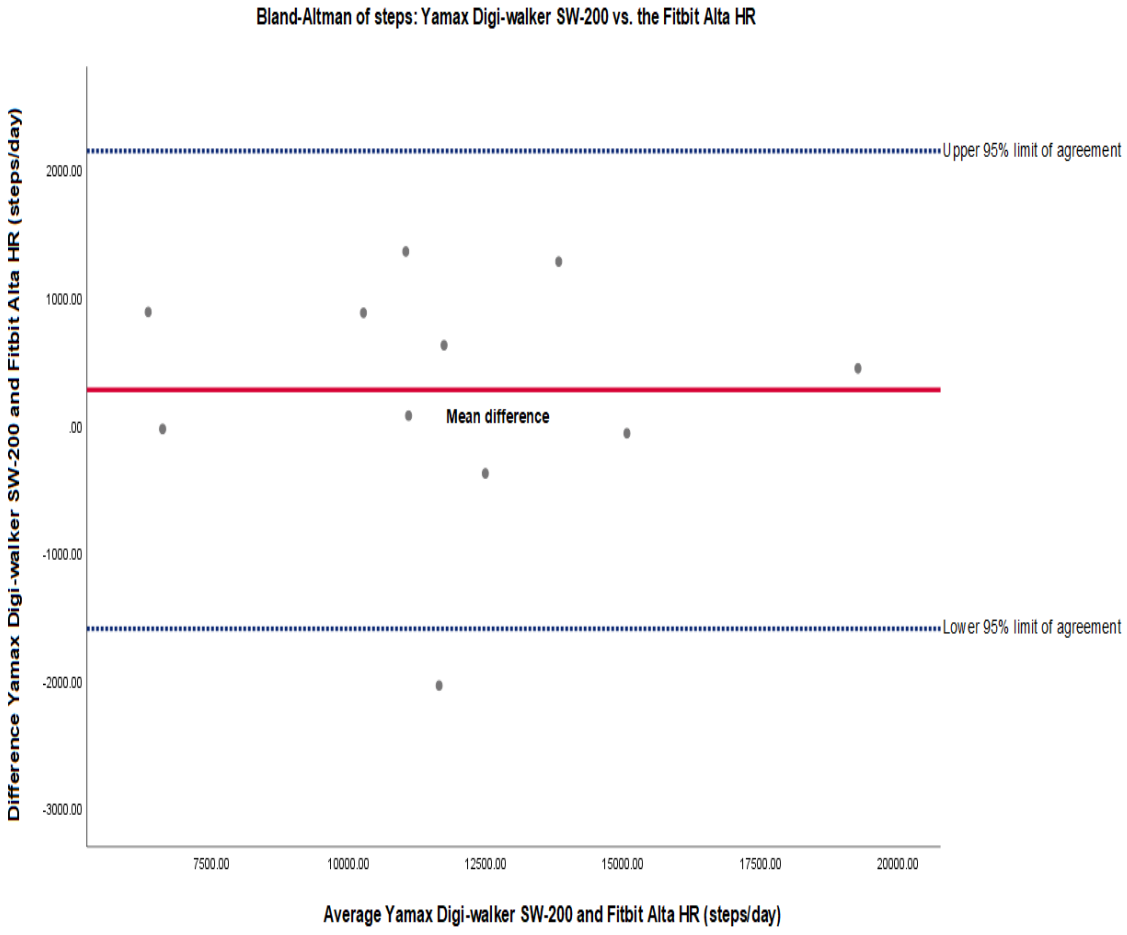


Figure 18: A) Pedometer (Yamax Digi-walker SW-200). B) Fitbit Alta HR (Fitbit Inc, USA).

Discussion

The aim of this study was to identify the level of agreement between the Yamax Digi-walker SW-200 pedometer and the Fitbit Alta HR (Fitbit Inc, USA) wristband on counting steps in healthy subjects. Eleven healthy subjects (7 males) were included in our study, with a mean age of 32 years old. The level of agreement between the wristband and the pedometer was almost perfect.

Our findings have demonstrated similar results to previous studies. Noah et al. compared a Fitbit tracker with an indirect calorimetry in 23 subjects. The Fitbit was found to be a reliable and a valid device in measuring steps (254). Additionally, Storm et al. found that the Fitbit was one of the most accurate devices when steps were counted when compared to seven activity monitors. However, the device requires charging, needs a smartphone connection, is relatively expensive, and can cause a rash. On the other hand, the Fitbit is light, easy to use, has an alarm which can be used to motivate physical activity,

and measures more than steps, for example heart rate and energy expenditure.

Our findings suggest that the pedometer correlated well with the Fitbit. Alahmari et al. have suggested that the pedometer (Yamax Digi-walker SW-200) correlated well with steps during 6MWT in COPD patients (255). The advantage of using a pedometer is that it is not expensive, it is simple to use, and it is unobtrusive. However, it does not provide the intensity, frequency, or distance of the physical activity.

Conclusion

The Yamax Digi-walker SW-200 and Fitbit Alta HR (Fitbit Inc, USA) showed almost perfect agreement in counting steps in healthy subjects. The Yamax Digi-walker SW-200 will be used in our main study.

4. Nutritional supplementation during pulmonary rehabilitation in COPD: A systematic review.

4.1 Introduction

Patients with COPD experience daily symptoms, reduced exercise capacity, and susceptibility to exacerbations, resulting in reduced health-related quality of life (3, 6, 7). The international GOLD strategy document summarises current approaches to COPD management (3). Cost-effective treatment approaches for COPD, described in the 'value pyramid' (53) include smoking cessation, influenza vaccination and PR. Multiple high-quality randomised controlled trials (RCTs) and meta-analyses have demonstrated that PR is an effective management strategy in COPD, since it improves exercise performance, reduces dyspnoea, reduces the risk of exacerbation and improves health-related quality of life (66-69, 71, 72).

Exercise limitation is one of the most common problems for COPD patients and this may be compounded by reduced muscle mass and malnutrition. Some COPD patients may lose body weight and skeletal muscle mass, which leads to muscle weakness and dysfunction, impacting functional ability and quality of life (135). Muscle disuse, caused by a prolonged sedentary lifestyle and voluntary immobilisation, leads to further muscle deconditioning and thus reduced muscle strength and endurance (136). It has also been postulated that COPD is associated with a myopathy, which may be driven by systemic inflammation (136). Being underweight is associated with an increased risk of mortality in COPD and weight loss predicts mortality and morbidity in chronic lung disease patients (68, 137). Therefore, patients with COPD are at risk of significant morbidity and mortality as a result of changes in body composition and nutritional and metabolic status.

It has been suggested that healthy older adults require additional nutrients compared with younger adults to preserve bone and lean mass. For instance, it is recommended that young adults require 0.7 g of protein/kg body weight per day while the recommendation for older adults is 1.2–1.5 g protein/kg body weight/day, especially for people with conditions that require higher levels of protein, such as COPD (146). Nutritional supplements have been used to overcome malnutrition in patients with COPD. It has been suggested that nutritional support integrated with exercise training may improve exercise activity, decrease mortality, and improve muscle strength in undernourished COPD patients (222, 223). A meta-analysis of nutritional supplementation for stable COPD by Ferreira et al. included 17 randomised clinical trials and concluded that nutritional supplements increased muscle mass and body weight and improved respiratory function and exercise tolerance in COPD patients who were poorly nourished (224, 258). Additionally, Collins et al. demonstrated in a meta-analysis of nutritional support and functional capacity in COPD that nutritional supplements improved weight and handgrip strength in COPD patients (225). Both reviews only included randomised clinical trials and it was not necessary for participants to be engaged in PR. We hypothesised that an integrated approach of exercise training and nutritional support might be the best way to seek functional improvements. However, the uptake of nutritional supplementation during PR, where the potential benefit may be greatest, has been limited by the absence of rigorous evidence-based studies supporting use. The objective of this systematic review was to report and summarise the current evidence for using nutritional supplementation during PR in stable COPD patients to enhance PR outcomes. This systematic review has been published in *Chronic Respiratory Disease* (226). Appendix 19

4.2 Methods

Search strategy

The preferred reporting items for systematic reviews and meta-analyses guidelines were used for this systematic review, with Prospero registration number CRD42018089142 (259). The search was conducted up to 7 July 2020 using Medical Literature Analysis and Retrieval System Online or MEDLARS Online, Excerpta Medica dataBASE, Allied and Complementary Medicine Database, the Cochrane Database of Systematic Reviews, Cumulative Index of Nursing and Allied Health Literature and Web of Science database (Tables A1 to A5). The search strategy and terms used in this systematic review are described in the Appendix 19. The bibliography of eligible articles and existing systematic reviews in the field were also screened.

Inclusion criteria

The PICO (P: population, patient, problem; I: intervention; C: control, comparison or comparator; O: outcome) criteria for included studies appear in Table 6. Studies were included in the systematic review if they met all of the following criteria: studies of patients with a confirmed diagnosis of COPD; no evidence of recent exacerbation, as described in the individual studies; patients enrolled on a PR or other exercise training programme and patients receiving nutritional supplementation (caloric, non-caloric, powder, liquid, capsule or tablets) during PR.

Table 6: PICO criteria used for inclusion of studies.

Criteria	Definition
Participants	Patients with a confirmed diagnosis of COPD, no evidence of recent exacerbation, enrolled on a pulmonary rehabilitation or other exercise training program
Intervention	Any nutritional supplement given during pulmonary rehabilitation
Comparator	Placebo, other nutritional supplement regime, no nutritional supplements
Outcome	Exercise function, body composition, peripheral muscle strength, respiratory muscle function, and quality of life.
Study Design	No restrictions

Abbreviations: COPD: chronic obstructive pulmonary disease; PICO: P—population, patient, problem; I—intervention; C—control, comparison or comparator; O—outcome.

Exclusion criteria

We excluded book chapters, systematic reviews (but screened the reference lists), non-English manuscripts, conference abstracts with no full-text and non-full text articles.

The main outcomes of interest were to investigate the impact of nutritional supplementation during PR programmes on exercise function, body composition, peripheral muscle strength, respiratory muscle function, and quality of life.

Data collection

Three authors screened the titles and abstracts to exclude irrelevant studies. Full texts of the relevant studies were read by the first author to evaluate if they fulfilled the inclusion criteria. The reference lists of included studies and excluded systematic reviews were also screened; two additional studies were

found, and the senior authors discussed eligibility. Disagreements between authors were resolved by discussion.

Quality assessment

The two authors performed risk of bias assessment using the Cochrane risk of bias tool to assess randomised studies, which comprises seven questions, and the modified Newcastle– Ottawa scale to assess cohort studies, which is also made up of seven questions (260, 261). For the randomised trials, we scored each of the seven domains as 0 (*low risk of bias*) or 1 (*high risk of bias or bias unclear*). There was, therefore, a total score between 0 and 7 in which a higher score equates to a higher risk of bias. For cohort studies, each of the seven domains was scored from 0 (*high risk of bias*) to 3 (*low risk of bias*) and we took a mean of the domains to result in a score between 0 and 3, where a higher score represents a lower risk of bias.

Synthesis of results

The main purpose of this systematic review was to report and summarise the current evidence of using nutritional supplementation during PR in stable COPD. A meta-analysis was not attempted due to methodological heterogeneity between studies. Our discussion focuses on the studies at lower risk of bias.

4.3 Results

Initially, 580 studies were considered potentially eligible. However, after removing duplicates, 449 titles and abstracts were included. Screening the titles and abstracts resulted in 30 of 449 studies being considered for full-text reading. After reading the full text of 30 studies, 10 further studies were

excluded (table A6 in Appendix 19). Screening the reference list of eligible studies revealed two further relevant studies. Thus 22 studies in total met the inclusion criteria for the systematic review (see Figure 19).

The 22 studies comprised 5 cohort studies and 17 RCTs. The sample size and study duration varied between 8 and 80 participants and 6 weeks to 4 months, respectively. A full description of the included RCTs and cohort studies appears in Tables 7 and 8, respectively. The risk of bias assessment for RCT and cohort studies appears in Tables A7 and A8 in Appendix 19, respectively.

Figure 19: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

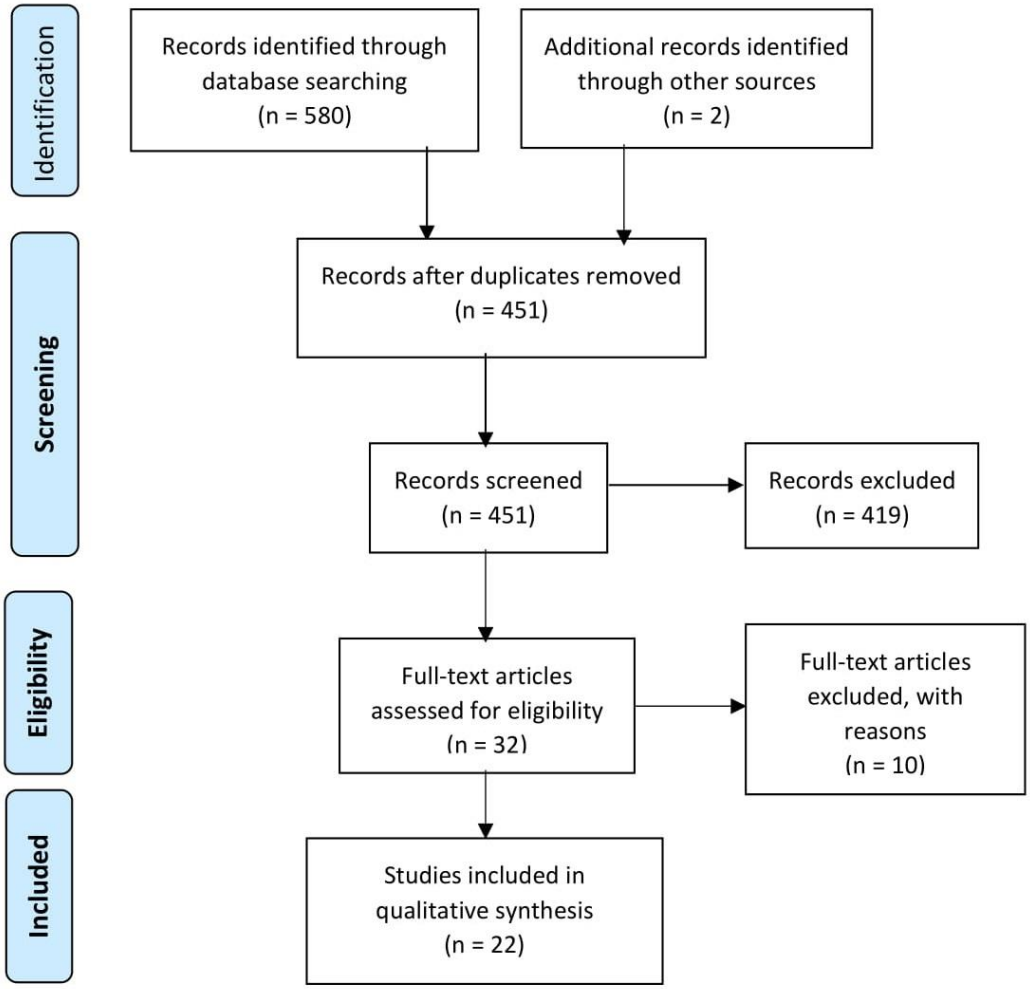


Table 7: Detailed description of the included RCT studies.

Author and Risk of Bias	Mean age, GOLD stage & BMI	Subject	Intervention	Pulmonary Rehabilitation	Outcome Measures	Results
Van de Bool et al. (262) (2017) Bias**:** 1/7	**Age**: 62 years old. **GOLD**: 2. **BMI**: 22.7 kg/m^2.	N= 73 ('low muscle mass').	**Intervention:** 125 mL of 9.4 g protein, 28.1 g carbohydrate and 4.1 g fat, leucine, n-3 PUFA and vitamin D once per day. **Placebo:** Flavoured non-caloric aqueous solution.	**Duration:** 4 months **Location:** outpatient. **Session detail:** 40 sessions two to three times per week. 1- High intensity endurance exercise by cycle ergometry. 2- Treadmill walking. 3- Progressive resistance exercise of upper and lower body. 4**-** Education session.	1. **Body Composition**: Body mass, BMC, SMM, and FM. 2. **Muscle Function**: Quadriceps muscle strength, MIP. 3**. Exercise Performance**: cycle endurance time (CET) & 6MWT. 4. **Anxiety/Depression**: HADS. 5. **Physical Activity**: 7 days.	1. **Body Composition**: Significant improvement in body mass (1.5 ± 0.6 kg, $p < 0.05$) and FM (1.6 ± 0.5 kg, $p < 0.01$) in the intervention group. 2. **Muscle Function**: No significant differences between the groups. 3. **Exercise Performance**: No significant differences between the groups. 4. **Anxiety/Depression**: No significant differences between the groups. 5**. Physical Activity**: Significant benefit in physical activity (929.5 ± 459.2 steps/day $p < 0.05$).
Paulin et al.(219) (2016) Bias: 1/7	**Age**: I versus P (56.5 vs. 65.2 years old). **GOLD**: 3 and 4. **BMI**: I versus P (24.5 vs.	N= 16	**Intervention (I)**: B_{12} 500 mg/ day for 8 weeks **Placebo (P):** Maltodextrin.	**Duration:** 8 weeks. **Location:** outpatient. **Session detail:** 3 days/week, 40 minutes of aerobic and resistance exercise.	1. **Cardiopulmonary Exercise Testing**: Incremental or constant-load protocols.	1. **Exercise Performance**: No significant differences between the groups.

	25.1 kg/m^2).					
Ahnfeldt et al.(218) (2015) Bias: 4/7	**Age**: I versus P (67 vs. 70 years old). **GOLD**: 2 and 3. **BMI**: I versus P (24.3 vs. 23.4 kg/m^2).	N= 35	**Intervention (I)**: Protein bar (each 134.8 kcal of energy, 9.3 g protein, 14.6 carbohydrate, 4.2 fat) two times per day for 9 weeks. **Placebo (P):** No.	**Duration:** 9 weeks. **Location:** outpatient **Session detail:** A- 1 hour two times per week and home-based one time per week of: 1- Endurance. 2- Resistance. 3- Interval training. 4- Educational class.	1. **Muscle Function**: lower muscle strength. 2. **Exercise Performance**: SWT. 3. **Quality of Life**: SGRQ.	1. **Muscle Function**: No significant differences between the groups. 2. **Exercise Performance**: No significant differences between the groups. 3. **Quality of Life**: No significant differences between the groups.
Gurgun et al.(263) (2013) Bias**:** 2/7	**Age**: I versus P (64 vs. 66 years old). **GOLD**: 3 and 4. **BMI**: I versus P (17.8 vs. 20 kg/m^2).	N= 30 ('wasted')	**Intervention (I):** 250 mL 83.3% carbohydrate, 30% fat, 16.7% proteins, three times per day. **Placebo (P):** No.	**Duration:** 8 weeks. **Location:** outpatient. **Session detail:** Two times per week 60–80 minutes/day: A- Education. B- Exercise training include: 1- Warm-up and bicycle ergometer for 15 minutes. 2- Treadmill (15 minutes). 3- Upper and lower extremity strength (5–10 minutes). 4- Breathing and relaxation therapies (15–20 minutes each).	1. **Body Composition**: Body weight, BMI, and FFMI. 2. **Exercise Performance**: 6MWT, ISWT, and ESWT. 3. **Quality of Life**: SGRQ. 4. **Anxiety/Depression**: HADS. 5. **Breathlessness Scale**: MRC and Borg. 6. **Muscle Size**: $Quad_{CSA}$.	1. **Body Composition**: Significant improvement in weight (1.1 ± 0.9 kg, p <0.05), BMI (0.2 ± 1.4 kg/m^2, p <0.05), and FFMI (0.6 ± 0.5 kg/m^2, p <0.05) in intervention group. 2. **Exercise Performance**: No significant differences between the groups. 3. **Quality of Life**: No significant differences between the groups. 4. **Anxiety/Depression**: No significant differences between the groups. 5. **Breathlessness Scale**: No significant differences between the groups. 6. **Muscle Size**: significant increase in $Quad_{CSA}$ (2.5 ± 4.1 cm^2, p < 0.05) in the intervention group.

Hornikx et al.(264) (2012) Bias**:** 3/7	**Age**: I versus P (67 vs. 69 years old). **GOLD**: 2, 3 and 4. **BMI**: I versus P (25 vs. 24 kg/ m^2).	N= 49	**Intervention (I):** vitamin D monthly dosage (100.000 UI cholecalciferol) **Placebo (P):** Arachidis oleum: 4 mL.	**Duration:** 3 months. **Location:** outpatient. **Session detail:** Three times per week 90 minutes training of: 1- Cycling. 2- Walking on treadmill. 3- Stair climbing and arm cranking. 4- Strength exercises for extremities.	1. **Muscle Function**: quadriceps strength, MIP and MEP. 2. **Exercise Performance**: incremental cycle ergometer and 6MWD. 3. **Quality of Life**: CRDQ.	1. **Muscle Function**: Significant increase in MIP (11 ± 12 cmH_2O, p = 0.004) but no differences between groups in quadriceps strength and MEP. 2. **Exercise Performance**: No significant differences between the groups. 3. **Quality of Life**: No significant differences between the groups.
Sugawara et al. (265) (2012) Bias: 1/7	**Age**: 77 years old. **GOLD**: 3. **BMI**: not recorded.	N= 31	**Intervention:** Mein (contains 200 kcal 20% protein, 25% lipid, 53.2% sugar, 1.8 fibre, Fisher is 3.7, antioxidant vitamin A, C and E) (two times per day 200 mL) for 12 weeks + provided meal with dietary instruction. **Placebo:** No.	**Duration:** 12 weeks. **Location:** Home-based. **Session detail:** A- Breathing retraining: 1- Pursed-lip breathing. 2- Diaphragmatic breathing. 3- Slow deep breathing. B- Exercise training: 1- Upper and lower limb exercises. 2- Respiratory muscle stretching calisthenics. 3- Level walking for least 15 minutes. 4- Inspiratory and expiratory muscle exercises. C- Education program.	1. **Body Composition**: Body weight, FFM, FMI, (AC), (AMC), %IBW. 2. **Muscle Function**: MIP and MEP, quadriceps strength 3. **Exercise Performance**: 6MWD. 4. **Quality of Life**: CRQ. 5. **Breathlessness Scale**: MRC.	Data reported as change in ratio in interventional group vs placebo group, not as absolute values. 1. **Body Composition**: Significant improvement in body weight (2.6 ± 3 kg vs. -0.2 ±1.4 kg, p = 0.0010), FMI (8.6 ± 10.7 kg/m^2 vs. 0.6 ± 10.6 kg/m^2, p = 0.048), %AC (2.4 ± 3.7% vs. -0.7 ± 2.4%, p = 0.0134) and %IBW (2.7 ± 3% vs. -0.2 ± 1.3%, p = 0.0017) in the intervention group. 2. **Muscle Function**: MIP (39.2 ± 38.9 cmH_2O vs. 0.1 ± 24.1 cmH_2O, p = 0.0030) and quadriceps strength (10.0 ± 13.3 kg/kg vs. -1.6 ± 9.5 kg/kg, p = 0.0079) increased significantly in the intervention group. 3. **Exercise Performance**: 6MWD (19.7 ± 24.7 m vs. -7.1 ± 50.8 m, p = 0.0137) improved significantly in the intervention group. 4. **Quality of Life**: total score (6.2 ± 7.5 vs. -2.7 ± 13.1, p = 0.0374)

				D- Physiotherapist supervision every 2 weeks in hospital. E- Periodic visits at home.		and emotional domain (8.9 ± 14.4 vs. -3.9 ± 12.2, p = 0.0097) increased significantly in the intervention group. 5**. Breathlessness Scale**: MRC 22.6 ± 40.6 vs. – 4.4 ± 17.2 (p = 0.0339) improved significantly in the intervention group.
Baldi et al.(266) (2010) Bias**:** 3/7	**Age**: I versus P (73 vs. 70 years old). **GOLD**: 3. **BMI**: I versus P (19.9 vs. 21 kg/m^2).	N= 28 depleted.	**Intervention (I):** Amino acids 4 g two times per day for 12 weeks. **Placebo (P)**: No.	**Duration**: 4 weeks. **Location**: inpatient **Session detail**: 5 days per week. 30 minutes submaximal cycle ergometry. 30 minutes walking and 1 arm exercise session. **Then:** **Duration:**8 weeks **Location:** Home **Session detail:** Twice per day 30 minutes unloaded bicycle training.	1. **Body Composition**: weight and FFM.	Data reported as change in interventional group vs change in placebo group. 1. **Body Composition**: Significant increase in weight (3.8 ± 2.6 kg, p = 0.0002) versus (-0.1 ± 1.1 kg, p = 0.81) and FFM (1.5 ± 2.6 kg, p = 0.05) versus (-0.1 ± 2.3 kg, p = 0.94).
Laviolette et al.(267) (2010) Bias**:** 2/7	**Age**: I versus P (63 vs. 68 years old). **GOLD**: 2 and 3. **BMI**: I versus P (29.7 vs.	N= 22.	**Intervention (I):** Whey protein 20 g in 120 mL/day for 16 weeks. (8 without PR and 8 with PR). **Placebo (P):** Casein 20 g in 120 mL/day for	**Duration:** 8 weeks **Location:** not specified **Session detail:** Three times per week. 90 minutes of: 1- Endurance. 2- Resistance exercise. 3- Education and self-management strategies.	Baseline, 8th, and 16th week: 1. **Body Composition**: weight. 2. **Muscle Function**: quadriceps muscle strength and fatigue. 3. **Exercise Performance**: constant work rate cycle endurance. 4. **Quality of Life**: CRQ.	1. **BODY COMPOSITION**: No significant differences between the groups. 2. **MUSCLE FUNCTION**: No significant differences between the groups. 3. **EXERCISE PERFORMANCE**: No significant differences between the groups. 4. **QUALITY OF LIFE**: No significant differences between the groups. 5. **LUNG FUNCTION**:

	26.7 kg/m^2).		16 weeks. (8 without PR and 8 with PR).		5. **Lung Function**: spirometry and lung volumes.	No significant difference between groups.
Wetering et al.(268) (2010) Bias**:** 3/7	**Age**: 64 years old. **GOLD**: 2. **BMI**: 21.7 kg/m^2.	N= 30 ('wasted')	**Intervention:** Respifor (high-carbohydrate supplement; 125 mL, 188 kcal) three times per day for 4 months. **Placebo:** No.	**Duration:** 4 months**.** **Location:** outpatient. **Session detail:** 1- Two times per week for 30 minutes of intensive exercise. 2- 1, 2 and 3 months dietician counselling for weight losing and muscle-wasted. 3- Education program. 4- Smoking cessation.	1. **Body Composition**: FFMI and BMI. 2. **Muscle Function**: MIP and quadriceps average power. 3. **Exercise Performance**: Peak exercise capacity (Wmax), cycle endurance test (CET) and 6MWD. 4. **Quality of Life**: SGRQ.	1. **Body Composition**: Significant increase in BMI (mean difference 1 kg/m^2, $p < 0.05$), and FFMI (mean difference 0.9 kg/m^2, $p < 0.05$). 2. **Muscle Function**: Significant increase in MIP (mean difference 1.4 kPa, $p < 0.05$) and QAP (mean difference 13.1 W, $p < 0.05$). 3. **Exercise Performance**: Significant increase in W_{max} (mean difference 11.7 W, $p < 0.05$), CET (mean difference 525 second, $p < 0.05$), and 6MWD (mean difference 27.2 m, $p < 0.05$). 4. **Quality of Life**: No statistically significant difference although absolute difference between groups at 6.1 units is greater than the MCID.
Deacon et al. (269) (2008) Bias**:** 2/7	**Age**: I versus P (68 vs. 68 years old). **GOLD**: 3. **BMI**: I versus P (28.1 vs. 25.7 kg/m^2).	N= 80.	**Intervention (I):** Creatine **Loading Phase:** 22 g daily, 4 divided doses for 5 days **Maintenance Phase:** (PR) 3.76 g daily. **Placebo (P):**	**Duration:** 7 weeks. **Location:** outpatient **Session detail:** Three times per week of: 1- Endurance training. 2- Individually prescribed resistance training using gym equipment and free weights.	1. **Body Composition**: weight, FFM, and FM. 2. **Muscle Function**: quadriceps, triceps, and biceps. 3. **Exercise Performance**: ISWT and ESWT. 4. **Quality of Life**: CRQ-SR.	1. **Body Composition**: No significant differences between the groups. 2. **Muscle Function**: No significant differences between the groups. 3. **Exercise Performance**: No significant differences between the groups. 4. **Quality of Life**: No significant differences between the groups.

			Lactose.			
Borghi-Silva et al. (270) (2006) Bias: 1/7	**Age**: I versus P (69 vs. 65 years old). **GOLD**: 3. **BMI**: I versus P (22 vs. 23 kg/m^2).	N= 16.	**Intervention (I):** Oral L-carnitine 2 g, twice per day in 10 mL bottle for 6 weeks. **Placebo (P):** Saline solution.	**Duration:** 6 weeks. **Location:** outpatient. **Session detail:** 1 hour three times per week: (30 minutes treadmill, inspiratory muscle training).	1. **Body Composition**: Triceps skinfold, mid-arm circumference, and BMI. 2. **Muscle Function**: MIP and MEP. 3. **Exercise Performance**: incremental exercise test (treadmill) and 6MWT. 4. **Breathlessness Scale**: Borg.	Data reported as change in interventional group vs change in placebo group. 1. **Body Composition**: No significant differences between the groups. 2. **Muscle Function**: MIP (40 ± 14 cmH_2O vs. 14 ± 5 cmH_2O, $p < 0.05$) but not MEP, increased significantly in the intervention group. 3. **Exercise Performance**: No significant differences between the groups. 4. **Breathlessness**: No significant differences between the groups.
Faager et al.(271) (2006) Bias**:** 1/7	**Age**: I versus P (67 vs. 64 years old). **GOLD**: 3. **BMI**: I versus P (25 vs. 22 kg/m^2).	N= 23.	**Intervention (I):** Creatine 0.3 g/kg body weight/day, divided in four doses per day for 7 days. Creatine 0.07 g/kg body weight/ day one dose/day for remaining 7 weeks. **Placebo (P):** Glucose.	**Duration:** 8 weeks. **Location:** outpatient. **Session detail:** Two times per week for 60-75 minutes of exercise training and education consisting of : 1- Ergometer cycling. 2- Arm muscle training with dumbbells. 3- Rising and getting up from a stool and getting up onto a low stool. 4- Thera band exercises for shoulder girdle.	1. **Body Composition**: weight. 2. **Muscle Function**: Grip strength, maximal right knee strength & fatigue. 3. **Exercise Performance**: ESWT. 4. **Quality of Life**: SGRQ. 5. **Lung Function**: spirometry.	1. **Body Composition**: No significant differences between the groups. 2. **Muscle Function**: No significant differences between the groups. 3. **Exercise Performance**: No significant differences between the groups. 4. **Quality of Life**: No significant differences between the groups. 5. **Lung Function**: No significant differences in FEV_1 between the groups.

				5- Thigh muscle training with weight cuffs. 6- Abdominal muscle training. 7- Flexibility exercises for thorax and adjacent joints.		
Broekhuizen et al.(272) (2005) Bias**:** 3/7	**Age**: I versus P (62 vs. 64 years old). **GOLD**: 3. **BMI**: I versus P (22.5 vs. 22.1 kg/m^2).	N= 80.	**Intervention (I):** PUFA 1 g 9 capsules/day. **Placebo (P):** 9 capsules/day of palm & sunflower oil, vitamin E. **Depleted patients** n=48 Respifor (see above) three times per day.	**Duration:** 8 weeks. **Location:** inpatient. **Session detail:** A- General physical training of: 1- Exercise in relation to daily activities. 2- Cycle ergometry. 3- Treadmill walking. 4- Swimming. B- Sports and games. C- Educational program. D- Regular meals.	1. **Body Composition**: BMI, weight, FFM, FM, and FFMI. 2. **Muscle Function**: quadriceps strength, handgrip and MIP 3. **Exercise Performance**: endurance time Incremental bicycle ergometry and Submaximal bicycle ergometry. 4. **Lung Function**: spirometry	1. **Body Composition**: No significant differences between the groups. 2. **Muscle Function**: No significant differences between the groups. 3. **Exercise Performance**: Maximal exercise capacity (peak workload (9.7 W difference, p = 0.009) and bicycle ergometry duration (4.3 minutes difference, p = 0.023) improved significantly in the intervention group. 4. **Lung Function**: No significant differences between the groups.

Fuld et al.(273) (2005) Bias: 3/7	**Age**: I versus P (64 vs. 62 years old). **GOLD**: 3. **BMI**: I versus P (23.2 vs. 24.3 kg/m^2).	N= 25.	**Intervention (I):** Creatine+ Glucose polymer (5 g Creatine and 35 g glucose/dose). **A-Loading phase**: three times per daily for 14 days. **B-Maintenance phase:** one time per daily for 10 weeks (PR). **Placebo (P):** Glucose polymer (40.7 g/dose).	**Duration:** 8 weeks **Location:** outpatient **Session detail:** Two times per week each 1 hour consisting of: 1- A warm-up. 2- Mobility training. 3- Dynamic strength training of all extremities. 4- Whole body endurance training. 5- Education and behavioural interventions.	1. **Body Composition**: Body mass, FFM, and FM. 2. **Muscle Function**: MIP, lower limb muscle performance and handgrip. 3. **Exercise Performance**: ISWT, ESWT, and cycle ergometry. 4. **Quality of Life**: SGRQ. 5. **Lung Function**: spirometry.	Data reported as change in interventional group vs change in placebo group. 1. **Body Composition**: FFM increased significantly by (2 kg vs. 0.4 kg, $p < 0.05$) in the Creatine group. FM and BM no significant differences between the groups. 2. **Muscle Function**: Significant increase in lower limb strength (19.5 N.m vs. 12.2 N.m, $p < 0.05$), endurance (1216 J vs. 362 J, $p < 0.05$), handgrip strength (2.9 N vs. 0.6 N, $p < 0.05$) and endurance (15.6 repetitions vs. 8.4 repetitions, $p < 0.05$) in the Creatine group. No significant change in MIP. 3. **Exercise Performance**: No significant differences between the groups. 4. **Quality of Life**: Total score decreased (5.9, $p < 0.05$) and activity domain deceased (5.3, $p < 0.01$) in the Creatine group. 5. **Lung Function**: No significant improvement in FEV_1.
Steiner et al. (250) (2003) Bias**:** 3/7	Age: I versus P (66 vs. 68 years old). GOLD: 3.	N= 60.	**Intervention (I):** Respifor (high-carbohydrate supplement; 125 mL, 188 kcal) three times per day for 7 weeks	**Duration:** 7 weeks. **Location:** outpatient**.** **Session detail:** Two times per week of: 1- Endurance training (walking exercise+ home walking program).	1. **Body Composition**: weight, BMI, BM, lean mass, and fat mass. 2. **Muscle Function**: quadriceps and handgrip strength. 3. **Exercise Performance**: ISWT and ESWT. 4. **Quality of Life**:	1. **Body Composition**: Significant improvement in weight (0.63 kg, $p = 0.004$), BMI (0.24 kg/m^2, $p = 0.002$), and fat mass (0.67 kg, $p = 0.001$) in the intervention group. 2. **Muscle Function**: No significant differences between the groups.

	BMI: I versus P (23.9 vs. 23.5 kg/m^2).		**Placebo (P):** Non-nutritive.	2- Circuit of low impact conditioning exercise. 3- Educational sessions.	CRQ-SR.	3. **Exercise Performance**: No significant differences between the groups. 4. **Quality of Life**: No significant differences between the groups.
Vermeeren et al. (274) (2000) Bias: 3/7	**Age**: Part I 65 versus Part II 62 years old. **GOLD**: 3. **BMI**: Part I 20.6 versus Part II 22.6 kg/m^2.	Part 1: N= 14 Part II: N= 11	***Part I:*** **Intervention 1:** 1046 kJ, 21% protein, 34% fat, 45% carbohydrate. **Intervention 2:** 2092 kJ, 21% protein, 36% fat, 43% carbohydrate. **Placebo:** 209 kJ coffee creamer and lemon syrup. ***Part II:*** (Respifor; see above) versus Pulmocare (high fat supplement) 200 mL.	**Duration:** not specified. **Location:** inpatient. **Session detail:** Not specified.	1. **Exercise Performance**: cycle ergometer. 2. **Lung Function**: spirometry. 3. **Self-Reported**: A- Change in breathlessness during meals. B- Leg pain.	1. **Exercise Performance**: **Part I:** No significant differences between the groups. 2. **Lung Function**: **Part I:** No significant differences between the groups. **Part II:** PEF (pre 3.1 L/s ±1.0, post 3.3 L/s ± 1.2) increased significantly after the Respifor supplement versus Pulmocare (pre 3.1 L/s ± 0.9, post 3.1 L/s ± 0.9) ($p < 0.05$). 3. **Self-Reported Symptoms**: **Part I:** Satiety changed significantly after the supplements for the 2092-kJ supplement ($p < 0.05$). **Part II:** Significant increase in breathlessness at 30 and 60 minutes following a meal with Pulmocare versus Respifor (raw data not provided, $p < 0.05$).

Schols et al. (275) (1995) Bias: 4/7	**Age**: not recorded. **GOLD**: 3. **BMI**: not recorded.	N= 71 (per protocol group).	Complex, three group study: P group: placebo steroid. N group: placebo steroid + nutritional supplement. N+A: 4 IM injections of nandrolone + nutritional supplement (not considered further). Nutrition: one time per day 200 mL for 57 days mixture of Nutri-drink (high energy), Protifar (high protein) and Fantomalt (high energy carbohydrate and oil).	**Duration:** 57 days. **Location:** inpatient. **Session detail:** 1- General physical training related to daily activates. 2- Cycle ergometry. 3- Treadmill walking. 4- Walking circuits. 5- Swimming.	Measurements were made at entry, 29 and 57 days: 1. **Body Composition**: weight, arm circumference, skinfolds, FFM. 2. **Muscle Function**: MIP. 3. **Exercise Performance**. 12MWT.	Comparing group P with group N. Patients were stratified to depleted group vs non-depleted group: **Depleted group:** 1. **Body Composition**: No significant difference in FFM or arm circumference between N and P but significant increase in skinfold and weight in the N groups (raw data not provided, $p < 0.03$). **Non-depleted group:** Only reported in per protocol analysis 2. **Muscle Function**: No significant differences between the groups. 3. **Exercise Performance**: No significant differences between the groups.

Abbreviation: I, intervention group; P, placebo or control group; 12MWT, Twelve-Minute Walk Test; 6MWD, six-minute walk distance; BM, body mass; BMC, bone mineral content; BMI, Body mass index; CRQ, Chronic Respiratory Disease Questionnaire; CWT, constant work rate test; ESWT, Endurance Shuttle Walk Test; FEV_1, forced expiratory volume in one second; FFM, Fat-free mass; FM, fat mass; FMI, fat mass index; IBW, Ideal body weight; ISWT, Incremental Shuttle Walking Test; MEP, Maximum expiratory pressure; FFMI: fat free mass index; MIP, Maximum inspiratory pressure; MMC, mid-arm muscle circumference; PEF, peak expiratory flow; QAP, quadriceps average power; $Quad_{CSA}$, quadriceps cross-sectional area; SGRQ, St. George's Respiratory Questionnaire; SMM, skeletal muscle mass; UI, International Unit; LBM, Lean body mass LBMI, Lean body mass Index; SMI, skeletal muscle mass index; BCM, Body cell mass; BMC, bone mineral content; ASM, appendicular skeletal muscle mass; EQ-5D-3L, EuroQoL Five-Dimensions Questionnaire.

Table 8: Detailed description of the included Cohort studies.

Author and Risk of Bias	Mean age, GOLD stage & BMI	Subject	Intervention	Pulmonary Rehabilitation	Outcomes Measures	Result
Kubo et al.(276) (2006) Bias: 2.4	**Age**: I versus P (70 vs. 71 years/ old). **GOLD**: 3. **BMI**: I versus P (18.8 vs. 18.3 kg/m^2).	N=8.	**Intervention (I)**: 400 kcal and 8 g protein and abundance of branched chain amino acids in 200 mL. **Placebo (P):** No.	**Duration:** 8 weeks. **Location:** outpatient. **Session detail:** One times per week for 8 weeks: 1- 90 minutes lecture and physical therapy: A- Breathing instruction B- Muscle strengthening exercise for lower limb.	1. **Exercise performance**: 6MWD. 2. **Quality of Life**: CRQ.	1. **Exercise Performance**: No significant differences between the groups. 2. **Quality of Life**: No significant differences between the groups.

Broekhuizen et al.(277) (2005) Bias: 1.1	**Age**: A versus B (62 vs. 63 years old). **GOLD**: 3. **BMI** A versus B (20 vs. 19.7 kg/m^2).	N= 19 Historical Controls: =20.	**Group A**: Respifor (as above) 125 mL three times per day G**roup B**: Historical One Ensini (high carbohydrate supplement), one Fortimel (high carbohydrate supplement), one Nutridrink (high carbohydrate supplement), 200 mL three times per day for 8 weeks.	**Duration:** 8 weeks. **Location:** inpatient. **Session detail:** Daily: 1- Two times 20 minutes submaximal cycle ergometry. 2- One time 20 minutes treadmill exercise. 3- One time 30 minutes gymnastics. 4- One session of unsupported arm endurance and strength exercise training. 5- Educational programme.	1. **Body Composition**: weight, FFM, FFMI, and FM. 2. **Exercise Performance**: incremental bicycle ergometry. 3. **Quality of Life**: SGRQ. 4. **Lung Function**: FEV_1.	1. **Body Composition**: **Group A:** 1- Significant weight gain (1.9 kg, p = 0.019) versus group B (1.2 kg) **Both groups:** Post PR, significant gain in weight (A: 1.9 kg, p <0.001; B: 1.2 kg, p < 0.001), FM (only group A 1.3 kg, p < 0.05), and FFM (A: 2 kg, p <0.001; B: 1.9 kg, p < 0.05). 2. **Exercise Performance**: **Both groups:** Peak workload increased significantly during the incremental bicycle ergometry test (Group A: 8.3 ± 17.1 W, p = 0.062; Group B: 9 ± 9.4 W, p = 0.002). 3. **Quality of Life**: SGRQ **Group A:** A- No significant differences (although numerical change in SGRQ was greater than the MCID). **Group B:** A- Worse score on the impact dimension. **Both groups:** No significant differences between the groups. 4. **Lung Function**: No significant differences between the groups.

Creutzberg et al. (251) (2003) Bias: 1.7	**Age**: I versus P (65 vs. 65 years old). **GOLD**: 3. **BMI**: I versus P (20.2 vs. 19.8 kg/m^2).	N= 64 ('depleted') Historical Controls = 28.	**Intervention (I):** Fortimel (as above), Ensini (as above), Fortipudding (high carbohydrate supplement) three times per day for 8 weeks. **Placebo (P):** No.	**Duration:** 8 weeks. **Location:** inpatient. **Session detail:** A- General physical training: 1- Swimming. 2- Sports. 3- Exercise in relation to daily activities. 4- Cycle ergometry. 5- Treadmill walking. B- Games. C- Educational program.	1. **Body Composition**: weight and FFM. 2. **Muscle Function**: MIP. 3. **Quality of Life**: SGRQ.	1. **Body Composition**: Significant increase in body weight (2.1 kg, $p < 0.05$) and FFM (1.1 kg, $p < 0.05$) in the intervention group. 2. **Muscle Function**: No significant differences between the groups. 3. **Quality of Life**: No significant differences between the groups.
Menier et al. (278) (2001) Bias: 2.4	**Age**: 63 years old. **GOLD**: not recorded. **BMI**: not recorded.	N=60	**Intervention (I):** Amino acids 1 capsule/7 kg body weight /day, 6 weeks. **Placebo (P)**: No.	**Duration**: 5 weeks. **Location**: not specified **Session detail:** 5 day/week. (40 minutes) Intensity training endurance until exhaustion	1.**Exercise performance**: Reached max power (Wmax)	1.**Exercise Performance**: No significant differences between the groups.
Creutzberg et al. (279) (2000) Bias: 2.2	**Age**: group 1, 2, and 3. (69, 65, vs. 59 years old). **GOLD**: 3 **BMI**: group 1,2, and 3. (39.9, 42.9, and 39.6 kg/m^2)	N= 24 (depleted group).	**Intervention:** Fortimel (as above), Ensini (as above), Fortipudding (as above) Three times per day for 8 weeks.	**Duration**: 8 weeks **Location**: inpatient **Session detail**: not specified. Intensity depending on the tolerance of the patient.	1. **Body Composition**: weight and FFM.	**Patients divided into (1) no weight gain<2%. (2) expected weight gain >5%. (3) medium weight gain 2 to 5%:** 1. **Body Composition**: Weight significantly increased for group 3 (5.8 ± 1.2 kg, $p < 0.001$) versus 1 and 2. FFM significantly increased for group 2 (FFM 1.5 ± 1.2 kg, $p < 0.05$) and group 3 (FFM 3.1 ± 1.8, $p < 0.001$) versus group 1.

Abbreviations: : I, intervention group; P, placebo or control group; 12MWT, twelve-minute walk test; 6MWD, six-minute walk distance; BMI, Body mass index; CRQ, Chronic Respiratory Disease Questionnaire; FEV_1, forced expiratory volume in one second, FFM, Fat-free mass; FFM, Fat-free mass; FFMI: fat free mass index; FM, fat mass; MIP, maximum inspiratory pressure; PR, Pulmonary rehabilitation; SGRQ, St. George's Respiratory Questionnaire.

Exercise capacity

Data on exercise function, performance, capacity or endurance were reported in 19 studies using the endurance shuttle walking test (ESWT), ISWT, 6MWT, 12-minute walk test, treadmill and incremental or constant work-load cycle ergometry. Seventeen studies found that using nutritional supplements such as high carbohydrates, vitamin D, creatine, or L carnitine in addition to PR programs had no statistical benefit compared to PR alone (218, 219, 250, 262-264, 267, 269-271, 273-278). Three studies found that using nutritional supplements, such as, polyunsaturated fatty acids (PUFAs) and respifor, which are high in carbohydrates, had a statistically significant benefit on top of PR (265, 268, 272).

There was only one study with positive findings at the lowest risk of bias (1/7), in which Sugawara et al. reported increases in 6-minute walk distance by 19.7 ±24.7 m with this addition of supplement (less than the minimum clinically important difference). In this RCT, the intervention group received ready-to drink oral ONS twice a day composed of 200 kilocalories, 60% carbohydrates, 15% protein, 25% fat, 248 µg of omega-3 PUFAs 0.6 with vitamins A, C and E and a 12-week exercise programme while the control group underwent a 12-week exercise programme only (265). There were four RCTs with a similar low risk of bias, which demonstrated no benefit of supplementation. Van de Bool et al.(262) reported that using a high carbohydrate supplementation once a day (125mL of 9.4 g protein, 28.1 g carbohydrate and 4.1 g fat, leucine, n-3 PUFA and vitamin D) over a period of 4 months within an outpatient PR did not show any significant improvement in exercise performance measured by cycle endurance time or 6MWT compared to the control PR group, who

received flavoured non-caloric aqueous solution as a placebo. Similarly, the study by Paulin et al. found that using vitamin B12 for 8 weeks during outpatient, PR did not show any significant improvement in exercise performance or endurance compared to PR alone (219). Borghi-Silva et al. reported that using L-carnitine twice a day for 6 weeks did not demonstrate a significant improvement in exercise performance measured by treadmill performance and 6MWT when compared to the placebo group, who received saline solution for the same duration (270). Finally, Faager et al. concluded that using creatine for 8 weeks during PR did not improve exercise performance when measured by ESWT compared to the placebo (glucose) group who underwent the same PR (271).

Body composition

Seventeen trials measured body composition including body weight, FFM, FFMI and BMI.

Body weight was one of the most frequent outcomes measured before and after giving nutritional supplementation; 11 studies measured body weight in COPD patients with normal BMI. Seven studies reported that body weight increased significantly following nutritional supplementation compared to the placebo groups (250, 251, 263, 265, 266, 275, 279), and the study by Broekhuizen et al.(277) compared two nutritional supplement regimes, respifor versus ensini, fortimel and nutridrink, which found that both interventions significantly increased body weight. Four studies reported that body weight did not significantly improve in the intervention groups when compared to the placebo groups (267, 269, 271, 272). Of the RCTs in which body weight significantly increased, there was only one study, by Sugawara et al., that had

a low risk of bias (265). This study reported a significant increase in body weight after 12 weeks of 2.6 ±3 kg in those receiving the ready-to-drink (ONS, described above) with mean baseline body weight of 50.8 kg, compared to those in the placebo group with the mean baseline body weight of 54.8 kg (265). In the study by Gurgun et al., there were significant improvements in body weight of 1.1 ±0.9 kg, BMI 0.2 ± 1.4 kg/m^2 and in FFMI (0.6 ±0.5 kg/m^2) in those who received 250 mL of 83.3% carbohydrate, 30% fat and 16.7% protein three times a day as an intervention (263). Of the four studies with negative findings, one study was at low risk of bias (271). This study found no significant difference in body weight between the creatine intervention group and the placebo group after eight weeks.

BMI was assessed before and after using supplementation in five of 24 studies (250, 263, 268, 270, 272). BMI significantly increased in the supplementation group when compared to the placebo group in three studies (250, 263, 268). Two studies reported no significant difference in BMI between participants who received nutritional supplementation with PR compared to PR only (270, 272). One RCT at the lowest risk of bias showed no improvement in BMI with carnitine (270). In contrast, Gurgun et al. reported that BMI significantly increased after receiving nutritional supplement (263).

FFM was evaluated in nine trials (251, 265, 266, 269, 272, 273, 275, 277, 279). Three studies demonstrated that FFM increased significantly in comparison with the placebo group but these studies all had some risk of bias (251, 273, 275). Two (263, 268) of four studies (263, 268, 272, 277) with some risk of bias reported that FFMI significantly increased in the supplemental group when compared to the placebo group. In contrast, the study by Broekhuizen et al.

reported no significant difference in FFMI between the group who received PUFA as an intervention and the placebo group who received palm and sunflower oil with vitamin E capsule as a placebo (272).

Peripheral muscle strength

Of the 24 studies included in this systematic review, 11 studies measured quadriceps muscles strength, handgrip strength or both (218, 250, 262, 264, 265, 267-269, 271-273).

Three studies reported that handgrip strength did not significantly improve in the intervention groups when compared to placebo (250, 271, 272). Faager et al. being at lowest risk of bias reported that using carnitine for 8 weeks during PR did not significantly improve handgrip strength when compared to the placebo group who received glucose (271). In contrast, the study by Fuld et al., which had a higher risk of bias, showed significant improvement in handgrip after using creatine three times a day for 2 weeks followed by once a day for 10 weeks (273).

Quadriceps muscle strength was assessed in 11 studies (218, 250, 262, 264, 265, 267-269, 271-273). Of the 11 RCTs, only three studies with 86 participants in total demonstrated positive findings (265, 268, 273). Sugawara et al., which had a low risk of bias, concluded that quadriceps muscle strength increased significantly after receiving a complex nutritional supplement when compared to the placebo group (265). However, eight studies reported that using nutritional supplementation during PR had no additional effect on quadriceps muscle strength (218, 250, 262, 264, 267, 269, 271, 272). Van de Bool et al. with a low risk of bias reported that using a high carbohydrate supplement showed no significant improvement in quadriceps strength when

compared to the placebo group (262). Similarly, the study by Faager et al. showed that using creatine for 8 weeks in COPD patients enrolled in an 8-week PR programme did not reveal significant differences in quadriceps muscle strength compared with those who used placebo (271).

Respiratory muscle function

Respiratory muscle function was assessed in nine of the 24 included studies (251, 262, 264, 265, 268, 270, 272, 273, 275), of which three were at lowest risk of bias (262, 265, 270). Sugawara et al. reported that maximum inspiratory pressure (MIP) significantly improved in the interventional group (39.2 ±38.9 cmH_2O) after receiving nutritional supplement embedded in 12 weeks of PR compared with placebo (0.1 ±24.1 cmH_2O) (265). A small study by Borghi-Silva et al. showed a significant improvement in MIP (40 ±14 cmH_2O) with carnitine compared to placebo (MIP; 14 ±5 cmH_2O) (270). In contrast, a larger study by van de Bool et al. did not show a significant improvement in MIP when compared with placebo, who received glucose (262). None of the studies that measured maximal expiratory pressure (MEP) showed a significant difference between interventional and placebo groups (268, 272, 275).

Quality of life

Quality of life was assessed in 14 of 24 studies (218, 250, 251, 262-265, 267-269, 271, 273, 276). Eight studies used SGRQ (218, 251, 263, 268, 271, 273, 277), and six used the Chronic Respiratory Questionnaire (CRQ) (250, 264, 265, 267, 269, 276). Overall, only two studies demonstrated a significant improvement in quality of life with supplementation in addition to PR (265, 273). Sugawara et al., which was at lowest risk of bias, measured quality of life using

the CRQ and showed a significant improvement in those receiving nutritional supplement compared with placebo, which was clinically significant (6.2 ±7.5 vs - 2.7 ±13.1) (265). Thirteen studies showed negative findings including two RCTs at lowest risk of bias, including the study by Faager et al. using creatine supplementation and the study by van de Bool et al. using the high carbohydrate supplement. Faager et al. using creatine for eight weeks during PR did not improve quality of life measured by SGRQ (271). Similarly, van de Bool et al. reported that four months of using oral nutritional intervention did not show symptoms of anxiety and depression (262).

4.4 Discussion

This review is the first to summarise the potential effects of using nutritional supplementation during PR in patients with COPD. The studies varied in design, used differing supplements, and measured different outcomes. In some, the primary purpose was to use the exercise component of PR to enhance the effect of nutrition, whereas others tested whether nutrition supplementation could enhance outcomes from PR. This results in considerable heterogeneity across studies, many of which were further limited by small sample size. It is, therefore, challenging to draw a single conclusion to address whether using a nutritional supplement has additional effects on exercise function, body composition, respiratory muscle function, and quality of life during PR. We were also unable to perform meta-analysis due to this heterogeneity. Consequently, appropriately powered double blinded RCT studies with suitable sample size using high energy/high protein nutritional supplement to investigate the effect of nutritional support in enhancing PR outcomes, and longer-term clinical outcomes, in COPD patients, are still

needed. This would be particularly important in the high-risk group of COPD patients who are undernourished. This would support recommendations to incorporate nutritional support in PR management (225, 280). High protein/high energy ONS is recommended by the British Association for Parenteral and Enteral Nutrition for patients with COPD due to high energy and protein requirements (188) and PR services in different health contexts that need to consider how best to integrate nutritional assessment and, where successful, intervention into diverse methods of PR delivery.

Exercise capacity has been used to quantify the direct effect of nutrition interventions and to predict mortality and morbidity in COPD patients and other diseases. In this systematic review, the majority of studies demonstrated no improvement in exercise outcomes with nutritional supplementation in addition to PR, compared to PR alone. There were four RCTs with negative findings at low risk of bias (219, 262, 270, 271) which tested carbohydrate, B12, creatine, and carnitine supplementation and just one small RCT with a positive finding, which used a ready-to-drink ONS twice a day composed of 200 kilocalories, 60% carbohydrates, 15% protein, 25% fat, and 248 μg of omega-3 PUFAs 0.6 with vitamins A, C, and E. These findings complement the meta-analysis of nutritional supplementation in stable COPD by Ferreira et al., which included 17 randomised clinical trials and concluded that nutritional supplements increased exercise tolerance in COPD patients who were poorly nourished when compared with baseline only, but which did not specifically consider use in the context of PR (224). A meta- analysis was not possible in our review due to considerable heterogeneity in studies, as described above.

Body composition is one of the outcome measures that might be expected to improve when using nutritional supplement in COPD. Being underweight is associated with an increased risk of mortality in COPD (137). Low body weight is observed in between 25% and 40% of COPD patients. Among these, 25% have moderate to severe weight loss and 35% have extremely low fat-free mass (281). In this systematic review, we found that ready-to-drink ONS during PR may increase body weight in a population with normal body weight, but not with carnitine or creatine. Importantly, improvements in body weight and FFM using nutritional supplementation during PR appear to occur especially in depleted, malnourished and muscle-wasted patients (who are at highest risk) (262, 263, 266, 268). In the meta-analysis by Ferreira et al, significant weight gain was noted compared to baseline in 11 RCTs and the meta-analysis of Collins et al. showed significant weight gain in favour of nutritional support when compared with control outside the context of a PR programme (224, 258).

In recent years, researchers have paid attention to the assessment of outcomes, such as quadriceps muscle strength and handgrip strength. Handgrip strength and quadriceps muscle strength are valid measurements of peripheral muscle strength and are associated with mortality, morbidity, and increased length of hospital stay (140, 225). In this systematic review, RCTs at low risk of bias did not support the concept that creatine, high carbohydrates, and L-carnitine increase peripheral muscle strength, and we found conflicting evidence for the benefits of a ready-to drink ONS with one study having positive and another study having negative results. Collins et al. concluded that handgrip strength improved significantly in the intervention group when compared to usual care group without PR (225).

Respiratory muscle weakness in COPD patients may be due to several factors, such as acute exacerbations, systemic inflammation and malnutrition (282). It has been suggested that nutritional supplements may improve respiratory muscle function. In this systematic review, we found two studies reporting that nutritional supplementation in addition to PR had an extra benefit in improving respiratory muscle function. This was demonstrated by measuring MIP and MEP. The effects were seen only on inspiratory measures, and the authors did not speculate on why they thought this was. Collins et al. concluded that MIP and MEP improved significantly in the intervention group when compared to usual care group. Ferreira et al. found that there was no significant difference between intervention control groups in MIP, but for malnourished patients with COPD, MIP, and MEP improved significantly with nutritional support (224, 225).

Quality of life may be affected through multiple mechanisms in COPD. The available evidence from this review included one small study demonstrating an improvement in QOL measured by CRQ using ready-to-drink ONS, and two studies with negative results, one of which used creatine and one of which also used ONS. The meta-analysis by Ferreira et al. reported significant improvement for quality of life measured using SGRQ for patients with COPD who were malnourished. Additionally, Naz and Sahin demonstrated that protein-rich nutritional supplement significantly improved the quality of life in patients with COPD who participated at PR when compared to PR alone (283).

Since the publication of our systematic review, we have updated our search and identified two additional studies. A double-blinded RCT was conducted by Gouzi et al. to investigate the effect of using oral antioxidant supplementation

with vitamin C, E, Zinc, and selenium during PR on 57 COPD patients (284). The PR programme comprised of 24 sessions of endurance training, strength exercises, and educational components, such as dietary counselling and smoking cessation for 28 days long. They measured quadriceps muscle endurance and strength, exercise capacity by 6MWD, BMI and FFMI. They concluded that quadriceps muscle strength significantly improved quadriceps muscle strength in favour of antioxidant supplementation when compared with placebo in the context of PR (intervention: 9 4 ±8 9 $N \cdot m^{-1}$ versus placebo: -0 4 ±15.8 $N \cdot m^{-1}$, $p < 0.001$). Nevertheless, it did not show significant improvements in quadriceps muscle endurance, exercise capacity, and body composition. Another double-blinded RCT was conducted by Pavitt et al. to investigate the effect of using 140 mL oral nitrate-rich beetroot juice which contained 12.9 mmol of nitrate twice a week three hours prior a PR session on 122 COPD patients (285). The PR programme comprised of 8 weeks (16 sessions) of supervised exercise programme and homebased exercises which included a mixture of aerobic and strength training. They measured exercise capacity using ISWT, body compositions (FFM and FFMI), health-related quality of life using the CAT, psychological status using the HADS, breathlessness using the MRC dyspnoea score and physical activity using accelerometer. They concluded that exercise capacity measured by ISWT significantly improved in favour of the treatment group when compared with placebo in the context of PR (intervention median (IQR): 60 m (10, 85) versus placebo: 30m (0, 70), $p = 0.027$), and the steps count increased significantly in the treatment group while a reduction was noticed in the placebo group (intervention median (IQR): 348 steps/day (−94; +1629) versus placebo: 329 steps/day (−915; +640), $p=0.02$).

Strengths and limitations

To our knowledge, this is the only review that reports the effect of nutritional supplementation during PR in stable COPD. PR is an evidence-based and cost effective intervention in COPD and thus maximising outcomes is of great interest to clinicians and patients alike. We have carefully searched the literature and registered our review in advance on PROSPERO. Three independent researchers examined the titles and abstracts for inclusion. Potential limitations include: we only accessed studies in English, and the inherent variation, many of which had a risk of bias, for example, with inadequate sample size or absence of a power calculation, variation in outcomes measured, variety in study design or different PR protocols. Additionally, outcomes varied between studies, and we have not specifically considered the diversity of nutritional outcomes in this review, which focuses on clinical PR outcomes. There was significant diversity in the type, available substrate, energy imbalance or ingredients of the supplement either caloric or non-caloric and powder, liquid or tablets. We also observed a variation in the amount, contents, and the duration of using supplements. Also, our review did not investigate the benefits of using nutritional supplements beyond the duration of PR, which could be important in clinical practice given that a major aim of PR programmes is to durably improve quality of life and reduce the risk of exacerbations and hospitalisations.

4.5 Conclusion

This is the first systematic review to report the value of nutritional supplementation during PR in patients with COPD. It is not possible to draw a definitive conclusion due to the heterogeneity of the supplements used,

rehabilitation programmes, and outcome measures. However, nutritional supplements may enhance the benefit of PR programmes, which would be of considerable benefit to those living with COPD. Not all studies showed positive results and there is a real need for further well-designed and rigorous research to address this area. This is particularly true in weight-losing and/or malnourished patients with COPD, who are at the highest risk of poor outcomes.

5. Prevalence and Association of Malnutrition in Patients referred to PR.

5.1 Introduction

Malnutrition is common in COPD and its consequences might lead to unfavourable outcomes. PR is an effective management strategy in COPD patients that improves exercise performance, reduces dyspnoea, reduces the risk of exacerbation, and improves health-related quality of life (66-69, 71, 72). Exercise intolerance/limitation is one of the most common problems for COPD patients, and this may be compounded by malnutrition. As previously mentioned, MUST is a simple validated questionnaire used to identify subjects who are malnourished or at risk of becoming malnourished. Current evidence on the prevalence of malnutrition with COPD patients referred to PR is limited. Therefore, this chapter aims to determine the prevalence of malnutrition in a COPD population referred to PR and to identify if there was an association between COPD severity and malnutrition.

5.2 Research questions

1. What is the prevalence of malnutrition among COPD patients who referred to PR?

2. What is the relationship between FEV_1, a marker of COPD severity, and BMI?

5.3 Study design

Prospective single centre study.

5.4 Methodology

Over a period of one year, we approached 221 patients who referred to a PR programme in Camden London Borough, UK. We included all patients who

were diagnosed with COPD with spirometry results defined as post-bronchodilator $FEV_1/VC < 0.70$ confirming COPD and an appropriate exposure history. Patients were stratified based on their risk of malnutrition (MUST: 0= low risk, 1= medium risk and ≥2= high risk). (Appendix 14)

Outcomes

1. Determine the prevalence of malnutrition using MUST tool
2. Identify the association between COPD severity measured by FEV_1 and the risk of malnutrition

Additional outcomes compared between nutritional groups (low risk, medium risk and high risk for malnutrition)

3. Smoking status
4. Smoking history (pack years)
5. BMI (calculated from height and weight)
6. Spirometry (FEV_1, and FEV_1/FVC ratio)

Study procedure

Recruitment

Over the year, subjects were approach at the Peckwater Centre and St. Pancras Hospital pulmonary rehabilitation classes. Age, gender, BMI, FEV_1/FVC ratio, and FEV_1 were measured. We also assessed smoking status and calculated smoking pack year history.

5.5 Analysis

The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse our data. To examine whether our data were normally distributed, Kolmogorov-Smirnov test was used. Normally distributed data (parametric) were presented as mean (SD) while non-normally distributed data (non-parametric) median (IQR) were used. Pearson or Spearman correlation tests were used to identify association between continuous variables. Pearson correlation was used for normally distributed data (parametric), and Spearman correlation was used for not normally distributed data (non-parametric). One-way ANOVA was used for normally distributed data (parametric) and Bonferroni correction was used to compare normally distributed data (parametric) for subgroups (low, medium, and high). Kruskal-Wallis was used for not normally distributed data (non-parametric).

5.6 Results

Over the year, 203 COPD patients (120:83; male: female) were included in the study. The overall prevalence of malnutrition in COPD patients enrolled in the PR programme was 17% (medium risk 8%, high risk 9%). Seventeen patients (9:8; male: female) were at medium risk of malnutrition, and 18 patients (10:8; male: female) were at high risk of malnutrition (Table 9). The patients were mainly classified as GOLD stage 2-3 with a mean age of 71 ±9 years. Out of 203 COPD patients, 64 patients (32%) were active smokers, of these 76% (49) were low risk, 11% (7) were medium risk and 13% (8) were high risk. The median for the smoking history of the total population was 43.5 pack years with no significant differences between low, medium and high risk groups ($p > 0.05$).

The mean FEV_1 was 1.3 ±0.4 L (low risk 1.4 ±0.4, medium risk 1 ±0.3, and high risk 0.76 ±0.2) and demonstrated a significant difference between groups ($p < 0.001$). The high risk group mean FEV_1 was significantly lower than low risk group (0.76 ±0.2 L vs 1.4 ±0.4 L, $p < 0.001$). When FEV_1 means compared between medium risk group and low risk group, medium risk group was significantly lower than low risk group (1 ±0.3 vs 1.4 ±0.4 $p < 0.001$). There was also significant difference between all groups in FEV_1% ($p < 0.05$). There was a significant difference between all groups in FEV_1/FVC ratio ($p < 0.001$). When we compared FEV_1/FVC ratio within each group, statistical significant differences were found between high risk and low risk group ($p < 0.05$), and medium risk with low risk groups ($p < 0.05$).

Table 9: Baseline characteristics of subjects with chronic obstructive pulmonary disease (COPD) stratified by malnutrition risk.

Subjects **Demographics**	**Total population (203)**	**Low risk**	**Medium risk**	**High risk**	**p-value**
Age (years)	71 ±9	71 ±9	68 ±9	69 ±10	0.53
Male	120 (59%)	102 (85%)	8 (7%)	10 (8%)	0.44
Female	83 (41%)	66 (79%)	9 (11%)	8 (10%)	
Active smoker	64 (32%)	49 (76%)	7 (11%)	8 (13%)	0.30
Ex-smoker	139 (68%)	119 (86%)	10 (7%)	10 (7%)	
Smoking history (pack-years)	43.5 (28 – 59)	41 (27 – 59)	51 (28 – 73)	46 (34 – 62)	0.54
Pulmonary function					
FEV_1 (L)	1.3 ±0.4	1.4 ±0.4	1 ±0.3	0.76 ±0.2	0.001

FEV_1 (% predicted)	52 (39, 67)	54 (44, 64)	48 (28 – 62)	34 (31 – 52)	0.01
FEV_1/FVC ratio	52 (43, 64)	55 (44, 64)	41 (38 – 57)	44 (38 – 51)	0.003
Body composition					
BMI (kg/m^2)	25.5 ±5.6	27 ±5	19 ±0.4	17 ±0.9	0.000

Data are presented as n (%), mean±SD, or median IQR
Abbreviations: BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements.

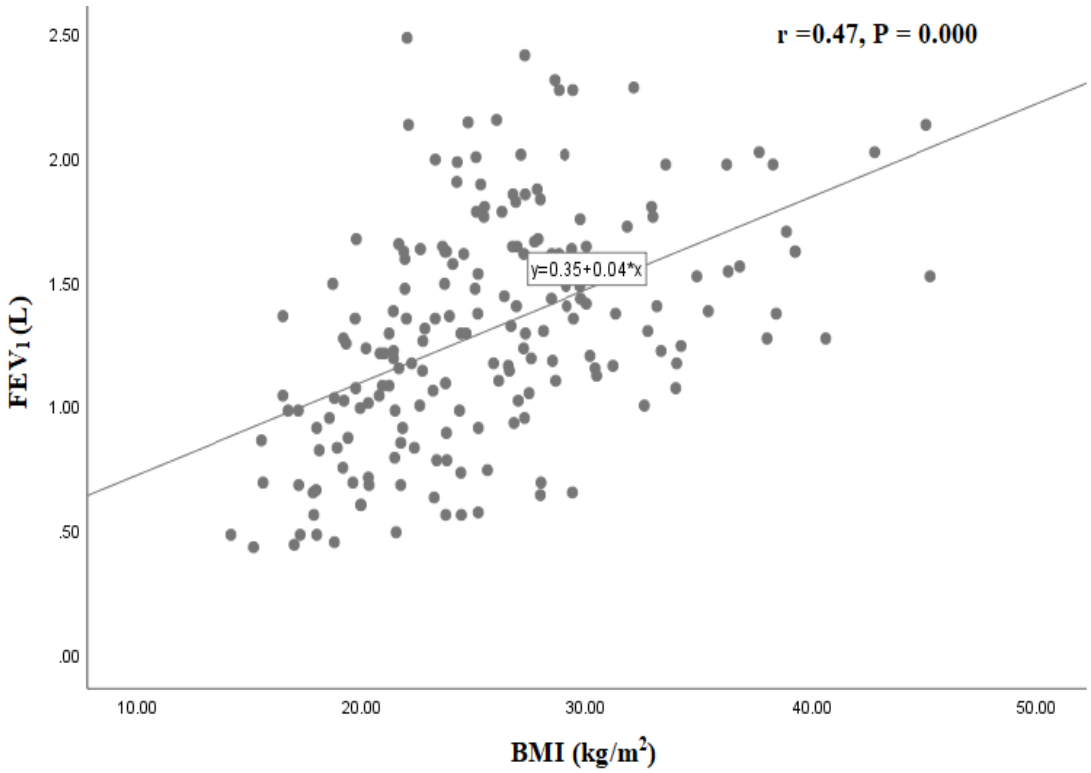
We also explored the relationship between BMI and pulmonary function includes FEV_1, FEV_1%, and FEV_1/FVC among all patients (Table 10). Amongst all patients, a statistical significant positive correlation was found between BMI and FEV_1 ($r = 0.47$, $p < 0.001$) (Figure 20). When the relationship between BMI and FEV_1% or BMI and FEV_1/FVC were compared, there were statistical significant positive correlations ($r = 0.34$, $p < 0.001$ and $r = 0.42$, $p < 0.001$), respectively. There were no significant correlations between BMI and age or smoking history.

Table 10: Correlations between BMI and pulmonary function in all participants.

Subjects	**Total population (203)**	
Outcome	**BMI**	
	r	P
FEV_1 (L)	0.47	<0.001
FEV_1 (% predicted)	0.34	<0.001
FEV_1/FVC %	0.42	<0.001

Abbreviations: r: Pearson's correlation; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements.

Figure 20: Correlation between FEV_1 and BMI.

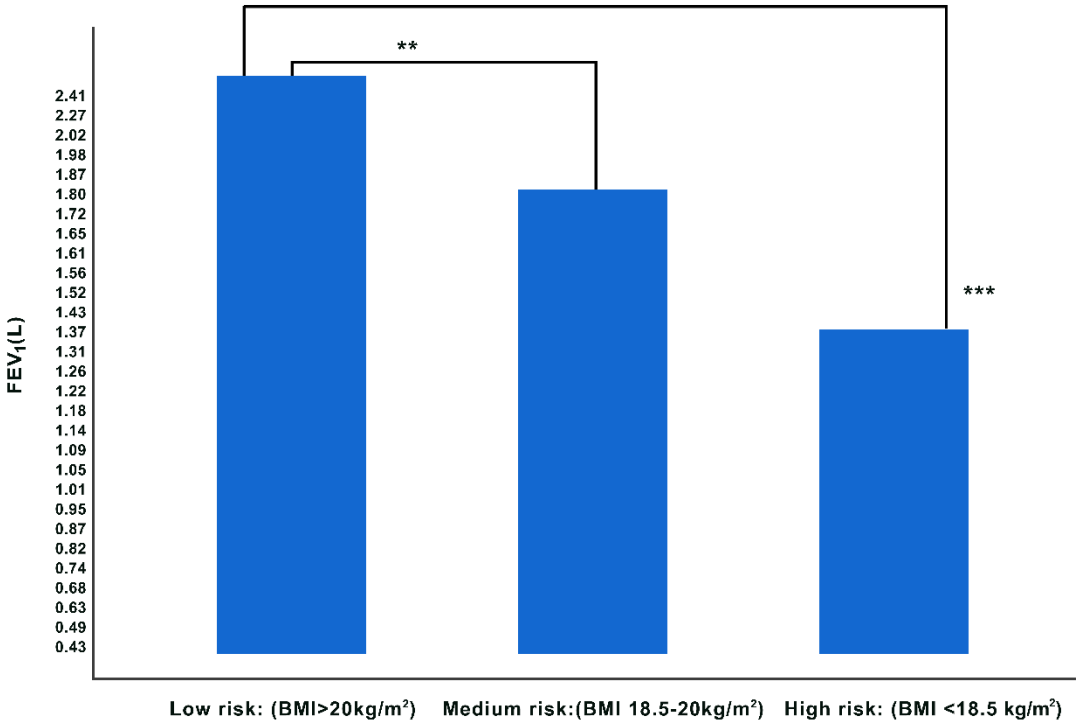


Additionally, we made comparisons across all groups (low risk, medium risk, and high risk groups). All groups were compared with each other to identify the differences between groups in pulmonary function (FEV_1, FEV_1%, and FEV_1/FVC) (Table 11).

There was no significant difference in FEV_1 between **high risk group** when compared with **medium risk** group ($p = 0.1$). FEV_1 was significantly higher in **low risk group** in comparison with **medium** ($p = 0.003$) and **high risk groups** ($p < 0.001$) (Figure 21). With regard to FEV_1%, it was found that low risk group was significantly different from high risk group ($p = 0.016$) (Figure 22). No other significant differences were found between groups with regard to FEV_1%. FEV_1/FVC were significantly different in low risk group when compared with medium ($p < 0.05$) and high risk groups ($p = 0.03$) (Figure 23). There was no

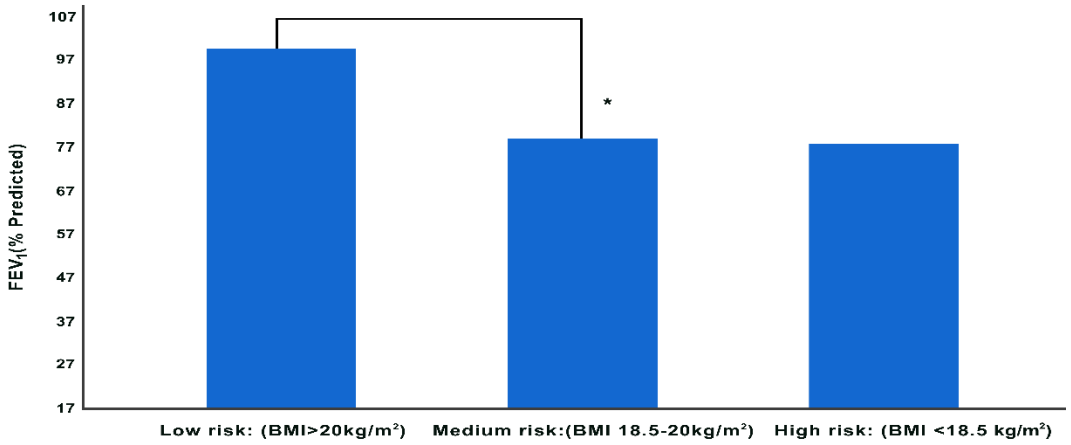
significant difference between high risk and medium risk groups in FEV_1/FVC ($p > 0.05$).

Figure 21: Comparison of forced expiratory volume in one second (L) between groups divided into three groups (low risk, medium risk and high risk).



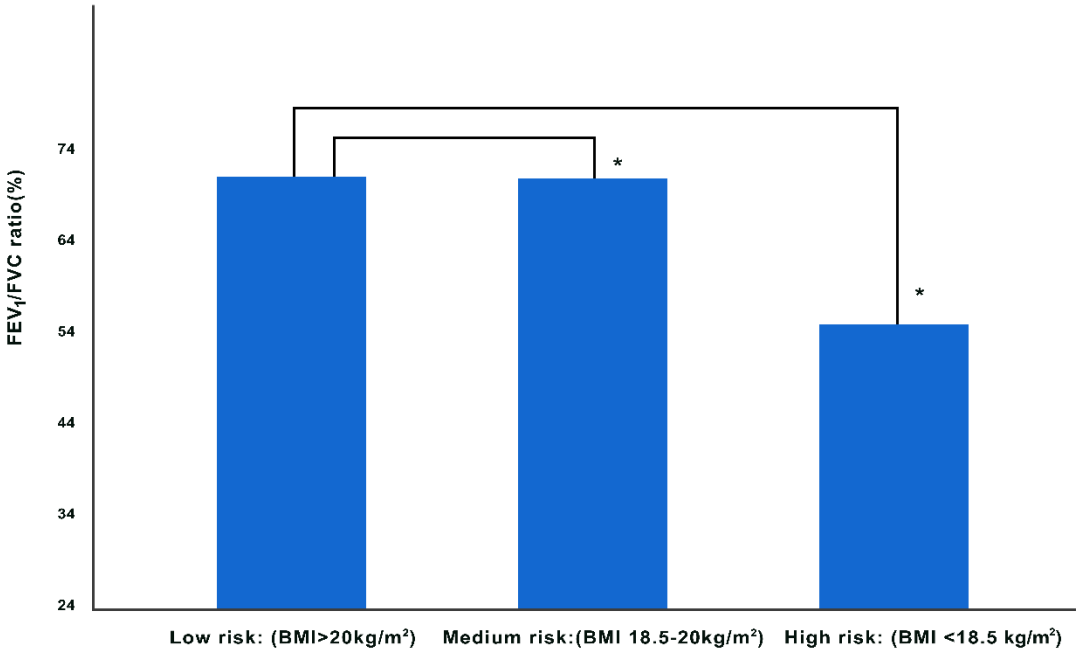
** p<0.01; *** p<0.001; α significant between the groups.

Figure 22: Comparison of forced expiratory volume in one second (% predicted) between groups divided into three groups (low risk, medium risk and high risk).



Graph does not start at zero.
* p < 0.05; α significant between the groups.

Figure 23: Comparison of FEV_1/FVC ratio (%) between groups divided into three groups (low risk, medium risk and high risk).



Graph does not start at zero.
* p < 0.05; α significant between the groups.

Table 11: Comparison of lung function between groups divided into three groups (low risk, medium risk and high risk).

Outcome	Group 1	Group 2	P value
FEV_1 (L)	Low risk (BMI >20 kg/m^2)	Medium risk (BMI 18.5–20 kg/m^2)	0.003
	Low risk (BMI >20 kg/m^2)	High risk (BMI <18.5 kg/m^2)	< 0.001
	Medium risk (BMI 18.5–20 kg/m^2)	High risk (BMI <18.5 kg/m^2)	0.1
FEV_1 (% predicted)	Low risk (BMI >20 kg/m^2)	Medium risk (BMI 18.5–20 kg/m^2)	0.01
	Low risk (BMI >20 kg/m^2)	High risk (BMI <18.5 kg/m^2)	0.54
	Medium risk (BMI 18.5–20 kg/m^2)	High risk (BMI <18.5 kg/m^2)	0.66
FEV_1/FVC ratio	Low risk (BMI >20 kg/m^2)	Medium risk (BMI 18.5–20 kg/m^2)	0.04
	Low risk (BMI >20 kg/m^2)	High risk (BMI <18.5 kg/m^2)	0.02
	Medium risk (BMI 18.5–20 kg/m^2)	High risk (BMI <18.5 kg/m^2)	1

Abbreviation: FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements; BMI, Body Mass Index.

5.7 Discussion

In our study, the prevalence of malnutrition in COPD patients who referred to PR was 17%. We found lower BMI was significantly associated with lower FEV_1, FEV_1% and FEV_1/FVC, but not with higher smoking history or age in COPD patients. In patients with low risk of malnutrition, FEV_1 was higher compared with other groups (medium and high). FEV_1% in low risk group was significantly higher than medium risk group only, and FEV_1/FVC in low risk group was significantly higher than medium and high risk groups.

Several studies have reported the prevalence of malnutrition in COPD, which vary between 11% to 33%, and its effect on patients' outcomes. According to

Steer et al. in a prospective study conducted in the UK which included 608 COPD patients who were hospitalised due to COPD exacerbation, the prevalence of malnutrition was 33% (190). Collins et al. reported that the prevalence of malnutrition in 425 outpatients with COPD who were screened with the Malnutrition Universal Screening Tool 'MUST' was 21% (192). Malnutrition Pathway, a group of experts in the field of malnutrition in the UK, concluded that around one in three hospitalised COPD patients or one in five outpatients are malnourished or at risk of being malnourished (188). In the UK, Ng and her colleagues reported in 2013 the overall prevalence of malnutrition for 778 stable COPD patients who were referred to PR was 11%; 6% were at medium risk and 5% were at high risk (191). As a consequence of malnutrition, Collins et al. have reported that the number of hospital admissions are doubled, and six- month mortality rate increased three fold in malnourished COPD patients when compared to those with normal weight (201).

Mete et al. compared spirometric values among COPD patients and concluded that patients with high risk of malnutrition (BMI < 18.5 kg/m^2) had significantly lower spirometric values compared with those who had BMI > 18.5 kg/m^2 (286). Wu et al. conducted a retrospective study to analyse the association between BMI and pulmonary function in Chinese COPD patients. They found FEV_1 was significantly increased with BMI and those with higher BMI had better pulmonary function result (287). Our study yielded a similar result, we discovered that there was a positive relationship between BMI and FEV1 and that this relation continued even in overweight and obese patients despite the risk of a restrictive pattern that might be expected with obesity. It is possible that this relationship is modified in people with COPD because of the co-existent airflow obstruction. Additionally, we discovered that lower BMI was

significantly associated with lower spirometric values, and FEV_1 was significantly lower for malnourished COPD patients. We speculated the relationship between BMI and lung function values, such as FEV_1 might be due to higher resting energy requirement, skeletal muscle atrophy and disuse, insufficient oxygenation, and systemic inflammation (186).

Our study did not showed any relationships between BMI and smoking history among COPD patients, although smoking is considered the most common risk factor for COPD occurrence, and accelerated FEV_1 decline.

Limitations of our study are that it has small sample size, so the result could not be generalised, and it is a single centre. We could not obtain additional body compositions measurements such as FFMI which an additional indicator for malnutrition in COPD. We could not asses recent weight lose among all patients as this indicate a risk of malnutrition. Finally, we could not conclude if the relationship between BMI and FEV_1 is considered a causative or not.

5.8 Conclusion

The prevalence of malnutrition of COPD in our single centre PR programme was 17%, and lower BMI was associated with lower lung function (FEV_1). In COPD patients with low risk of malnutrition, FEV_1 was higher compared with other groups (medium and high).

6. A Double-Blind, Randomised, Controlled Trial of Protein Supplementation to Enhance Exercise Capacity in Chronic Obstructive Pulmonary Disease during Pulmonary Rehabilitation.

6.1 Introduction

As described in detail in the introduction, patients with COPD tend to have daily symptoms and reduced exercise capacity, all of which lead to impaired health-related quality of life (6, 7). Peripheral muscle dysfunction is common among COPD patients, which is caused by reduced muscle mass, altered muscle metabolism or muscle fiber structure (133). COPD patients may lose skeletal muscle mass, leading to muscle weakness and dysfunction and/or muscle disuse, thus negatively affecting functional capacity, mobility, gait speed, overall strength and fertility (133, 135). Muscle disuse, caused by a prolonged sedentary lifestyle and voluntary immobilisation, leads to further muscle deconditioning and thus reduced muscle strength and endurance (135). PR is a fundamental management strategy in COPD patients that improves exercise performance, reduces dyspnoea and the risk of exacerbation, improves health-related quality of life, and promotes self-dependency in relation to activities of daily living (66-69, 71, 72, 161). Maximising the value and response to PR is of great interest to clinicians and patients alike.

Malnutrition is common in COPD and may unfavourably affect PR outcomes. Therefore; nutritional supplements have been used to overcome malnutrition, and may improve exercise activity, decrease the risk of mortality, and improve muscle strength in undernourished COPD patients (222, 223). COPD patients need a higher level of protein supplementation, which is recommended by the British Association for Parenteral and Enteral Nutrition, due to a higher protein requirement to preserve lean mass (188). As summarised in my systematic review, several studies have investigated the benefit of using nutritional support during PR and yielded conflicting outcomes; this is due to variations in PR

protocols and measured outcomes, type, ingredients amount, contents, or the duration of nutritional supplementation (226).

An integrated approach of exercise training and nutritional support may offer the greatest potential benefit and might be the best way to seek functional improvements with COPD patients. We hypothesised that a low volume, high energy, high protein oral nutritional supplement taken by stable COPD patients over the course of PR will enhance exercise capacity, peripheral muscle strength, anthropometrics measurements, health related quality of life, and physical activity compared to those taking a high carbohydrate oral nutritional supplement without protein. This study investigated the effect of a nutritional supplement (Fortisip Compact Protein) during a PR program on exercise capacity, peripheral muscle strength, anthropometrics measurements, health related quality of life, and physical activity in stable COPD patients.

6.2 Method

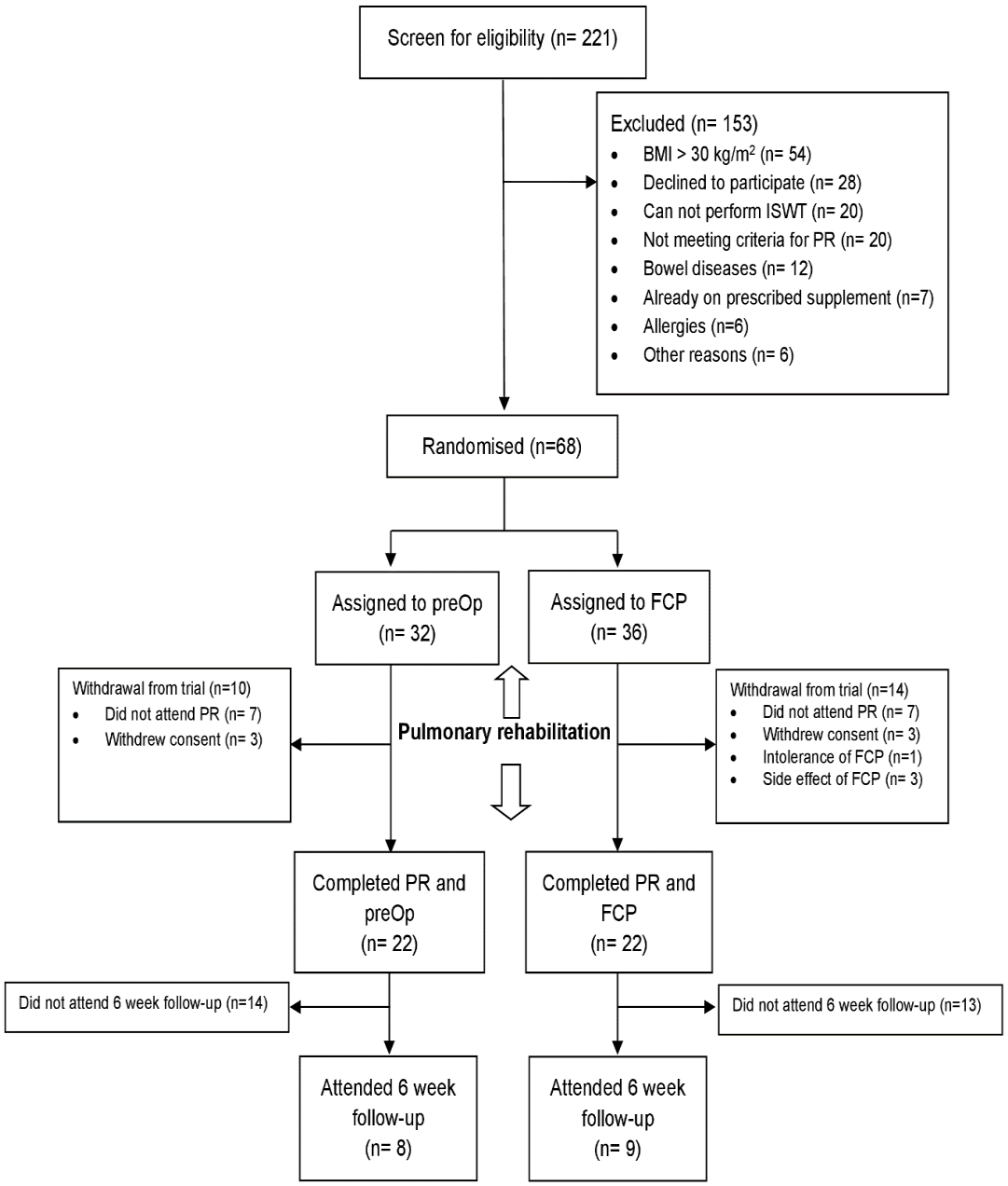
Ethical approval was obtained from the Central Research Ethics Committee and HRA (reference 18/LO/1842) (Appendix 1). Written informed consent was obtained for each participant before participating in the study. The study was registered at ClinicalTrials.gov (227).

6.2.1 Participants

Briefly, we approached and screened patients attending PR assessments at Central and North West London NHS Foundation Trust (two sites: the Peckwater Centre and St. Pancras Hospital) in London. COPD patients who agreed to participate were asked to sign a consent form (appendix 4).

Patients with appropriate exposure history and confirmed COPD diagnosis (post-bronchodilator FEV_1: FVC ratio <0.7) were recruited. Each participant was randomised to receive either the intervention of twice a day of FCP or twice a day of preOp.

Figure 24: Consolidated Standards of Reporting Trials (CONSORT) recruitment diagram for enrolment and study completion.



Abbreviation: BMI, body mass index; ISWT, Incremental Shuttle Walk Test; PR, pulmonary rehabilitation; FCP, Fortisip compact protein.

6.2.2 Pulmonary rehabilitation

PR is a comprehensive out-patient rehabilitation programme consisting of one hour of exercise training and one hour of education which participants attend twice a week for a total of 12 sessions. The PR programme is supervised by respiratory physiotherapists and follows BTS guidelines (228). The exercise training portion starts with a warm-up and is followed by low intensity aerobic exercises such as cycling, treadmill walking and level walking, and resistance exercise, such as progressive resistance of upper and lower body with free weights, step up, thigh muscle training with or without weight cuffs and sit to stand. Intensity of exercises were depends upon the tolerance of each individual. The education part includes but is not limited to: stress management, signs of chest infection: early recognition of exacerbation, dyspnoea and symptom management, nutrition, techniques using inhalers and nebulizers, energy conservation, smoking cessation and chest clearance techniques. Education topics were delivered by a multidisciplinary team.

6.2.3 Measurements

Demographic data and a comprehensive medical history for each participant were collected. Details of the number of chest infections and hospital admissions due to COPD exacerbation in the past 12 months were gathered. Post-bronchodilator hand-held spirometry was performed to confirm the diagnosis of COPD with appropriate risk factor exposure. Health-related quality of life was assessed by CAT and SGRQ questionnaires; breathlessness was assessed by MRC dyspnoea and BORG scales; anxiety and depression was assessed by HADS questionnaire; and risk of malnutrition was assessed by MUST. With each participant, a practice and second ISWT,

body composition (height/ weight/ FM/ FFM/ FFMI), anthropometric measurements (waist, hip, and mid-thigh circumferences), right and left handgrip, and STS5 were conducted. Additionally, participants were given a pedometer to record their daily steps for 14 days before the start date and 14 days after the completion date of the PR programme and were provided with instruction on how to complete the supplement and step count diaries.

All measurements were carried out at the start and the end of the rehabilitation programme. Further details about all measurements are described in Chapter 3.

6.3 Statistical analysis

Data were analysis based on intention- to- treat analysis which included all participants who completed PR and nutritional supplementation for both arms. Data were assessed for normality by visual inspection of the histogram, and the Kolmogorov-Smirnov test. Baseline characteristics of each group (interventional group vs control group) were reported using mean and standard deviation/ median and interquartile range and percentage as appropriate. For the main outcome (ISWT), between-group differences were compared by ANCOVA considering pre-ISWT value as a covariate. Pre and post PR measurements for each group (intervention group vs. control group) were compared using paired t-test analysis for normally distributed data and Wilcoxon signed-rank test if not normally distributed. Independent t-tests were used to compare the mean difference between both groups for normally distributed data and Mann-Whitney U tests for non-normally distributed data. Participants in the intervention group were classified as responders (improvement in the distance walked exceeded 36.1 m in ISWT) or non-

responders (improvement in the distance walked did not exceeded 36.1 m in ISWT) and compared. Participants in the intervention group were also stratified based on BMI ≤21 kg/m^2 and/or FFMI ≤15 kg/m^2 for women or 16 kg/m^2 for men into depleted and non-depleted groups to compare the effect of intervention in these subsets (251). Interim analysis were planed when we reach half of the sample size so we had stop the recruitment and only 44 who completed the trial were included in the main analysis. The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse our data.

6.4 Results

We approached and screened 221 consecutive patients between 7 January 2018 and 31 January 2020. Of these, 54 patients were excluded due to BMI > 30 kg/cm^2, 28 declined to participate, 20 were unable to perform ISWT, 20 did not meet the criteria to be included in PR, and 12 had bowel diseases. The CONSORT diagram is illustrated in Figure 21. Ultimately, 68 participants (42 male, 26 female) were randomised to receive FCP (intervention, n= 36) or preOp (control, n= 32) and started PR. After randomisation and PR had started, 24 (35%) individuals withdrew from the trial (FCP intervention= 14, preOp control= 10). Of the 68 participants, only 44 (intervention= 22; control = 22) completed PR and nutritional supplementation with pre- and post-measurements available, with the last visit for the last participant completed on the 13th March 2020. Twenty-four did not complete the trial, 14 withdrew from the PR class (intervention: 7; control: 7), six withdrew consent (intervention: 3; control: 3), one participant withdrew from the study due to intolerance of the supplement related to taste and three developed mild

diarrhoea, with no serious adverse reaction being reported. The baseline characteristics of both groups (completers and non-completers) are presented in Table 12 and 13.

Table 12: Demographic data, respiratory and non-respiratory medications, and baseline pulmonary function test of subjects with Chronic Obstructive Pulmonary Disease (COPD) divided into two groups; completers and non-completers.

Subjects Demographics	**Total population (68)**	**Completers (44)**	**Non-completers (24)**	**p-value** completers vs. non-completers
Age (years)	72 ±8	73 ±8	70 ±9	0.16
Male n (%)	42 (62%)	28 (64%)	14 (58%)	0.67
Female n (%)	26 (38%)	16 (36%)	10 (42%)	
Active smoker n (%)	26 (38%)	15 (34%)	11 (46%)	0.34
Ex-smokers n (%)	42 (62%)	29 (66%)	13 (54%)	
Smoking history (pack-years)	41.5 (28 – 58)	45 (28 – 61)	39 (30 – 58)	0.75
Exacerbation within last year	1 (0 – 2)	1 (0 – 2)	2 (0 – 3)	0.09
Hospitalisation due to exacerbations within last year n (%)	15 (22%)	7 (16%)	8 (33%)	0.09
Medications				
SABA n (%)	44 (65%)	31 (70%)	13 (54%)	0.18
LABA n (%)	40 (59%)	25 (57%)	15 (63%)	0.65
SAMA n (%)	0	0	0	^
LAMA n (%)	36 (53%)	24 (55%)	12 (50%)	0.70
ICS n (%)	33 (49%)	19 (43%)	14 (58%)	0.20
Other non-Respiratory medications n (%)	60 (88%)	38 (86%)	22 (92%)	0.52

Diabetes n (%)	0	0	0	^
Pulmonary function				
FEV_1 (L)	1.3 (1 – 1.9)	1.6 (1.1 – 2.4)	1.2 (1.1 – 1.2)	0.77
FEV_1 (% predicted)	58 (39 – 70)	64 (43 – 74)	49 (37 – 60)	0.89
FEV_1/FVC %	52 ±12	54 ±12	51 ±13	0.36

Data are presented as n (%), mean ±SD or median IQR. p value represent a comparison between completers and non-completers. ^ No data to compare with.
Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; BMI, FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements.

Table 13: Baseline anthropometric measurements, body composition, functional outcomes, health related quality of life and anxiety and depression questionnaires, and physical activity of subjects with Chronic Obstructive Pulmonary Disease (COPD) divided into two groups; completers and non-completers.

Subjects	**Total population (68)**	**Completers (44)**	**Non-completers (24)**	**p-value** completers vs. non-completers
Anthropometric measurements				
Weight (kg)	69 ±14	71 ±14.6	66 ±12	0.13
Waist circumference (cm)	92.7 ±13	94 ±14	90 ±11	0.30
Hip circumference (cm)	100 ±10	101 ±10	98 ±8	0.33
Mid-thigh circumference (cm)	57 ±8	58 ±7	56 ±9	0.46
Body composition				
Fat mass (kg)	24.7 ±6	25 ±6	24 ±6	0.49
BMI kg/cm^2	24 (21 – 27)	24 (21 – 27)	24 (21 – 27.5)	0.98
FFM (kg)	45 ±11	47.9 ±12	41.9 ±3.7	0.11
FFMI (kg/cm^2)	15.3 ±2.6	15.8 ±2.6	14 ±0.9	0.60

Functional outcomes				
ISWT (m)	266 ±134	267 ±130	264 ±144	0.94
mMRC grade	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.82
(R) Handgrip (kg)	27 ±9	28 ±10	24 ±7	0.09
(L) Handgrip (kg)	25 ±8	27 ±9	23 ±5	0.05
STS5 (sec)	10.3 (8.6 – 12.8)	11 (7 – 15)	9.8 (9.8 – 9.9)	0.70
Questionnaires				
CAT	20 ±7	19 ±7	21 ±7	0.34
Anxiety scores (HADS)	7 ±4	6 ±4	8 ±4	0.25
Depression scores (HADS)	6 (3 – 9)	6 (3 – 8.5)	7 (2 – 12)	0.45
SGRQ total	49 ±17	46 ±16	55 ±18	0.07
SGRQ symptoms	61 ±21	57 ±22	68 ±17	0.07
SGRQ activity	67 ±20	66 ±18	71 ±23	0.30
SGRQ impact	35 ±18	32 ±17	42 ±20	0.06
MUST	0	0	0	0.99
Physical activity (steps/ day)	3014 (1765 – 5914)	2961 (1860 – 5922)	3479 (2505 – 4660)	0.93

Data are presented as n (%), mean ±SD, or median IQR.
p value represent a comparison between completers and non-completers. ^ No data to compare with.
Abbreviations: BMI,Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

The mean age of the participants was 72 ±8 years: 62% were male, and 62% were ex-smokers. The non-completers had a trend towards higher numbers of exacerbations and hospital admissions but these were not statistically significant when compared with completers (p >0.05). Our participants were mainly GOLD 2 and 3, with median FEV_1 1.3L (57% predicted). There were no significant differences between the groups in the ISWT, weight, FFM, FM,

physical activity measured by steps, CAT, anxiety and depression scores, risk of malnutrition, SGRQ scores, and STS5 ($p > 0.05$). Overall, there were no statistical differences in baselines characteristics between completers and non-completers. The baseline characteristics of 44 completers in both groups (control: 22; intervention: 22) are presented in Table 14 and 15.

Table 14: Demographic data, respiratory and no respiratory medications, and baseline pulmonary function test of COPD patient who completed the study divided into two groups; control and intervention.

Subjects Demographics	**Control (22)**	**Intervention (22)**	**p-value**
Age (years)	70 ±9	75 ±6	**0.04**
Male n (%)	13 (59%)	15 (68%)	0.53
Female n (%)	9 (41%)	7 (32%)	
Active smoker n (%)	10 (45%)	5 (23%)	0.20
Ex-smokers n (%)	12 (55%)	17 (77%)	
Smoking history (pack-years)	39 (24 – 59)	45 (28 – 93)	0.41
Exacerbation within last year	1 (0 – 2.5)	0 (0 – 1)	0.21
Hospitalisation due to exacerbations within last year	0 (0 – 1.25)	0 (0 – 0)	**0.03**
Medications			
SABA n (%)	15 (68%)	15 (68%)	0.81
LABA n (%)	15 (68%)	9 (41%)	0.09
SAMA n (%)	0	0	^
LAMA n (%)	16 (73%)	8 (36%)	**0.02**
ICS n (%)	12 (54%)	7 (32%)	0.16
Other non-Respiratory medications n (%)	17 (77%)	20 (91%)	0.09
Diabetes n (%)	0	0	^
Pulmonary function			

FEV_1 (L)	1.2 (0.95 – 1.6)	1.6 (1 – 2.5)	0.27
FEV_1 (% predicted)	52 ±19	59 ±22	0.18
FEV_1/FVC %	54 ±12	53 ±13	0.90

Data are presented as n (%), mean ±SD, or median IQR. ^ No data to compare with.
p value was calculated using chi square, paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented a comparison between control and intervention groups.
Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements.

Table 15: Baseline anthropometric measurements, body composition, functional outcomes, health related quality of life and anxiety and depression questionnaires, and physical activity of subjects with Chronic Obstructive Pulmonary Disease (COPD) divided into two groups; control and intervention.

Subjects	**Control (22)**	**Intervention (22)**	**p-value**
Anthropometric measurements			
Weight (kg)	68 ±13	75 ±16	0.12
Waist circumference (cm)	92 ±14	95.6 ±15	0.46
Hip circumference (cm)	98 ±9	104 ±11	**0.04**
Mid-thigh circumference (cm)	56 ±8	59 ±6	0.16
Body composition			
FM (kg)	24 ±6.6	26 ±6	0.50
BMI kg/cm^2	23 ±4	24 ±4	0.36
FFM (kg)	43 ±10	49 ±13	0.12
FFMI (kg/cm^2)	15 ±3	16 ±3	0.17
Functional outcomes			
ISWT (m)	265 ±133	269 ±130	0.92
mMRC grade	3 (2 – 3)	3 (2 – 3)	0.87
(R) Handgrip (kg)	26 ±19	30 ±10	0.15
(L) Handgrip (kg)	25 ±9	29 ±9	0.16
STS5 (sec)	10.6 (7.5 – 13)	10.5 (9 – 12)	0.94

Questionnaires

CAT	20 ±8	18 ±6	0.37
Anxiety scores (HADS)	6.5 (4.5 – 9.5)	4.5 (3 – 10)	0.42
Depression scores (HADS)	6.5 ±3	5 ±3.5	0.19
SGRQ total	52 ±17	41 ±13	**0.02**
SGRQ symptoms	63 ±23	52 ±21	0.14
SGRQ activity	57 (57– 86)	57 (53 – 69)	**0.03**
SGRQ impact	38 ±19	27 ±12	**0.03**
MUST	0 (0, 1)	0 (0, 0)	0.50
Physical activity (steps/ day)	2663 (1947– 4912)	4297 (1726 – 7211)	0.33

Data are presented as n (%), mean ±SD, or median IQR. ^ No data to compare with.
p value was calculated using chi square, paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented a comparison between control and intervention groups.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

The intervention group was older than the control group (control: 70 years ±9 vs. intervention: 75 years ±6; $p < 0.05$). There were fewer ex-smokers in the control than the intervention groups (control: 55%; intervention: 77%). Hospitalisation due to COPD exacerbation was significantly higher in the control group ($p <0.05$), but COPD exacerbation was not significantly different between the groups ($p > 0.05$). There were no significant differences in waist and mid-thigh circumference measurements. However, there was a statistical difference between the control and the intervention groups in hip circumference (control: 98 cm ±9 vs. intervention: 104 cm ±11; $p <0.05$) that is unlikely to be clinically significant. There were significantly more participants in the control group using LAMA as a prescribed medication than in the intervention group (73% vs. 36%; $p < 0.05$). There were no statistical differences between the groups in body composition, including weight, FM,

FFM, and FFMI, and functional outcomes, including ISWT, right and left handgrips, and STS5. When health-related quality of life was measured at baseline by CAT and SGRQ, CAT did not show a significant difference ($p > 0.05$); however, SGRQ total score, activity, and impact domains showed significantly higher impact of COPD in the control group when compared with the intervention group (SGRQ total: 52 ±17 vs. 41 ±13, $p < 0.05$; activity domain: 57 (57– 86) vs. 57 (53 – 69), $p < 0.05$; impact domain: 38 ±19 vs. 27 ±12, $p < 0.05$). Physical activity measured by steps and risk of malnutrition were similar ($p >0.05$).

The changes after PR and supplementation within each group and the mean differences between them are presented in table 16 and 17. Within the control group, there were significant improvements after PR in ISWT (40 m ±60; $p < 0.01$), right handgrip (2.5 kg ±4; $p < 0.05$), left handgrip (3 kg ±5, $p < 0.05$), STS5 (-3 sec (-5 – (-0.6)); $p < 0.01$), body weight (1.3 kg ±1.8; $p < 0.05$) and mid-thigh circumference (1.8 cm ±4; $p < 0.05$). However, there were no significant improvements in CAT, MRC, anxiety and depression, SQRG scores in all domains, hip & waist circumferences, body composition, risk of malnutrition and physical activity measured by steps.

Table 16: Within group changes and mean difference for functional and anthropometric outcomes after the pulmonary rehabilitation.

Outcomes	Control (22)			Intervention (22)			p- value (The change between the mean differences)
	Pre	Post	Mean difference	Pre	Post	Mean difference	
Functional outcomes							
ISWT (m)	265 ±133	305 ±148	40 ±60α ‡	269 ±129	342 ±149	73 ±68α ‡	0.10
mMRC grade	3 (2 – 3)	3 (2 – 3)	0 (0 – 0)	3 (2 – 3)	3 (2 – 3)	0 (0 – 0)	1
(R) Handgrip (kg)	26 ±19	29 ±9	2.5 ±4α †	30 ±10	32 ±10	1.7 ±3α †	0.44
(L) Handgrip (kg)	25 ±9	28 ±10	3 ±5α †	29 ±9	30 ±10	1.7 ±3α ‡	0.33
STS5 (sec)	10.6 (7.5 – 13)	7.5 (6 – 10)	-3((-5) – (-0.6))α ‡	10.5 (9 – 12)	9 (7 – 12)	-1.6((-2) – (-0.8))α ‡	0.08
Anthropometric measurements							
Weight (kg)	68 ±13	69± 13	1.3 ±1.8α †	75 ±16	76 ±16	0.9 ±1.6α ‡	0.50
Waist circumference (cm)	94 (78 – 105)	94 (77 – 102)	-1 ((-2) – 3.5)	93 (87 – 105)	96.5 (85 – 111)	0.8 ((-1) – 2.3)	0.38
Hip circumference (cm)	98 ±9	98 ±9	0.25 ±2	104 ±11	103 ±9	-1.6 ±5	0.11
Mid-thigh circumference (cm)	56 ±8	58 ±6	1.8 ±4α †	59 ±6	61 ±5	1.5 ±3α †	0.75

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting baseline from post rehabilitation measurements.
p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
† $p<0.05$; ‡ $p<0.01$; α significant within the group.

Abbreviations: ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand–Five Test.

Table 17: Within group changes and mean difference for body composition, health related quality of life and anxiety and depression questionnaires, and physical activity outcomes after the pulmonary rehabilitation.

Outcomes	Control (22)			Intervention (22)			p- value
	Pre	Post	Mean difference	Pre	Post	Mean difference	(The change between the mean differences)
Body composition							
Fat mass (kg)	26 (18-30)	25 (18.5 – 30)	-0.4 ((-0.6) – 2.8)	27 (21 – 32)	27 (19.5 – 33)	-0.5 ((-1.5) – 2)	0.24
FFM (kg)	41 (34 – 52)	42 (34 – 56)	0.5 ((-2) – 2)	52 (37 – 61)	49 (38 – 59)	0.8 ((-0.8) – 1.4)	0.88
FFMI (kg/cm^2)	15 ±3	15 ±3	0.02 ±1.4	16 ±3	17 ±4	0.8 ±4	0.38
Questionnaires							
CAT	20 ±8	19 ±8	-1 ±5	18 ±6	17 ±7.5	-0.1 ±6	0.98
Anxiety scores (HADS)	7 ±4	6.5 ±5	-0.4 ±2	6 ±5	5 ±5	-1 ±3	0.55
Depression scores (HADS)	6.5 ±3	6 ±3	-0.3 ±2	5 ±3.5	4 ±4	-1 ±2	0.39
SGRQ total	52 ±17	51 ±17	-2.4 ±11.5	41 ±12.6	43 ±16	0 ±10	0.48
SGRQ symptoms	63 ±23	57 ±20	-6 ±20	52 ±21	49 ±27	-5 ±17	0.76
SGRQ activity	71.6 ±18	71 ±19	-2 ±10	60 ±17	66 ±21	4 ±16	0.2

SGRQ impact	38 ±19	36.6 ±20	-2 ±16	27 ±12	28.5 ±16.5	-0.1 ±11	0.74
MUST	0 (0 – 1)	0 (0 – 1)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	1
Physical activity (steps/ day)	2663 (1947 – 4912)	2903 (1800 – 4753)	72((-749) – 825)	4297 (1726 – 7211)	5973 (2000 – 6812)	294 ((-365) – 661)	0.88

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting baseline from post rehabilitation measurements.
p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
† $p<0.05$; ‡ $p<0.01$; α significant within the group.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Within the intervention group, there were significant improvements after PR in ISWT (73 m ±68; $p < 0.01$), right handgrip (1.7 kg ±3; $p < 0.05$), left handgrip (1.7 kg ±3, $p < 0.01$), STS5 (-2 sec ((-2) – (-0.8)); $p < 0.01$), body weight (0.9 kg ±1.6; $p < 0.01$) and mid-thigh circumference (1.5 cm ±3; $p < 0.05$). However, there were no significant improvements in CAT, MRC, anxiety and depression, SQRG scores in all domains, hip and waist circumferences, body composition, risk of malnutrition and physical activity measured by steps.

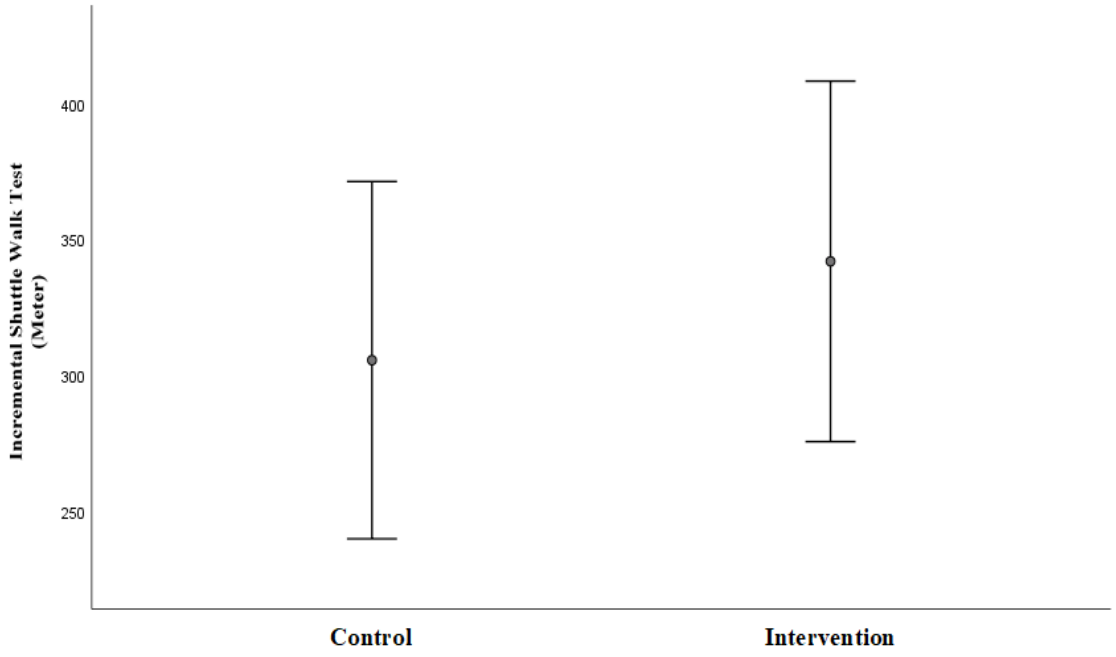
There were no significant differences between the groups in the ISWT, right and left handgrips, STS5, body weight, mid-thigh, hip, and waist circumferences, CAT, MRC, anxiety and depression, SQRG scores in all domains, body composition, risk of malnutrition and physical activity.

Primary outcome: Incremental Shuttle Walk Test

Adjusted for baseline ISWT, there was no statistically significant difference between the groups in post ISWT (control: 305 m ±148 vs. intervention: 342 m ±149, $p > 0.05$); however, this would be a clinically meaningful difference (MCID) in ISWT: more than 36.1 m. This difference in the ISWT is illustrated in Figure 22.

Next, we wanted to assess the baseline characteristics for those who responded compare to those who did not respond based on a change greater than the MCID of the ISWT which is more than 36.1 m. The baseline characteristics of responders and non-responders are presented in Table 18 and 19.

Figure 25: Post pulmonary rehabilitation mean ±SE of ISWT in the intervention and control groups.



Abbreviation: SE, standard error.

Table 18: baseline characteristics between responders and non-responders to ISWT in the interventional group.

Subjects Demographics	**Non-responders (9)**	**Responders (13)**	**p-value**
Age (years)	78 ±6	74 ±5	0.15
Male n (%)	6 (66%)	9 (69%)	0.90
Female n (%)	3 (33%)	4 (31%)	
Active smoker n (%)	2 (22%)	3 (23%)	0.96
Ex-smokers n (%)	7 (78%)	10 (77%)	
Smoking history (pack-years)	45 (21 – 49)	49 (28 – 105)	0.34
Exacerbation within last year n (%)	5 (56%)	5 (38%)	0.43
Hospitalisation due to exacerbations within last year n (%)	1 (11%)	0 (0%)	0.22
Anthropometric measurements			
Weight (kg)	71 ±18	78 ±14	0.32

Waist circumference (cm)	92 ±18	98 ±12	0.33
Hip circumference (cm)	102 ±15	106 ±8.5	0.44
Mid-thigh circumference (cm)	55 ±6.2	62 ±4.5	**0.006**
Medications			
SABA n (%)	7 (87%)	8 (61%)	0.20
LABA n (%)	4 (50%)	5 (38%)	0.60
SAMA n (%)	0	0	^
LAMA n (%)	4 (50%)	4 (31%)	0.38
ICS n (%)	3 (37%)	4 (31%)	0.75
Other non-Respiratory medications n (%)	8 (100%)	12 (92%)	0.42
Diabetes n (%)	0	0	^
Pulmonary function			
FEV_1 (L)	1.2 (0.95 – 1.6)	1.6 (1 – 2.5)	0.26
FEV_1 (% predicted)	52 ±19	59 ±22	0.28
FEV_1/FVC %	54 ±12	53 ±13	0.75
Body Composition			
Fat mass (kg)	25.5 ±7	26 ±6	0.87
BMI kg/cm^2	24 ±5	25 ±3	0.50
FFM (kg)	45 ±14	52± 13	0.29
FFMI (kg/cm^2)	15 ±3	16.5 ±2	0.38
Functional outcomes			
ISWT (m)	274 ±132	265 ±134	0.88
mMRC grade	3 (2 – 3)	3 (2 – 3)	0.95
(R) Handgrip (kg)	28.5 ±8	32 ±12	0.45
(L) Handgrip (kg)	27 ±8	30 ±10	0.43
STS5 (sec)	11 ±4	11 ±3	0.89
Questionnaires			
CAT	18 ±7	19 ±6	0.78

Anxiety scores (HADS)	3 (2 – 7.5)	6 (2.5 – 13)	0.26
Depression scores (HADS)	3 ±2	6.5 ±4	**0.04**
SGRQ total	39 ±12	42 ±14	0.56
SGRQ symptoms	52 ±23	52 ±21	0.99
SGRQ activity	56 (53 – 60)	62 (54 – 77)	0.25
SGRQ impact	26 ±11	27 ±14	0.95
MUST	0 (0 – 1.7)	0 (0 – 0)	0.36
Physical activity (steps/ day)	3930 ±3495	4909 ±2851	0.49

Data are presented as n (%), mean ±SD, or median IQR.
Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Between the responders and non-responders in the intervention group, there were significant differences in mid-thigh circumference (responder: 62 cm ±4.5 vs. non-responder: 55 cm ±6.2; $p < 0.05$) and depression scores (responders: 6.5 ±4 vs. non-responders: 3 ±2; $p < 0.05$) but clinically within normal range, although this difference is higher than the MCID, 1.4 points. There were no significant differences between the responders and non-responders in demographic data, hip and waist circumferences, respiratory and non-respiratory medications, pulmonary function, body composition, mMRC grade, both handgrips, STS5, anxiety score, health-related quality of life, risk of malnutrition and steps. The change in anthropometric measurements, body composition, dyspnoea scale, functional outcomes, health-related quality of life, anxiety, and depression, risk of malnutrition and physical activity measured by steps were assessed after rehabilitation but there were no

statistical between responders and non-responders in the intervention group ($p > 0.05$).

Table 19: Baseline characteristics between responders and non-responders to ISWT in the control group.

Subjects Demographics	**Non-responders (8)**	**Responders (14)**	**p-value**
Age (years)	71 ±11	69 ±7	0.55
Male n (%)	5 (62%)	8 (57%)	0.80
Female n (%)	3 (38%)	6 (43%)	
Active smoker n (%)	3 (38%)	7 (50%)	0.57
Ex-smokers n (%)	5 (62%)	7 (50%)	
Smoking history (pack-years)	42 ±30	42 ±24	0.97
Exacerbation within last year n (%)	4 (50%)	9 (64%)	0.51
Hospitalisation due to exacerbations within last year n (%)	2 (25%)	4 (28%)	0.85
Anthropometric measurements			
Weight (kg)	80 (52 – 85)	66 (55 – 73)	0.29
Waist circumference (cm)	92 ±17	92 ±12	0.99
Hip circumference (cm)	99 ±11	97 ±8	0.56
Mid-thigh circumference (cm)	57 ±8	66 ±8	0.66
Medications			
SABA n (%)	5 (62%)	10 (71%)	0.66
LABA n (%)	6 (75%)	9 (64%)	0.60
SAMA n (%)	0	0	^
LAMA n (%)	6 (75%)	10 (71%)	0.85
ICS n (%)	6 (75%)	6 (43%)	0.14
Other non-Respiratory medications n (%)	8 (100%)	9 (64%)	0.05
Diabetes n (%)	0	0	^

Pulmonary function			
FEV_1 (L)	1.5 (0.98 – 2.3)	1 (0.95 – 1.4)	0.25
FEV_1 (% predicted)	59 ±26	48 ±13	0.19
FEV_1/FVC %	47 ±15	58 ±8	**0.03**
Body Composition			
Fat mass (kg)	24 ±8	25 ±5	0.72
BMI kg/cm^2	24 ±5	23 ±3	0.36
FFM (kg)	47 ±11	41 ±10	0.17
FFMI (kg/cm^2)	16 ±3	14 ±2	0.08
Functional outcomes			
ISWT (m)	281 ±153	255 ±126	0.68
mMRC grade	3 (2 – 4)	2.5 (2 – 3)	0.13
(R) Handgrip (kg)	26 ±8	26 ±9	0.95
(L) Handgrip (kg)	24 ±8	25 ±9	0.71
STS5 (sec)	12 ±5	12 ±6	0.99
Questionnaires			
CAT	22 ±7	19 ±9	0.50
Anxiety scores (HADS)	8 ±5	6 ±4	0.39
Depression scores (HADS)	8 ±3	6 ±3	0.16
SGRQ total	59 ±18	48 ±16	0.18
SGRQ symptoms	61 ±26	63 ±22	0.87
SGRQ activity	81 ±14	66 ±18	0.08
SGRQ impact	46 ±23	34 ±16	0.17
MUST	0 (0 – 1)	0 (0 – 0.5)	0.71
Physical activity (steps/ day)	3489 (2411 – 5752)	2437 (1455 – 4426)	0.30

Data are presented as n (%), mean ±SD, or median IQR.

Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Between the responders and non-responders in the control group, there was a significant difference in FEV_1/FVC % (responder: 58 ±8% vs. non-responder: 47 ±15%; $p < 0.05$). There was a clinically higher SGRQ total score in non-responders compared with responders that exceeded the MCID of 4 units (responder: 48 ±16 vs. non-responder: 59 ±18; $p > 0.05$). There were no significant differences between the responders and non-responders in demographic data, anthropometric measurements, respiratory and non-respiratory medications, FEV1 and FEV1 percent predicated, body composition, ISWT, mMRC grade, both handgrips, STS5, anxiety and depression scores, health-related quality of life, risk of malnutrition and steps.

Next, we wanted to assess the changes after rehabilitation within the intervention and control groups for those who were depleted (defined as BMI ≤21 kg/m^2 and/or FFMI ≤15 kg/m^2 for women or 16 kg/m^2 for men) compared to those who were not depleted in the intervention and control groups. The mean differences between depleted and non-depleted participants in the intervention and control groups are presented in Table 20 and 21. Within intervention, between depleted and non-depleted groups, there were significant differences in hip circumference (depleted hip circumference: 1 ((-2) – 1.5) vs. non- depleted hip circumference: -2 ((-4) – (-1)); $p < 0.05$) FFM (depleted FFM: 1 (1 – 3) vs. non- depleted FFM: -0.4 ((-4) – 0.8); $p < 0.01$) and FFMI (depleted: 0.4 (0.3 – 0.8) vs. non-depleted: -0.1 ((-1) – 0.3); $p < 0.01$) . There were no significant differences in ISWT, mMRC grade, right and left handgrips, weight, waist and mid-thigh circumferences, CAT, anxiety and depression scores and SQRG scores in all domains and physical activity measured by steps ($p > 0.05$). However, SGRQ scores improved in the

depleted group but these improvements were only clinically meaningful (SGRQ total: -5 ±9, SGRQ symptoms: -11 ±17 and SGRQ impact: -5.5 ±9).

Within the control group, between depleted and non-depleted groups, there were significant differences in left handgrip (depleted left handgrip: 1 ±3 kg vs. non- depleted left handgrip: 6 ±7 kg p = 0.01) and FM (depleted FM: -0.3 ((-0.7) – 1) vs. non- depleted FFM: 2 (0.7 – 6); p = 0.04). There were no significant differences in ISWT, mMRC grade, right handgrip, STS5, weight, waist, hip, and mid-thigh circumferences, FFM, FFMI, CAT, anxiety and depression scores, SQRG scores in all domains and physical activity measured by steps (p > 0.05).

Table 20: The mean difference between depleted and non-depleted participants in the intervention group.

Outcomes	**Non-depleted (11)**	**Depleted (11)**	**p-value**
Functional outcomes			
ISWT (m)	84 ±85	62 ±48	0.47
mMRC grade	0 (0 – 0)	0 (0 – 0)	1
(R) Handgrip (kg)	1 ±3	2 ±3	0.50
(L) Handgrip (kg)	1.4 ±2	2 ±3	0.62
STS5 (sec)	-0.8 ±2	-2 ±0.8	0.20
Anthropometric measurements			
Weight (kg)	1 ±2	0.7 ±1	0.59
Waist circumference (cm)	0 ((-1) – 1.5)	1.7 ((-1) – 3)	0.52
Hip circumference (cm)	-2 ((-4) – -1)	1 ((-2) – 1.5)	**0.02**
Mid-thigh circumference (cm)	1 ((-0.5) – 3)	0 ((-2) – 1.5)	0.95
Body composition			
FM (kg)	0.4 ((-1.4) – 7)	-0.8 ((-3) – 0.1)	0.05

FFM (kg)	-0.4 ((-4) – 0.8)	1 (1 – 3)	**0.002**
FFMI (kg/cm^2)	-0.1 ((-1) – 0.3)	0.4 (0.3 – 0.8)	**0.007**
Questionnaires			
CAT	-0.3 ±8	-2 ±4	0.57
Anxiety scores (HADS)	-0.5 ±2	-1.2 ±3	0.59
Depression scores (HADS)	0.5 ±2	-1.2 ±2	0.47
SGRQ total	4 ±9	-5 ±9	0.05
SGRQ symptoms	-0.1 ±16	-11 ±17	0.18
SGRQ activity	9 ±16	-3 ±16	0.11
SGRQ impact	4 ±10.5	-5.5 ±9	0.06
Physical activity (steps/ day)	-111 ±1422	476 ±770	0.32

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting baseline from post rehabilitation measurements. P value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Table 21: The mean difference between depleted and non-depleted participants in the control group.

Outcomes	Non-depleted (8)	Depleted (14)	p-value
Functional outcomes			
ISWT (m)	18 ±68	54 ±54	0.18
mMRC grade	0 (0 – 0)	0 (0 – 0)	1
(R) Handgrip (kg)	4 (0.8 – 8)	-0.2 ((-1) – 4)	0.06
(L) Handgrip (kg)	6 ±7	1 ±3	**0.01**
STS5 (sec)	-4 ±4	-3 ±4	0.60
Anthropometric measurements			
Weight (kg)	1.4 (0.3 – 2)	0.6 (0.05 – 1)	0.24
Waist circumference (cm)	0.5 ±3	-0.4 ±4	0.58
Hip circumference (cm)	0.2 ±2	0.3 ±2	0.91
Mid-thigh circumference (cm)	0.8 ±2	2 ±5	0.08
Body composition			
FM (kg)	2 (0.7 – 6)	-0.3 ((-0.7) – 1)	**0.04**
FFM (kg)	-2 ((-4) – 1)	1 ((-0.1) – 2)	0.14
FFMI (kg/cm^2)	-0.5 ±2	0.4 ±1	0.17
Questionnaires			
CAT	-1 ±5	-1 ±5	0.98
Anxiety scores (HADS)	-0.25 ±2	-0.5 ±3	0.82
Depression scores (HADS)	-0.25 ±3	-0.4 ±2	0.92
SGRQ total	-2 ±17	-3 ±8	0.83
SGRQ symptoms	-10 ±27	-5 ±15	0.58
SGRQ activity	2 ±11	-4 ±10	0.27
SGRQ impact	-1 ±24	-2 ±11	0.95
Physical activity (steps/ day)	64 ((-1078)– 522)	134 ((-730) – 1680)	0.53

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting baseline from post rehabilitation measurements. P value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip,

left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

6.5 Discussion

To our knowledge, this the first study that has investigated the effect of high protein supplementation during PR in COPD; other studies have tested different supplements. The main findings of this study were that, in individuals with COPD who were enrolled in a six-week PR programme and received high protein nutritional supplementation, no significant difference between groups in exercise capacity measured by ISWT was detected, however, there was a clinically meaningful difference favouring the intervention group and individuals who reached that improvement had larger mid-thigh circumference and higher baseline depression score.

PR is recognised as an effective non-pharmacological management approach for improving exercise capacity with COPD, and this improvement can be sustained for one year (288). The ISWT is commonly used to measure exercise capacity, assess the effect of interventions such as PR, and to predict hospitalisation and mortality for COPD patients. In our study, there was no statistically significant difference in improvement in the exercise capacity between the intervention and control groups, this is in keeping with other RCTs that used creatine, high carbohydrate and other protein supplements (250, 263, 267, 269, 273). However, in our study, there was an improvement in ISWT that reached the MCID, on top of the usual improvement seen in PR, in the intervention group (250, 285). The intervention group was older than the control group, which may have reduced the effect size of the intervention as ageing induces frailty and sarcopenia thus reducing exercise capacity. The control group had more active smokers, higher number of hospitalisations due

to COPD exacerbations, greater COPD severity, higher SGRQ scores, although not significant, and lower daily steps which may all have negatively affected the improvement in this group. This study suggests that using a high protein supplement that is tolerable might enhance exercise capacity gains during PR.

Muscle fitness is usually assessed by peripheral muscle strength. A reduction in muscle strength, measured by handgrip strength, is associated with longer length of stay in hospital, poorer quality of life, and higher morbidity and mortality rates in COPD patients (158, 159). Handgrip strength, which is a valid measurement of peripheral muscle strength or performance, can be used to assess the effectiveness of PR and nutritional supplementation. According to Pitta et al, handgrip strength improved in 29 COPD patients after three months of PR (289). In our study, the improvement in handgrip was only noted within each group itself, with no difference between groups, which is similar to results in previous studies (250, 271, 272). Faager et al. reported that using carnitine for eight weeks during PR did not significantly improve handgrip strength when compared to the placebo group who received glucose (271). In contrast, the study by Fuld et al., showed significant improvement in handgrip after using creatine three times a day for two weeks followed by once a day for 10 weeks (273).

The five-repetition sit-to-stand exercise is considered to assess daily activities that rely on lower limb muscle performance (290, 291). In COPD, STS5 has been measured and correlated with health-related quality of life and strength of the lower limb (292). In our study, we were unable to show a significant difference between groups, although there were significant improvements

within each group. In COPD patients who underwent outpatient PR, STS5 was responsive to PR and significantly correlated with exercise capacity (244).

Recently, research on nutritional supplementation has focused on the quality of provided nutritional supplement rather than providing nutritional supplement with sufficient energy to preserve or improve body weight in COPD patients. Underweight COPD patients who enrolled in a PR programme may be susceptible to weight loss due to the exercise and energy imbalance. In our study, body weight did not decline and we did not find any difference between the groups; this might be due to the control group having received a carbohydrate supplement, as high carbohydrate supplementation could increase or maintain body weight (250, 263). In the study by Gurgun et al., there were significant improvements in body weight of 1.1 ±0.9 kg in those who received 250 mL of high carbohydrate supplement three times a day as an intervention (263).

This data has demonstrated that participants who received the intervention and reached or exceeded 36 m (MCID) in the ISWT had larger mid-thigh circumference at baselines. Similar associations were reported previously in a study where leg circumference, such as mid-thigh circumference, was positively associated with exercise capacity in a COPD population (293). Additionally, thigh muscles such as quadriceps have been positively associated with exercise capacity (294). As muscle mass increased, strength and endurance improved (294). This suggests that those who responded to the intervention might initially have higher muscle mass, especially in the lower limbs. We did not find any difference between the groups in hip and waist circumferences.

Body composition abnormalities are common in COPD patients, especially those who are referred to PR. Over the years, measuring body composition has been a concern for many researchers due to its association with exercise capacity, quality of life, and COPD severity (211, 213). In our study, we found that FFM and FFMI did not improve when we compared the intervention group with the control group; however, FFM and FFMI improved more in the depleted intervention group compared with the non-depleted intervention group, which suggests that high protein supplementation was most beneficial for depleted participants. Improvements in FFM and FFMI have been reported previously using nutritional supplementation during PR in depleted, malnourished, and muscle-wasted patients (251, 263, 268). We observed declines in FFM and FFMI in the non-depleted intervention group which might be related to other factors, such as protein metabolism disorders, medication use, muscle disuse or inactivity (250).

CAT has been used in PR with COPD patients to assess symptom burden. Several studies have reported a CAT score improvement in stable and post exacerbation COPD patients after enrolment in a PR class (295-297). In our study, we found no differences between CAT scores before and after the PR within and between the groups which might be due to the small sample size. According to the National PR audit report in July 2020, 58% of PR patients experienced an improvement in health status measured by CAT questionnaire (179). In the Pavitt study, there was no difference between groups in the CAT (285).

Anxiety and depression are independently responsible for a significant reduction in quality of life (126). The effect of PR on anxiety and depression

was reported by Gordon et al, in that PR had a positive effect in these conditions (298). When nutritional supplementation was implemented with COPD patents during PR in two RCTs, the supplementation did not improve anxiety and depression measured by HADS (262, 285). Our study show no improvements in HADS scores between groups (intervention and control; responders and non-responders; and depleted and non-depleted). Our participants tended to have anxiety and depression scores within normal range and this might be the reason that no improvement were observed. In our study, we found that participants who received the intervention supplement with PR and reached or exceeded MCID in the ISWT had higher baseline depression score (although still within normal range), and higher than in the non-responder group by more than the MCID which is 1.4 points (235). In COPD patients, depression has a negative impact on PR outcomes such as exercise capacity and dyspnoea which might unfavourably affect the distance walked in ISWT during the baseline visit (299). Our PR programme involved exercise and education, including stress management. Treating depression might positively impact exercise capacity allowing further distance to be covered at the end of PR.

SGRQ scores at baseline were higher in our control group and this might affect other outcomes such exercise capacity. Few studies have reported a significant correlation between SQRG total score and exercise capacity measured by 6MWT. As 6MWT distance increased, SGRQ score decreased (300, 301). Additionally, we found that SGRQ scores did not improve in the depleted group when compared with the non-depleted group. My systematic review found that out of seven studies using SGRQ to measure quality of life,

only one reported significant improvements in the SGRQ total and activity domain scores (using creatine supplementation during PR) (226, 273).

Physical inactivity is an important issue reported by COPD patients and it correlates with exercise performance. Our study found that there were no differences between groups in physical activity measured by steps, which contradicts other studies. Pavitt et al. and Van de Bool et al. reported that physical activities measured by steps improved in the intervention groups enrolled in PR programmes and who received nutritional supplementation (262, 285).

We had planned to conduct an interim analysis when we reached half of the required sample size, which was 49 participants; however, we were required to stop the recruitment due to the COVID-19 pandemic; consequently we had 44 completers. Based on that number, we completed an interim analysis and new power calculation. The mean improvement and standard deviation of the ISWT in the control group after pulmonary rehabilitation programme and nutritional supplementation were 40 ±60 m. The mean improvement and standard deviation of the ISWT after pulmonary rehabilitation programme and nutritional supplementation in the intervention group were 73 ±68 m. The dropout rate from the current trial was 35%. A new sample size was calculated in conjunction with statisticians at UCL, with 80% power at 5% significance level and standard deviation of 65 m (the average SD of ISWT for both groups) to ensure we could detect this additional increase in ISWT performance in the intervention group, and to account for the 35% dropout rate. To achieve this, we would needed to recruit 190 COPD patients (95 per group), with 124 completing a definitive study.

6.5.1 Limitations

We failed to recruit the required sample size due to the COVID-19 pandemic, which put the country in complete lockdown, additionally the strict criteria for inclusion, such as BMI > 30 kg/m^2 limited recruitment. We had to exclude 54 patients. In addition, based on interim data, we would not have been able to reach the required number of participants in a single centre study. We were not able to use ultrasound and scan thigh muscles as planned and we did not measure quadriceps strength. This might more accurately quantify the effect of intervention. Thigh circumference may not be the most accurate measurement, especially in obese patients. There were some differences between groups in baseline characteristics such as age, number of hospital admission and quality of life which may have impacted outcomes. Our stratification was only based on BMI and we might also have stratified participants based on disease severity as we had a higher number of hospitalisations in the control group. We could not provide a placebo identical to the intervention used in term of size or ingredients, but were able to relabel both products. There was heterogeneity in the exercise capacity measured by ISWT between participants. To check compliance with the supplement, we only provided participants with a diary card and we were not able to collect empty bottles.

6.6 Conclusion

Using a high protein nutritional supplementation in individuals with COPD who were enrolled in PR, we found no statistically significant difference between groups in exercise capacity measured by ISWT or in other secondary outcomes; however, there was a clinically meaningful difference favouring the

intervention, and individuals who reached that improvement had larger mid-thigh circumference.

The results of this chapter are currently being written up as a peer-review publication.

7. Change in Exercise Capacity and Other Outcomes Following Completion of a Double-Blind, Randomised, Controlled Trial of Protein Supplementation to Enhance Exercise Capacity in Chronic Obstructive Pulmonary Disease.

7.1 Introduction

As described in detail in the introduction, nutritional supplements are used to overcome malnutrition in patients with COPD, and nutritional support integrated with exercise training may improve exercise capacity, decrease the risk of mortality, and improve muscle strength in undernourished COPD patients (222, 223). In the previous chapter, I reported the effects of protein supplementation during a pulmonary rehabilitation programme.

The benefit of nutritional supplementation (Respifor, Nutricia) two years after PR was tested in muscle-wasted COPD patients who were enrolled in PR versus usual care group who received verbal dietary recommendation. It was found that there was a significant improvement in MIP and limb muscles, compared to participants who were in the usual care group (268). Additionally, deterioration was noticed in the usual care only group in exercise capacity, quality of life measured by SGRQ, and the cycle endurance test (268). Only one study has addressed the effect of supplementation following PR; however, supplementation were continued upon indication after PR for the muscle-wasted patients and the participants in the usual care group did not participate in PR programme. Whether the effects of nutritional supplements can be sustained for six weeks following the cessation of PR is unknown. Therefore, we offered participants who completed the study a six-week follow-up to evaluate the longer-term effect of nutritional supplementation following PR. We did not continue the nutritional supplementation during this period.

Our study investigated the effect of FCP compared with preOp supplement on exercise capacity, anthropometrics measurements and body composition (body weight, BMI, FM, and FFMI, waist, hip, and mid-thigh circumference),

peripheral muscle strength, level of anxiety and depression and health related quality of life at six weeks post discharge. We hypothesised that the benefits of FCP on exercise capacity, anthropometrics measurements and body composition (body weight, BMI, FM, and FFMI, waist, hip, and mid-thigh circumference), peripheral muscle strength, level of anxiety and depression, and health-related quality of life may be maintained up to six weeks following PR completion compared with the control group.

7.2 Methods

This study is an extension of my previous study reported in chapter 6. The participants are the same. Ethical approval was obtained from Central Research Ethics Committee and Health Research Authority (HRA) (reference 18/LO/1842) Appendix 1. The study was registered at ClinicalTrials.gov (227).

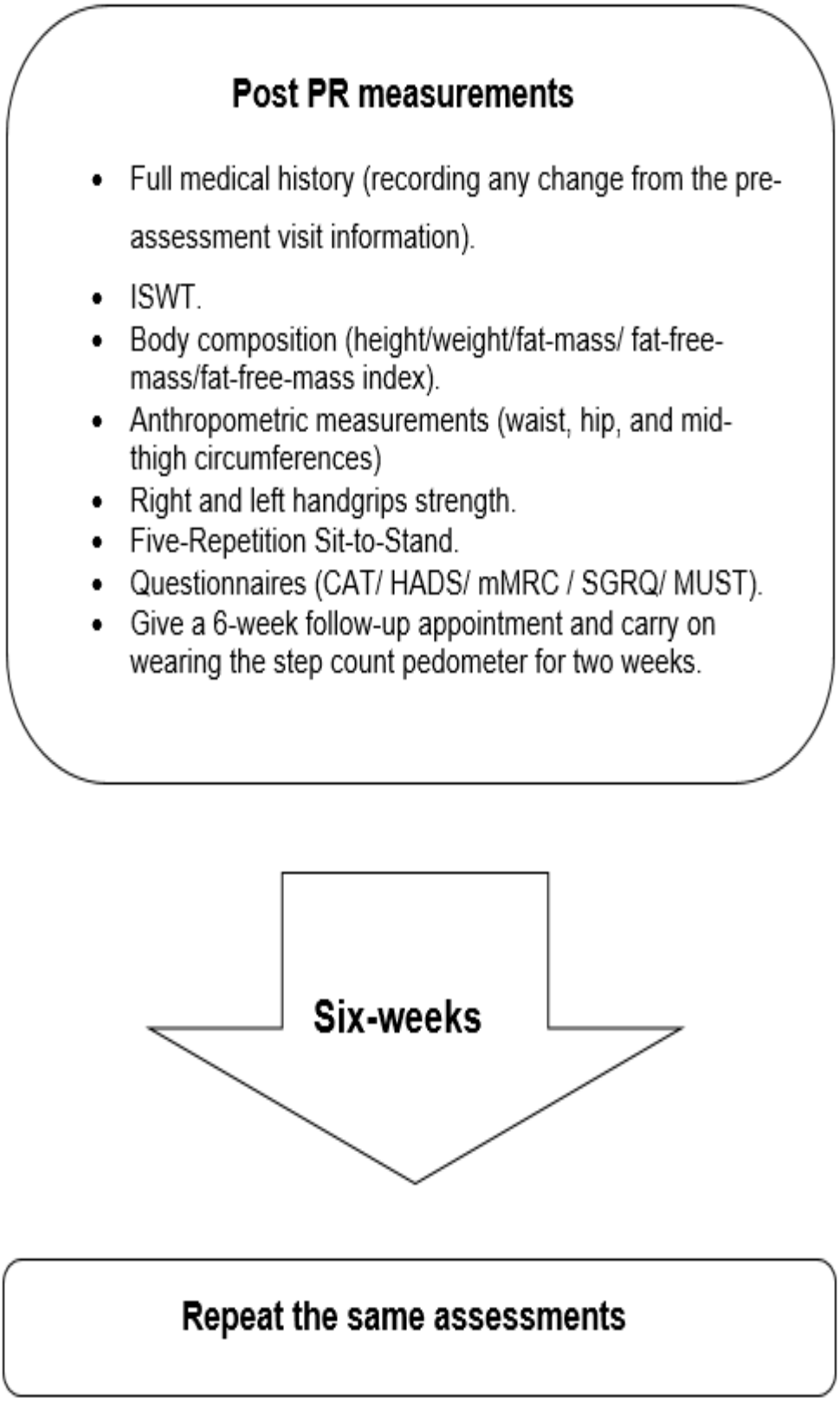
7.2.1 Participants

Participants who completed the PR programme were asked to attend a follow-up visit six weeks after the end of PR for re-assessment. Nutritional supplementation was not continued during this time. Participants were given a simple step-counter (pedometer) and asked to record daily steps post-PR for 14 consecutive days (appendix 8), except during showering and sleeping. At the end of the six weeks, the participants were re-assessed by completing the same evaluations described in the previous chapter and the methods.

7.2.2 Measurements

A detailed explanation of all measurements made reported in the methods chapter. An overview of the methods for this chapter is reported in Figure 23.

Figure 26: Method overview.



7.3 Statistical Analysis

Data were assessed for normality by visual inspection of the histogram, and the Kolmogorov-Smirnov test. Baselines characteristics for subjects who attended the follow-up visit six weeks after the end of PR and did not attend were compared. Baseline characteristics of each group (interventional group vs control group) were reported using mean and standard deviation/ median and interquartile range and percentage as appropriate. For ISWT, between-group differences were compared by ANCOVA considering baseline ISWT value as a covariate. Baseline and post visits with six-week follow-up measurements for each group (intervention group vs. control group) were compared by using paired t-test analysis for normally distributed data and Wilcoxon signed-rank test if not normally distributed. Independent t-tests were used to compare the mean difference between both groups for normally distributed data and Mann-Whitney U tests for non-normally distributed data. The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse our data.

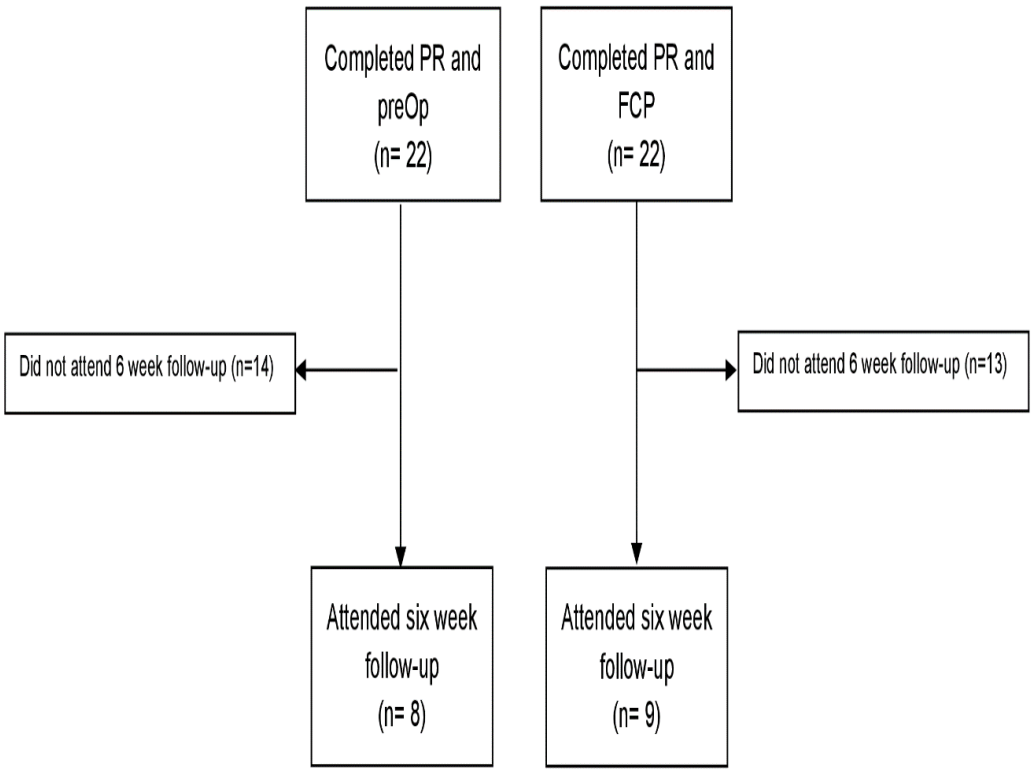
7.4 Results

Baseline characteristics of the participants

We approached 44 consecutive patients who completed the PR programme (Figure 24). Of the 44 participants who completed the trial, 11 follow-up visits were cancelled due to the COVID-19 pandemic. Only 17/44 (preOp control: eight; FCP intervention: nine) attended the follow-up assessment visit six weeks after PR completion (Figure 24). The baseline characteristics of participants who attended the follow-up and did not attended the follow-up visits are presented in Tables 22 and 23.

The mean age of the 17 participants who attended follow-up was 74 years and 65% were female, with a median FEV_1 of 1.35L (64% predicted). Comparisons were made between the baseline characteristics of the 17 who attended the follow-up assessment visit with the 27 who did not attend. The groups were generally similar but a higher percentage of females attended the six-week visits than males (did not attend: 5 females (18%) vs. 11 females (65%); $p < 0.05$). Additionally, participants who attended the six-week visit had significantly lower right handgrip strength (25 kg ±9 vs 31 kg ±9; $p < 0.05$).

Figure 27: Consort diagram of the approached participants.



Abbreviation: BMI, body mass index; ISWT, Incremental Shuttle Walk Test; PR, pulmonary rehabilitation; FCP, Fortisip compact protein.

Table 22: Demographic data, respiratory and non-respiratory medications, and baseline pulmonary function test of subjects with chronic obstructive pulmonary disease (COPD) who completed PR, divided into 17 participants who did attend the six-week follow-up visit and 27 who did not.

Subjects Demographics	**Total population (44)**	**Did not attend F/U (27)**	**Did attend F/U (17)**	**p-value** Attended vs. didn't attend F/U
Age (years)	73 ±8	73 ±6	71 ±10	0.28
Male n (%)	28 (64%)	22 (82%)	6 (35%)	**0.002**
Female n (%)	16 (36%)	5 (18%)	11 (65%)	
Active smoker n (%)	15 (34%)	10 (37%)	5 (29%)	0.60
Ex-smokers n (%)	29 (66%)	17 (63%)	12 (71%)	
Smoking history (pack-years)	45 (28 – 61)	49 (30 – 61)	34 (25 – 60)	
Exacerbation within last year n (%)	23 (52%)	14 (60%)	9 (40%)	0.94
Hospitalisation due to exacerbations within last year n (%)	7 (16%)	4 (15%)	3 (18%)	0.80
Medications				
SABA n (%)	31 (70%)	19 (70%)	12 (70%)	0.92
LABA n (%)	25 (57%)	16 (59%)	9 (53%)	0.76
SAMA n (%)	0	0	0	^
LAMA n (%)	24 (55%)	13 (48%)	11 (65%)	0.34
ICS n (%)	19 (43%)	12 (44%)	7 (41%)	0.75
Non-Respiratory medications n (%)	38 (86%)	22 (81%)	16 (94%)	0.22
Diabetes n (%)	0	0	0	^
Pulmonary function				
FEV_1 (L)	1.6 (1.1 – 2.4)	1.2 (1 – 2.2)	1.4 (1 – 2)	0.74
FEV_1 (% pred)	64 (43 – 74)	44 (38 – 71)	64 (39 – 73)	0.51
FEV_1/FVC %	55 ±12	56 ±11	51 ±12	0.18

Data are presented as n (%), mean ±SD, or median IQR.
p value represent a comparison between participants who did attend the six-week follow-up visit and did not. ^ No data to compare with.

Abbreviations: SABA, Short-acting beta-agonists; LABA; Long-acting beta-agonists; SAMA, Short-acting muscarinic antagonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroids; FEV_1, Forced Expiratory Volume in 1 second; FEV_1%, Predicted Forced Expiratory Volume in 1 second; FEV_1/FVC, calculated ratio between both measurements.

Table 23: Baseline anthropometric measurements, body composition, functional outcomes, health related quality of life and anxiety and depression questionnaires, and physical activity of subjects with Chronic Obstructive Pulmonary Disease (COPD).

Subjects	**Total population (44)**	**Did not attend F/U (27)**	**Did attend F/U (17)**	**p-value** Attended vs. didn't attend F/U
Anthropometric measurements				
Weight (kg)	71±15	73 ±14	69 ±15	0.32
Waist circumference (cm)	96 ±12	95 ±13	91 ±16	0.36
Hip circumference (cm)	104 ±10	100 ±9	103 ±13	0.30
Mid-thigh circumference (cm)	58 ±7	58 ±6	56 ±8	0.34
Body composition				
Fat mass (kg)	27 ±6	25 ±5	25 ±8	0.73
BMI kg/cm^2	24 (21 – 27)	25 (22 –28)	23.5 (20 – 27)	0.48
FFM (kg)	48 ±12	48 ±12	43 ±12	0.20
FFMI (kg/cm^2)	16 ±2.6	16 ±3	15 ±2	0.17
Functional outcomes				
ISWT (m)	267 ±130	270 ±123	261 ±144	0.81
mMRC grade	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.65
(R) Handgrip (kg)	29 ±11.5	31 ±9 ¥ †	25 ±9	**0.03**
(L) Handgrip (kg)	27 ±10	29 ±9	24 ±9	0.06
STS5 (sec)	11 (7 – 15)	11 (8.6 – 12)	10 (8 – 15)	0.96
Questionnaires				
CAT	19 ±7	20 ±7	19 ±8	0.85

Anxiety scores (HADS)	8 ±5	6 ±5	7 ±4	0.33
Depression scores (HADS)	6 (3 – 8.5)	5 (3 – 8)	6 (2.5 – 8.5)	0.69
SGRQ total	51 ±16	46 ±16	47 ±15	0.76
SGRQ symptoms	63 ±21	56 ±23	59 ±21	0.74
SGRQ activity	68 ±17	64 ±20	68 ±15	0.59
SGRQ impact	38 ±18	32 ±17	33 ±17	0.92
MUST	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.99
Physical activity (steps/ day)	4102 (2148 – 6385)	2416 (1488 – 5277)	4818 (2095 – 7528)	0.05

Data are presented as n (%), mean ±SD, or median IQR**.**
p value represent a comparison between participants who did attend the six-week follow-up visit and did not. ^ No data to compare with.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool

The mean change based on the differences between the post-PR and six-week follow-up within each group and between groups (control: 8; intervention: 9) are presented in Tables 24 and 25.

Table 24: The mean differences for functional and anthropometric measurements between then end of PR and six-week follow-up divided into two groups; control and intervention.

Outcomes	Control (8)	Intervention (9)	p-value (between groups)
Functional outcomes			
ISWT (m)	10 ((-7.5) – 25)	0 ((-30) – 0)	0.09
mMRC grade	0 (0 – 0)	0 (0 – 0)	0.67
(R) Handgrip (kg)	0.80 ±2.1	-0.33 ±3.4	0.42
(L) Handgrip (kg)	-0.02 ±2.3	-0.02 ±3	0.87
STS5 (sec)	-1 ±1.1 α †	-0.7 ±1	0.59
Anthropometric measurements			
Weight (kg)	0.1 ±0.8	0.4 ±1.5	0.67
Hip circumference (cm)	-0.3 ±1.7	-0.4 ±2.2	0.99
Waist circumference (cm)	1 ±4	1 ±4	0.99
Mid-thigh circumference (cm)	0.75 ±3	0.3 ±5	0.81

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting before rehabilitation from the six-week follow-up measurements.
p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
† p<0.05; ‡ p<0.01; α significant within the group.
Abbreviations: ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test.

Table 25: The mean differences between then end of PR and six-week follow-up divided into two groups; control and intervention.

Outcomes	Control (8)	Intervention (9)	p-value (between groups)
Body composition			
Fat mass (kg)	1 ±2	0.1 ±2.5	0.42
FFM (kg)	-1 ±2	0.3 ±2	0.27
FFMI (kg/cm^2)	-0.35 ±0.88	1 ±0.8	0.31
Questionnaires			
CAT	-1.5 ±5	-0.7 ±2	0.67
Anxiety scores (HADS)	-0.4 ±2	1 ±2	0.07
Depression scores (HADS)	-0.75 ±2	0.1 ±1.5	0.36
SGRQ total	-4 ±8	0.5 ±6	0.26
SGRQ symptoms	8 ±14	2 ±8	0.25
SGRQ activity	-5 ±11	-5 ±5 α †	0.94
SGRQ impact	-4 ±13	0.7 ±5	0.35
MUST	0 (0 – 1)	0 (0 – 1)	1

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting before rehabilitation from the six-week follow-up measurements.
p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
† p<0.05; ‡ p<0.01; α significant within the group.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

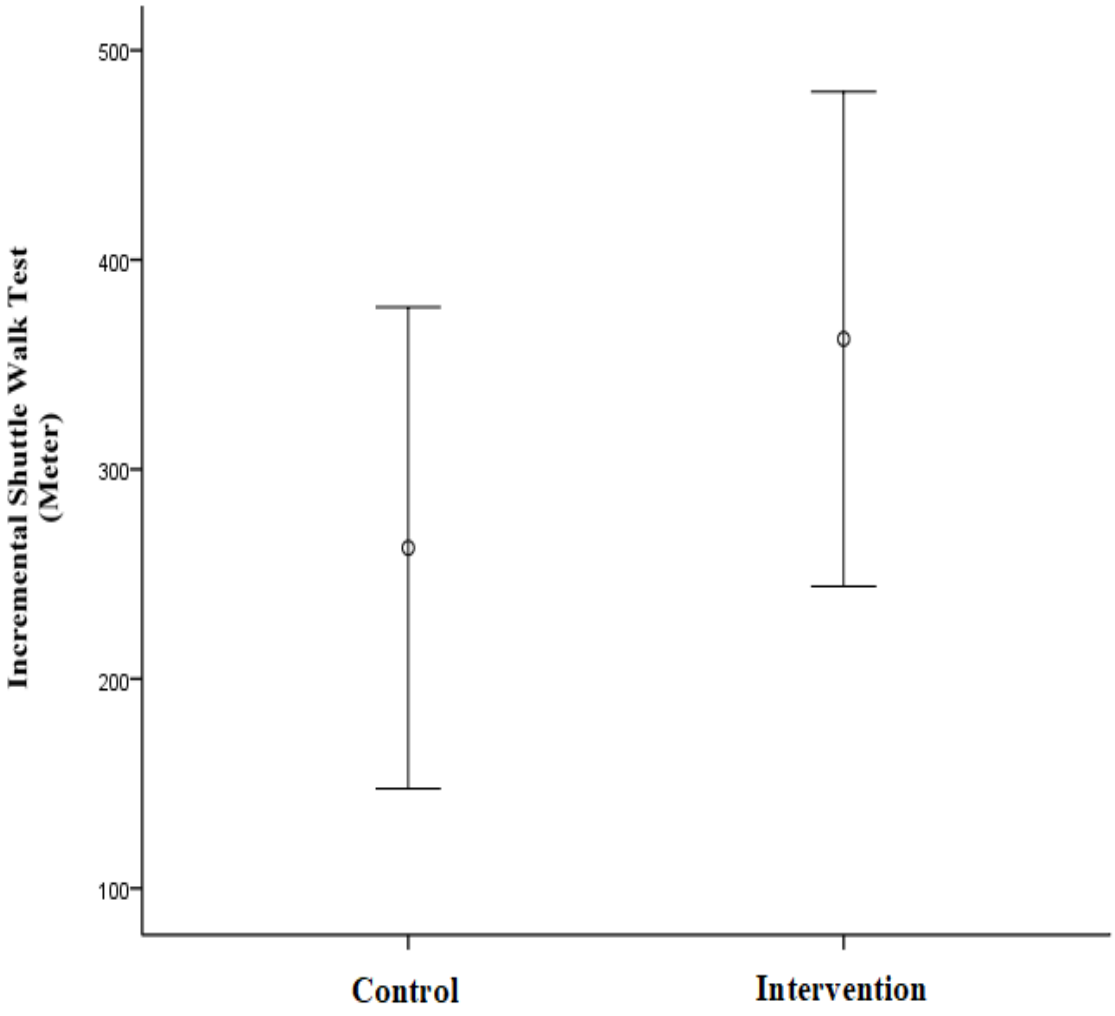
Within the control group, there no were significant improvements or declines in ISWT, mMRC scale, right and left handgrips, anthropometric measurements, body composition, anxiety and depression, health-related quality of life and risk of malnutrition, but only a significant improvement in STS5 (mean difference: -1 sec ±1.1; $p < 0.05$) was noticed between the end of PR and follow-up (Tables 24 and 25).

Within the intervention group, there no were significant improvements or declines in ISWT, body weight, anthropometric measurements, body composition, anxiety and depression, risk of malnutrition, and SQRG scores except activity domain. Within the intervention group, there was a significant improvement in the activity domain of SGRQ (mean difference: -5 ±5; $p < 0.05$) between the end of PR and follow-up. When we compared the changes between both groups, there were no significant differences in any of the outcome measures between the end of PR and follow-up visit (Tables 24 and 25).

Next, we wanted to assess the improvement in ISWT at six-week follow-up visit. There was no statistical significant difference between the groups in ISWT at six-week follow-up visit (control; 262.5 m ±137; intervention: 362 m ±154; $p > 0.05$); however, this would be a clinically meaningful difference (MCID) in ISWT: more than 36.1 m. This difference in the ISWT is illustrated in Figure 25.

Thereafter, we wanted to assess the mean change based in the differences between pre PR measurements and the six-week follow-up for both groups. The mean change based on the differences between the pre PR and the six-week visits within each group (control: 8; intervention: 9) are presented in Table 26 and 27.

Figure 28: Mean and ±SE of ISWT at six-week follow-up in the intervention and control groups.



Abbreviation: SE, standard error.

Table 26: The mean differences for functional and anthropometric outcomes between pre PR and six-week follow-up visit divided into two groups; control and intervention.

Outcomes	Control (8)	Intervention (9)	p-value (between groups)
Functional outcomes			
ISWT (m)	45 ±38 α †	62 ±78 α †	0.58
mMRC grade	0 (0 – 0)	0 (0 – 0)	0.67
(R) Handgrip (kg)	0.7 ±2.3	1.5 ±4	0.67
(L) Handgrip (kg)	1.1 ±2	1.5 ±3.5	0.77
STS5 (sec)	-3 ±2 α †	-2.5 ±2.3 α †	0.74
Anthropometric measurements			
Weight (kg)	0.1 ±0.8	0.4 ±1.5	0.67
Hip circumference (cm)	1 ±7	0.05 ±3.6	0.54
Waist circumference (cm)	0.25 ((-0.8) – 2.7)	0 ((-3.7) – 1.7)	0.75
Mid-thigh circumference (cm)	4.7 ±4	2.7 ±4.5	0.41

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting before rehabilitation from the six-week follow-up measurements.
p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
† $p<0.05$; ‡ $p<0.01$; α significant within the group.
Abbreviations: ISWT, incremental shuttle walk test; mMRC; modified medical research council dyspnoea scale; (R) handgrip, right handgrip; (L) handgrip, left handgrip; STS5, Sit to Stand– Five Test.

Table 27: The mean differences for body composition, health related quality of life and anxiety and depression questionnaires, and physical activity outcomes between baseline and six-week follow-up visit divided into two groups; control and intervention.

Outcomes	Control (8)	Intervention (9)	p-value (between groups)
Body composition			
Fat mass (kg)	1.6 ±2	0.7 ±3	0.53
FFM (kg)	0.4 ((-1.5)– 1.2)	0.8 ((-0.1) – 1)	0.92
FFMI (kg/cm^2)	0.11 ±0.85	0.08 ±0.99	0.96
Questionnaires			
CAT	0 (0 – 0)	0 (0 – 0)	0.53
Anxiety scores (HADS)	-1.5 ±4	-0.3 ±3	0.40
Depression scores (HADS)	-1.4 ±3	-1 ±3	0.80
SGRQ total	-10 ±8	-2 ±11	0.20
SGRQ symptoms	-5 ±9	-1.5 ±15.5	0.62
SGRQ activity	-12 ±9	-2 ±18	0.31
SGRQ impact	-11 ±10	-2 ±10	0.13
MUST	0 (0 – 1)	0 (0 – 1)	1

Data are presented as n (%), mean ±SD, or median IQR.
Mean difference for each group was calculated by subtracting before rehabilitation from the six-week follow-up measurements.
p value was calculated using paired t-test for normally distributed and Wilcoxon signed-rank test for non-normally distributed data, and represented the difference between the mean differences in control and intervention groups.
† $p<0.05$; ‡ $p<0.01$; α significant within the group.
Abbreviations: BMI, Body Mass Index; FFM, fat-free-mass; FM, fat-mass; FFMI, fat-free-mass index; CAT; COPD assessment test; HADS, hospital anxiety and depression scale; SGRQ, St. George's respiratory questionnaire; MUST, malnutrition universal screening tool.

Within the control group, there were significant improvements in ISWT (mean difference 45 m ±38; $p < 0.05$), STS5 (mean difference: -3 sec ±2; $p < 0.05$) between pre PR and follow-up visit. Within the control group, there were no significant improvements or declines in mMRC, right and left handgrips, body weight, hip, waist and mid-thigh circumferences, body composition, anxiety

and depression, health-related quality of life and risk of malnutrition between pre PR and follow-up visit.

Within the intervention group, there were significant improvements in ISWT (mean difference 62 m ±78; $p < 0.05$) and STS5 (mean difference: - 2.5 sec ±2.3; $p < 0.05$) only between pre PR and follow-up visit. Within the intervention group, there no were significant improvements or declines in mMRC, body weight, right and left handgrips, hip, waist and mid-thigh circumferences, body composition, anxiety and depression, health-related quality of life and risk of malnutrition.

When we compared the changes between both groups, there were no significant differences in any of the outcome measures.

7.5 Discussion

In the previous chapter, I reported that individuals with COPD had no statistically significant change in exercise capacity measured by ISWT (or in other outcomes) when given protein supplementation during PR; however, there was a clinically meaningful improvement in ISWT favouring the intervention group, and individuals who had that improvement had a larger baseline mid-thigh circumference. In this chapter, we observed no decline in ISWT or other outcomes at six weeks following PR. This study showed an improvement in ISWT in both group when compared with pre PR values and no decline was noticed in both group when compared with the end of PR. When comparisons were made between the end of PR and the six-week visits, no changes were observed between or within groups, except an improvement in the activity domain of SGRQ in the intervention group compared to end of PR.

To our knowledge, this is the only study that re-assessed patients at six weeks following PR to assess if any changes associated with nutritional supplementation during PR were sustainable. We approached 44 patients who had completed the main trial. Seventeen attended and were successfully assessed at follow-up. Eight patients were in the control group and nine patients were in the intervention group. After comparing those who did and did not attend follow-up assessments, we have shown that they were generally similar, but those who did not attend were more likely to be male and had a stronger (right) handgrip.

The improvement in COPD following PR has been investigated by different researchers. The benefit of PR has been well-established, but uncertainty remains on how best to maintain that benefit over a longer period of time. A longitudinal RCT was conducted by Brooks et al. to investigate the effect of post-pulmonary rehabilitation on exercise capacity and quality of life on 85 COPD patients (302). Participants were followed up to a year and results show that exercise capacity was initially maintained but gradually declined over the year. Additionally, Beauchamp et al. reported in a systematic review that PR benefit was not sustained for 12 months in 619 moderate to severe COPD patients (303). In our study, when we assessed exercise function at six weeks after PR and nutritional supplementation with a second visit, there was no change in the intervention group, which is similar to the findings of a study conducted by Wetering et al, (268) who investigated the effect of four months of PR and nutritional supplementation, and followed up participants for two years. At 24 months, the intervention group who received nutritional supplementation were consistently stable, compared with the usual care group who had deteriorated over this period.

The five-repetition sit-to-stand test is used in PR to assess exercise capacity and is positively correlated well with ISWT (292, 304). Jones et al., reported that STS5 significantly improved in 80 COPD patients following PR (304). We are not aware of any data that has tested if that improvement is sustained over time. In our study, we found the STS5 improved in both groups with PR and that improvement correlated with ISWT improvement.

Compared to baseline, FFM in the control group and the intervention group were stable in our study following PR. However, Wetering et al., found a significant improvement in FFMI compared to the baseline after 24 months in the intervention group (268).

Improving health-related quality of life is of interest to patients and health care providers. Following PR, there has been an improvement in quality of life in different contexts, but this effect starts to deteriorate in COPD patients after 12 months (288, 305). Wetering et al., also examined the effects of PR and nutritional supplementation and found that intervention groups remained stable, while the control group declined (268). In our study and within the intervention group, only the SGRQ activity score improved with other domain being stable and the control group did not deteriorate when comparison was made with post-PR data.

Anxiety and depression scores improved after a PR programme in a study conducted by Griffiths et al. that included 200 patients, in which the majority had COPD; however, these improvements had declined by one year follow-up, especially in COPD patients with diminished exercise function (288). In our study, patients were stable and no deterioration was detected in either group following PR and nutritional supplementation six weeks after completion.

7.5.1 Limitations

My follow-up study is limited by the small sample size and high dropout rate due to the COVID-19 pandemic, which put the country in complete lockdown, additionally the strict criteria for inclusion, such as BMI > 30 kg/m^2 limited recruitment. Based on interim data, we would not have been able to reach the required number of participants in a single centre study. We were not able to use ultrasound and scan thigh muscles as planned and we did not measure quadriceps strength. This might more accurately quantify the effect of intervention. Thigh circumference may not be the most accurate measurement, especially in obese patients. There was a difference between participants who attended the follow-up and did not attended follow-up visit in right handgrip strength which may be due to more males dropping out.

7.6 Conclusion

At six-week follow-up, there was no further change in exercise capacity or other secondary outcomes between intervention and control groups.

8. Participants' Experience Using Nutritional Supplements during Pulmonary Rehabilitation: a survey

8.1 Introduction

Many studies have incorporated nutritional supplementation into COPD management to identify the effects of supplementation on patients' muscle strength and exercise capacity.

However, there is little evidence from COPD patients about the experience of the consumption of nutritional supplements during the course of PR. Patients' feedback is essential in achieving better quality healthcare and is likely to "facilitate reflective discussion to encourage the formulation of change" (306). Recommendations on ONS state the importance of testing patients' preferences regarding products, as well as monitoring the daily intakes of COPD patients commencing ONS (188). Patients' compliance with the 'starter pack' supplements can be monitored and flavours can be changed based on patient preference. Further investigation into information on COPD patients' experience and preferences has the potential to improve supplements used in the future for managing COPD patients.

8.2 Aims

To investigate COPD patients' experience taking FCP (Nutricia, *Zoetermeer*, *Netherlands*) and preOp (Nutricia, *Zoetermeer*, *Netherlands*) during a six-week PR programme.

8.3 Materials and Methods

Participants who had already enrolled in a double-blinded, randomised controlled trial were included. Data were collected in the form of a printed survey covering a total of six questions. There were three multiple choice questions regarding patients' preference of the taste of the supplement, its

effect on their appetite, and if they would continue consumption of the product in the future. The other three questions in the survey were open-ended and addressed the following: ‘What do you like or dislike about the supplement?’, ‘What could be changed about the supplement that would make you more likely to take it?’, and ‘What do you feel about having to take it twice a day?’

These questions were discussed with experts in the field of respiratory medicine to establish if they would meet the aims of the research. The survey was initially given to ten volunteers in order to confirm the readability. Feedback was taken into account and the survey was modified accordingly. To clarify, these volunteers were not involved in the actual study (Appendix 9).

The surveys were collected and scanned for any questions left unanswered. Those patients who left any questions unanswered were interviewed in person. All data were manually transcribed on to an Excel spreadsheet. In the first question, patients were asked to state if their appetite was affected (increased, decreased, or stayed the same). Secondly, they needed to rate how satisfied they were with the supplement, using a 4-point scale: 1 = not satisfied at all, 2 = slightly satisfied, 3 = satisfied, 4 = very satisfied. The third multiple choice question required a ‘yes’ or ‘no’ answer in regard to whether patients would choose to continue taking the supplement in the future. For the three open-ended questions, responses were read several times to identify meaningful responses to the study. All responses were coded as phrases to produce meaningful data. Coded phrases were collected to identify any similarities in the answers given and to establish an overarching idea (theme). All themes were reviewed by an independent expert to ensure clarity and accuracy that each theme was fit and appropriate for the assigned coded phrases. The

evaluated answers were organised into categories. The categories used were, 'no answer', 'capability', 'compliance', 'health-related', 'product', and 'poor understanding of intervention' (Table 28). Answers were separated within each category into 'positive', 'negative' or 'mixed positive and negative' answers.

Table 28: Category descriptions for thematic analysis of the three open-ended questions.

Category	Description
No answer	No feedback given
Capability	How the product affects patients' capability to take the supplement (E.g. bottles are heavy)
Compliance	Anything that enables the patient to choose to consume or not consume the supplement (E.g. easy to take, too thick, etc.)
Health-related	Patients make comments related to how they feel about the product benefitting them or the general population
Product	Anything related to the product's taste
Poor understanding of intervention	When the purpose of consumption of supplement is not understood by the patients

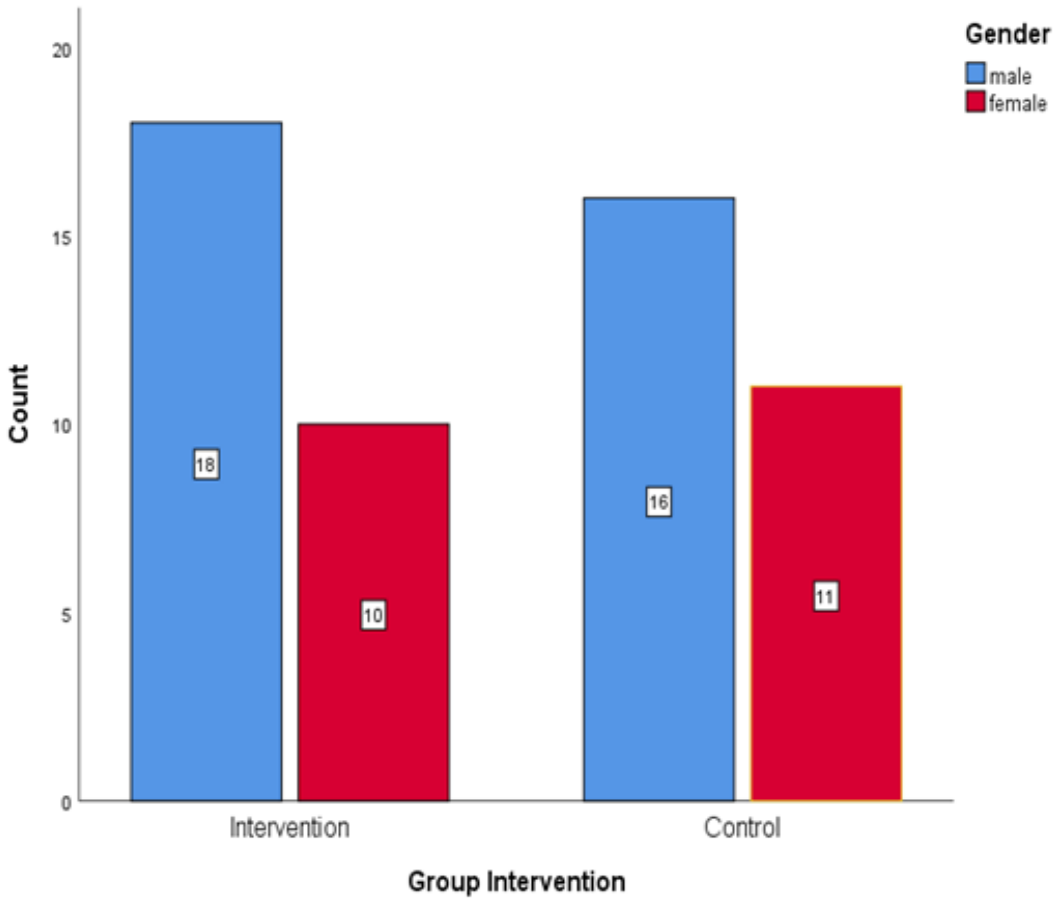
8.3.1 Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), Version 26 (IBM Corp, Armonk, USA) software was used to analyse the quantitative responses. Data were presented as mean (SD) for normally distributed data or median (IQR) for non-normally distributed data. A chi-square test was used to compare responses from two groups. Comparing two groups, logistic regression was applied to the question about patients' preference regarding the continuation of the product in the future. Participants were stratified to BMI < or ≥ 21 kg/m^2. Results were considered statistically significant when p-value < 0.05.

8.4 Results

Fifty-five responses were collected. Around 33% of the responses were only partly completed (18 out of 55 surveys). The mean (SD) age was 71.4 ±9 years old. Men accounted for 62% and females 38% of the respondents (FCP: 18 men, 10 females; preOp: 16 men, 11 females) (Figure 26). There was a balanced number of participants in both arms, FCP (intervention, n= 28) or preOp (control, n= 27) (Figure 26). Eighty percent of these patients had a BMI of ≥ 21kg/m^2 and 20% had a BMI of < 21kg/m^2.

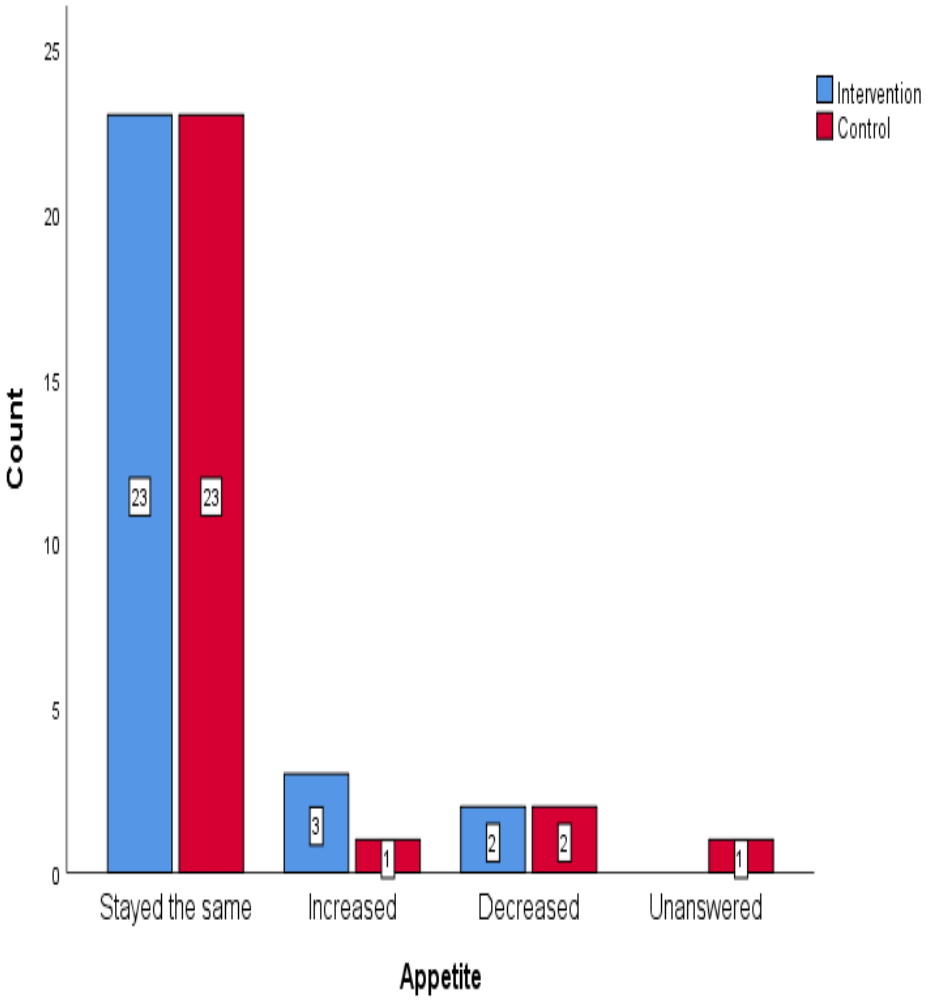
Figure 29: Bar chart indicating the number of males and females in each group.



8.4.1 Multiple-choice questions

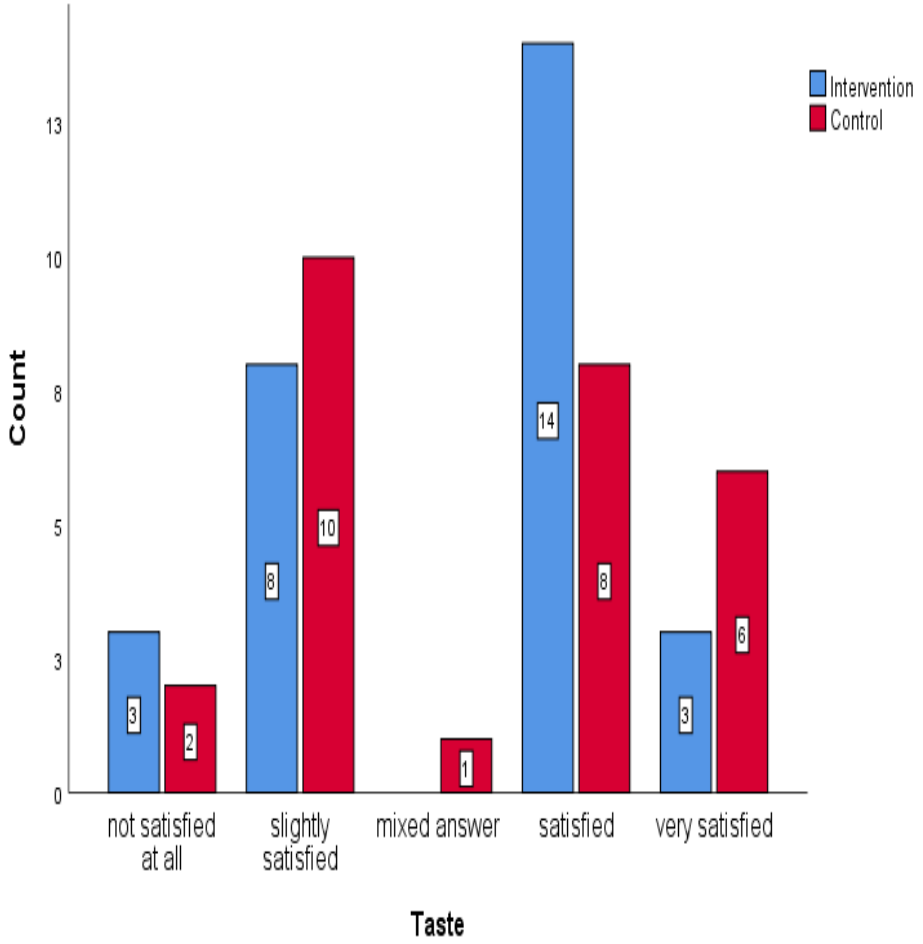
The first question regarding the effect of the supplements on appetite had 84% of the participants' responses stating no change to their appetite, of which FCP (intervention: 23) or preOp (control: 23) groups. There was no significant difference between the groups, $p > 0.05$ (Figure 27).

Figure 30: Bar chart showing that the majority of patients experience no effect on their appetite when they take nutritional supplements.



Question two investigated the taste satisfaction of the supplements and showed the majority of responses generally falling under the “slightly satisfied” and “satisfied” category (70-79%) of the patients within each group; p =0.4) (Figure 28). The ‘mixed answer’ category for this question was a response from a patient who circled both ‘slightly satisfied’ and ‘satisfied’ and could not decide which answer was more suitable.

Figure 31: Bar chart showing the different levels of satisfaction as regards the taste of the supplements.



In response to the third multiple-choice question about whether to continue taking the supplements if they were available, 17 out of 27 in the control group (63%) preferred to continue taking the preOp while 12 out of 28 (43%) in the intervention group preferred to continue taking the FCP product if it was made available in the future. When gender was compared in this section, males in the intervention group were more likely (n = 9) to continue taking the FCP, but not significantly. Overall, the results were not significant (intervention: $p = 0.39$; placebo: $p > 0.05$) (Table 29). Additionally, when responses were stratified based on BMI of < or ≥ 21 kg/m^2, it did not affect a person's response (responding 'yes' or 'no') in choosing to continue taking supplements ($p > 0.05$). However, only 49 patients were included as six patients did not provide an answer.

Table 29: Summary of responses from males and females in both intervention and control groups for continuation of product.

	Intervention (24)		**Control (25)**	
Gender	Male	Female	Male	Female
No answer (n)	3	1	2	0
Yes (n)	9	3	9	8
No (n)	6	6	5	3

8.4.2 Open-ended questions

This section of the survey allowed the patients to comment on any other aspect of the supplements they consumed over the course of PR. The results of the three open-ended questions were tabulated and compared between both groups.

For question number three (Table 30), addressing what patients liked or disliked about the nutritional supplements used between the intervention group (FCP) and the control (preOp) group, the results showed no significant statistical difference in any of the categorical descriptions. Ten out of 55 (18%) patients did not answer this question (intervention: 4; control: 6). In general, the majority of patients' answers fell under the 'compliance' (35%) or 'product' (34%) category. Within the compliance category, more than half of the comments were negative, ranging from the non-preferred yoghurt texture to finding it filling or taking appetite away. Some simply stated that they did not like the drink. Positive comments on compliance involved feeling refreshed and finding the supplements easy to consume. Product-related responses were mostly about how the patients liked the flavour. Eleven patients thought that the products were either too sweet, bland, artificial or had a boring flavour. Under the 'capability' category, there were only four responses, of which all four were negative. Those from the intervention group who consumed FCP complained that the 'bottles were heavy' and they were 'shocked by the size of the delivery box'. The patients in the control group who consumed preOp mentioned that the bottles were 'difficult to clean' and not 'reusable'. In terms of comments related to health, about half of the comments were positive and related to improved health. A patient who enjoyed taking the preOp supplement mentioned how her mouth ulcers healed and thought it might be due to the supplements' effect. Interestingly, three patients in the intervention group who consumed the FCP withdrew from the study reported mild diarrhoea. Other negative comments mentioned supplements affecting their consumption of their usual foods and drinks or feeling bloated after consumption of the product.

Table 30: Reported responses summarised for question three divided into (intervention: 24; control: 21).

Category		Intervention	Control	p-value
No answer		4	6	0.45
Capability	Negative	2	2	0.97
Compliance	Positive	3	6	0.39
	Negative	11	7	
	Mixed Answer	3	1	
Health Related	Positive	1	3	0.43
	Negative	4	1	
	Mixed Answer	1	1	
Product	Positive	10	9	0.82
	Negative	5	4	
	Mixed Answer	1	1	
Poor Understanding	Negative	0	2	0.14

Question four asked about how supplements could be altered so that participants were more likely to consume them. Around 44% of the responses fell under the 'no answer' category because the patients didn't fill in this section or had no changes to make (Table 31). The next largest category of responses was 23% from the 'product' category. Only three of the responses in this category mentioned the supplement having a good flavour (intervention:1; control: 2). All other responses on the product's flavour were negative and varied in opinions from 'lacking flavour', 'bitter', to being 'too sweet', while some contrasting comments suggested that the product needs more flavour or should 'taste like juice'. Under the 'capability' category, the comments were similar to question three, namely that there were too many bottles, they were

too big, or ‘not recyclable’. The texture of a product makes a patient feel more willing to take the supplement. Some patients in the intervention group who consumed FCP thought that the creamy, nutty flavour and aroma allowed them to enjoy the supplement more, while the rest in either groups felt that the texture was dry in the mouth or too milky. All health-related responses were negative, and some participants addressed how they could not see any effects of the supplement, regardless of which group some of these patients were in. Others were worried about calories they might gain or assumed the products might cause diabetes because they were too sweet. A participant from the intervention (FCP) group mentioned that after taking the supplements, his urine had a strong medicinal smell and he was unsure if it was due to the supplement or from other medications he took. Other participants felt that two bottles a day made them feel bloated. One participant had ‘poor understanding of the intervention’, did not understand what the supplementation could potentially do, and just took it as a matter of course.

Table 31: Reported responses summarised for question number four.

Category		**Intervention**	**Control**	**P-value**
No answer		16	12	0.19
Capability	Negative	2	3	0.61
Compliance	Positive	2	0	0.30
	Negative	2	1	
Health Related	Negative	5	5	0.95
Product	Positive	1	2	0.59
	Negative	5	7	
Poor Understanding	Negative	1	0	0.32

Thirty eight percent of the participants did not answer the last open-ended question, 'What do you think about having to take the supplements twice a day?' (Table 32). Almost 53% of the responses fell under the compliance category, mainly because this question had to do with how each participant was instructed to drink a fixed number of supplements per day. More than half of the participants favoured taking two bottles a day; the others thought that one bottle would be more convenient or a smaller bottle might be more suitable. One response fell under the 'capability' category, suggesting that the bottle size should be reduced, but with double the concentration of the nutrients in it. The other comments were not related to the question but were still written in this text box and stated the following: 'a nutritious intake' (health-related), 'cool, fruity drink' and 'don't want to take sweet drinks when returning home late' (product-related). In addition, one participant complained that the verbal and written instructions about the consumption of the supplement were contradictory (poor understanding related).

Table 32: Reported responses summarised for question number five.

Category		Intervention	Control	P-value
No answer		14	8	0.08
Capability	Negative	1	0	0.32
Compliance	Positive	8	10	0.51
	Negative	5	6	
	Mixed Answer	0	1	
Health Related	Positive	1	1	0.98
Product	Positive	0	1	0.37
	Negative	1	0	
Poor Understanding	Negative	1	0	0.32

8.5 Discussion

To the best of our knowledge, this is the first study that has investigated the experiences of a COPD population taking nutritional supplementation during PR. We found that appetite did not change in the majority of participants in both groups, and that the majority were satisfied with the taste of the products. The majority of participants in the preOp group preferred to continue taking the product, and almost half of the participants in the FCP group preferred to continue taking the product if it was made available to them in the future. Also, almost half of participants in both groups recommended no changes were needed for either product. Finally, more than half of the participants favoured taking two bottles a day in both groups.

Despite being in the FCP or preOp group, patients' opinions of the two supplements were similar and not affected by gender, BMI, or age. The absence of any differences in groups might be due to a small sample size. There was no pattern in the patients' comments in either group. Since there were no significant correlations that could be drawn from the results in the two groups, we took a different approach to this analysis.

Our study confirmed that most participants who took the available supplements did not experience any effect on their appetite which is a potential cause for concern, especially in older people, because it could lead to nutritional deficiencies (307). Al-Sharefi et al. conducted a survey and found that 36% of patients had to discontinue calcium supplements and calcium supplementation confirmed through patients' feedback (308).

However, taste is subjective and varies between individuals, which may explain why 70% of our participants fell under the 'slightly satisfied' or 'satisfied' category.

Since there were no significant differences between the two groups in the open-ended questions, the general comments were related to the number of supplements consumed, taste, and the sustainability of the product packaging used. Based on participants' feedback, consuming two bottles a day was the most preferred, which coincides with recommendations (188). Generally, participants preferred the products not to be in large bottles and not to be sweet, as the perception was that sweetness is unhealthy as it is associated with sugar and health conditions such as diabetes.

When research accounts for feedback from COPD patients there could be a potential improvement in patient adherence to taking nutritional supplements during their PR if their preferences were met.

8.5.1 Strengths and Limitations.

The key strength of our survey research is that there is currently no available evidence of how COPD patients feel about taking nutritional supplements during PR. Thus, if there are any notable observations made, it could help in improving the nutritional interventions we provide them. Potential disadvantages would be the sample size of this study. The opinions on the supplements were also limited to people of older ages and could be generally confined to older generation's perceptions of healthcare, which could be different to those from a younger generation with advanced technology and knowledge of innovations in healthcare. People are now more pro-active about improving their lifestyle and preventing diseases.

8.6 Conclusion

Pulmonary rehabilitation incorporating nutritional supplements could potentially have many benefits, such as reducing COPD symptoms, improving exercise performance, reducing future exacerbations, and enhancing quality of life. Receiving feedback from patients themselves covers aspects that clinical outcome results may not convey. The feedback we received gives an idea that nutritional supplements are acceptable to patients. The supplements can be easily consumed, as long as the amount prescribed is manageable and convenient to take, while also considering the flavour, sweetness, and texture of the supplement. The above-mentioned feedback could help to tailor future nutritional supplements for COPD patients based on their preferences, which may in turn lead to an improvement in patients' adherence. More research is needed to identify experiences of COPD patients consuming nutritional supplementation during PR programmes and should be a component of future studies.

9. Conclusion, discussion, and suggested future studies

This chapter summarises the main findings of this PhD thesis and includes suggestions for future work.

The main findings of this PhD are summarised as follows:

1- Systematic review.

- Nutritional supplementation may enhance the benefit of PR programmes with COPD, especially in weight-losing and/or malnourished patients, but some studies showed contradictory results.
- There remains insufficient evidence for nutritional supplementation improving outcomes during PR in COPD patient due to heterogeneity in supplements used, outcome measures, and PR programmes.

2- Prevalence and Association of Malnutrition in Patients referred to PR.

- The prevalence of malnutrition of COPD measured by the MUST screening tool in our single centre PR programme was 17%.
- Lower BMI was associated with lower lung function (FEV_1), as has been previously reported
- FEV_1 was higher in COPD patients at low risk of malnutrition, compared with other groups (medium and high).

3- A Double-Blind, Randomised, Placebo-Controlled Trial of Protein Supplementation to Enhance Exercise Capacity in Chronic Obstructive Pulmonary Disease: A pilot study.

- The study was stopped early, analyses demonstrated no statistically significant differences in exercise capacity in patients with COPD receiving

high-protein supplementation during PR, compared to those on control supplement. However, there was a clinically meaningful difference in improvement favouring the intervention group.

- Individuals who improved (defined as patients who reach or exceeded the MCID of ISWT, which is between 35.0 and 36.1 m) had larger mid-thigh circumference and higher baseline depression score.

4- Change in exercise capacity and other outcomes following completion of nutritional trial during PR in COPD.

- The study was stopped early, analyses demonstrated no statistically significant change in exercise capacity and other secondary outcomes in patients with COPD who received high-protein supplementation during PR, compared to those on control supplement at six weeks post PR.

5- Participants' Experience Using Nutritional Supplements during Pulmonary Rehabilitation: a survey.

- The majority were satisfied with the taste of the supplement, and appetite did not change with either of the products.
- Almost half of the participants in the FCP (protein) group wished to continue taking the product.
- Almost half of participants in both groups suggested no changes were needed for either product.
- More than half of the participants favoured taking two bottles a day in both groups.

Discussion:

I aimed to investigate relationships between malnutrition, nutritional supplementation, and PR in COPD. I proposed to address the prevalence of malnutrition among COPD patients referred to PR, the effect of nutritional supplementation on exercise capacity during PR and other PR outcomes, and the experience of utilising nutritional supplements in COPD patients. As the number of individuals diagnosed with COPD is rising globally, and with malnutrition significantly increasing the risk of mortality in COPD, finding better solutions to their health needs through integrating nutritional supplementation into exercise programmes is needed.

This work has confirmed that prevalence of malnutrition among COPD patients who are referred to PR is high, that lower BMI is significantly associated with lower spirometric values, and that FEV_1 was significantly lower in malnourished COPD patients. However, it is clear that the current approach used to identify the risk of malnutrition using the MUST screening tool is inadequate due to its limited ability in assessing FFM. We speculated that the relationship between BMI and lung function values may be due to higher resting energy requirement, skeletal muscle atrophy and disuse, insufficient oxygenation, and systemic inflammation. We did not find any relationships between BMI and smoking history, although smoking is considered the most common risk factor for COPD (and accelerated FEV_1 decline). Malnutrition doubles the number of hospital admissions, and increases the six- month mortality rate three fold (201).

PR is recognized as an effective non-pharmacological management approach for improving exercise capacity with COPD, and this improvement can be

sustained for one year (288). Maximising the value and response to PR is of great interest to clinicians and patients alike. The results of my RCT demonstrate that in individuals with COPD who were enrolled in six-week PR and received high protein nutritional supplementation, there was no significant difference between groups in exercise capacity measured by ISWT, however, there was a clinically meaningful difference improvement favouring the intervention group, and individuals who reached that improvement had larger mid-thigh circumference. Two studies have reported significant improvements in exercise capacity measured by ISWT favouring the intervention groups, however, these improvements in ISWT did not reached the MCID (250, 285). Previous RCTs using creatine, high carbohydrate and protein supplements found no significant difference in improvement in the exercise capacity between the intervention and control groups (250, 263, 267, 269, 273). We note that the intervention group in our RCT were older than the control group, which may have reduced the effect of the intervention on exercise capacity and other outcomes as ageing induces frailty. Leg circumference, such as mid-thigh circumference was positively associated with exercise capacity in a COPD population (293). Additionally, thigh muscles such as quadriceps have been positively associated with exercise capacity (294). As muscle mass increased, strength and endurance improved (294). This explains that those who responded to intervention might initially had higher muscle mass, especially in the lower limbs. FFM and FFMI improved in the depleted intervention group compared with the non-depleted intervention group, which means the high protein supplementation was beneficial for the depleted participants. The result of this thesis highlighted the importance of integrating

nutritional supplementation in PR programmes, especially for depleted patients.

The benefit of PR has been well-established, but gradually declines over a year following the programme. This thesis also confirmed that improvement in exercise capacity following PR was maintained for six weeks after the cessation of PR and nutritional supplementation, however, the sample size was too small to be conclusive, and this raises the question for how long the effect of nutritional supplementation could be maintained.

One way to improve nutritional adherence in patients who required nutritional supplementation is to provide patients with their preferences. Patient feedback is essential in achieving better quality of healthcare and facilitate reflective discussion to encourage the formulation of change (306) which has the potential to improve supplements used among COPD patients. This thesis also confirmed that the appetite of our participants did not change, the majority were satisfied with the taste of the products and preferred to continue taking the products in the future, and that the amount of supplements consumed was suitable.

Due to the COVID-19 pandemic, which put the U.K in a complete lockdown status on 23 March 2020, we were required to stop recruiting further patients. As a result of that, we failed to recruit the required sample size and 11 follow-up visits were cancelled.

Further advances in understanding malnutrition and its consequences could offer a solution to mitigate the burden on COPD patients. The existing literature did not show a solid evidence of efficacy due to variation among the current studies. Therefore, future studies must focus on conducting appropriately

powered double-blinded RCT studies with suitable sample size using high energy/high protein nutritional supplements to investigate the effect of nutritional support in enhancing PR outcomes, and longer-term clinical outcomes are still needed, especially undernourished and weight losing patients. Only by doing this we could better explain the additional benefit of nutritional supplementation during PR which may help to improve patients' quality of life and may lower the mortality and morbidity associated with COPD.

Future work suggestions

1- Definitively demonstrating the effect of high-protein supplementation on PR outcomes in COPD?

We have shown the potential effect of using FCP on exercise capacity and other PR outcomes; however, our study was under powered and the control product was not a true placebo. We have now completed a revised power calculation that can be used in a future definitive RCT. An appropriately powered, likely multicentre double-blind randomised controlled trial using FCP nutritional supplement as an intervention with an identical placebo in size and taste should be conducted to definitely demonstrate the effect of nutritional supplementation in enhancing exercise capacity, quadriceps muscle strength, rectus femoris muscle cross-sectional area (RF_{CSA}), anthropometrics measurements, health related quality of life, physical activity and longer-term effect, in stable and malnourished COPD patients who are referred to a PR programme. If positive, this would be practice-changing for nutritional assessment and supplementation for COPD during PR. Professor Hurst's team are in active discussion about such a study with *Nutricia*.

2- What is the benefit of Fortisip compact protein on hospitalised patients?

Acute exacerbations of COPD are accompanied by weight loss, reduction in muscle mass and strength, elevated energy requirements, and lower health-related quality of life. Hospitalised exacerbations have a profound effect on patients and health services. Reduction in muscle mass and strength may result in reduced exercise capacity and lower the amount of daily physical activity. Loss of appetite has been reported in COPD and might cause insufficient dietary intake. Thus, an appropriately powered double-blinded

randomised controlled trial using FCP nutritional supplement as an intervention with identical placebo in size and taste to investigate the effect of high protein supplementation on exercise capacity, physical activity, body composition, upper and quadriceps muscle strength and whether supplementation preserves body weight and muscle mass in malnourished COPD patients who are currently hospitalised due to COPD exacerbation would be an important further study.

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Appendices

List of Appendices

Publications

Appendix 19: Nutritional Supplementation during Pulmonary Rehabilitation in Stable Chronic Obstructive Pulmonary Disease: A Systematic Review (PAPER).

Appendix 20: Prevalence of Malnutrition in Patients Referred for Pulmonary Rehabilitation (ABSTRACT).

Appendix 21: The relationship between malnutrition and severity of airflow obstruction in COPD patients (ABSTRACT).

Appendix 22: Nutritional Supplementation during Pulmonary Rehabilitation in Stable Chronic Obstructive Pulmonary Disease: A Systematic Review (ABSTRACT).

Appendix 1: HRA approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

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19 November 2018

Dear Dr Mandal

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A Double-Blind, Randomised, Placebo-Controlled Trial of Protein Supplementation to enhance Exercise Capacity in Chronic Obstructive Pulmonary Disease.**
IRAS project ID:	**244023**
Protocol number:	**18/0329**
REC reference:	**18/LO/1842**
Sponsor	**University College London**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Abdulelah Aldhahir
Email: abdulelah.aldhahir.17@ucl.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **244023**. Please quote this on all correspondence.

Yours sincerely,

Natalie Wilson
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Suzanne Emerton, UCL/UCLH Joint Research Office, Sponsor contact*
Ms Mabel Saili, Camden and Islington NHS Foundation Trust, Lead NHS R&D contact

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [MODEL AGREEMENT FOR NON-COMMERCIAL RESEARCH]	2.1	01 August 2018
Covering letter on headed paper [Cover letter - reply to ethics review]		14 November 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Verification of Insurance]		25 July 2018
HRA Schedule of Events	1.0	19 November 2018
HRA Statement of Activities	1.0	19 November 2018
IRAS Application Form [IRAS_Form_28092018]		28 September 2018
IRAS Checklist XML [Checklist_14112018]		14 November 2018
IRAS Checklist XML [Checklist_28092018]		28 September 2018
Letter from funder [Financial letter from funder]	1.0	20 September 2018
Letter from sponsor [UCL Insurance Confirmation Letter]	13	21 September 2018
Letter from statistician [Trial statistician letter]	1.0	06 August 2018
Non-validated questionnaire [products compliance]	1.0	13 September 2018
Participant consent form	3.0	19 November 2018
Participant information sheet (PIS)	3.0	19 November 2018
Participant information sheet (PIS) [Patient information sheet]	1.0	13 September 2018
Referee's report or other scientific critique report [Peer review]	1.0	11 June 2018
Referee's report or other scientific critique report [Peer review]	1.0	16 July 2018
Research protocol or project proposal [Research protocol]	2.0	14 November 2018
Sample diary card/patient card [Food Diary]	2.0	14 November 2018
Summary CV for Chief Investigator (CI) [Chief Investigator CV]	1.0	16 July 2018
Summary CV for student [Student researcher CV]	1.0	16 July 2018
Summary CV for supervisor (student research) [Academic supervisor CV]	1.0	16 July 2018
Summary CV for supervisor (student research) [Chief Investigator CV]	1.0	16 July 2018
Validated questionnaire [Must screening tool]	1.0	13 September 2018
Validated questionnaire [COPD assessment questionnaire]	1.0	13 September 2018
Validated questionnaire [Medical Research Council dyspnoea scale]	1.0	13 September 2018
Validated questionnaire [Hospital Anxiety and Depression Scale]	1.0	13 September 2018
Validated questionnaire [Borg scale]	1.0	13 September 2018
Validated questionnaire [ST. GEORGE'S RESPIRATORY QUESTIONNAIRE]	1.0	13 September 2018

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	Minor amendments have been made to the PIS/ICF documentation post REC to ensure conformity to HRA-HCRW standards.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial, single site study taking place in the NHS. A statement of activities has been submitted and the sponsor is intending to use a separate site agreement. The agreement is unmodified.
4.2	Insurance/indemnity arrangements assessed	Yes	UCL will be liable for any damage caused to or by the device.
4.3	Financial arrangements assessed	Yes	Sponsor is not providing funding to participating NHS organisations.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	
5.3	Compliance with any applicable laws or regulations	Yes	No comments

Section	Assessment Criteria	Compliant with Standards	Comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	
6.3	Devices – MHRA notice of no objection received	Not Applicable	
6.4	Other regulatory approvals and authorisations received	Not Applicable	

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial, single site study. There is one site-type involved in the research. Activities and procedures as detailed in the protocol will take place at participating NHS organisations. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS or on the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net, or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator (PI) is expected at participating NHS organisations. Sponsor does not expect research staff to undertake any specific or additional training for the study. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Central and North West London NHS
NHS Foundation Trust

Recruitment Team
CNWL NHS Offices
Argo House
180 Kilburn Park Road
London
NW6 5FA

Thursday, 27th December 2018

Private and Confidential
Mr Abdulelah Mastour Aldhahir

United Kingdom

Your Ref: 333-JAMESON-AS

Dear Mr Abdulelah Aldhahir,

APPOINTMENT OF HONORARY STATUS

Dear Abdulelah Aldhahir,

I am pleased to inform you that you have successfully completed all your ID/Pre-Employment checks. I would like to offer you an honorary appointment with Central and North West London NHS Foundation Trust! We are looking forward to you starting with us.

Your role will be a Honorary Trainee based at St Pancras Hospital from 10-Dec-2018 until **December 2019**, with an option to renew the contract for a further period. You will normally be based at St Pancras Hospital but may be asked to visit/work at other sites within the Trust, which would be negotiated with you in advance.

The appointment and duties

This appointment is without remuneration and covers your duties as they affect patients and/or services and equipment on NHS premises. As you are employed in an honorary capacity no employment rights are conferred by this appointment.

You will be required to complete a medical questionnaire or to allow our Occupational Health Department access to your medical details via your own Occupational Health Department. For some staff a medical examination may be necessary on appointment.

The duties relating to the appointment are determined byHeidi Ridsdale to whom you are responsible.

Appendix 2: CNWL honorary contract

Central and North West London NHS
NHS Foundation Trust

Recruitment Team
CNWL NHS Offices
Argo House
180 Kilburn Park Road
London
NW6 5FA

Thursday, 27th December 2018

Private and Confidential
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The appointment and duties

This appointment is without remuneration and covers your duties as they affect patients and/or services and equipment on NHS premises. As you are employed in an honorary capacity no employment rights are conferred by this appointment.

You will be required to complete a medical questionnaire or to allow our Occupational Health Department access to your medical details via your own Occupational Health Department. For some staff a medical examination may be necessary on appointment.

The duties relating to the appointment are determined byHeidi Ridsdale to whom you are responsible.

Confidentiality

During the course of your employment you may have access to data and information (computerised, written or oral) of a confidential nature. You are expected to maintain confidentiality about information relating to all aspects of your employment both during and after your period of employment with the Trust.

Disclosures of information in whatever way it is held relating to patients e.g. diagnosis, treatment, personal data; staff e.g. personnel records; business sensitive or commercial information e.g. contractual and rental agreements, financial arrangements; or that which you acquire during the course of your employment e.g. computer software, research projects, inventions and designs; may only be disclosed with the agreement of your manager. All employees have a responsibility for ensuring security of information and to comply with the Data Protection Act, Access to Health Records Act and Computer Misuse Act. Disclosure of personal, medical, business sensitive or commercial information, systems passwords or other information of a confidential nature to any unauthorised person or persons will be considered as gross misconduct and will lead to disciplinary action which may include dismissal.

Moreover the Data Protection Act 1998 also renders an individual liable for prosecution in the event of unauthorised disclosure of information, or an action for civil damages under the same Act.

As an employee you have a responsibility to ensure you maintain a high quality of data and record management.

No unreasonable restriction is placed on staff in talking to the media on general matters relating to clinical or non-clinical issues except matters, which are confidential. Disclosures of confidential information to the media should only to taken following authorisation from the Chief Executive or their delegated representative.

Health and Safety

You are reminded that, under the Employment Rights Act 1996, you have a joint obligation with the Trust in ensuring good physical working conditions and that health and safety standards are maintained throughout the organisation. You must have regard at all time to your own health and safety and that of your colleagues and visitors to the Trust's premises. Any hazards or accidents must be reported immediately to your manager (or duty manager out of hours) and this should be documented on the appropriate form.

Personal Property

Central and North West London NHS Foundation Trust accepts no liability for loss by theft, fire or other means of personal property. It is therefore recommended that you take out an insurance policy to cover your personal property.

NHS Indemnity

You will be indemnified by the Trust for all NHS work undertaken as part of services provided to the Trust. You are advised to take out adequate defence cover for any work, which does not fall within scope of the indemnity scheme.

You should fully co-operate with the Trust and its legal advisors in the investigation of any patient complaint/incident including but not limited to any allegation of negligence or misconduct. You are required to provide the Trust on request a full written statement concerning any patient complaint/incident. This obligation will continue after this appointment has ceased.

Smoking and Alcohol Consumption

Smoking is not permitted on the premises. Consumption of alcohol is not permitted whilst on duty.

Notification of Actual or Intended Criminal Proceedings

You must immediately notify your Executive Director if you are charged with or convicted of a criminal offence. If in any doubt you must seek the advice of your manager.

Registration

It is a condition of the honorary appointment that you maintain registration with your recognised professional association/General Medical Council. You should present a copy of your certificate to the HR Directorate on an annual basis. Failure to maintain registration could lead to your honorary appointment being withdraw.

Equal Opportunities

You are expected to comply with the Trust's Equal Opportunities Policy and to ensure that no individual (patient, member of staff, visitors etc) receives less favourable treatment on the grounds of their gender, sexual orientation, marital status, disability, religion, creed, colour, race, ethnic, national origin, HIV status, age, social background, trade union membership or non-membership and is not placed at a disadvantage by requirements or conditions which cannot be shown to be justifiable.

You are expected to comply with Trust standards, in accordance with Trust Policies and Procedures

at all times. This includes notifying your manager should you be unable to carry out the duties of your appointment for any reason. Should any of the terms of this contract be breached your appointment with the Trust may be affected and your appointment may be terminated.

If you wish to accept this appointment on the foregoing terms, please sign the form of acceptance at the end of this letter and return it to me. Please sign and retain the copy letter for your records.

Yours sincerely,

Miss Alima Sultana
Recruitment Adminstrator
Tel: 442033173314

Signed on behalf of the Trust

I Abdulelah Aldhahir hereby accept the position of Honorary on the terms and conditions as set out herein.

Name:

Signed

Date

I Abdulelah Aldhahir hereby confirm I will return a signed copy of this honorary contract within 5 days of receipt via scan and email within the electronic recruitment system.

Appendix 3: Patient information sheet.

Central and North West London NHS
NHS Foundation Trust

Patient Information Sheet

Nutritional Supplementation to Enhance Exercise Capacity in COPD

You are being invited to take part in a research study. Please take the time to read the following information carefully and discuss it with others. Please ask us if there is anything that you do not understand or if you would like more information.

What is the study about? Why is it being done?

Chronic obstructive pulmonary disease (COPD) is a lung condition where patients go through difficulties in emptying air out of their lungs due to the narrowing of their airways. Therefore, finding it hard to breath with ease. COPD causes weakness and limits the ability to do daily tasks due to limited exercise capacity from breathlessness and weakness. Improving exercise performance is very important. Pulmonary Rehabilitation (PR) is– a specific exercise and education class for COPD that you have been enrolled on, it has been shown to reduces difficulty in breathing, also the risk of frequent chest infections, and had proven benefits for exercise performance and overall quality of life.

Other researches had shown that high protein supplements improve exercise endurance in athletic people; but, the effect of protein supplements in COPD have not been studied in enough detail. Our research project is designed to address this.

We will collect information about the effect of using a protein supplement before, during, and after the PR class.

What Happens in The Study?

At your first visit, your muscle strength and exercise performance are tested. You shall receive a diary card to record food intake and a special watch (that measures activity) to wear for 14 consecutive days. All volunteers will be assigned to one of two groups. Those in group 1 shall receive the protein supplementation drink while those in group 2 shall be issued the carbohydrate supplement. For the purpose of improving the research outcomes, both the volunteers and

researchers will be unaware of what supplementation they are assigned to. This is in order to investigate the true effects of supplement without bias. You will be assigned to one of our supplements by equal chance. This is so that, you have the chance of 50% to be in either group like almost like tossing a coin. Heads means you are given the protein supplementation and tail means you are given the carbohydrate supplement instead.
Volunteers are assessed at the beginning of the study, at the end of your PR program and six weeks after the PR program. This information is then used to determine the outcome of this study

How do I use my drink?

We will provide you with the drink during the study time only. You are required to drink the supplement twice a day between your meals, every day until the completion of your PR program. If you are unable to attend a class or miss a class you will still need to continue to drink your supplement.

Why Have I Been Invited?

You have been invited to join this study because you have COPD and you have been enrolled on the PR program.

Do I Have to Take Part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you decide to withdraw at any time, the data already collected with consent would be used in the study, unless you refused. No further data would be collected or any other research procedures will be carried out on or in relation to the participant who wishes to withdraw from the study.

What Does The Study Involve?

At the first visit before you start the PR program, the researcher will collect information including age and smoking history. Also you will receive a watch to wear which measures your activity levels for 14 consecutive days, and questionnaires to fill in. Additionally, the researcher will give you a diary card to record food and drink before, during, and after PR program for 3 consecutive days. We will take additional measurements including:

1- Exercise performance (by doing a walk test)
2- Height and weight.
3- Waist, hip, and mid-thigh perimeter with a tape.
4- Muscle and fat percentage.
5- Tests to measure your hand and thigh muscles.
6- Thigh muscle image will be taken using an ultrasounds machine.

One week after the first visit we will contact you to make sure that you are getting on okay with the watch. No extra visits are required for the main study. As you will be already enrolled in the PR program for six weeks. . You will not be required for longer than the duration of our study. When you have completed the PR program, all the measurements will be repeated and you will be given the watch again to wear it for 14 consecutive days. You will be asked to attend once more, six weeks after the PR program to repeat the tests. If you agree to take part, the total study time will be 12 weeks. The actual study will only involve one additional visit. Unfortunately, we are not able to pay you for travel costs to this visit.

What are the possible risks of taking part?

We are not changing any of your treatment; therefore we do not expect any significant harm or risk to come to you if you take part. We will exclude anyone who might have a side effect from drinking either of the supplements.

What are the potential for benefit to research participants?

We hope that being part of the research project will be a positive experience for you. You might not benefit directly from taking part in the study but it is hoped that findings from the study my benefit future patients.

Participation

It is your decision to be in this study. If you do not want to be in this study, your usual NHS care will continue as normal. You can also withdraw from the study at any time without giving a reason. Your doctor will still look after you as normal. We hope, though, that you will tell us why you wish to withdraw from the study. The data already collected with consent would be used in the study, unless you refused. No further data would be collected or any other research procedures will be carried out on or in relation to the participant who wishes to withdraw from the study.

Confidentiality

If you join the study, some parts of your medical records and data collected for the study will be looked at by researchers who are not part of your direct healthcare team. The sponsoring organization and the NHS Trust may also check these records to ensure that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant. The researchers will also need to keep a record of your telephone number and address to contact you. This information will be kept securely at protected UCL computers with password access and will not be disclosed to anyone outside of the research team. All data collected on the consent form and questionnaires will be confidential and will be coded with a study ID number. Participant's data that have been collected will be confidential. Study code and number will be set for storing all confidential information. In the study, original paper questionnaires ، assessment forms and participants' contacts will be collected from patients in accordance with the patient consent form and patient information sheet of this protocol. The participants' data (original paper questionnaires assessment forms and participants' contacts) will be appropriately kept within locked space at UCL Respiratory, Royal Free Campus, London, NW3 2QG. Dr.John Hurst will act as the data controller for the study. Only the investigators involved with this study will have the original code for patient identifiable data. However, the information collected about

you will be used to support other research in the future, and may be shared anonymously with other researchers.
Mr. Abdulelah Aldhahir (primary researcher), University College London will process, store and dispose of original paper questionnaires assessment forms and participants' contact details in accordance with all applicable legal and regulatory requirements under supervisor of the Chief Investigator/Academic Supervisor. This project is covered by the UCL Data Protection Registration, reference No Z6364106/2018/06/10 health research.

GDPR

[Central and North West London NHS Foundation Trust] will keep your name, [NHS number] and contact details confidential and will not pass this information to [University College London]. [Central and North West London NHS Foundation Trust] will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from [University College London] and regulatory organisations may look at your medical and research records to check the accuracy of the research study. [University College London] will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.
Central and North West London NHS Foundation Trust will keep identifiable information about you from this study 20 years after the study has finished.

UCL is the sponsor for this study based in [the United Kingdom/ country]. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will keep identifiable information about you for 20 years after the study has finished
Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information http://www.ucl.ac.uk/jro/who-are-we/data-protection data-protection@ucl.ac.uk

NHS will collect information from you and/or your medical records for this research study in accordance with our instructions.

What happens when the research study stops?

Written reports of the study findings will be available from the primary researcher and if you wish, a copy of the report can be requested from Mr. Abdulelah Aldahir at the address given at the end.

What will happen to the results of the research study?

The data will be analysed and will be available to a range of people, including the research team, health professionals and researchers through written reports, established website reports, presentations and journal publications. However, it will not be possible to identify any individual participant from these reports or publications.

This research is being funded by the Saudi Ministry of Higher Education as part of a PhD award to Mr. Aldhahir to study at UCL. The study has been academically peer-reviewed, and was given a favorable ethical opinion for conduct in the NHS by the xxxx REC. The study is sponsored by University College London (UCL)

What if there is a problem" or "What happens if something goes wrong?

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: 020 7794 0500 Extension 34301. If you remain unhappy, you can make a formal complaint through the National Health Service (NHS) complaints procedure. Details can be obtained through the University College London Hospitals (UCLH) Patient Advice and Liaison Service (PALS) on 0207 3447 3041, email: PALS@uclh.nhs.uk, address: PALS, Ground Floor Atrium, University College Hospital, 235 Euston Road, London, NW1 2BU. University College London (UCL) holds insurance against

claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Thank you for taking time to consider this study. Please ask any questions and let us know if there are things that you do not understand, or would like more information about.

Thank you for taking the time to read this information sheet

Appendix 4: consent form

Central and North West London NHS
NHS Foundation Trust

Study Number:
Participant Identification:
Researcher name: Abdulelah Aldhahir
IRAS Project ID: 244023

CONSENT FORM

Nutritional Supplementation to Enhance Exercise Capacity in COPD

Please initial box

1. I confirm that I have read the information sheet dated **19 November 2018 (version 3.0)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the academic respiratory research team from the University College London, and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. I understand that the study information held and maintained by the respiratory research team (chief investigator, researcher, and research assistants) from UCL and other central UK NHS bodies may be used to help contact me or provide information about my health status. ☐

6. We will need to keep a record of your contact information to enable contact. Source documentation will be on paper files stored in a locked office at UCL. Electronic files will be kept on password protected, UCL computers. ☐

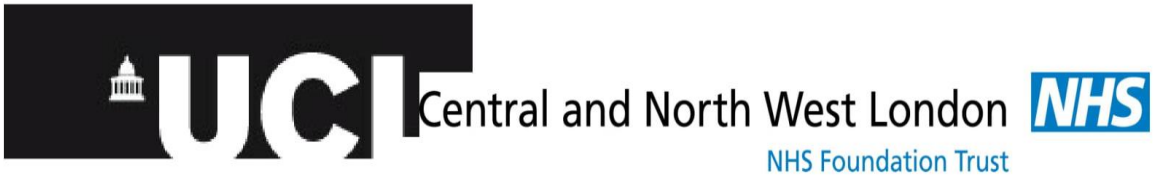
7. If I withdraw from the study, the collected data with consent would be retained and used in the study with no further data would be collected or any other research procedures. ☐

8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
_____	_____	_____

Name of Person Taking consent	Date	Signature

Appendix 5: Main project participant's assessment sheet.



Name: **Mobile:**

General information			
NHS number:	Study number:	Date:	
Address:			
Gender: □ Male □Female	Height (cm): Weight (Kg):	DOB:	BMI:
Date of the start PR:	Date of completion:	Session #:	
Clinical information			
Smoking Status:	□ current smoker □ Ex-smoker □ Never smoked □ Not recorded If current or ex-smoker: Age started: Age stopped: Maximum number/day: Smoke anything else other than cig: Yes/No if yes, please specify: (age started/ended, max/day)		
Do you have any other significant medical conditions other than COPD? ☐ No ☐ Yes	***Medical records if possible:*** ☐ Diabetes type1 ☐ diabetes type2 ☐ Bowel disease ☐ Other medical conditions: 1. 2. 3. 4.		
	Other personal records if any:		

Have you lost weight in the last 6 months?	☐ NO ☐ Yes ☐ Not Known How many Kg:
Do you take any respiratory or other medication?	□ Yes □ No □ Not known ***If yes***, please specify: Drug: …….. Dose: …… Frequency: …… Drug: ……..… Dose: ……..…… Frequency: ……..… Drug: ……..... Dose: ……..…… Frequency: …… Drug: ……..…… Dose: …… Frequency: …… Drug: ……..…… Dose: …… Frequency: ……
Are you allergic to cow's milk? □ **Yes** □ **No** □ **Not known**	
Step counter given Pre? □ Yes □ No Date given: Date of return: Step Counter given Post? □ Yes □ No Date given: Date of return:	

COPD Exacerbation (chest infection)

Waist circumference cm	First: Second: Mean:		First: Second: Mean:		First: Second: Mean:	
Hip circumference cm	First: Second: Mean:		First: Second: Mean:		First: Second: Mean:	
Mid-thigh circumference (cm)	R L		R L		R L	
Handgrip Kg	R	L	R	L	R	L
	1th: 2nd: 3rd:	1th: 2nd: 3rd:	1th: 2nd: 3rd:	1th: 2nd: 3rd:	1th: 2nd: 3rd:	1th: 2nd: 3rd:
Step Counter (mean/total days)	Pre PR days: Counts:		Post PR days: Counts:			

Pulmonary function	
Outcomes:	**Date:**
FEV1	
FEV1 %	
FVC	
FVC%	
FEV1/FVC	

Body composition			
Outcomes:	**PRE**	**POST**	**6 Weeks Post**
Fat %			
FM (kg)			
Lean %			
Lean (kg)			
Dry Lean (kg)			
TBW%			
Waist/ Hip			
Body weight			

Ultrasound			
Outcomes:	**PRE**	**POST**	**6 Weeks Post**
(RF_{CAS}) cm^2	First: Second: Third: Mean:	First: Second: Third: Mean:	First: Second: Third: Mean:

Appendix 6: before PR diary card

Daily Step-Count (before Pulmonary Rehab class)

First Week

Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:

Second Week

Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:

Appendix 7: Drink diary

Did you drink your shake?
Please tick the boxes as appropriate.

Week 1

Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐

Week 2

Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐
Date ……..…	Morning ☐	Afternoon ☐

Appendix 8: After PR diary card

Daily Step-Count (After PR class)

First Week

Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:

Second Week

Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:
Date:	Steps:

Thanks for completing this booklet

Please address any questions to:

Appendix 9: Bespoke survey of patient experience

Nutritional Supplementation to Enhance Exercise Capacity in COPD Patients

Thank you for taking part in this survey.

1. Since starting the supplement, which of the following applies to your appetite? Please circle below.

1. Increased 2. Decreased 3. Stayed the same.

2. How satisfied are you with the taste of your supplement? Please Circle below.

1 = Not satisfied at all 2 = slightly satisfied 3 = satisfied 4 = very satisfied

3. What did you like or dislike about the supplement?

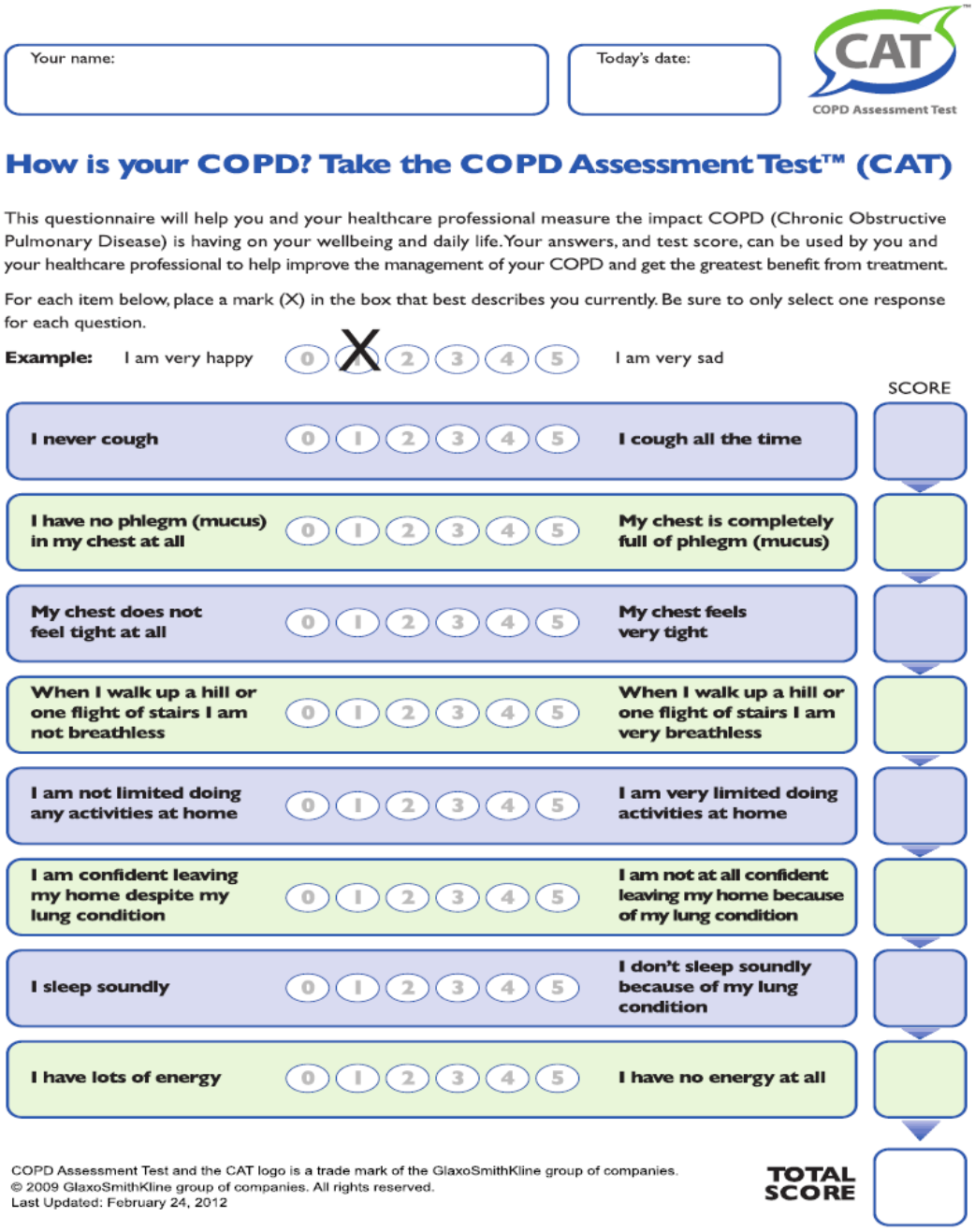
4. If it was available, would you continue to take your supplement? Please circle below.

   1. Yes 2. No

5. What can be changed about the supplement to make you more likely to take it?

6. What do you think about having to take it twice a day?

Appendix 10: COPD assessment (CAT)



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

Last Updated: February 24, 2012

Appendix 11: H.A.D.S questionnaire.

Hospital Anxiety and Depression Score (HADS)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time (occ.)	1
	Not at all	0
D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	**I can enjoy a good book or radio/TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Appendix 12: MRC dyspnoea scale

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Appendix 13: St George's Respiratory Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

Appendix 14: Malnutrition Universal Screening Tool (MUST)

BAPEN
www.bapen.org.uk

'Malnutrition Universal Screening Tool'

MAG
Malnutrition Advisory Group
A Standing Committee of BAPEN

BAPEN is registered charity number 1023927 www.bapen.org.uk

'MUST'

'MUST' is a five-step screening tool to identify **adults,** who are malnourished, at risk of malnutrition (undernutrition), or obese. It also includes management guidelines which can be used to develop a care plan.

It is for use in hospitals, community and other care settings and can be used by all care workers.

This guide contains:

- A flow chart showing the 5 steps to use for screening and management
- BMI chart
- Weight loss tables
- Alternative measurements when BMI cannot be obtained by measuring weight and height.

The 5 'MUST' Steps

Step 1

Measure height and weight to get a BMI score using chart provided. *If unable to obtain height and weight, use the alternative procedures shown in this guide.*

Step 2

Note percentage unplanned weight loss and score using tables provided.

Step 3

Establish acute disease effect and score.

Step 4

Add scores from steps 1, 2 and 3 together to obtain overall risk of malnutrition.

Step 5

Use management guidelines and/or local policy to develop care plan.

Please refer to *The 'MUST' Explanatory Booklet* for more information when weight and height cannot be measured, and when screening patient groups in which extra care in interpretation is needed (e.g. those with fluid disturbances, plaster casts, amputations, critical illness and pregnant or lactating women). The booklet can also be used for training. See *The 'MUST' Report* for supporting evidence. Please note that 'MUST' has not been designed to detect deficiencies or excessive intakes of vitamins and minerals and is of **use only in adults.**

Appendix 15: Record Keeping, archiving, finance, risk assessment and insurance

Record Keeping and archiving

At the end if the trial, essential documents and data will be securely archived by the researcher for twenty years. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

Finance

This PhD research study was funded by the student's sponsor, Jazan University through the Saudi Arabia Cultural Bureau (SACB) in London.

Risk assessment

This is an interventional study where the patient takes the nutritional supplement. We do not anticipate any harm from that product. This product is not suitable for galactosaemia, infants, and patients with delayed gastric emptying, so they were excluded. There might be slight discomfort or participants may become tired when taking measurements, therefore, the research team ensured that there were an adequate rest gap between measurements as needed.

Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this trial shall provide negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request. (Appendix 16)

Appendix 16: University College London Insurance

University College London Hospitals NHS
NHS Foundation Trust

UCL

UCL/UCLH Joint Research Office

Office Location:
1st Floor Maple House
149 Tottenham Court Road
London W1T 7DN

Postal Address:
UCL,
Gower Street
London WC1E 6BT

Email uclh.randd@nhs.net Tel No. 020 3447 5199
Web-sites: www.uclh.nhs.uk; www.ucl.ac.uk/iro

21/09/18

Dr Swapna Mandal
UCL Division of Medicine
London
SE1 7EH

Dear Swapna

Chief Investigator: Dr Swapna Mandal

Study/Trial Title: Nutritional supplementation during Pulmonary Rehabilitation in COPD

Funder: Royal Embassy of Saudi Arabia Cultural Bureau

UCL Project ID No. **18/0329**

Re: Insurance for studies not involving a Clinical Trial of an Investigational Medicinal Product (non-CTIMP) sponsored by UCL

Thank you for completing the UCL Insurance Registration Form dated **03/07/2017** I am pleased to inform you that the above study, as described in the registration form, is now insured under UCL's policy. A copy of the current insurance summary (Verification of Insurance) is attached to this letter.

The policy provides for the legal liabilities (negligence) of UCL and its' employees or agents.

This confirmation letter, together with the attached summary, needs to be submitted to the Research Ethics Committee in support of question A76 for both your NHS REC and, where applicable, NHS R&D applications submitted via the Integrated Research Application System (IRAS).

.../Continued

Appendix 17: Borg scale.

0	No breathlessness* at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximal)
10	Maximal

Appendix 18. Data bases search strategies, excluded studies, risk of bias of the included cohort and RCT studies.

Table A1. Medline Search Strategy.

1 exp Pulmonary Disease, Chronic Obstructive/	(51369)
2 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(110202)
3 emphysema.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(33167)
4 (copd or coad or cobd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(42175)
5 (chronic adj3 bronchitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(11093)
6 1 or 2 or 3 or 4 or 5	(147446)
7 exp Dietary Supplements/	(68218)
8 exp Nutritional Support/	(43349)
9 ((diet$ or food or nutrition$ or herbal) adj3 (supplement$ or support$ or enhance$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(110391)
10 7 or 8 or 9	(158546)
11 exp Rehabilitation/	(285709)
12 rehab$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(304313)
13 11 or 12	(497231)
14 6 and 10 and 13	(140)

Table A2. Embase Search Strategy.

1 exp chronic obstructive lung disease/ (51369)
2 exp emphysema/ (14325)
3 exp chronic bronchitis/ (1712)
4 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, (110202) keyword, floating subheading word, candidate term word]
5 emphysema.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (33167)
6 (copd or coad or cobd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (42175)
7 (chronic adj3 bronchitis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (11093)
8- 1 or 2 or 3 or 4 or 5 or 6 or 7 (149229)
9 exp diet supplementation/ (0)
10 exp nutritional support/ (43349)
11 ((diet$ or food or nutrition$ or herbal) adj3 (supplement$ or support$ or enhance$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword,

(110391) floating subheading word, candidate term word]

---

12 9 or 10 or 11 (142817)

---

13 exp rehabilitation/ (285709)

---

14 rehab$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

(304313)

15- 13 or 14 (497231)

16- 8 and 12 and 15 (140)

Table A3. Allied and Complementary Medicine Database Search Strategy.

1	exp Pulmonary Disease, Chronic Obstructive/ (48121)
2	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (104520)
3	emphysema.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (32308)
4	(copd or coad or cobd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (38816)
5	(chronic adj3 bronchitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10902)
6	1 or 2 or 3 or 4 or 5 (141003)
7	exp Dietary Supplements/ (61794)
8	exp Nutritional Support/ (42221)
9	((diet$ or food or nutrition$ or herbal) adj3 (supplement$ or support$ or enhance$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (102371)
10	7 or 8 or 9 (148194)
11	exp Rehabilitation/ (272399)
12	rehab$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (170043)
13	11 or 12 (380519)
14	6 and 10 and 13 (125)
15	pulmonary disease chronic obstructive/ or bronchitis/ or pulmonary emphysema/ or lung diseases obstructive/ (80818)
16	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (104520)
17	emphysema.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (32308)
18	(copd or coad or cobd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

(38816)

19 (chronic adj3 bronchitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10902)

20 15 or 16 or 17 or 18 or 19 (151650)

21 dietary supplements/ (46793)

22 ((diet$ or food or nutrition$ or herbal) adj3 (supplement$ or support$ or enhance$)).mp. mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (102371)

23 21 or 22 (102371)

24 exp rehabilitation/
(272399)

25 rehab$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
(170043)

26 24 or 25
(380519)

27 20 and 23 and 26 (120)

Table A4. CINHAL

S1	(MH "Pulmonary Disease, Chronic Obstructive+")
S2	(MH "Emphysema+")
S3	obstruc* N3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)
S4	emphysema
S5	COPD OR COAD OR COBD
S6	chronic N3 bronchitis
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	(MH "Nutritional Support+")
S9	(diet* OR food OR nutrition* OR herbal) N3 (supplement* OR support* OR enhance*)
S10	S8 OR S9
S11	(MH "Rehabilitation+")
S12	rehab*
S13	S11 OR S12
S14	S7 AND S10 AND S13 (52)

Table A5. Web of Science

# 1	TOPIC: (obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) (93750)
# 2	TOPIC: (obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR TOPIC: (emphysema) OR TOPIC: (chronic NEAR/3 bronchitis) OR TOPIC: (COPD OR COAD OR COBD) (135223)
# 3	TOPIC: (obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR TOPIC: (emphysema) OR TOPIC: (chronic NEAR/3 bronchitis) OR TOPIC: (COPD OR COAD OR COBD) AND TOPIC: ((diet* or food or nutrition* or herbal) NEAR/3 (supplement* or support* or enhance*) (114803)
# 4	TOPIC: (obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR TOPIC: (emphysema OR (chronic NEAR/3 bronchitis) OR (COPD OR COAD OR COBD)) (135223)
# 5	TOPIC: ((obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR emphysema OR (chronic NEAR/3 bronchitis) OR (COPD OR COAD OR COBD)) (135223)
# 6	TOPIC: ((obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR emphysema OR (chronic NEAR/3 bronchitis) OR (COPD OR COAD OR COBD)) AND TOPIC: ((diet* or food or nutrition* or herbal) NEAR/3 (supplement* or support* or enhance*)) (491)
# 7	TOPIC: ((obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR emphysema OR (chronic NEAR/3 bronchitis) OR (COPD OR COAD OR COBD)) AND TOPIC: ((diet* or food or nutrition* or herbal) NEAR/3 (supplement* or support* or enhance*)) AND TOPIC:(rehab*) (102)
# 8	TOPIC: ((obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR emphysema OR (chronic NEAR/3 bronchitis) OR (COPD OR COAD OR COBD)) AND TOPIC: ((diet* or food or nutrition* or herbal) NEAR/3 (supplement* or support* or enhance*)) AND TOPIC:(rehab*) (102)
# 9	TS=(obstruct* NEAR/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) (93750)
# 10	TS=(emphysema) (22729)
# 11	TS=(COPD OR COAD OR COBD) (57609)
# 12	TS=(chronic NEAR/3 bronchitis) (9926)
# 13	#12 OR #11 OR #10 OR #9 (135223)
# 14	TS=((diet* or food or nutrition* or herbal) NEAR/3 (103028)
# 15	TS=(rehab*) (205904)
# 16	#15 AND #14 AND #13 (102)

Table A6. Excluded Studies

First Author	Study Title	Reason
Schols, 1998	*Weight Loss is a Reversible Factor in the Prognosis of COPD*	The study was designed to answer different research questions
Curtis, K, 2015	Acute Dietary Nitrate Supplementation and Exercise Performance in COPD: A Double-Blind, Placebo-Controlled, Randomised Controlled Pilot Study.	Participants were not in Pulmonary rehabilitation
Pison, C, 2011	Multimodal Nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomized controlled trial.	Population were not only COPD
Slinde, F, 2001	Individual dietary Intervention in patients With COPD during Multidisciplinary rehabilitation.	No nutritional supplement
Marinari, S, 2013	Effects of nutraceutical diet integration, with coenzyme Q10 (Q-Ter multicomposite) and creatine, on dyspnea, exercise tolerance, and quality of life in COPD patients with chronic respiratory failure.	Participants were not in Pulmonary rehabilitation
Candemir, I, 2017	Oral nutritional support in patients with COPD who completed the pulmonary rehabilitation program; Six months and one-year follow-ups	Table are not in English
Olveira, G, 2015	Oral supplement enriched in HMB combined with pulmonary rehabilitation improves body composition and health related quality of life in patients with bronchiectasis (Prospective, Randomised Study)	Participants were not COPD
Beer M, 2019	Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial	Duplicated to an original study included already.
Constantin D, 2013	Skeletal muscle molecular responses to resistance training and dietary supplementation in COPD	Participants were not in Pulmonary rehabilitation.
Ogasawara T, 2018	Effect of eicosapentaenoic acid on prevention of lean body mass depletion in patients with exacerbation of chronic obstructive pulmonary disease: A prospective randomized controlled trial	Participants were at hospital.

Table A7. Risk of bias of the included RCT studies.

First Author	Random Sequence generation	Allocation concealment	Selective reporting	Blinding subject+ personnel	Blinding outcome assessment	incomplete outcome data)	Other source of bias	OVERALL (0-7, higher score = higher risk of bias)
Bool, 2017	Low	Low	Low	Low	Low	Low	Unclear	1
Sugawara, 2012	Low	Low	Low	Low	Low	Low	Unclear	1
Paulin, 2016	Low	Unclear	Low	Low	Low	Low	Low	1
Faager, 2006	Low	Unclear	Low	Low	Low	Low	Low	1
Laviolette, 2010	Low	Unclear	Low	Low	Low	Low	Unclear	2
Borghi-Silva, 2006	Low	Low	Low	Low	High	Low	Low	1
Gurgun, 2013	Low	Low	Low	High	Unclear	Low	Low	2
Beers, 2019	Low	Unclear	Low	Low	Low	Low	Unclear	2
Deacon, 2008	Low	High	Low	Low	Low	Low	Unclear	2
Vermeeren, 2000	High	Unclear	Low	Low	Low	Low	Unclear	3
Baldi, 2010.	Low	Unclear	Low	High	High	Low	Low	3
Fuld, 2005	Low	Unclear	Low	Low	Low	High	High(design)	3
Wetering, 2009	Low	Low	Low	High	Low	High	Unclear	3
Broekhuizen, 2005	Low	High	High	Low	Low	Low	Unclear	3
Steiner, 2003	Low	High	Low	Low	Low	High(drop rate)	Unclear	3
Schols, 1995	Low	Unclear	Low	High	High	Low	unclear	4
Hornikx, 2012	High	High	Low	Low	Low	Low	High	3
Ogasawara, 2018	Low	Low	High	High	High	Low	Unclear	4
Ahnfeldt, 2015	Low	Low	Low	High	High	High	Unclear	4

Table A8. Risk of bias of the included cohort studies.

First author	Population representative	Sample size adequate	Confounders	Statistical analysis	Missing data	Methodology of the outcome	Objective assessment	OVERALL (0-3, higher score = lower risk of bias)
Creutzberg, 2000	3	0	2	3	3	3	3	2.4
Broekhuizen, 2005	3	2	0	3	3	3	2	2.3
Creutzberg, 2003	3	2	0	3	3	3	3	2.4
Menier, 2001	3	2	0	0	3	1	3	1.7
Kubo, 2006	3	0	0	0	3	0	2	1.1

0 = definitely no (high risk of bias); 1 = mostly no; 2 = Mostly yes; 3 = definitely yes (low risk of bias)

Publications

Appendix 19: Systematic review

Review

Chronic Respiratory Disease

Chronic Respiratory Disease
Volume 17: 1–21

DOI: 10.1177/1479973120904953
journals.sagepub.com/home/crd
SAGE

Nutritional supplementation during pulmonary rehabilitation in COPD: A systematic review

Abdulelah M Aldhahir[1,2], Ahmed M Al Rajeh[3], Yousef S Aldabayan[3], Salifu Drammeh[1], Vanitha Subbu[4], Jaber S Alqahtani[1,5], John R Hurst[1] and Swapna Mandal[4]

Abstract

Uptake of nutritional supplementation during pulmonary rehabilitation (PR) for people with chronic obstructive pulmonary disease (COPD) has been limited by an absence of rigorous evidence-based studies supporting use. The objective was to report and summarise the current evidence supporting the use of nutritional supplementation to improve outcomes during PR in stable COPD patients. A systematic search was conducted up to 7 August 2019 (registration number CRD42018089142). The preferred reporting items for systematic reviews and meta-analyses guidelines were used. Six databases were included: Medical Literature Analysis and Retrieval System Online or MEDLARS Online, Allied and Complementary Medicine Database, the Cochrane Database of Systematic Reviews, Excerpta Medica dataBASE, Cumulative Index of Nursing and Allied Health Literature and Web of Science. This systematic search generated 580 initial matches, of which 22 studies (917 COPD participants) met the pre-specified criteria and were included. Sixteen of 19 studies that used nutritional supplements in addition to PR did not show additional benefit compared to PR alone when measuring exercise capacity. Nutritional supplements significantly increased body weight in 7 of 11 studies. Body mass index increased significantly in two of six studies. Handgrip strength did not improve, while quadriceps muscle strength significantly improved in 3 of 11 studies. Four of eight studies showed a significant improvement in inspiratory muscle function. Only 2 of 14 studies demonstrated a significant improvement in quality of life with supplementation in addition to PR. There remains insufficient evidence on the effect of nutritional supplementation on improving outcomes during PR in patients with COPD due to heterogeneity in supplements, outcome measures and PR programmes. Therefore, controversy remains and further research is needed.

Keywords

Chronic obstructive pulmonary disease, pulmonary rehabilitation, nutrition, nutritional supplementation

Date received: 23 August 2019; accepted: 10 December 2019

Introduction

Patients with chronic obstructive pulmonary disease (COPD) experience daily symptoms, reduced exercise capacity and susceptibility to exacerbations, resulting in reduced health-related quality of life.[1–3] The international Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document summarises current approaches to COPD management.[1] Cost-effective treatment approaches for

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COPD, described in the 'value pyramid'[4] include smoking cessation, influenza vaccination and pulmonary rehabilitation (PR). Multiple high-quality randomised controlled trials (RCTs) and meta-analyses have demonstrated that PR is an effective management strategy in COPD, since it improves exercise performance, reduces dyspnoea, reduces the risk of exacerbation and improves health-related quality of life.[5–10]

Exercise limitation is one of the most common problems for COPD patients and this may be compounded by reduced muscle mass and malnutrition. Some COPD patients may lose body weight and skeletal muscle mass, which leads to muscle weakness and dysfunction, impacting functional ability and quality of life.[11] Muscle disuse, caused by a prolonged sedentary lifestyle and voluntary immobilisation, leads to further muscle deconditioning and thus reduced muscle strength and endurance.[12] It has also been postulated that COPD is associated with a myopathy, which may be driven by systemic inflammation.[12] Being underweight is associated with an increased risk of mortality in COPD and weight loss predicts mortality and morbidity in chronic lung disease patients.[8,13] Therefore, patients with COPD are at risk of significant morbidity and mortality as a result of changes in body composition and nutritional and metabolic status.

It has been suggested that healthy older adults require additional nutrients compared with younger adults to preserve bone and lean mass. For instance, it is recommended that young adults require 0.7 g of protein/kg body weight per day while the recommendation for older adults is 1.2–1.5 g protein/kg body weight/day, especially for people with conditions that require higher levels of protein, such as COPD.[14] Nutritional supplements have been used to overcome malnutrition in patients with COPD. It has been suggested that nutritional support integrated with exercise training may improve exercise activity, decrease mortality and improve muscle strength in undernourished COPD patients.[15,16] A meta-analysis of nutritional supplementation for stable COPD by Ferreira et al. included 17 randomised clinical trials and concluded that nutritional supplements increased muscle mass and body weight and improved respiratory function and exercise tolerance in COPD patients who were poorly nourished.[17,18] Additionally, Collins et al. demonstrated in a meta-analysis of nutritional support and functional capacity in COPD that nutritional supplements improved weight and handgrip strength in COPD patients.[19] Both reviews only included randomised clinical trials and it was not necessary for participants to be engaged in PR. We hypothesised that an integrated approach of exercise training and nutritional support might be the best way to seek functional improvements. However, the uptake of nutritional supplementation during PR, where the potential benefit may be greatest, has been limited by the absence of rigorous evidence-based studies supporting use. The objective of this systematic review was to report and summarise the current evidence for using nutritional supplementation during PR in stable COPD patients to enhance PR outcomes.

Methods

Search strategy

The preferred reporting items for systematic reviews and meta-analyses guidelines were used for this systematic review, with Prospero registration number CRD42018089142.[20] The search was conducted up to 7 August 2019 using Medical Literature Analysis and Retrieval System Online or MEDLARS Online, Excerpta Medica dataBASE, Allied and Complementary Medicine Database, the Cochrane Database of Systematic Reviews, Cumulative Index of Nursing and Allied Health Literature and Web of Science database (Supplemental Material Tables A1 to A5). The search strategy and terms used in this systematic review are described in Supplemental Material. The bibliography of eligible articles and existing systematic reviews in the field were also screened.

Inclusion criteria

The PICO (P: population, patient, problem; I: intervention; C: control, comparison or comparator; O: outcome) criteria for included studies appear in Table 1. Studies were included in the systematic review if they met all of the following criteria: studies of patients with a confirmed diagnosis of COPD; no evidence of recent exacerbation, as described in the individual studies; patients enrolled on a PR or other exercise training programme and patients receiving nutritional supplementation (caloric, non-caloric, powder, liquid, capsule or tablets) during PR.

Exclusion criteria

We excluded book chapters, systematic reviews (but screened the reference lists), non-English

Table 1. PICO criteria used for the inclusion of studies.

Criteria	Definition
Participants	Patients with a confirmed diagnosis of COPD, no evidence of recent exacerbation, enrolled on a pulmonary rehabilitation or other exercise training program
Intervention	Any nutritional supplement given during pulmonary rehabilitation
Comparator	Placebo, other nutritional supplement regime, no nutritional supplements
Outcome	Exercise function, body composition, peripheral muscle strength, respiratory muscle function and quality of life.
Study design	No restrictions

COPD: chronic obstructive pulmonary disease; PICO: P—population, patient, problem; I—intervention; C—control, comparison or comparator; O—outcome.

manuscripts, conference abstracts with no full-text and non-full text articles.

The main outcomes of interest were to investigate the impact of nutritional supplementation during PR programmes on exercise function, body composition, peripheral muscle strength, respiratory muscle function and quality of life.

Data collection

Three authors (AMA, JRH, and SM) screened the titles and abstracts to exclude irrelevant studies. Full texts of the relevant studies were read by the first author (AMA) to evaluate if they fulfilled the inclusion criteria. The reference lists of included studies and excluded systematic reviews were also screened; two additional studies were found, and the senior authors (JRH and SM) discussed eligibility. Disagreements between authors were resolved by discussion.

Quality assessment

The first and seventh authors (AMA and JRH) performed risk of bias assessment using the Cochrane risk of bias tool to assess randomised studies, which comprises seven questions, and the modified Newcastle–Ottawa scale to assess cohort studies, which is also made up of seven questions.[21,22] For the randomised trials, we scored each of the seven domains as 0 (*low risk of bias*) or 1 (*high risk of bias* or *bias unclear*). There was, therefore, a total score between 0 and 7 in which a higher score equates to a higher risk of bias. For cohort studies, each of the seven domains was scored from 0 (*high risk of bias*) to 3 (*low risk of bias*) and we took a mean of the domains to result in a score between 0 and 3, where a higher score represents a lower risk of bias.

Synthesis of results

The main purpose of this systematic review was to report and summarise the current evidence of using nutritional supplementation during PR in stable COPD. A meta-analysis was not attempted due to methodological heterogeneity between studies. Our discussion focuses on the studies at lower risk of bias.

Results

Initially, 580 studies were considered potentially eligible. However, after removing duplicates, 449 titles and abstracts were included. Screening the titles and abstracts resulted in 30 of 449 studies being considered for full-text reading. After reading the full text of 30 studies, 10 further studies were excluded (Supplemental Material Table A6). Screening the reference list of eligible studies revealed two further relevant studies. Thus, 22 studies in total met the inclusion criteria for the systematic review (see Figure 1).

The 22 studies comprised 5 cohort studies and 17 RCTs. The sample size and study duration varied between 8 and 80 participants and 6 weeks to 4 months, respectively. A full description of the included RCTs and cohort studies appears in Tables 2 and 3, respectively. The risk of bias assessment for RCT and cohort studies appears in Tables A7 and A8 in Supplemental Material, respectively.

Exercise capacity

Data on exercise function, performance, capacity or endurance were reported in 19 studies using the endurance shuttle walking test (ESWT), incremental shuttle walking test, 6-minute walk test (6MWT), 12-minute walk test, treadmill and incremental or constant work-load cycle ergometry. Seventeen studies found that using nutritional supplements such as high carbohydrates, vitamin D, creatine, or L-carnitine in addition to PR programs had no statistical benefit compared to PR alone.[23–27,30,32–34,36–41,43] Three studies found that using nutritional supplements, such as, polyunsaturated fatty acids (PUFAs) and respifor, which are high in carbohydrates, had a statistically significant benefit on top of PR.[28,31,35]

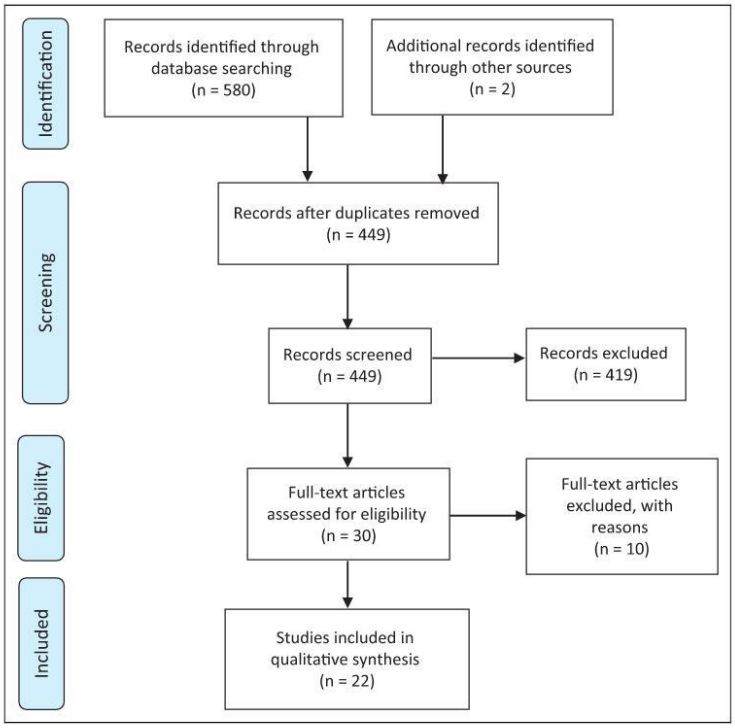

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram.

There was only one study with positive findings at the lowest risk of bias (1/7), in which Sugawara et al. reported increases in 6-minute walk distance by 19.7 $\pm$ 24.7 m with this addition of supplement (less than the minimum clinically important difference). In this RCT, the intervention group received ready-to-drink oral nutritional supplement (ONS) twice a day composed of 200 kilocalories, 60% carbohydrates, 15% protein, 25% fat, 248 µg of omega-3 PUFAs 0.6 with vitamins A, C and E and a 12-week exercise programme while the control group underwent a 12-week exercise programme only.[28] There were four RCTs with a similar low risk of bias, which demonstrated no benefit of supplementation. van de Bool et al.[23] reported that using a high carbohydrate supplementation once a day (125 mL of 9.4 g protein, 28.1 g carbohydrate and 4.1 g fat, leucine, n-3 PUFA and vitamin D) over a period of 4 months within an outpatient PR did not show any significant improvement in exercise performance measured by cycle endurance time or 6MWT compared to the control PR group, who received flavoured non-caloric aqueous solution as a placebo. Similarly, the study by Paulin et al. found that using vitamin B12 for 8 weeks during outpatient, PR did not show any significant improvement in exercise performance or endurance compared to PR alone.[24] Borghi-Silva et al. reported that using L-carnitine twice a day for 6 weeks did not demonstrate a significant improvement in exercise performance measured by treadmill performance and 6MWT when compared to the placebo group, who received saline solution for the same duration.[33] Finally, Faager et al. concluded that using creatine for 8 weeks during PR did not improve exercise performance when measured by ESWT compared to the placebo (glucose) group who underwent the same PR.[34]

Body composition

Seventeen trials measured body composition including body weight, fat-free mass (FFM), fat-free mass index (FFMI) and body mass index (BMI).

Table 2. Detailed description of the included RCT studies.

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
van de Bool et al.[23] Bias: 1/7	Age: 62 years old. GOLD: 2. BMI: 22.7 kg/m^2.	$N = 73$ ('low muscle mass').	Intervention: 125 mL of 9.4 g protein, 28.1 g carbohydrate and 4.1 g fat, leucine, n-3 PUFA and vitamin D once per day. Placebo: Flavoured non-caloric aqueous solution.	Duration: 4 months Location: outpatient. Session detail: 40 sessions, two to three times per week. 1. High intensity endurance exercise by cycle ergometry. 2. Treadmill walking. 3. Progressive resistance exercise of upper and lower body. 4. Education session.	1. Body composition: Body mass, BMC, SMM and FM. 2. Muscle function: Quadriceps muscle strength, MIP. 3. Exercise performance: cycle endurance time (CET) and 6MWT. 4. Anxiety/depression: HADS. 5. Physical activity: 7 days.	1. Body composition: Significant improvement in body mass (1.5 $\pm$ 0.6 kg, $p < 0.05$) and FM (1.6 $\pm$ 0.5 kg, $p < 0.01$) in the intervention group. 2. Muscle function: No significant differences between the groups. 3. Exercise performance: No significant differences between the groups. 4. Anxiety/depression: No significant differences between the groups. 5. Physical activity: significant benefit in physical activity (929.5 $\pm$ 459.2 steps/day, $p < 0.05$).
Paulin et al.[24] Bias: 1/7	Age: I versus P (56.5 vs. 65.2 years old). GOLD: 3 and 4. BMI: I versus P (24.5 vs. 25.1 kg/m^2).	$N = 16$	Intervention (I): B_{12} 500 mg/day for 8 weeks. Placebo (P): Maltodextrin.	Duration: 8 weeks. Location: outpatient. Session detail: 3 days/week, 40 minutes of aerobic and resistance exercise.	1. Cardiopulmonary exercise testing: Incremental or constant-load protocols.	1. Exercise performance: No significant differences between the groups.
Ahnfeldt et al.[25] Bias: 4/7	Age: I versus P (67 vs. 70 years old). GOLD: 2 and 3. BMI: I versus P (24.3 vs. 23.4 kg/m^2).	$N = 35$	Intervention (I): Protein bar (each 134.8 kcal of energy, 9.3 g protein, 14.6 carbohydrate, 4.2 fat) two times per day for 9 weeks. Placebo (P): No.	Duration: 9 weeks. Location: outpatient Session detail: A—1 hour 2 times per week and home-based one time per week of: 1. Endurance. 2. Resistance. 3. Interval training.	1. Muscle function: lower muscle strength. 2. Exercise performance: SWT. 3. Quality of life: SGRQ.	1. Muscle function: No significant differences between the groups. 2. Exercise performance: No significant differences between the groups. 3. Quality of life: No significant differences between the groups.

(continued)

Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
Gurgun et al.[26] Bias: 2/7	Age: I versus P (64 vs. 66 years old). GOLD: 3 and 4. BMI: I versus P (17.8 vs. 20 kg/m^2).	$N = 30$ ("wasted")	Intervention (I): 250 mL 83.3% carbohydrate, 30% fat, 16.7% proteins, three times per day. Placebo (P): No.	4. Educational class. Duration: 8 weeks. Location: outpatient. Session detail: Two times per week 60–80 minutes/day: A—Education. B—Exercise training include: 1. Warm-up and bicycle ergometer for 15 minutes. 2. Treadmill (15 minutes). 3. Upper and lower extremity strength (5–10 minutes). 4. Breathing and relaxation therapies (15–20 minutes each).	1. Body composition: Body weight, BMI, FFMI. 2. Exercise performance: 6MWT, ISWT, and ESWT. 3. Quality of life: SGRQ. 4. Anxiety/depression: HADS. 5. Breathlessness scale: MRC and Borg. 6. Muscle size: $Quad_{CSA}$.	1. Body composition: Significant improvement in weight (1.1 $\pm$ 0.9 kg, $p < 0.05$), BMI (0.2 $\pm$ 1.4 kg/m^2, $p < 0.05$) and FFMI (0.6 $\pm$ 0.5 kg/m^2, $p < 0.05$) in the intervention group. 2. Exercise performance: No significant differences between the groups. 3. Quality of life: No significant differences between the groups. 4. Anxiety/depression: No significant differences between the groups. 5. Breathlessness scale: No significant differences between the groups. 6. Muscle size: Significant increase in $Quad_{CSA}$ (2.5 $\pm$ 4.1 cm^2, $p < 0.05$) in the intervention group.
Hornikx et al.[27] Bias: 3/7	Age: I versus P (67 vs. 69 years old). GOLD: 2, 3 and 4. BMI: I versus P (25 vs. 24 kg/m^2).	$N = 49$	Intervention (I): vitamin D monthly dosage (100.000 UI cholecalciferol). Placebo (P): Arachidis oleum: 4 mL.	Duration: 3 months. Location: outpatient. Session detail: Three times per week 90 minutes training of: 1. Cycling. 2. Walking on treadmill. 3. Stair climbing and arm cranking. 4. Strength exercises for extremities.	1. Muscle function: quadriceps strength, MIP and MEP. 2. Exercise performance: incremental cycle ergometer and 6MWD. 3. Quality of life: CRDQ.	1. Muscle function: Significant increase in MIP (11 $\pm$ 12 cmH_2O, $p = 0.004$) but no differences between groups in quadriceps strength and MEP. 2. Exercise performance: No significant differences between the groups. 3. Quality of life: No significant differences between the groups.

(continued)

Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
Sugawara et al.[28] Bias: 1/7	Age: 77 years old. GOLD: 3. BMI: not recorded.	$N = 31$	Intervention: Mein (contains 200 kcal 20% protein, 25% lipid, 53.2% sugar, 1.8 fibre, Fisher is 3.7, antioxidant vitamins A, C and E) (two times per day 200 mL) for 12 weeks + provided meal with dietary instruction. Placebo: No.	Duration: 12 weeks. Location: Home-based. Session detail: A—Breathing retraining: 1. Pursed-lip breathing. 2. Diaphragmatic breathing. 3. Slow deep breathing. B—Exercise training: 1. Upper and lower limb exercises. 2. Respiratory muscle stretching calisthenics. 3. Level walking for least 15 minutes. 4. Inspiratory and expiratory muscle exercises. C—Education program. D—Physiotherapist supervision every 2 weeks in hospital. E—Periodic visits at home.	1. Body composition: Body weight, FFM, FMI, (AC), (AMC), %IBW. 2. Muscle function: MIP and MEP, quadriceps strength. 3. Exercise performance: 6MWD. 4. Quality of life: CRQ. 5. Breathlessness scale: MRC.	Data reported as change in ratio in interventional group versus placebo group, not as absolute values. 1. Body composition: Significant improvement in body weight (2.6 $\pm$ 3 kg vs -0.2 $\pm$1.4 kg, $p = 0.0010$), FMI (8.6 $\pm$ 10.7 kg/m^2 versus 0.6 $\pm$ 10.6 kg/m^2, $p = 0.048$), %AC (2.4 $\pm$ 3.7% vs -0.7 $\pm$ 2.4%, $p = 0.0134$), and %IBW (2.7 $\pm$ 3% vs. $-0.2 \pm$ 1.3%, $p = 0.0017$) in the intervention group. 2. Muscle function: MIP (39.2 $\pm$ 38.9 cmH_2O vs. 0.1 $\pm$ 24.1 cmH_2O, $p = 0.0030$) and quadriceps strength (10.0 $\pm$ 13.3 kg/kg vs. $-1.6 \pm$ 9.5 kg/kg, $p = 0.0079$) increased significantly in the intervention group. 3. Exercise performance: 6MWD (19.7 $\pm$ 24.7 m vs. $-7.1 \pm$ 50.8 m, $p = 0.0137$) improved significantly in the intervention group. 4. Quality of life: total score (6.2 $\pm$ 7.5 vs. $-2.7 \pm$ 13.1, $p = 0.0374$) and emotional domain (8.9 $\pm$ 14.4 vs. $-3.9 \pm$ 12.2, P = 0.0097) increased significantly in the intervention group. 5. Breathlessness scale: MRC 22.6 $\pm$ 40.6 vs. $-4.4 \pm$ 17.2 ($p = 0.0339$) improved significantly in the intervention group.

(continued)

Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
Baldi et al.[29] Bias: 3/7	Age: I versus P (73 vs. 70 years old). GOLD: 3. BMI: I versus P (19.9 vs. 21 kg/m^2).	$N = 28$ depleted	Intervention (I): Amino acids 4 g two times per day for 12 weeks. Placebo (P): No.	Duration: 4 weeks. Location: inpatient Session detail: five days per week. 30 minutes submaximal cycle ergometry. 30 minutes walking and 1 arm exercise session. Then: Duration: 8 weeks Location: Home Session detail: Twice per day 30 minutes unloaded bicycle training.	1. Body composition: weight and FFM.	Data reported as change in the interventional group versus change in the placebo group. 1. Body composition: Significant increase in weight (3.8 $\pm$ 2.6 kg, p versus = 0.0002). ($-$0.1 $\pm$ 1.1 kg, $p = 0.81$) and FFM (1.5 $\pm$ 2.6 kg, p versus = 0.05). ($-$0.1 $\pm$ 2.3 kg, $p = 0.94$).
Laviolette et al.[30] Bias: 2/7	Age: I versus P (63 vs. 68 years old). GOLD: 2 and 3. BMI: I versus P (29.7 vs. 26.7 kg/m^2).	$N = 22$	Intervention (I): Whey protein 20 g in 120 mL/day for 16 weeks (8 without PR and 8 with PR). Placebo (P): casein 20 g in 120 mL/day for 16 weeks (8 without PR and 8 with PR).	Duration: 8 weeks Location: not specified Session detail: Three times per week. 90 minutes of: 1. Endurance. 2. Resistance exercise. 3. Education and self-management strategies.	Baseline, 8th, and 16th week: 1. Body composition: weight. 2. Muscle function: quadriceps muscle strength and fatigue. 3. Exercise performance: constant work rate cycle endurance. 4. Quality of life: CRQ. 5. Lung function: spirometry and lung volumes.	1. Body composition: No significant differences between the groups. 2. Muscle function: No significant differences between the groups. Exercise performance: No significant differences between the groups. 4. Quality of life: No significant differences between the groups. 5. Lung function: No significant difference between groups.
Wetering et al.[31] Bias: 3/7	Age: 64 years old. GOLD: 2. BMI: 21.7 kg/m^2.	$N = 30$ ("wasted")	Intervention: respifor (high-carbohydrate supplement; 125 mL, 188 kcal) three times per day for 4 months. Placebo: No.	Duration: 4 months. Location: outpatient. Session detail: 1. Two times per week for 30 minutes of intensive exercise.	1. Body composition: FFMI and BMI. 2. Muscle function: MIP and quadriceps average power. 3. Exercise performance: Peak exercise capacity	1. Body composition: Significant increase in BMI (mean difference 1 kg/m^2, $p < 0.05$), and FFMI (mean difference 0.9kg/m^2, $p < 0.05$). 2. Muscle function: Significant increase in MIP (mean

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Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
				2. 1, 2 and 3 months dietician counselling for weight losing and muscle-wasted patients. 3. Education program. 4. Smoking cessation.	(W_{max}), cycle endurance test (CET) and 6MWD. 4. Quality of life: SGRQ.	difference 1.4 kPa, $p < 0.05$) and QAP (mean difference 13.1 W, $p < 0.05$). 3. Exercise performance: Significant increase in W_{max} (mean difference 11.7 W, $p < 0.05$), CET (mean difference 525 second, $p < 0.05$), and 6MWD (mean difference 27.2 m, $p < 0.05$). 4. Quality of life: No statistically significant difference although absolute difference between groups at 6.1 units is greater than the MCID.
Deacon et al.[32] Bias: 2/7	Age: I versus P (68 vs. 68 years old). GOLD: 3. BMI: I versus P (28.1 vs. 25.7 kg/m^2).	$N = 80$	Intervention (I): Creatine Loading phase: 22 g daily, 4 divided doses for 5 days. Maintenance phase: (PR) 3.76 g daily. Placebo (P): lactose.	Duration: 7 weeks. Location: outpatient Session detail: three times per week of: 1. Endurance training. 2. Individually prescribed resistance training using gym equipment and free weights.	1. Body composition: weight, FFM and FM. 2. Muscle function: quadriceps, triceps and biceps. 3. Exercise performance: ISWT and ESWT. 4. Quality of life: CRQ-SR.	1. Body composition: No significant differences between the groups. 2. Muscle function: No significant differences between the groups. 3. Exercise performance: No significant differences between the groups. 4. Quality of life: No significant differences between the groups.
Borghi-Silva et al.[33] Bias: 1/7	Age: I versus P (69 vs. 65 years old). GOLD: 3. BMI: I versus P (22 vs. 23 kg/m^2).	$N = 16$	Intervention (I): Oral L-carnitine 2 g, twice per day in 10 mL bottle for 6 weeks. Placebo (P): Saline solution.	Duration: 6 weeks. Location: outpatient. Session detail: 1 hour three times per week: 30 minutes treadmill, inspiratory muscle training.	1. Body composition: Triceps skinfold, mid-arm circumference and BMI. 2. Muscle function: MIP and MEP. 3. Exercise performance: incremental exercise test (treadmill) and 6MWT. 4. Breathlessness scale: Borg.	Data reported as change in interventional group vs change in the placebo group. 1. Body composition: No significant differences between the groups. 2. Muscle function: MIP (40 $\pm$ 14 cmH_2O vs. 14 $\pm$ 5 cmH_2O, $p < 0.05$) but not MEP, increased significantly in the intervention group.

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Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
						3. Exercise performance: No significant differences between the groups. 4. Breathlessness: No significant differences between the groups.
Faager et al.[34] Bias: 1/7	Age: I versus P (67 vs. 64 years old). GOLD: 3. BMI: I versus P (25 vs. 22 kg/m^2).	$N = 23$	Intervention (I): creatine 0.3 g/kg body weight/day, divided in four doses/day for 7 days. Creatine 0.07 g/kg body weight/day one dose/day for remaining 7 weeks. Placebo (P): Glucose.	Duration: 8 weeks. Location: outpatient. Session detail: Two times per week for 60–75 minutes of exercise training and education consisting of: 1. Ergometer cycling. 2. Arm muscle training with dumbbells. 3. Rising and getting up from a stool and getting up onto a low stool. 4. Thera band exercises for shoulder girdle. 5. Thigh muscle training with weight cuffs. 6. Abdominal muscle training. 7. Flexibility exercises for thorax and adjacent joints.	1. Body composition: weight. 2. Muscle function: Grip strength, maximal right knee strength and fatigue. 3. Exercise performance: ESWT. 4. Quality of life: SGRQ. 5. Lung function: spirometry.	1. Body composition: No significant differences between the groups. 2. Muscle function: No significant differences between the groups. 3. Exercise performance: No significant differences between the groups. 4. Quality of life: No significant differences between the groups. 5. Lung function: No significant differences in FEV_1 between the groups.
Broekhuizen et al.[35] Bias: 3/7	Age: I versus P (62 vs. 64 years old. GOLD: 3. BMI: I versus P (22.5 vs. 22.1 kg/m^2).	$N = 80$	Intervention (I): PUFA 1 g 9 capsules/day. Placebo (P): 9 capsules/day of palm and sunflower oil, vitamin E. Depleted patients $n = 48$ respifor (see above) 3times per day.	Duration: 8 weeks. Location: inpatient. Session detail: A—General physical training of: 1. Exercise in relation to daily activities. 2. Cycle ergometry. 3. Treadmill walking.	1. Body composition: BMI, weight, FFM, FM and FFMI. 2. Muscle function: quadriceps strength, handgrip and MIP. 3. Exercise performance: endurance time incremental bicycle	1. Body composition: No significant differences between the groups. 2. Muscle function: No significant differences between the groups. 3. Exercise performance: Maximal exercise capacity (peak workload (9.7 W difference, *P*

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Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
				4. Swimming. B—Sports and games. C—Educational program. D—Regular meals.	ergometry and submaximal bicycle ergometry. 4. Lung function: spirometry.	= 0.009) and bicycle ergometry duration (4.3 minutes difference, $p = 0.023$) improved significantly in the intervention group. 4. Lung function: No significant differences between the groups.
Fuld et al.[36] Bias: 3/7	Age: I versus P (64 vs. 62 years old). GOLD: 3. BMI: I versus P (23.2 vs. 24.3 kg/m^2).	$N = 25$	Intervention (I): Creatine + glucose polymer (5 g creatine and 35 g glucose/dose). A—Loading phase: three times daily for 14 days. B—Maintenance phase: one time daily for 10 weeks (PR). Placebo (P): Glucose polymer (40.7 g/dose).	Duration: 8 weeks Location: outpatient Session detail: Two times per week each 1 hour consisting of: 1. A warm-up. 2. Mobility training. 3. Dynamic strength training of all extremities. 4. Whole body endurance training. 5. Education and behavioural interventions.	1. Body composition: Body mass, FFM and FM. 2. Muscle function: MIP, lower limb muscle performance, handgrip. 3. Exercise performance: ISWT, ESWT, cycle ergometry. 4. Quality of life: SGRQ. 5. Lung function: Spirometry.	Data reported as change in interventional group versus change in the placebo group. 1. Body composition: FFM increased significantly by (2 kg vs. 0.4 kg, $p < 0.05$) in the creatine group. FM and BM: No significant differences between the groups. 2. Muscle function: Significant increase in lower limb strength (19.5 N.m vs. 12.2 N.m, $p < 0.05$), endurance (1216 J vs. 362 J, $p < 0.05$), handgrip strength (2.9 N vs. 0.6 N, $p < 0.05$) and endurance (15.6 repetitions vs. 8.4 repetitions, $p < 0.05$) in the creatine group. No significant change in MIP. 3. Exercise performance: No significant differences between the groups. 4. Quality of life: Total score decreased (5.9, $p < 0.05$) and activity domain deceased (5.3, $p < 0.01$) in the creatine group. 5. Lung function: No significant improvement in FEV_1.

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Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
Steiner et al.[37] Bias: 3/7	Age: I versus P (66 vs. 68 years old). GOLD: 3. BMI: I vs. P (23.9 vs. 23.5 kg/m^2).	$N = 60$.	Intervention (I): respifor (high-carbohydrate supplement; 125 mL, 188 kcal) three times per day for 7 weeks Placebo (P): non-nutritive.	Duration: 7 weeks. Location: outpatient. Session detail: two times per week of: 1. Endurance training (walking exercise + home walking program). 2. Circuit of low impact conditioning exercise. 3. Educational sessions.	1. Body composition: weight, BMI, BM, lean mass, fat mass. 2. Muscle function: quadriceps and handgrip strength. 3. Exercise performance: ISWT and ESWT. 4. Quality of life: CRQ-SR.	1. Body composition: Significant improvement in weight (0.63 kg, $p = 0.004$), BMI (0.24 kg/m^2, $p = 0.002$), and fat mass (0.67 kg, $p = 0.001$) in the intervention group. 2. Muscle intervention: No significant differences between the groups. 3. Exercise performance: No significant differences between the groups. 4. Quality of life: No significant differences between the groups.
Vermeeren et al.[38] Bias: 3/7	Age: part I 65 versus part II 62 years old. GOLD: 3. BMI: part I 20.6 versus part II 22.6 kg/m^2.	Part I: $N = 14$ Part II: $N = 11$	Part I: Intervention 1: 1046 kJ, 21% protein, 34% fat, 45% carbohydrate. Intervention 2: 2092 kJ, 21% protein, 36% fat, 43% carbohydrate. Placebo: 209 kJ coffee creamer and lemon syrup. Part II: respifor (see above) versus pulmocare (high fat supplement) 200 mL.	Duration: not specified. Location: inpatient. Session detail: Not specified.	1. Exercise performance: cycle ergometer. 2. Lung function: spirometry. 3. Self-reported: A—Change in breathlessness during meals. B—Leg pain.	1. Exercise performance: Part I: No significant differences between the groups. 2. Lung function: Part I: No significant differences between the groups. Part II: PEF (pre 3.1 L/second ± 1.0, post 3.3 L/second ± 1.2) increased significantly after the respifor supplement versus pulmocare (pre 3.1 L/second ± 0.9, post 3.1 L/second ± 0.9) ($p < 0.05$). 3. Self-reported symptoms: Part I: Satiety changed significantly after the supplements for the 2092-kJ supplement ($p < 0.05$). Part II: Significant increase in breathlessness at 30 and 60 minutes following a meal with pulmocare versus respifor (raw data not provided, $p < 0.05$).

(continued)

Table 2. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
Schols et al.[39] Bias: 4/7	Age: not recorded. GOLD: 3. BMI: not recorded.	$N = 71$ per protocol group.	Complex, three group study: *p* group: placebo steroid. *N* group: placebo steroid + nutritional supplement. N + A: 4 IM injections of nandrolone + nutritional supplement (not considered further). Nutrition: one time per day 200 mL for 57 days mixture of nutridrink (high energy), protifar (high protein) and fantomalt (high energy carbohydrate and oil).	Duration: 57 days. Location: inpatient. Session detail: 1. General physical training related to daily activates. 2. Cycle ergometry. 3. Treadmill walking. 4. Walking circuits. 5. Swimming.	Measurements were made at entry, 29 and 57 days: 1. Body composition: weight, arm circumference, skinfolds, FFM. 2. Muscle function: MIP. 3. Exercise performance: 12MWT.	Comparing group *p* with group *N*. Patients were stratified to depleted group versus non-depleted group: Depleted group: 1. Body composition: No significant difference in FFM or arm circumference between N and P but significant increase in skinfold and weight in the *N* groups (raw data not provided, $p < 0.03$). Non-depleted group: Only reported in per protocol analysis 2. Muscle function: No significant differences between the groups. 3. Exercise performance: No significant differences between the groups.

I: intervention group; P: placebo or control group; 12MWT: 12-minute walk Test; 6MWD: 6-minute walk distance; BM: body mass; BMC: bone mineral content; BMI: body mass index; CRQ, Chronic Respiratory Disease Questionnaire; CWT: constant work rate test; ESWT: endurance shuttle walk test; FEV_1: forced expiratory volume in 1 second; FFM: fat-free mass; FM: fat mass; FMI: fat mass index; IBW: ideal body weight; ISWT: incremental shuttle walking test; MEP: maximum expiratory pressure; FFMI: fat-free mass index; MIP: maximum inspiratory pressure; MMC: mid-arm muscle circumference; PEF: peak expiratory flow; QAP: quadriceps average power; $Quad_{CSA}$: quadriceps cross-sectional area; SGRQ: St. George's Respiratory Questionnaire; SMM: skeletal muscle mass; UI: International unit; LBM: lean body mass; LBMI: lean body mass index; SMI: skeletal muscle mass index; BCM: body cell mass; BMC: bone mineral content; ASM: appendicular skeletal muscle mass; EQ-5D-3 L: EuroQoL five-dimensions Questionnaire; W, Watt.

Table 3. Detailed description of the included cohort studies.

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
Kubo et al.[40] Bias: 2.4	Age: I vs. P (70 vs. 71 years old). GOLD: 3. BMI: I vs. P (18.8 vs. 18.3 kg/m^2).	$N = 8$	Intervention (I): 400 kcal and 8 g protein and abundance of branched chain amino acids in 200 mL. Placebo (P): No.	Duration: 8 weeks. Location: outpatient. Session detail: one time per week for 8 weeks: 1–90 minutes lecture and physical therapy: A: Breathing instruction B: Muscle strengthening exercise for lower limb.	1. Exercise performance: 6MWD. 2. Quality of life: CRQ.	1. Exercise performance: No significant differences between the groups. 2. Quality of life: No significant differences between the groups.
Broekhuizen et al.[41] Bias: 1.1	Age: A vs. B (62 vs. 63 years old). GOLD: 3. BMI A vs. B (20 vs. 19.7 kg/m^2).	$N = 19$ Historical controls: = 20	Group A: respifor (as above) 125 mL three times per day. Group B: historical One ensini (high carbohydrate supplement), one fortimel (high carbohydrate supplement), one nutridrink (high carbohydrate supplement), 200 mL three times per day for 8 weeks.	Duration: 8 weeks. Location: inpatient. Session detail: Daily: 1. 2 times 20 minutes submaximal cycle ergometry. 2. 1 time 20 minutes treadmill exercise. 3. 1 time 30 minutes gymnastics. 4. One session of unsupported arm endurance and strength exercise training. 5. Educational programme.	1. Body Composition: weight, FFM, FFMI and FM. 2. Exercise performance: incremental bicycle ergometry. 3. Quality of life: SGRQ. 4. Lung function: FEV_1.	1. Body composition: Group A: 1. Significant weight gain (1.9 kg, $p = 0.019$) vs. group B (1.2 kg). Both groups: Post-PR, significant gain in weight (A: 1.9 kg, $p < 0.001$; B: 1.2 kg, $p < 0.001$), FM (only group A 1.3 kg, $p < 0.05$), and FFM (A: 2 kg, $p < 0.001$; B: 1.9 kg, $p < 0.05$). 2. Exercise performance: Both groups: Peak workload increased significantly during the incremental bicycle ergometry test (group A: 8.3 $\pm$ 17.1 W, $p = 0.062$; group B: 9 $\pm$ 9.4 W, $p = 0.002$). 3. Quality of life: SGRQ Group A: A: No significant differences (although numerical change in SGRQ was greater than the MCID). Group B: A: Worse score on the impact dimension. Both groups: No significant differences between the groups. 4. Lung function: No significant differences between the groups.
Creutzberg et al.[42] Bias: 1.7	Age: I vs. P (65 vs. 65 years old). GOLD: 3.	$N = 64$ ("depleted") Historical controls = 28	Intervention (I): fortimel (as above), ensini (as above), fortipudding (high carbohydrate supplement) three times per day for 8 weeks. Placebo (P): No.	Duration: 8 weeks. Location: inpatient. Session detail: A—General physical training: 1. Swimming.	1. Body composition: weight and FFM. 2. Muscle function: MIP.	1. Body composition: Significant increase in body weight (2.1 kg, $p < 0.05$) and FFM (1.1 kg, $p < 0.05$) in the intervention group. 2. Muscle function: No significant differences between the groups.

(continued)

Table 3. (continued)

Author and risk of bias	Mean age, GOLD stage and BMI	Subject	Intervention	Pulmonary rehabilitation	Outcomes measures	Result
	BMI: I vs. P (20.2 vs. 19.8 kg/m^2).			2. Sports. 3. Exercise in relation to daily activities. 4. Cycle ergometry. 5. Treadmill walking. B—Games. C—Educational program.	3. Quality of life: SGRQ.	3. Quality of life: No significant differences between the groups.
Menier et al.[43] Bias: 2.4	Age: 63 years old. GOLD: not recorded. BMI: not recorded.	$N = 60$	Intervention (I): amino acids 1 capsule/7 kg body weight/day, 6 weeks. Placebo (P): No.	Duration: 5 weeks. Location: not specified Session detail: 5 days/week. (40 minutes). Intensity training endurance until exhaustion	1. Exercise performance: Reached max power (W_{max})	1. Exercise performance: No significant differences between the groups.
Creutzberg et al.[44] Bias: 2.2	Age: group 1, 2, and 3 (69, 65, vs. 59 years old). GOLD: 3 BMI: group 1, 2, and 3 (39.9, 42.9, and 39.6 kg/m^2)	$N = 24$ (depleted group)	Intervention: fortimel (as above), ensini (as above), fortipudding (as above) three times per day for 8 weeks.	Duration: 8 weeks Location: inpatient Session detail: not specified. Intensity depending on the tolerance of the patient.	1. Body composition: Weight and FFM.	Patients divided into (1) no weight gain <2%. (2) expected weight gain >5%. (3) medium weight gain 2–5%: 1. Body composition: Weight significantly increased for group 3 (5.8 $\pm$ 1.2 kg, $p < 0.001$) vs. 1 and 2. FFM significantly increased for group 2 (FFM 1.5 $\pm$ 1.2 kg, $p < 0.05$) and group 3 (FFM 3.1 $\pm$ 1.8, $p < 0.001$) vs. group 1.

I: intervention group; P: placebo or control group; 12MWT: 12-minute walk test; 6MWD: 6-minute walk distance; BMI: body mass index; CRQ: Chronic Respiratory Disease Questionnaire; FEV_1: forced expiratory volume in 1 second, FFM: fat-free mass; FFMI: fat-free mass index; FM, fat mass; MIP: maximum inspiratory pressure; PR: pulmonary rehabilitation; SGRQ: St. George's Respiratory Questionnaire.

Body weight was one of the most frequent outcomes measured before and after giving nutritional supplementation; 11 studies measured body weight in COPD patients with normal BMI. Seven studies reported that body weight increased significantly following nutritional supplementation compared to the placebo groups,[26,37,39,28,29,42,44] and the study by Broekhuizen et al.[41] compared two nutritional supplement regimes, respifor versus ensini, fortimel and nutridrink, which found that both interventions significantly increased body weight. Four studies reported that body weight did not significantly improve in the intervention groups when compared to the placebo groups.[30,32,34,35] Of the RCTs in which body weight significantly increased, there was only one study, by Sugawara et al., that had a low risk of bias.[28] This study reported a significant increase in body weight after 12 weeks of 2.6 $\pm$ 3 kg in those receiving the ready-to-drink (ONS, described above) with the mean baseline body weight of 50.8 kg, compared to those in the placebo group with the mean baseline body weight of 54.8 kg.[28] In the study by Gurgun et al., there were significant improvements in body weight of 1.1 $\pm$ 0.9 kg, BMI 0.2 $\pm$ 1.4 kg/m^2 and in FFMI (0.6 $\pm$0.5 kg/m^2) in those who received 250 mL of 83.3% carbohydrate, 30% fat and 16.7% protein three times a day as an intervention.[26] Of the four studies with negative findings, one study was at low risk of bias.[34] This study found no significant difference in body weight between the creatine intervention group and the placebo group after 8 weeks.

BMI was assessed before and after using supplementation in 5 of 24 studies.[26,33,37,31,35] BMI significantly increased in the supplementation group when compared to the placebo group in three studies.[26,37,31] Two studies reported no significant difference in BMI between participants who received nutritional supplementation with PR compared to PR only.[33,35] One RCT at the lowest risk of bias showed no improvement in BMI with carnitine.[33] In contrast, Gurgun et al. reported that BMI significantly increased after receiving nutritional supplement.[26]

FFM was evaluated in nine trials.[32,36,39,41,28,35,29,42,44] Three studies demonstrated that FFM increased significantly in comparison with the placebo group but these studies all had some risk of bias.[36,39,42] Two[26,31] of four studies[26,41,31,35] with some risk of bias reported that FFMI significantly increased in the supplemental group when compared to the placebo group. In contrast, the study by Broekhuizen et al. reported no significant difference in FFMI between the group who received PUFA as an intervention and the placebo group who received palm and sunflower oil with vitamin E capsule as a placebo.[35]

Peripheral muscle strength

Of the 24 studies included in this systematic review, 11 studies measured quadriceps muscle strength, handgrip strength or both[23,25,27,30,32,34,36,37,28,31,35]

Three studies reported that handgrip strength did not significantly improve in the intervention groups when compared to placebo.[34,37,35] Faager et al. being at lowest risk of bias reported that using carnitine for 8 weeks during PR did not significantly improve handgrip strength when compared to the placebo group who received glucose.[34] In contrast, the study by Fuld et al., which had a higher risk of bias, showed significant improvement in handgrip after using creatine three times a day for 2 weeks followed by once a day for 10 weeks.[36]

Quadriceps muscle strength was assessed in 11 studies.[23,25,27,30,32,34,36,37,28,31,35] Of the 11 RCTs, only three studies with 86 participants in total demonstrated positive findings.[36,28,31] The study by Sugawara et al., which had a low risk of bias, concluded that quadriceps muscle strength increased significantly after receiving a complex nutritional supplement when compared to the placebo group.[36,28,31] However, nine studies reported that using nutritional supplementation during PR had no additional effect on quadriceps muscle strength.[23,25,27,30,32,34,37,35] van de Bool et al. with a low risk of bias reported that using a high carbohydrate supplement showed no significant improvement in quadriceps strength when compared to the placebo group.[23] Similarly, the study by Faager et al. showed that using creatine for 8 weeks in COPD patients enrolled in an 8-week PR programme did not reveal significant differences in quadriceps muscle strength compared with those who used placebo.[34]

Respiratory muscle function

Respiratory muscle function was assessed in 9 of the 24 included studies,[23,27,33,36,39,28,31,35,42] of which 3 were at lowest risk of bias.[23,33,28] Sugawara et al. reported that maximum inspiratory pressure (MIP) significantly improved in the interventional group (39.2 $\pm$ 38.9 cmH_2O) after receiving nutritional supplement embedded in 12 weeks of PR compared with placebo (0.1 $\pm$ 24.1 cmH_2O).[28] A small study by

Borghi-Silva et al. showed a significant improvement in MIP (40 ± 14 cmH_2O) with carnitine compared to placebo (MIP; 14 ± 5 cmH_2O).[33] In contrast, a larger study by van de Bool et al. did not show a significant improvement in MIP when compared with placebo, who received glucose.[23] None of the studies that measured maximal expiratory pressure (MEP) showed a significant difference between interventional and placebo groups.[39,31,35]

Quality of life

Quality of life was assessed in 14 of 24 studies.[23,25–27,30,32,34,36,37,40,28,31,42] Eight studies used the St. George Respiratory Questionnaire (SGRQ),[25,26,34,36,41,31,42] and six used the Chronic Respiratory Disease Questionnaire (CRQ).[27,30,32,37,40,28] Overall, only two studies demonstrated a significant improvement in quality of life with supplementation in addition to PR.[36,28] Sugawara et al., which was at lowest risk of bias, measured quality of life using the CRQ and showed a significant improvement in those receiving nutritional supplement compared with placebo, which was clinically significant (6.2 ± 7.5 vs. −2.7 ± 13.1).[28] Thirteen studies showed negative findings including two RCTs at lowest risk of bias, including the study by Faager et al. using creatine supplementation and the study by van de Bool et al. using the high carbohydrate supplement. Faager et al. using creatine for 8 weeks during PR did not improve quality of life measured by SGRQ.[34] Similarly, van de Bool et al. reported that 4 months of using oral nutritional intervention did not show symptoms of anxiety and depression.[23]

Discussion

This review is the first to summarise the potential effects of using nutritional supplementation during PR in patients with COPD. The studies varied in design, used differing supplements and measured different outcomes. In some, the primary purpose was to use the exercise component of PR to enhance the effect of nutrition, whereas others tested whether nutrition supplementation could enhance outcomes from PR. This results in considerable heterogeneity across studies, many of which were further limited by small sample size. It is, therefore, challenging to draw a single conclusion to address whether using a nutritional supplement has additional effects on exercise function, body composition, respiratory muscle function and quality of life during PR. We were also unable to perform meta-analysis due to this heterogeneity. Consequently, appropriately powered double-blinded RCT studies with suitable sample size using high energy/high protein nutritional supplement to investigate the effect of nutritional support in enhancing PR outcomes, and longer-term clinical outcomes, in COPD patients, are still needed. This would be particularly important in the high-risk group of COPD patients who are undernourished. This would support recommendations to incorporate nutritional support in PR management.[19,45] High protein/high energy ONS is recommended by the British Association for Parenteral and Enteral Nutrition for patients with COPD due to high energy and protein requirements[46] and PR services in different health contexts that need to consider how best to integrate nutritional assessment and, where successful, intervention into diverse methods of PR delivery.

Exercise capacity has been used to quantify the direct effect of nutrition interventions and to predict mortality and morbidity in COPD patients and other diseases. In this systematic review, the majority of studies demonstrated no improvement in exercise outcomes with nutritional supplementation in addition to PR, compared to PR alone. There were four RCTs with negative findings at low risk of bias,[23,24,33,34] which tested carbohydrate, B12, creatine and carnitine supplementation and just one small RCT with a positive finding, which used a ready-to-drink ONS twice a day composed of 200 kilocalories, 60% carbohydrates, 15% protein, 25% fat and 248 µg of omega-3 PUFAs 0.6 with vitamins A, C and E. These findings complement the meta-analysis of nutritional supplementation in stable COPD by Ferreira et al., which included 17 randomised clinical trials and concluded that nutritional supplements increased exercise tolerance in COPD patients who were poorly nourished when compared with baseline only, but which did not specifically consider use in the context of PR.[17] A meta-analysis was not possible in our review due to considerable heterogeneity in studies, as described above.

Body composition is one of the outcome measures that might be expected to improve when using nutritional supplement in COPD. Being underweight is associated with an increased risk of mortality in COPD.[13] Low body weight is observed in between 25% and 40% of COPD patients. Among these, 25% have moderate to severe weight loss and 35% have extremely low FFM.[47] In this systematic review, we

found that ready-to-drink ONS during PR may increase body weight in a population with normal body weight but not with carnitine or creatine. Importantly, improvements in body weight and FFM using nutritional supplementation during PR appear to occur especially in depleted, malnourished and muscle-wasted patients (who are at highest risk).[23,26,31,29] In the meta-analysis by Ferreira et al, significant weight gain was noted compared to baseline in 11 RCTs and the meta-analysis of Collins et al. showed significant weight gain in favour of nutritional support when compared with control outside the context of a PR programme.[17,18]

In recent years, researchers have paid attention to the assessment of outcomes, such as quadriceps muscle strength and handgrip strength. Handgrip strength and quadriceps muscle strength are valid measurements of peripheral muscle strength and are associated with mortality, morbidity and increased length of hospital stay.[19,48] In this systematic review, RCTs at low risk of bias did not support the concept that creatine, high carbohydrates, and L-carnitine increase peripheral muscle strength, and we found conflicting evidence for the benefits of a ready-to-drink ONS with one study having positive and another study having negative results. Collins et al. concluded that handgrip strength improved significantly in the intervention group when compared to usual care group with PR.[19]

Respiratory muscle weakness in COPD patients may be due to several factors, such as acute exacerbations, systemic inflammation and malnutrition.[49] It has been suggested that nutritional supplements may improve respiratory muscle function. In this systematic review, we found two studies reporting that nutritional supplementation in addition to PR had an extra benefit in improving respiratory muscle function. This was demonstrated by measuring MIP and MEP. The effects were seen only on inspiratory measures, and the authors did not speculate on why they thought this was. Collins et al. concluded that MIP and MEP improved significantly in the intervention group when compared to usual care group. Ferreira et al. found that there was no significant difference between intervention control groups in MIP, but for malnourished patients with COPD, MIP and MEP improved significantly with nutritional support.[17,19]

Quality of life may be affected through multiple mechanisms in COPD. The available evidence from this review included one small study demonstrating an improvement in QOL measured by CRQ using ready-to-drink ONS, and two studies with negative results, one of which used creatine and one of which also used ONS. The meta-analysis by Ferreira et al reported significant improvement for quality of life measured using SGRQ for patients with COPD who were malnourished. Additionally, Naz and Sahin demonstrated that protein-rich nutritional supplement significantly improved the quality of life in patients with COPD who participated at PR when compared to PR alone.[50]

Strengths and limitations

To our knowledge, this is the only review that reports the effect of nutritional supplementation during PR in stable COPD. PR is an evidence-based and cost-effective intervention in COPD and thus maximising outcomes is of great interest to clinicians and patients alike. We have carefully searched the literature and registered our review in advance on PROSPERO. Three independent researchers examined the titles and abstracts for inclusion. Potential limitations include we only accessed studies in English, and the inherent variation, many of which had a risk of bias, for example, with inadequate sample size or absence of a power calculation, variation in outcomes measured, variety in study design or different PR protocols. Additionally, outcomes varied between studies, and we have not specifically considered the diversity of nutritional outcomes in this review, which focuses on clinical PR outcomes. There was significant diversity in the type, available substrate, energy imbalance or ingredients of the supplement either caloric or non-caloric and powder, liquid or tablets. We also observed a variation in the amount, contents and the duration of using supplements. Also, our review did not investigate the benefits of using nutritional supplements beyond the duration of PR, which could be important in clinical practice given that a major aim of PR programmes is to durably improve quality of life and reduce the risk of exacerbations and hospitalisations.

Conclusion

This is the first systematic review to report the value of nutritional supplementation during PR in patients with COPD. It is not possible to draw a definitive conclusion due to the heterogeneity of the supplements used, rehabilitation programmes and outcome measures. However, nutritional supplements may enhance the benefit of PR programmes, which would

be of considerable benefit to those living with COPD. Not all studies showed positive results and there is a real need for further well-designed and rigorous research to address this area. This is particularly true in weight-losing and/or malnourished patients with COPD, who are at the highest risk of poor outcomes.

Authors' note

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Author contributions

AMA, JRH, and SM conceived and designed the study. AMA performed the initial search and data extraction, while JRH and SM checked the eligibility of the included articles. AMA and JRH performed the quality assessment for the included articles. AMA wrote the initial manuscript and YSA, JSA, SD, and AMR contributed to the writing of the manuscript. JRH, SM, and VS revised the manuscript. All authors read and approved the final manuscript.

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Supplemental material

Supplemental material for this article is available online.

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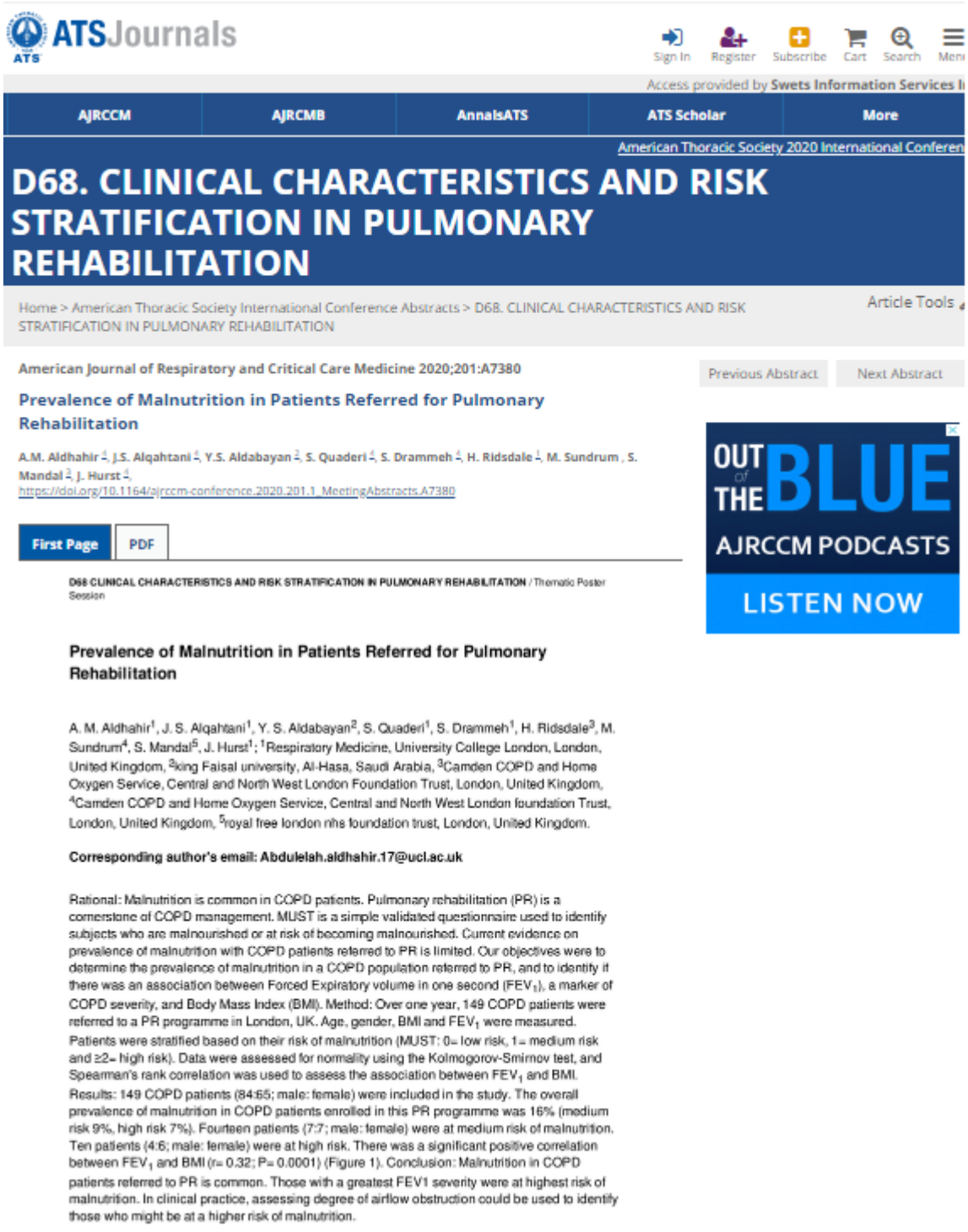
Appendix 20: Prevalence of Malnutrition in Patients Referred for Pulmonary Rehabilitation.



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D68 CLINICAL CHARACTERISTICS AND RISK STRATIFICATION IN PULMONARY REHABILITATION / Thematic Poster Session

Prevalence of Malnutrition in Patients Referred for Pulmonary Rehabilitation

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Rational: Malnutrition is common in COPD patients. Pulmonary rehabilitation (PR) is a cornerstone of COPD management. MUST is a simple validated questionnaire used to identify subjects who are malnourished or at risk of becoming malnourished. Current evidence on prevalence of malnutrition with COPD patients referred to PR is limited. Our objectives were to determine the prevalence of malnutrition in a COPD population referred to PR, and to identify if there was an association between Forced Expiratory volume in one second (FEV_1), a marker of COPD severity, and Body Mass Index (BMI). Method: Over one year, 149 COPD patients were referred to a PR programme in London, UK. Age, gender, BMI and FEV_1 were measured. Patients were stratified based on their risk of malnutrition (MUST: 0= low risk, 1= medium risk and ≥2= high risk). Data were assessed for normality using the Kolmogorov-Smirnov test, and Spearman's rank correlation was used to assess the association between FEV_1 and BMI. Results: 149 COPD patients (84:65; male: female) were included in the study. The overall prevalence of malnutrition in COPD patients enrolled in this PR programme was 16% (medium risk 9%, high risk 7%). Fourteen patients (7:7; male: female) were at medium risk of malnutrition. Ten patients (4:6; male: female) were at high risk. There was a significant positive correlation between FEV_1 and BMI (r_s= 0.32; P= 0.0001) (Figure 1). Conclusion: Malnutrition in COPD patients referred to PR is common. Those with a greatest FEV1 severity were at highest risk of malnutrition. In clinical practice, assessing degree of airflow obstruction could be used to identify those who might be at a higher risk of malnutrition.

Appendix 21: The relationship between malnutrition and severity of airflow obstruction in COPD patients.

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Obstructive Lung Diseases

TYPE: Abstract Publication

TOPIC: Obstructive Lung Diseases

THE RELATIONSHIP BETWEEN MALNUTRITION AND SEVERITY OF AIRFLOW OBSTRUCTION IN COPD PATIENTS

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PURPOSE: To identify the relationship between Malnutrition and Forced Expiratory volume in one second (FEV_1)

METHODS: COPD patients referred to the pulmonary rehabilitation underwent assessment. Gender, Body Mass Index (BMI) and FEV_1 were measured. Patients were stratified based on risk of malnutrition using Malnutrition Universal Screening Tool (MUST: 0= low risk, 1= medium risk and ≥2= high risk). MUST is used to identify subjects who are malnourished or at risk of becoming malnourished.

RESULTS: 148 COPD patients included in the study. Low risk accounted for 83% (n= 73; 51 female), medium risk 9.5 %(n= 7; 7 female) and high risk 6.8% (n= 4; 6 female). A significant difference were found between all groups in FEV_1 (low, medium, high risk) (p=0.011). A significant difference was noted in FEV_1 between high risk and medium risk groups (p= 0.03) and also between high risk and low risk groups (p= 0.008) with these in the high risk group having a lower FEV_1. See Table 1.

CONCLUSIONS: The severity of malnutrition was associated with severity of airflow obstruction.

CLINICAL IMPLICATIONS: The degree of airflow obstruction could be used in clinical practice to identify COPD patients who might be at a higher risk of malnutrition.

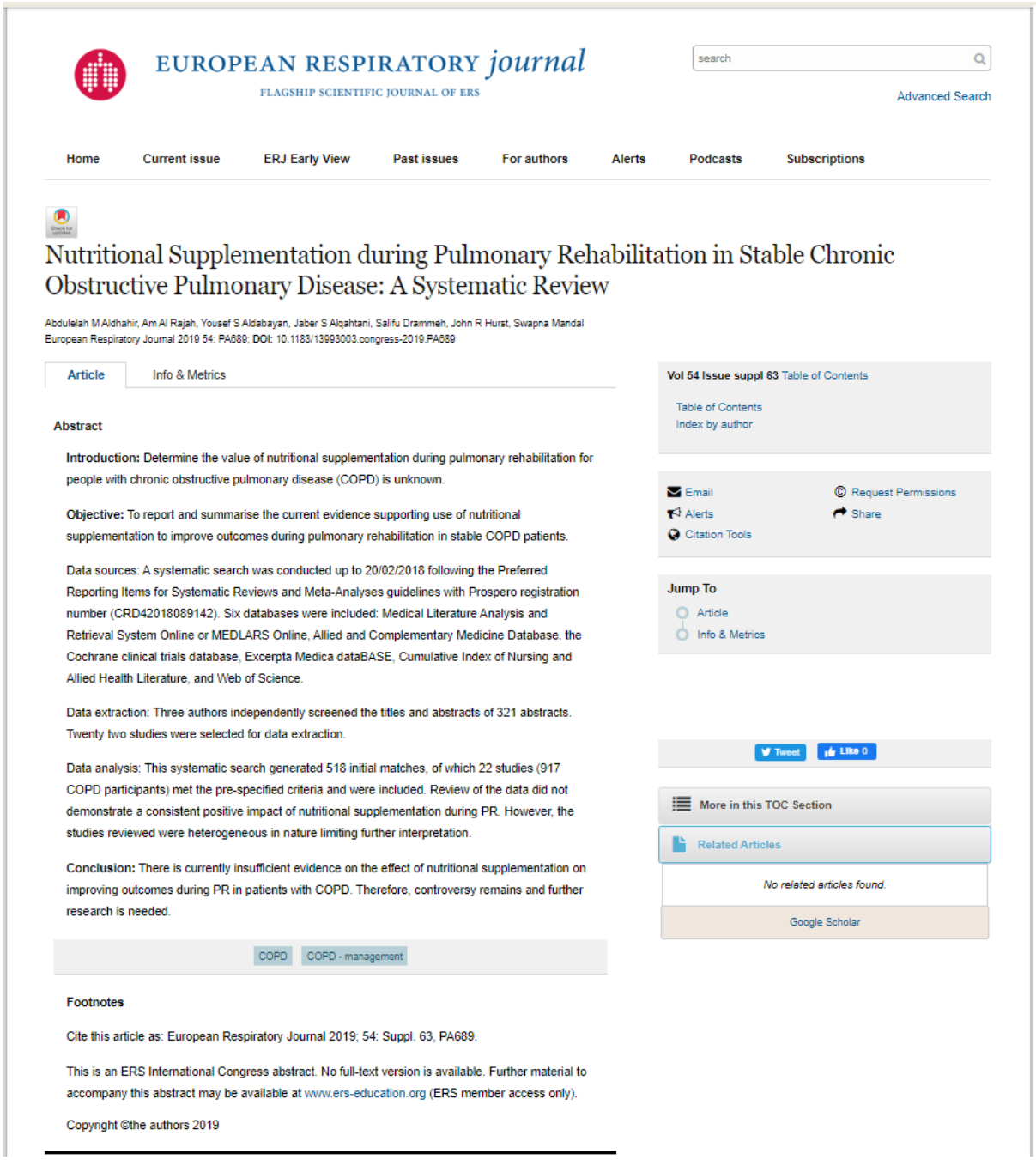
DISCLOSURE: No significant relationships.

KEYWORDS: Rehabilitation, COPD, Malnutrition

DOI: https://doi.org/10.1016/j.chest.2020.05.340

OBSTRUCTIVE LUNG DISEASES

Appendix 22: Nutritional Supplementation during Pulmonary Rehabilitation in Stable Chronic Obstructive Pulmonary Disease: A Systematic Review.



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Nutritional Supplementation during Pulmonary Rehabilitation in Stable Chronic Obstructive Pulmonary Disease: A Systematic Review

Abdulelah M Aldhahir, Am Al Rajah, Yousef S Aldabayan, Jaber S Alqahtani, Salifu Drammeh, John R Hurst, Swapna Mandal

European Respiratory Journal 2019 54: PA689; DOI: 10.1183/13993003.congress-2019.PA689

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Abstract

Introduction: Determine the value of nutritional supplementation during pulmonary rehabilitation for people with chronic obstructive pulmonary disease (COPD) is unknown.

Objective: To report and summarise the current evidence supporting use of nutritional supplementation to improve outcomes during pulmonary rehabilitation in stable COPD patients.

Data sources: A systematic search was conducted up to 20/02/2018 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines with Prospero registration number (CRD42018089142). Six databases were included: Medical Literature Analysis and Retrieval System Online or MEDLARS Online, Allied and Complementary Medicine Database, the Cochrane clinical trials database, Excerpta Medica dataBASE, Cumulative Index of Nursing and Allied Health Literature, and Web of Science.

Data extraction: Three authors independently screened the titles and abstracts of 321 abstracts. Twenty two studies were selected for data extraction.

Data analysis: This systematic search generated 518 initial matches, of which 22 studies (917 COPD participants) met the pre-specified criteria and were included. Review of the data did not demonstrate a consistent positive impact of nutritional supplementation during PR. However, the studies reviewed were heterogeneous in nature limiting further interpretation.

Conclusion: There is currently insufficient evidence on the effect of nutritional supplementation on improving outcomes during PR in patients with COPD. Therefore, controversy remains and further research is needed.

COPD | COPD - management

Footnotes

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