Journal Pre-proof

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PII: S0954-6111(20)30388-7

DOI: https://doi.org/10.1016/j.rmed.2020.106248

Reference: YRMED 106248

To appear in: *Respiratory Medicine*

Received Date: 16 September 2020

Accepted Date: 18 November 2020

Managing Malnutrition in COPD: A review

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Abstract

In the UK approximately 1.2 million people have COPD with around 25-40% being underweight and 35% have a severely low fat-free mass index. Measuring their body mass index is recommended and Health care professionals should endeavour to ensure that COPD patients are achieving their nutritional requirements.

A narrative review summarizes evidence from 28 original articles identified through a systematic searches of databases, grey literature and hand searches covering 15 years, focusing on two themes, on the impact of malnutrition on COPD, and the management of malnutrition in COPD.

Malnutrition causes negative effects on exercise and muscle function and lung function as well as increasing exacerbations, mortality and cost. Management options include nutritional supplementation which may increase weight and muscle function. Nutritional education has short-term improvements.

Malnutrition affects multiple aspects of COPD, but treatment is of benefit. Clinical practice should include nutrition management.

Key Words: Chronic Obstructive Pulmonary Disease, Malnutrition, BMI, FFMI, Mortality, Exacerbation, Cost, Nutritional Support, Management.

Introduction

In 2016 there were 3 million deaths worldwide as a result of chronic obstructive pulmonary disease, COPD, ranking it the third most common cause of death after ischaemic heart disease and stroke. Approximately 1.2 million people in the U.K. have a diagnosis of COPD and its incidence is on the rise [1]. COPD is characterised by symptoms of dyspnoea, cough and sputum production. Although COPD is not curable it is manageable and the National Institute for Health and Care Excellence, NICE (2018) COPD guidelines recommend smoking cessation, inhaled therapy and pulmonary rehabilitation [2]. However, before commencing pulmonary rehabilitation it is suggested that the patient's nutritional status is evaluated, and action taken based on the result of this assessment [3]. Similarly, NICE (2018) recommend that patients with COPD have their body mass index, BMI, calculated routinely [2].

BMI provides guidance on the nutritional status of the person and places them into one of four categories. NICE recommend that if the patient's weight is abnormal, the best course of action would be to refer the patient to a dietician for assessment [2]. Yet these recommendations have not been updated since the NICE COPD guidelines of 2004 [4]. Recent studies have estimated that 25-40% of COPD patients are underweight while 35% of patients have severely low fat-free mass index (FFMI) [5]. Fat-free mass is associated with muscle mass and if low it can impact negatively on exercise ability and muscle function [6]. As the prevalence of malnutrition appears to be high in COPD patients, better recognition is required in order to optimise management. NICE states that in the UK identifying and managing malnutrition is inadequate in all health sectors [4]. Malnutrition is defined as a condition where there is a lack of nutrients which negatively affects the body's structure and/or ability to function. In addition, a diagnosis of malnutrition can be made when there is a low BMI or unplanned weight loss with a reduced BMI or a low FFMI adjusted for sex. Furthermore, poor health can cause malnutrition, but malnutrition can also lead to illness and a reduction in health status.

Consequently, appropriate screening tools that are validated should be used to assess for malnutrition [7].

Rawal and Yadav (2015) state the exact cause of malnutrition in COPD is poorly understood but that several factors such as a raised resting energy expenditure, inflammation, hypoxia and medication use may contribute [5]. According to Shepherd (2013) all health care professionals must ensure that patients meet their nutritional requirements to avoid malnutrition [8].

This review aims to identify the impact that malnutrition has on people with COPD and the management options that have been used to improve malnutrition. This will allow recommendations to inform best practice.

Methods

A combined database search of CINAHL, Academic Search Complete, EBSCO and MEDLINE were completed multiple search words and search strings were created to find literature. Key search words were “Chronic Obstructive Pulmonary disease” (OR “COPD” OR “Chronic Obstructive Pulmonary Disease” OR “Chronic Obstructive Lung Disease), Malnutrition (OR “underweight” OR “low BMI” OR “Undernutrition” OR “Undernourishment”), “Diet” (OR “Feeding” OR “Eating” OR “Nutrition” OR “Supplements” OR “Nutritional Supplementation” OR “Food” OR “Food intake” OR “Inadequate diet” OR “Dietary deficiency”), “Management”, “Education” (OR “Advice” OR “Input”). A combination of search strings were combined using the Boolean search words, and/or. Research finished and/or published between 2004-2019 were included. Other inclusion criteria consisted of limiting the research to peer reviewed literature published in the English language. The database searches were undertaken between July and August 2019.

Separate searches of Wiley online library, PubMed and Science Direct was completed using the above search strings and filters. In addition, grey literature was investigated in order to minimise publication bias via Open Grey, NHS RightCare Casebooks and the World Health Organisation International Clinical Trials Registry Platform (ICTRP). Finally, hand searches of prominent journals in respiratory medicine were conducted. Thorax and European Respiratory Journal were searched via online editions for publications related to nutrition/malnutrition and COPD. Other hand searches included examining reference lists of research studies and other journal articles related to the current topic. Exclusion criteria were studies that examined malnutrition in people during exacerbation or those who were obese, malnutrition management of the obese COPD patient, and studies which examine the effect of specific supplements such as whey protein and vitamins. In addition, research which reports the effect of enteral feeding in COPD was omitted.

In total, database searches yielded 2,881 publications which were narrowed down by title. Following removal of duplications there were 33 research articles to be included for further review by title and abstract. Grey literature yielded twenty-five hits, however 24 were not appropriate for inclusion. One study seemed appropriate by title, but access to the study or abstract was not possible. In addition, searches of Thorax found five publications which were suitable for further review. European Respiratory Journal was searched based on inclusion and exclusion criteria and based on full text availability only one article was suitable for review. Similarly, scanning of reference lists uncovered seven studies which were evaluated. Duplicates were removed before studies were reviewed by title and abstract. A total of 28 articles being suitable for inclusion and for review (Fig 1).

Results

The 28 studies reviewed were conducted principally in Europe and Asia, 19 examined the impact of malnutrition on patients with COPD. Seven studies explored the effect of oral nutritional supplementation on people with COPD while two studies trialled counselling as an alternative (Table 1 and 2).

1. Impact of malnutrition on COPD

1.1 Exercise ability and muscle function

Dyspnoea inhibits mobility and general exercise which can result in an inability to complete daily activities. Consequently, muscle wasting can occur [9]. Yet Holst *et al.* (2019) undertook a cross-sectional study to examine whether a relationship between nutrition and physical ability existed [10].

The study included 79 people with a varying severity of COPD who were recruited from five pulmonary rehabilitation centres in Denmark. To obtain information about the patient's dietary intake a 3-day diary was completed as well as an additional 24-hour food recall at the time of the diary collection. However, it is unclear what the total population was so there is the risk of selection bias. Furthermore, the patients had other co-morbidities which could affect malnutrition. Yet, this makes the study more 'real world' as patients in the clinical setting can have more than just one illness [11]. The study found that protein intake below 75% of the recommended requirements was positively associated to a six-minute walk test, 6-MWT, ($<75\%$ Mean 6-MWT=332 $\pm$ 115 M, $\geq 75\%$ Mean 6-MWT=393 $\pm$ 108 M, $P = 0.023$). However, an energy intake below 75% of the recommended requirements was not associated with a reduced 6-MWT ($P = 0.388$). Conversely, a reduced energy intake was associated with a poorer 30 second–chair stand test, 30s-CST, ($P=0.01$) when linear regression was applied protein was not associated ($P = 0.08$).

In contrast, Lee *et al.* (2013) found that an estimated energy requirement, EER, below 75% was associated with a shorter 6-MWT (<75% EER 337 ± 84 M, ≥75% EER 366 ±80 M, P = 0.008) [12]. While those patients with higher calorie intake had a longer 6-MWT. This study was also a cross-sectional descriptive study and patients were recruited from five respiratory outpatient departments in South Korea. There was a larger sample size of 251 patients in comparison to Holst *et al.* (2019) [10] and patients mostly had mild to moderate disease severity. However, collection of information regarding dietary intake relied solely upon a 24-hour food recall method and there is the risk of underreporting with this tool [13].

In addition, total calorie, protein, iron and carbohydrate intake were significantly linked to the 6-MWT (P<0.001, P = 0.001, P<0.001 and P = 0.002 respectively).

Similarly, Katsura, Yamada and Kida, (2005) undertook a cross-sectional study in an outpatient department in Japan and found that COPD patients classified as underweight based on a BMI of ≤ 20kg/m^2 had a significantly lower 6-MWT than those who had a normal weight (underweight: 349 ± 18 M, normal weight: 396 ± 9 M, P<0.05) [14]. Conversely, a cohort study in Spain found no difference in 6-MWT between those who were malnourished (387± 119 M) and nourished groups (401 ± 119 m) [15].

Luo *et al.* (2016) also conducted a cross-sectional study in a respiratory clinic. The aim was to assess the relationship between nutrition and exercise ability, symptom burden and respiratory muscle function [16]. A sample size of 251 people of all disease severities were included but of these only 51 were female. The data show a weak correlation between a low FFMI and a shorter 6-MWT distance where r = 0.26 and P< 0.001.

Similar results were not seen in a cross-sectional study conducted by Hallin *et al.* (2011) in Sweden [17]. This study was smaller and only consisted of 49 COPD patients with moderate to severe disease who were already partaking in a study comparing different exercise regimes at one centre. The study did not find any correlation between FFMI and a 12 minute walking test, 12-MWT, distance or incremental shuttle walk test, ISWT, P = 0.2 and P = 0.56 respectively.

The BMI was not related to ISWT or 12-MWT (P = 0.4 and P = 0.9 respectively). Furthermore, peak working capacity in watts (W_{peak}) positively correlated to FFMI and BMI (coefficient: 2.8 and 1.5 respectively, P = 0.01). Also, FFMI, arm and leg circumference were significantly related to hand-grip strength (coefficient=18, P = 0.001, coefficient = 8, P = 0.007 and coefficient = 5.7, P<0.0001 respectively). Hand-grip strength is a predictor of mortality as well as physical frailty [18]. A similar result was seen in a cross-sectional study conducted in the Netherlands where handgrip strength was significantly lower in the malnourished group verses the nourished (31 ± 9 verses 38 ±11 kg) where P <0.01 when adjusted for sex). Handgrip strength showed a weak correlation to FFMI with r = 0.22 and P<0.001 [6].

Finally, Mkacher, Tabka and Trabelsi (2016) carried out a cross-sectional study in Tunisia to establish whether a relationship existed between balance, nutrition, exercise ability[19]. The participants had moderate to severe COPD. Nutritional status was assessed using the MNA which has been shown to be a reliable tool when assessing nutrition in COPD patients [20].

Balance was assessed using multiple techniques; Timed Up and Go test, TUG, Unipodal Stance Test, UST, Tinetti test and Berg Balance Scale, BBS. TUG has been shown to be valid and reliable at measuring patients' risk of falls. Tinetti is also a tool to assess patients' risk of falls. UST measures the patient's ability to stand on foot for 45 seconds. BBS was used to assess the patients functional balance. It was shown that those who were at risk of falls and had poor balance had a shorter 6-MWT (P<0.05). However, those with lower MNA scores (at risk of malnutrition) had significantly reduced scores measured by TUG and Tinnetti (P<0.01). Furthermore, the balance scores were also significantly correlated to BMI and 6-MWT (except for UST). The data suggest that balance is linked to exercise ability and nutrition.

1.2 Disease severity

The aim of COPD management is to prevent disease progression [21]. Consequently, Humphreys *et al.* (2008) undertook a cross-sectional study in a respiratory outpatient department in Australia with the objectives to assess if malnutrition was related to lung function and quality of life [22]. Sixty six patients with moderate COPD were recruited and 9 patients did not complete the diary. There was no significant difference in age, lung function, BMI or FFMI between those that did complete the diary and those that didn't. FFMI was measured using a tetra-polar bio-impedance spectroscopy. This test is easy to use and reliable in healthy people with normal hydration but may not be as reliable in those with electrolyte imbalances or exceptionally high or low weight [23]. The study showed that a low BMI and/or decreased FFMI was linked to a reduced forced expiratory volume in one second, FEV_1 ($P = 0.003$) and worse obstruction ($P = 0.038$) than those with normal body composition. A weak correlation between FEV_1 and BMI was seen ($r = 0.310$ and $P = 0.015$) while FEV_1 and FFMI exhibited a weak correlation only in male participants ($r = 0.373$ and $P = 0.046$). In comparison, Yazdanpanah *et al.* (2010) carried out a cross-sectional study in Iran [24]. Patients were recruited when acutely unwell in hospital but were stable at the time of the study. Sixty three patients with stage 2-4 COPD as per GOLD guidelines were included. Patients kept a 24-hour food diary for the previous day and a food frequency questionnaire, FFQ. The stability of the patients and if they were at home when completing the diary is unclear. FFQ was used as an acute exacerbation may affect dietary intake. However, if the patient was stable then dietary intake should be normal. The results showed that protein and energy intake were not significantly correlated to FEV_1 from either tool. However, it is reported that protein intake from the FFQ was correlated to the forced vital capacity, FVC, $P = 0.02$, $r = 0.2$ and to vital capacity, VC, $P=0.008$, $r = 0.3$. Another cross-sectional study was undertaken by Baig *et al.* (2018) to investigate the potential relationship between dyspnoea and COPD severity using

BMI and mid-upper arm circumference, MUAC [25]. One hundred and thirty eight patients were included, and the mean percent predicted FEV_1 was 28 ± 5%.

It is reported that lung function tended to be in the very severe category in those malnourished according to BMI (P = 0.001) and MUAC (P<0.001) but only 21 patients had severe COPD.

Luo *et al.* (2016) found that as COPD severity worsened patients' malnutrition as measured by FFMI also deteriorated (FFMI $\leq$15kg/m^2 for men and $\leq$16kg/m^2 for women) [16]. The most severe had a significantly worse FFMI (P<0.001). The correlation between FFMI and FEV_1 percent predicted was low (r = 0.17, P = 0.01).

In comparison, a cross-sectional study carried out in Turkey by Dilektasli *et al.* (2009) found that BMI was positively correlated to FEV_1 (r = 0.457 and P = 0.007) [26]. In the study were 35 participants with moderate to severe COPD. This study also found that those categorised as cachectic had significant difference in FEV_1 and diffusion capacity, DLCO, in comparison to those that were non-cachectic (FEV_1: 1.3 ± 0.6 L versus 1.6 ± 0.9 L, DLCO: 3.9 ± 1.6 versus 6.2 ± 2.0 mmol/kPa/min, P<0.05). Cachexia is described as severely low body weight as a result of reduced tissue mass other than fat [27]. Correspondingly, Gupta *et al.* (2014) undertook a cross-sectional study in an outpatient department in India to assess whether a relationship existed between BMI and oxygen saturations [28]. Patients (n = 147) with different COPD severities were included and BMI decreased as severity worsened (P<0.001). Also, peripheral capillary oxygen saturation, SpO_2 as measured by a pulse oximeter was inversely linked to BMI.

1.3 Exacerbation, mortality and associated cost

COPD exacerbations lead to decreased quality of life, reduced lung function and an increased risk of mortality. Exacerbations can occur due to viral or bacterial infection or inhaling a foreign substance [9]. Yet, Hallin *et al.* (2006) concluded from a multi-centre prospective cohort study of 87 people with COPD that being underweight or losing weight increased the risk of an exacerbation [29]. This Swedish study recruited patients when they were acutely unwell and followed them up one year later at home. Prior to the one-year review patients completed a seven-day food diary. However, only 41 patients were included due to incomplete data, diaries or death. Twenty four patients had an exacerbation, and participants who were underweight or normal weight were no more likely to exacerbate (P = 0.07). Furthermore, weight loss and a low BMI was found to decrease the time until the next exacerbation when a multivariate analysis was applied (BMI risk ratio: 0.78 95% CI: 0.65-0.93 P=0.003, Weight change: 0.76 95% CI 0.63-0.93 P=0.006). Yet, a cross-sectional Turkish study found that the rate of exacerbations was not affected by malnutrition (P = 2.37, odds ratio (OR): 0.234 95% CI 0.021-2.592) [30].

Hallin *et al.* (2006) also mention a small increase in weight in some patients in the underweight group within one year, which suggests patients may have lost weight just prior to their exacerbation [29]. Also, the results showed that the underweight group had 1.2 ± 1.2 admissions during the 12-month period whereas the normal group had less at 0.3 ± 0.6, $P<0.05$.

Similarly, Lee *et al.* (2013) found through a X^2 analysis of 251 patients, 21.1% of those with a low energy intake had attended the emergency department in the previous 6 months verses 8.2% of those with normal or above normal intake (x^2=6.661, p=0.012) [12].

Marco *et al.* (2019) conducted a cohort study at a Spanish pulmonary rehabilitation to assess the impact of malnutrition on hospital admission and mortality[15]. The study lasted for two years and included 118 patients with moderate to very severe disease. The study showed that 67 % of patients required at least one hospital admission. Those that were identified as being malnourished using European Society for Clinical Nutrition and Metabolism, ESPEN, criteria and admitted to hospital tended to have a longer length of stay (median (P_{25}, P_{75}) of 18 (1, 53.5) days in malnourished patients, compared to 9 (3, 20.5) days in patients who were nourished (P = 0.041). When variables (age and lung function) were adjusted the findings were still of significance. In addition, the 2-year mortality risk was increased when malnutrition was diagnosed by ESPEN (Hazard ratio, HR: 3.85 95% CI 1.4-10.62, P = 0.009) and by using the Mini-Nutritional Assessment tool Short form, MNA-SF (HR 3.96, 95% CI: 1.12-14.03, P=0.033). The MNA-SF has been shown to be a valid tool for assessing malnutrition [31]. Low FFMI increased the risk of mortality 17 times (HR 17.06, 95% CI: 2.24-129.82, P = 0.006).

Schols *et al.* (2005) conducted a large cohort study over five years in the Netherlands where patients were also recruited from a pulmonary rehabilitation centre [32]. The study recruits (n = 412) were allocated to one of four categories; cachectic, semi-starvation, muscle atrophy and no impairment. During the study 46% of patients died. BMI, FFMI and fat mass index were significantly associated with an increased risk of death (Relative risk: 0.94, 95% CI 0.90, 0.97, P=0.001, RR: 0.88, 95% CI 0.83, 0.94, P=0.001, RR: 0.93, 95% CI 0.88, 0.99, P=0.009 respectively). In addition, Cox regression models showed that FFMI was an independent predictor of mortality with and without alterations for stage of disease (RR: 0.90, 95% CI: 0.84, 0.96 P=0.003). However, FFMI was a better predictor than BMI of mortality risk.

Similarly, Hoong *et al.* (2016) undertook a cohort study in Australia where 834 patients were included after being identified as having had lung function testing completed [33]. The admissions to hospital were monitored for one year and mortality was assessed at year 1 and 2. There were 286 admissions, but patients may have been admitted to other local hospitals meaning the admissions could have been missed.

Patients that were admitted tended to have a lower BMI (27.4 ± 6.6 kg/m^2 in comparison to 28.6 ± 7.3 kg/m^2, P = 0.016), although the level would not be considered underweight. Mortality rate was greater in the group that was malnourished than the group that wasn't at 1 year and 2 years (27.7 vs 12.1 %, P = 0.006 and 40.4 vs 18%, P = 0.001). When confounding variables were removed (age, lung function, DLCO and BMI) malnutrition was still a strong factor in associated mortality at 1 year. The OR was 2.93 95% CI 1.10, 7.93 and P=0.009. Cox regression was also applied, and malnutrition was significantly important when assessing mortality risk (OR: 0.42 95% CI 0.19 – 0.91 P=0.028). Patients with malnutrition also had a longer length of stay, 11.6 ± 11 days, in comparison to 6.7 ± 10.2 days in nourished patients P = 0.003). Consequently, hospitalisation cost was increased in the malnourished group $23,652 ± 26,472) versus $12, 362 ± $21,865, P=0.002.

Larger cohort studies have also examined nutrition and mortality in COPD. McDonald *et al.* (2017) conducted a retrospective cohort study which combined data from the ECLIPSE study and the COPDGene study which included 12 countries and in 21 centres in the USA respectively [34]. The ECLIPSE study had 1,518 participants while the COPDGene study had 3,121. A calculation was tested on half of the ECLIPSE patients to measure the pectoralis muscle area, PMA, and then applied to all the other patients. $FFMI_{PMA}$ of <16kg/m^{-2} for men higher risk of death than those above these values. When variables were accounted for and Cox regression was applied then a low $FFMI_{PMA}$ was still linked to an increased risk of death by 60% (HR: 1.6, 95% CI 1.2-1.8 P<0.001). In the COPDGene study there were 729 deaths.

McDonald *et al.* (2019) also undertook a low bias study when they examined the prevalence of cachexia and the link with mortality, COPD severity and BMI [35]. Similarly, data was obtained from the cohort study ECLIPSE and 1,483 patient's data was suitable for inclusion. The duration for these patients was 3 years. The standard BODE test was adjusted to replace the B for BMI with a C for cachexia or W for weight loss. BODE represents BMI, airflow Obstruction, Dyspnoea and Exercise capacity and is used to assess patients' risk of hospital admission and death [9]. Patients with cachexia were more likely to die using all tools when evaluated using Kaplan-Meier. Cox-regression was then applied and covariates (smoking history, sex, age and BMI) were controlled for and cachexia was still linked to an increased risk of death as assessed by CODE and WODE (Hazard ratio: 3.2, 95% CI 1.6-6.6, P = 0.001, Hazard ratio: 3.2 95% CI: 1.8–5.6, P<0.001 respectively). Furthermore, COPD patients were 3 times more likely to die if they were cachectic.

1.4 Quality of life and symptom burden

Assessing QOL in chronic illness has become central to disease management. Katsura, Yamada and Kida, (2005) studied the effect that malnutrition has on the QOL of people with COPD [14]. The sample consisted of 83 patients who were recruited to the cross-sectional study from an outpatient department in Japan. Participants were categorised as underweight (BMI $\leq$20kg/m^2) or normal weight ($\geq$20kg/m^2 BMI $\leq$26kg/m^2). The participants needed to complete The Saint Georges Respiratory Questionnaire (SGRQ) and the SF-36 questionnaire. These had been translated into Japanese and to ensure the validity they were then re-translated back into English. The underweight group had worse scores in all the categories of SGRQ than the normal weight groups (Total score: mean difference: 12.83 P<0.05, Symptoms: mean difference: 9.28 P<0.01, Activity: mean difference 13.06 P<0.05 and Impact: mean difference: 14.44 P<0.05). Breathlessness had the largest impact on SGRQ after multiple regression was applied, but BMI was a contributing factor. All the results from the SF-36 were lower in the underweight group. Physical functioning, role emotional, bodily pain and general health were significantly worse (P<0.05 for all measurements except for bodily pain where P<0.001). Like SGRQ, BMI affected role emotional, bodily pain and general health as assessed by SF-36. Breathlessness was worse in the 34 participants who were considered underweight as measured by the oxygen cost diagram (OCD) (62.47 ± 3.3 versus 77.67 ± 2.3, P<0.001).

Similarly, Mete *et al.* (2018) found that malnutrition was more of a risk in patients with an mMRC of 3-4 [30]. When logistic regression was applied according to mMRC breathlessness was significantly worse where the OR was 22.9 95% CI (2.1-249) and P = 0.010. These data were obtained from a cross-sectional study which included 105 people, 80% of the participants were recruited from outpatient department and the other 20% consented while acutely unwell in hospital. Although Lee *et al.* (2013) found that total calorie, protein, iron and carbohydrate intake was inversely correlated to mMRC (r = -0.18, P = 0.004, r = -0.13, P = 0.043, r = -0.15 P = 0.021 and r = -0.14, P = 0.025 respectively) [12]. Similar findings were not seen in a study conducted by Vermeeren *et al.* (2006) [6]. This study used data from a single visit collected during the double-blind intervention study in 39 centres in the Netherlands, 389 people with stage 2 and 3 COPD were included and categorised as nourished or nutritionally depleted (defined as BMI $\leq$21kg/m^2 and/or FFMI of $\leq$15kg/m^2 (females) or $\leq$16kg/m^2 (males)). However, breathlessness as measured by the MRC did not vary between groups. In addition, SGRQ scores were not significantly different between groups. Equally, Humphreys *et al.* (2008) didn't find any difference in quality of life measured by SGRQ between those with a low BMI ± FFMI and those with normal body composition [20].

2. Management of malnutrition

Given the impact of malnutrition on COPD it is imperative that management options are understood by health care professionals providing care to patients with COPD. Knowledge of the benefit and weakness of treatment options are required so that patients can make an informed decision. Consequently, this will mean that health care professionals can obey the ethical principles of autonomy, beneficence and non-maleficence [36]. Furthermore, this knowledge is particularly relevant for nurses, as they are normally the first people to identify poor nutrition and therefore have an important role in managing malnutrition [37].

2.1 Nutritional supplementation

Oral nutritional supplements (ONS) are used during acute illnesses but also for those with chronic long-term conditions who find it challenging to meet their daily nutritional requirement. They should be used in conjunction with meals and not as a meal replacement [38]. Yet COPD patient's energy requirements may be greater than their peers without COPD [5]. Planas *et al.* (2005) undertook a randomised trial over 12 weeks in Spain to explore the effect of two different nutritional interventions on the quality of life of people with COPD [39]. Baseline measurements were taken and both groups had dietary intake requirements calculated but for group A this was multiplied by 1.7 and for group B it was multiplied by 1.3. To achieve the daily energy requirements all patients needed ONS's. Quality of life scores from the Chronic Respiratory Disease Questionnaire (CRDQ) did not improve significantly. However, this had been translated to Spanish. In group A, body weight was significantly improved from a mean 55.3 ± 8.1 to 58.5 ± 9 kg (P = 0.001). Skin fold thickness improved (P = 0.02). However, FFMI reduced from 14.6 ± 1.3 to 13.9 ± 1.6 kg/m^2 (P = 0.02). Also, lung function decreased along with handgrip strength. Group B did not gain weight (55.2 ± 8.6 to 55.6 ± 9.6 kg) nor did fat mass change. FEV_1 improved to 40.4±17.7 % predicted from 37.3 ± 18.5 % predicted. The authors conclude that an addition of 1.3 to dietary intake is superior and does not negatively affect respiratory function.

Similarly, Broekhuizen *et al.* (2005a) compared the effect of smaller volume ONS to larger volumes in a retrospective control trial in the Netherlands [40]. The population were patients admitted to a single pulmonary rehabilitation centre and identified as malnourished. Nineteen COPD patients (group A) admitted between 2000-2002 requiring three 125ml cartons of ONS were matched against 20 patients also admitted to the rehabilitation centre between 1995-1997 (group B) and received three 200ml cartons of ONS.

After two weeks the participants took part in an 8-week exercise programme which comprised of endurance and strength training. Data collection was complex and potentially made more difficult due to assessments being compared with retrospective data. Group A and B had significant increases in body weight and FFM from baseline (weight change: 3.3 ± 1.9 kg and 2.0 ± 1.2 kg, P<0.001, FFM group A: 2.2 ± 2.0 kg P<0.001 and group B 1.4 ±1.9 kg, P = 0.004). While fat mass, FM was greatly improved in A (1.1 ± 1.3 kg, P=0.002), this was not seen in B. Also, group A gained more weight than those in B which was significant (P=0.019). SGRQ changes were not statistically significant in either group, however there was a clinically significant change in group A where the total score decreased by 4 points. The exercise ability measured by incremental bicycle ergometry test was improved in A and B but did not differ between groups (A, 8·3 ± 17.1 W, within-group change P=0·062; group B, 9·0 ± 9.4 W, within-group change P = 0·002; between-group change, P=NS). Lung function did not change significantly.

Sugawara *et al.* (2010) undertook a prospective randomised control trial in Japan with patients receiving nutritional support in combination with an exercise regime [41]. COPD patients (n = 32) with moderate to severe disease were recruited from a pulmonary rehabilitation centre. To be eligible patients had to have a BMI of less than 19kg/m^2. Patients were randomised to either the intervention or control group.

The intervention group were given two ONS drinks which provided 400 kCal per day. Both groups received a 45-minute education class once a month. Following 12 weeks of ONS, the intervention group had an improvement in body weight and fat free mass in comparison to the control group (P = 0.002 and 0.038 respectively). The total CRDQ change was significant (P = 0.028). This tool had been translated into Japanese and validated previously. In addition, the intervention group had better 6-MWT, quadricep muscle force and maximum inspiratory pressure when compared to the control (P = 0.001, P = 0.002, and 0.003 respectively).

In contrast, Gurgun *et al.* (2013) showed 6-MWT and ISWT were not altered by adding ONS to pulmonary rehabilitation in a Turkish randomised control trial [42]. Malnourished patients with severe to very severe COPD admitted to a pulmonary rehab centre were randomised to one of three arms; pulmonary rehabilitation only (PR), pulmonary rehabilitation and ONS (PRNS) or control. The 46 patients completed the 8-week programme and then received 16 weeks of normal care. The PRNS group received three 250ml drinks to consume in addition to their normal meals. Quality of life scores were significantly improved in the PR group in all areas as measured by the SGRQ ($p<0.05$). However, the PRNS had improvements SGRQ except for the impact section (P = 0.112). The PRNS group had 10 patients with anxiety and 8 of them had depression (two patients needed to start anti-depressants). In the PR group five patients suffered from anxiety and seven with depression.

After treatment the PRNS group had four patients with anxiety and six with depression, while the PR group continued to have two with anxiety and five were depressed. Anxiety improved in participants in the PR and PRNS groups (P = 0.001 and P = 0.007 respectively) but depression was unchanged. Body weight increased in the PR and PRNS groups significantly (1.1 ± 0.9kg, P = 0.002 and 0.6 ± 0.7kg, P = 0.007 respectively). In comparison to the controls the results were significant (P = 0.001 and P<0.001, respectively). The PRNS had a greater increase in body weight, BMI, FFMI in comparison to the PR group (P<0.05). Mid-thigh CSA increased greatly in the PRNS group (2.5 ± 4.1 cm^2, P = 0.011). Yet the PR and control group did not see any improvement.

Furthermore, the results of a Danish randomised control trial showed that nutritional support did not improve ISWT (P=0.91) [43]. COPD patients (n =53) with varying severity were recruited from a pulmonary rehabilitation centre. Patients were randomised to an exercise only group or an exercise group plus nutritional support. The nutritional support came in the form of a protein bar. However, for inclusion BMI had to be less than 30 kg/m^2. The mean BMI in the exercise only group and exercise plus nutritional support group was 24.3 ± 3.9 and 23.4 ± 4.3 kg/m^2 respectively.

Similarly, van de Bool *et al.* (2017) found that nutritional support in combination with exercise did not yield better 6-MWT in comparison to an exercise only group [44]. This study was a randomised placebo-controlled study that took place in five pulmonary rehabilitation centres in the Netherlands. For inclusion in the study patients had to have a FFMI less than the 25th percentile for sex and age. The intervention group was given an ONS drink of 125ml containing 187.5 Kcal and the control had a placebo drink over 4 months. Afterwards there was an 8-month maintenance period. The nutrition group had an increase in fat mass (pre: 19.8 ± 1.1, post: 21 ± 1.1 kg, P<0.001) and body weight (pre: 63.8 ±1.7 kg, post: 65.7 ± 1.7 kg, P<0.001). The between-group difference in body weight and fat mass was of importance (P<0.05 and P<0.01 respectively). Skeletal muscle mass was substantially better in both groups but between group difference was not significant (placebo; pre: 18.5 ± 0.6, post: 18.8 ± 0.6 kg, P<0.001 Nutrition; pre: 17.2 ± 0.6, post:17.8 ± 0.7 kg, P<0.001). Improvements were seen in CET and quadriceps muscle strength (P<0.001 for both in the nutrition group, and in the placebo group P<0.001 for CET and P<0.01 in quadriceps muscle strength), but no difference was identified between groups. The nutrition group continued to have a stable daily step count, but the placebo group decreased. The between group difference was significant (P<0.05). HADS total score was pointedly better in the nutrition group and the placebo (P<0.001 and P<0.01 respectively). No between group difference was identified.

This study had an extension, in which patients were followed-up 3 months after the 8-months maintenance phase. After 12 months there was no difference between the intervention and control group in terms of CET and QMS. Yet, activity levels were lower in the placebo group than in the intervention group (P = 0.05). Steps were significantly greater in the intervention group by 1030 steps (P = 0.025). Intervention group had improvements in HADS from baseline

(P = 0.05). The EQ-5D scores were significantly better in the nutrition group (P = 0.034). The results of the EQ-5D was correlated to body weight change (r = 0.406, p = 0.008).

2.2 Nutrition advice and education

A systematic review has found that compliance with oral nutritional support is good at 78% [45]. Nevertheless, patients report difficulty with oral nutritional supplementation due to poor taste and side effects like nausea, vomiting and diarrhoea [46]. Consequently, an alternative method may be required. Dietary counselling has been studied as a method to support nutritional needs and increase body composition. Weekes, Emery and Elia (2009) undertook a randomised control trial in the UK of patients with COPD in the outpatient setting who were labelled as being at risk of malnutrition [47]. The patients were randomised to either the control or the intervention group. The intervention lasted for six months and then the patients were followed-up six months later. The intervention arm was provided with a leaflet about dietary intake and with milk fortification supplements. In addition, patients were offered dietary counselling. Similarly, the control group were given the leaflet and milk supplementation, but none received any education or advice about dietary intake.

Patients were seen at baseline and then month 1, 3, 6, 7, 9 and 12. Sixty six patients were investigated within a population (n =125) that were suitable based on inclusion and exclusion criteria. However, by the end of the study only 37 patients remained. The authors report that the main reason for participants dropping out was due to a deterioration in health. The difference in characteristics between patients that dropped out and remained was not significant. To reduce data collection disparities the same person undertook all assessments. Dietary intake at baseline was calculated using a recall method but for all other visits a 5-day diary was completed. The diaries were analysed by two dieticians who were blinded. After the six-month intervention period the intervention group were consuming more calories and protein (2,064 kcal versus 1,715 kcal, P=0.02 and 77.1g versus 56.9 g, P<0.001 respectively) in comparison to the control group. Yet, this significance was not seen at the follow-up point. Furthermore, it was noted that 24 participants from the intervention group used the milk powder supplement for 14 days or more but nobody from the control group did. The intervention group gained weight and managed to maintain this during the follow-up period, unlike the control group who lost weight as the study took place (3.1 (0.5-5.7) 95% CI P=0.02). Similarly, the control group lost muscle mass and fat mass, but the intervention group gained both. The difference in the sum of four skinfold thickness was significant between the groups when measured by intention-to-treat at six and twelve months (difference 6.6 mm, P=0.02; 12 months: difference 9.7 mm, P = 0.01).

Yet, the difference in mid-upper arm muscle circumference was not of important at the sixth month but was at the twelfth month (difference 0.9cm, P = 0.04). SGRQ total scores were better in the intervention group from the intention to treat analysis (53.4 ±2.2 versus 61.1 ± 2.4, P = 0.02 at six months, 50.6 ± 2.7 versus 63.9 ± 2.8, P=0.002 at 12 months). The impact scores were significant (P = 0.004), but the symptoms and physical activity were not (P = 0.73 and P = 0.06 respectively). Likewise, intention to treat analysis showed SF-36 scores were better at 6 and 12 months in the intervention group (P = 0.001 and P = 0.003 respectively). Yet the MRC score was improved in the intervention group (difference in 1-point P = 0.03). The Townsend score was not statistically significant (difference 1.5, P = 0.06).

Similarly, Farooqi *et al.* (2010) undertook an intervention study in Sweden to explore the effect of nutritional education on people with COPD [47]. Patients were recruited from a pulmonary rehabilitation centre following referral but did not complete any specific exercise programme during the period. The study does not describe whether patients received this support after the study. Forty one patients were included in the study, and 36 at the follow-up period, as one had died and four withdrew consent.

Patients were provided with education about COPD individually and as part of a group by the multi-disciplinary team. Recommended dietary intake was calculated for each patient and advice given based on current intake. The method of data collection included patients completing a 24-hour food recall diary at baseline but at the 3-month and 1-year follow-up they completed a 3-day food diary. At the initial visit 17 patients were underweight, 18 had normal weight and 6 were overweight. Like Weekes, Emery and Elia (2009) [47], body weight at 3 months and 1 year had increased significantly (1 ± 2kg, P<0.004 and 1.3 ± 3kg P<0.02). Handgrip strength had also improved at 3 months (1.4 ± 3.4 kg, P = 0.02). However, at one year the change was no longer significant (P = 0.07).

Walking distance had improved significantly at 3 months and 1 year (95.1 ± 118.3 M, P = 0.001 and 83.2 ± 170.1 M, P = 0.007). Additionally, energy intake was noted to be significantly greater at 3 months and 1 year (13.9 ±18.4 %, 15 ±17.5% respectively, P<0.001). Similarly, protein intake at 3 months had improved significantly (8.3 ± 21.9 %, P<0.03) but at this was not the case at 1-year follow-up (P<0.09).

Discussion

The available literature shows that malnutrition has many negative effects on people with COPD. Malnutrition measured by BMI or FFMI may affect the distance that patients can walk. Six of the studies examined this relationship but only one study found that 6-MWT was not related to nutrition (Table 1). These studies were all moderate quality but Marco *et al.* (2019) was of marginally higher quality and found no relationship [15]. Yet they were all at risk of selection bias while Luo *et al*. (2016), [16] and Holst *et al.* (2019) were at risk of study design bias [10]. Furthermore, Hallin *et al.* (2011) did not show that malnutrition affected exercise ability [29]. However, this study used an alternative exercise test to the 6-MWT in the form of the 12-MWT which has been linked to patients tiring due to the increased time [49]. Malnutrition was found to be positively related to hand-grip strength in two studies of moderate quality [6, 29]. In addition, only one study examined the effect malnutrition has on balance and the risk of falls [19]. This study found that malnutrition was related to these variables. This was a study of moderate quality, but the risk of potential bias was apparent. In addition, all the sample were male. It is noted that the method to identify malnutrition is different but also comparator groups are different. Some studies used BMI [10, 14] and some used dietary intake [12] and others [16] used FFMI or both FFMI and BMI [15].

While the assessment method used may affect the outcome, the review shows that there is no link between nutrition status, exercise and muscle strength.

The association between severity of disease and malnutrition has been examined in six studies but one low quality study showed that dietary intake was not related to FEV_1 but was to FVC [24]. Nevertheless, three of the studies were of low quality while the other three were moderate. All studies were potentially at risk of selection bias while study design bias was seen in two [16,24]. Channelling bias was probable in the study by Baig *et al.* (2018) [25]. It appears that malnutrition is present in those with worse COPD.

Muscle strength is likely affected by poor nutrition which could potentially worsen respiratory muscle function coincidently. Yet, it is challenging to understand whether malnutrition causes worsening of COPD, or vice versa, but as a result of the research available it is not possible to make a firm conclusion. There has only been a weak or low correlation shown. Nevertheless, most of the studies have included GOLD stage 2-4 COPD and have shown malnutrition in all categories but poorer nutrition is more prevalent in GOLD stage 4.

In addition, there were conflicting findings on the effect of malnutrition on exacerbation rate. Hallin *et al.* (2006) [29] found the rate was increased but Mete *et al.* (2018) did not [30]. Therefore, exacerbation may be affected.

Furthermore, hospital admissions and mortality rates are increased along with cost to the health system. The findings were produced from six studies and five of these were moderate quality and one was high quality (Table 2). There was the potential for selection bias in four of the studies. Nevertheless, these findings are in an era where financial constraints are prominent in the NHS and the budget per person has dropped. Consequently, funding must be spent in a more sensible manner and in a way that reduces further costs. As mortality is significantly affected, malnutrition management should be incorporated into patient care. Yet it is not clear how many patients are routinely screened for malnutrition as part of their routine care. Odencrants, Ehnfors, and Ehrenberg (2009) discuss how many nurses in primary care have been found to assess nutrition based solely on previous experiences [50]. Additionally, health care professionals endeavour to improve the life of the patients by delivering holistic care.

Quality of life is an important measurement and various assessment tools have been used in the studies included in this review. There are conflicting findings as to whether SGRQ is affected by malnutrition. Katsura, Yamada and Kida, (2005) [14] report that it is, but Vermeeren *et al.* (2006) [6] and Humphreys *et al.* (2008) [22] found no difference. Veremeeren *et al.* (2006) [6] was a much larger study and like Humphreys *et al*. (2008) [22] patients were classified based on BMI or FFMI. This is dissimilar to Katsura, Yamada and Kida, (2005) who categorised patients based on BMI only [14]. All three studies were of moderate quality. Vermeeren *et al.* (2006) [6] also found no difference between groups in breathlessness score measured by MRC while Mete *et al.* (2018) [30] and Lee *et al.* (2013) [12] did find a difference with mMRC. Similarly, Katsura, Yamada and Kida, (2005) found breathlessness was worse in malnourished patients by using OCD [14].

Mete *et al.* (2018), Lee *et al.* (2013) did not distinguish between body composition but examined dietary intake [12,30]. If breathlessness is worse in those with poorer nutrition, then it may be associated with those that also have reduced 6-MWT.

Furthermore, the benefit of nutritional intervention was examined in seven studies. Two studies were considered high quality while three were moderate and two were low. Five studies showed that body weight was significantly improved in the nutritional groups. However, it is noted that lower volumes may be more suitable as those given greater calories gained fat and lost FFMI [39].

Lung function improved in the group with lower calories in the study by Planas *et al.* (2005) [39] but worsened in those given more calories. Yet, Broekhuizen *et al.* (2005) found lung function changes were not clinically significant but this study is at risk of chronology bias [40]. Furthermore, Sugwara *et al.* (2010) found that inspiratory pressures and quadricep muscle force increased following nutrition [41]. In contrast the higher quality study by van de Bool *et al.* (2017) [44] found that CET and quadriceps muscle strength changes were not different between groups. Yet, a systematic review by Collins *et al.* (2013) showed by meta-analysis that respiratory muscle function was improved with supplementation [51].

Also, studies examined the effect of nutrition on exercise ability. Broekhuizen *et al.* (2005) and Sugwara *et al.* (2010) found that intervention improved 6-MWT [40,41].

Yet, these were low quality studies which differ to the results of three other studies showing no significant change in exercise ability measured by 6-MWT or ISWT [42-44]. Yet, van de Bool *et al.* (2017) did show an increase in daily steps with nutrition which was continued at the 3-month follow-up study [44, 50]. Collins *et al.* (2013) reported that four of five studies examining exercise reported that intervention improved exercise, but a meta-analysis was not possible. As mentioned, it is likely malnutrition affects exercise ability so perhaps longer duration of treatment is required to reverse this effect [51].

Quality of life was not seen to improve in several studies (Table 1 and 2). Sugwara *et al.* (2010) showed that intervention improved health related QOL, however, not being a blinded study there was a risk of bias [41]. Unfortunately, different tools to measure quality of life and breathlessness were used in the studies (Table 1 and 2). As a result, comparison between studies is challenging. In one study HADS did not improve between groups after initial treatment, yet, after a further 3 months there was a significant difference between groups [44,52]. In addition, exercise was not improved in the intervention group in comparison to the control group in any of the studies. Nonetheless, it is interesting that most of the studies combined nutrition programmes as part of pulmonary rehabilitation. Not all patients will be suitable for referral and those with more severe COPD may be housebound [53]. Therefore, there is potentially a gap in the current knowledge.

Two studies examined the benefit of dietary education and counselling and both were of moderate quality (Table 1 and 2). Weekes, Emery and Elia (2009) report that patients consumed more calories, increased their weight and improved quality of life and global health scores [47]. Yet, the increase in calories was not continued after the programme. Although this study was at risk of design bias as it was non-blinded (Table 1 and 2). Similarly, Faroorqi *et al.* (2010) showed that an education programme could increase weight after three months which was maintained at one year [48] . However, this study was also at risk of transfer bias. In addition, hand-grip strength improved but this result did not remain significant at one year. Consequently, these studies show that dietary counselling is likely to have an important role on the management of malnutrition in COPD. Nevertheless, although it is seen as a positive event that patients have gained weight in the studies, it is not clear to what level of nutrition patients with COPD need to reach in order to lower the risk of negative effects associated with malnutrition.

More research which examines the impact of malnutrition on COPD is necessary. Given that most of the studies are cross-sectional, a longitudinal cohort study over 2-5 years should be conducted. The study should primarily examine the effect of malnutrition on COPD severity, quality of life and exercise ability. A sample size of approximately fifty COPD patients from each GOLD stage should be used. In addition, research should explore the long-term effect of nutritional support. It would seem appropriate to undertake a randomised control trial over one year which involves the use of nutritional supplements and education. Patients with a low BMI and FFMI would be recruited from the respiratory outpatient department. As many of the studies have small numbers, a sample size of 150 patients may be appropriate. Furthermore, the nurse is an important contact for the patient with COPD. The nurse may be the first health care professional that the patient with COPD meets. The patient will continue to have ongoing nurse-led appointments. As a result, the nurse might be ideally placed to assess and implement a nutrition plan with the patient [50]. Consequently, the randomised control trial would involve nurses providing education and support during the study. An additional part of this study would preferably examine whether nutritional support is cost-effective.

Ideally, further studies should be done independent of pulmonary rehabilitation programmes.

Conclusion

Malnutrition affects a high proportion of people with COPD. There are multiple ways in which malnutrition is being measured in studies including BMI and FFMI. Yet, malnutrition is affecting exacerbation rates and increasing hospital admission and associated costs. Mortality is significantly associated with malnutrition which infers that health care professionals have a duty to include malnutrition assessment into the care of COPD patients. Furthermore, malnutrition worsens the patients' exercise ability and potentially severity of disease and quality of life. Consequently, oral nutritional supplementation may help the patient by avoiding further weight loss and increasing FFMI. Yet, smaller volumes/calories to support intake may be more appropriate. Finally, education and advice on nutrition may offer short term effects at improving intake. This knowledge is imperative to health care professionals to allow holistic care to be delivered. Furthermore, if malnutrition is not properly addressed then health care professionals may be failing the patient with COPD. Consequently, clinical practice must incorporate robust plans to monitor nutrition in COPD patients and tailor a nutrition plan with the patient that is regularly reviewed.

Acknowledgements

No funding was received by the authors and the Review was submitted towards an MSc in Respiratory Medicine, University of South Wales.

Conflict of Interest

The authors have no conflict of interest.

References

1. British Lung Foundation (BLF). Chronic Obstructive Pulmonary Disease (COPD) statistics. *(2019),* https://statistics.blf.org.uk/copd (Accessed: 04/06/20).

2. NICE. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. (2006). https://www.nice.org.uk/guidance/cg32/resources/nutrition-support-for-adults-oral-nutrition-support-enteral-tube-feeding-and-parenteral-nutrition-pdf-975383198917 (Accessed: 04/06/20).

3. Nici L, Donner C, Wouters E. et al. American thoracic society/European respiratory society statement on pulmonary rehabilitation. Am J Respir Crit Care Med (2006), 173: 1390-1413.

4. NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. (2018).https://www.nice.org.uk/guidance/ng115 (Accessed: 04/06/20).

5. Rawal G. and Yadav S. Nutrition in chronic obstructive pulmonary disease: A review. J Trans Int Med (2015) 3: 151-154.

6. Vermeeren MAP, Creutzberg EC, Schols AMWJ, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Resp Med, (2006), 100: 1349-1355.

7. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutri *(2017)*, 36: 49-64.

8. Shepherd AA. Nutrition through the life span. Part 2: children, adolescents and adults. Br J Nutri (2013), 17: 2052-2819.

9. Chapman S, Robinson G, Stradling J, et al. *Oxford handbook of respiratory medicine*. 3rd edn. (2014), Oxford: Oxford University Press UK.

10. Holst M, Beck AM, Rasmussen HH. et al. (2019) ‘Insufficient intake of energy and protein is related to physical functional capacity among COPD patients referred to municipality based pulmonary rehabilitation. Clin Nutri ESPEN (2019), 30: 35-41.

11. Harari S. Randomised controlled trials and real-life studies: two answers for one question. Eur Resp Rev (2018), 27: 1-2.

12. Lee H, Kim S, Lim Y.et al. Nutritional status and disease severity in patients with chronic obstructive pulmonary disease (COPD). Arch Geronto Geriatrics. (2013), 56: 518-523.

13. Ma Y, Olendzki BC, Pagoto SL, et al. Number of 24-Hour Diet Recalls Needed to Estimate Energy Intake. Ann Epidemiol (2009), 19: 553-559.

14. Katsura H, Yamada K, and Kida K. Both generic and disease specific health related quality of life are deteriorated in patients with underweight COPD. Resp Med (2005), 99: 624-630.

15. Marco E, Sanchez-Rodríguez D, Davalos-Yerovi VN, et al. Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease. Clin Nutri (2019), 38: 2180-2186.

16. Luo Y, Zhou L, Li Y, et al. Fat-Free Mass Index for Evaluating the Nutritional Status and Disease Severity in COPD. Resp Care (2016), 61: 680-688.

17. Hallin R, Janson C, Arnardottir RH, et al. Relation between physical capacity, nutritional status and systemic inflammation in COPD. Clin Resp J (2011), 5:136-142.

18. Massy-Westropp NM, Gill TK, Taylor AW, et al. Hand Grip Strength: age and gender stratified normative data in a population-based study. BMC Res Notes (2011), 4: 2-5.

19. Mkacher W, Tabka Z. and Trabelsi Y. Relationship between postural balance, lung function, nutritional status and functional capacity in patients with chronic obstructive pulmonary disease. Sci Sport (2016) 31: 88-94.

20. Hsu, MF, Ho SC, Kuo HP, et al. Mini-Nutritional Assessment (MNA) is Useful for Assessing the Nutritional Status of Patients with Chronic Obstructive Pulmonary Disease: A Cross-sectional Study. J Chron Ob Pulmon Dis (2014), 11: 325-332.

21. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Pocket Guide to COPD diagnosis, management, and prevention. (2019).

22. Humphreys K, Cross G, Frith P. et al. Nutritional status and dietary intake of outpatients with chronic obstructive pulmonary disease. Nutri Dietet, (2008), 65:168-174.

23. Kyle UG, Bosaeus I, De Lorenzo AD, et al. Bioelectrical impedance analysis - part II: utilization in clinical practice. Clin Nutri, (2004), 23:1430-1453.

24. Yazdanpanah L, Shidfar F, Moosavi AJ. et al. Energy and Protein Intake and Its Relationship with Pulmonary Function in Chronic Obstructive Pulmonary Disease (COPD) Patients. Acta Med Iranica, (2010) 48: 374-379.

25. Baig MMA, Hashmat N, Adnan M. et al. The relationship of dyspnea and disease severity with anthropometric indicators of malnutrition among patients with chronic obstructive pulmonary disease. Pakistan J Med Sci (2018), 34: 1-6.

26. Dilektaşli AG, Ulubay G, Bayraktar N, et al. The effects of cachexia and related components on pulmonary functions in patients with COPD. Tüberküloz ve Toraks Dergisi (2009), 57: 298-305.

27. Wagner PD. Possible mechanisms underlying the development of cachexia in COPD. Eur Resp J, (2008), 31: 492-501.

28. Gupta SS, Gothi D, Narula G. et al. Correlation of BMI and oxygen saturation in stable COPD in Northern India. Lung India (2014), 31: 29-34.

29. Hallin R, Koivisto-Hursti UK, Lindberg E. et al. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). Resp Med (2006), 100: 561-567.

30. Mete B, Pehlivan E, Gulbas G. et al. Prevalence of malnutrition in COPD and its relationship with the parameters related to disease severity. Int J COPD, (2018) 13: 3307-3312.

31. Kaiser MJ, Bauer JM, Ramsch C, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutri Health Aging (2009), 13: 782-788.

32. Schols A, Broekhuizen R, Weling-Scheepers CA et al. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutri (2005) 82: 53-59.

33. Hoong JM, Ferguson M, Hukins C. et al. Economic and operational burden associated with malnutrition in chronic obstructive pulmonary disease. Clin Nutri (2017) 36: 1105-1109.

34. McDonald MLN, Diaz AA, Rutten E, et al. Chest computed tomography-derived low fat-free mass index and mortality in COPD. Eur Resp J (2017), 50, 1-20.

35. McDonald ML, Wouters EF, Rutten E, et al. It's more than low BMI: prevalence of cachexia and associated mortality in COPD. Resp Res (2019), 20: 1-9.

36. Beauchamp T. and Childress J. Principals of Biomedical Ethics. 7TH ed. (2013), Oxford University Press, Oxford, UK.

37. Sauer AC, Alish CJ, Strausbaugh K, et al. Nurses needed: identifying malnutrition in hospitalized older adults. Nursing Plus Open (2016) 2: 21-25.

38. BAPEN. Oral Nutritional Supplements (ONS) (2016).

39. Planas M, Alvarez J, Garcia-Peris PA, et al. Nutritional support and quality of life in stable chronic obstructive pulmonary disease (COPD) patients. Clin Nutri (2005) 24: 433-441.

40. Broekhuizen R, Creutzberg EC, Weling-Scheepers CAPM, et al. Optimizing oral nutritional drink supplementation in patients with chronic obstructive pulmonary disease. Brit J Nutri (2005), 93: 965-971.

41. Sugawara K, Takahashi H, Kasai C, et al. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. Resp Med (2010) 104: 1883-1889.

42. Gurgun A, Deniz S, Argin M. et al. Effects of nutritional supplementation combined with conventional pulmonary rehabilitation in muscle-wasted chronic obstructive pulmonary disease: A prospective, randomized and controlled study. Respir (2013), 18: 495-500.

43.Ahnfeldt-Mollerup P, Hey H, Johansen C, et al. The effect of protein supplementation on quality of life, physical function, and muscle strength in patients with chronic obstructive pulmonary disease. Eur J Physical Rehab Med (2015) 51: 447-456.

44. van de Bool C, Rutten EPA, van Helvoort A, et al. A randomised clinical trial investigating the efficacy of targeted nutrition as adjunct to exercise training in COPD. J Cachexia Sarco Muscle (2017), 8: 748-758.

45. Hubbard GP, Elia M, Holdoway A. et al. Compliance to oral nutritional supplements and its association with increased total energy intake: results from a systematic review. Proc Nutri Soc (2011) 70: OCE5.

46. Drug and Therapeutics Bulletin. What role for oral nutritional supplements in primary care? *British Medical Journal*, 56(8) Brit Med J (2018) 56.

47. Weekes CE, Emery PW and Elia M. Dietary counselling and food fortification in stable COPD: a randomised trial. Thorax (2009), 64: 326-331.

48. Farooqi N, Nordström L, Lundgren R. et al. Changes in body weight and physical performance after receiving dietary advice in patients with chronic obstructive pulmonary disease (COPD): 1-year follow-up. Arch Geront Geriatrics (2010) 53: 70-75.

49. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Resp Crit Care Med (2002) 166: 111-117.

50. Odencrants S, Ehnfors M, and Ehrenberg A. Nutritional status and body composition among persons with chronic obstructive pulmonary disease. J Nursing Healthcare Chron Ill (2009) 1: 60-70.

51. Collins, PF, Elia M. and Stratton RJ. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Resp (2013), 18: 616-29.

52. van Beers M, Rutten-van Molken, MPMH, van de Bool C, et al. Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial. Clin Nutri (2019), 19: 1-9.

53. Bolton CE, Bevan-Smith EF, Blakey JD, et al . BTS Guideline on Pulmonary Rehabilitation in Adults. Thorax (2013), 68: 1-30.

Table 1 Theme 1 Study Design and Quality Assessment Score.

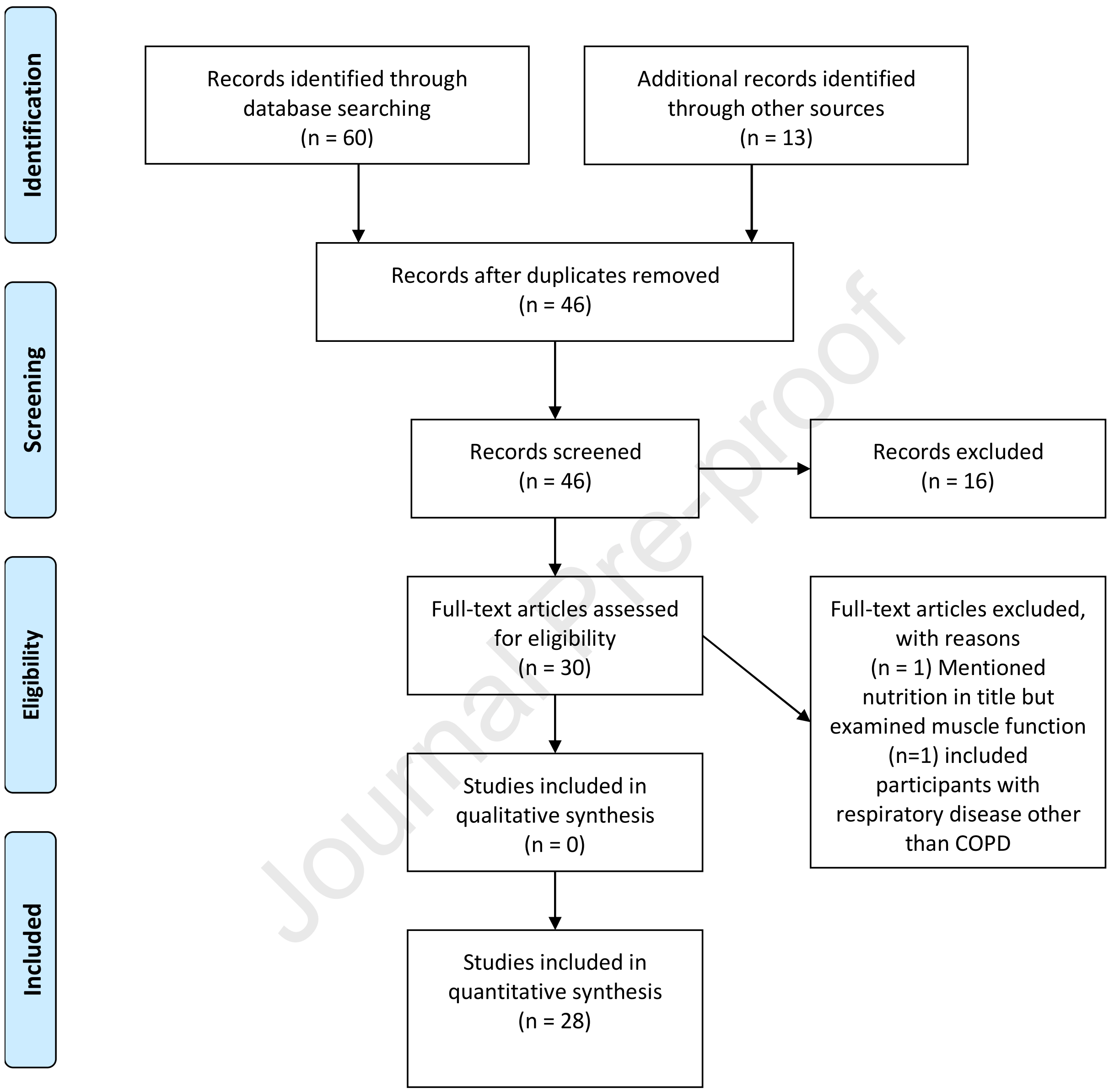
Study	**Type of study And Sample size (Male:Female)**	**Characteristics**	**Comparison**	**Outcome Measurements**	**Bias**	**QAS** (max 36)
Baig *et al.* (2018) [25]	Cross-sectional 138 (106:32)	Outpatient clinic Mean BMI=18.9kg/m^2	Underweight patients compared to normal weight	Lung function, BMI, MUAC, mMRC	Selection bias. Possible channelling bias (severe patients)	16
Dilektaşli *et al.* (2009) [26]	Cross-sectional 35 (30:5)	Setting not specified BMI <20 kg/m^2	Comparison made between groups based on BMI.	TNF-α, DLCO, MUAC, TSF	Selection bias	22
Gupta *et al.* (2014) [28]	Cross-sectional 147 (139:8)	Outpatient department	Comparison made between groups based on BMI.	BMI, Lung function Oxygen saturation	Selection bias	16
Hallin *et al.* (2006) [29]	Prospective cohort 41 (14:27)	Hospital and home setting.	Comparison made between groups based on BMI.	Admission, BMI, Energy intake, Exacerbation rate	Study design bias	24
Hallin *et al.* (2011) [17]	Cross-sectional 49 (14:35)	Exercise department	Comparison made between groups based on BMI and FFMI.	BMI, FFMI, ISWT, 12-MWT, Arm and leg circumference, Hand-grip strength, Peak working capacity	Selection bias. Study design bias by following people up post admission	22
Holst *et al.* (2019) [10]	Cross-sectional 79 (37: 42)	Pulmonary rehabilitation centre	Dietary intake below <75% compared to intake ≥75%	Dietary intake, Weight loss Symptom burden, Malnutrition risk , 6-MWT 30-s CST	Selection bias Study design bias (including people with conditions that may affect nutrition)	23
Hoong *et al.* (2017) [33]	Observational Cohort 834 (194:92)	Hospital	Comparison of those who died and had admissions	Malnutrition, Mortality Admission Cost	Selection bias	27
Humphreys *et al.* (2008) [22]	Cross-sectional study 66 (32:34)	Outpatient clinic and home setting.	Comparison made between groups based on BMI and FFMI.	BMI, FFMI, Dietary intake SGRQ, Activity, Lung function	Selection bias	25
Katsura *et al.* (2005) [14]	Cross sectional study 83 (73:10)	Outpatient department BMI <26kg/m^2	Comparison made between groups based on BMI	Lung function, Body composition, SGRQ, SF-36 6-MWT, OCD	Selection bias	24
Lee *et al.* (2013) [12]	Cross-sectional descriptive study 251(232:19)	Respiratory outpatients in five hospitals	Dietary intake below <75% compared to intake ≥75%	Dietary intake, BMI, BODE 6-MWT, Admission, mMRC	Study design bias as 24-hour collection may not have been long enough.	25

Luo *et al.* (2016) [16]	Cross sectional study 235 (184:51)	Outpatient clinic	Comparison between GOLD groups and FFMI	GOLD, FFMI, Exacerbation 6-MWT, mMRC, PImax PEmax	Selection bias Study design bias(including people with conditions that may affect nutrition)	24
Marco *et al.* (2018) [15]	Cohort 118, (95:23)	Pulmonary rehab centre	Comparison between those identified as malnourished with those nourished	BMI, FFMI, Lung function DLCO, 6-MWT, MRC Mortality	Selection bias	27
McDonald *et al.* (2017) [34]	Cohort ECLIPSE 1,518 (979: 539) COPDGene 3,121 (y:x)	Recruited for a clinical trial	Patients with low $FFMI_{PMA}$ were compared to those with normal $FFMI_{PMA.}$	FFMI Mortality	Potential recall bias	27
McDonald *et al.* (2019) [35]	Cohort 1483 (968:515)	46 centres	Patients were compared based BODE, WODE and CODE	Lung function, BMI, FFMI Functional Assessment of Chronic Illness Therapy score. 6-MWT, BODE, CODE, WODE, Mortality	Bias associated with using tools not validated	29
Mete *et al.* (2018) [30]	Cross sectional 105 (97:8)	Outpatient department (80% were from this setting) and referred hospitalised patients	Those at risk of malnutrition were compared to those that weren't.	Lung function, Exacerbation rate, MNA, Waist circumference, Dietary intake, mMRC	Selection bias, Analysis bias Study design bias (recruiting some patients who were inpatient and including people with conditions that may affect nutrition	20
Mkacher *et al.* (2016) [19]	Cross sectional study 58 (58:0)	Hospital setting	Those with poor balance or at risk of falls compared to those who weren't in terms of nutrition and physical ability.	6-MWT, BMI, MNA,TUG Unipodal stance test,Tinetti test, Berg balance scale	Selection bias	25
Schols *et al.* (2005) [32]	Cohort 412 (318:94)	Pulmonary rehab clinic	Patients were split into 4 groups	Lung function, SMI, FFMI BMI, Mortality	Selection bias	23
Vermeeren *et al.* (2005) [6]	Cross-sectional study 389 (271:118)	Outpatients at 39 sites.	Comparison of those identified as malnourished with those nourished.	Lung function, SGRQ, MRC FFMI, FFM, BMI	Study design bias (including people with conditions that may affect nutrition).	25
Yazdanpanah *et al.* (2010) [24]	Cross sectional study 63 (unknown)	Patients were recruited when acutely unwell in hospital but were stable at the time of the study.	Comparison of energy intake in comparison to lung function.	Lung function Dietary intake Exacerbation	Selection bias Study design bias (including people with conditions that may affect nutrition).	18

Table 2 Theme 2 Study Design and Quality Assessment Score.

Study	**Type of study And Sample size (Male:Female)**	**Characteristics**	**Comparison**	**Outcome Measurements**	**Bias**	**QAS (max 36)**
Ahnfeldt-Mollerup *et al.* (2015) [43]	RCT 53 (23:30)	Pulmonary rehabilitation BMI <30kg/m^2	Comparison between intervention group given energy bar and control group	ISWT, SGRQ, Muscle strength, Calorie intake, MRC	Selection bias	27
Broekhuizen *et al.* (2005) [40]	Retrospective control 39 (30:9)	Pulmonary rehab Inclusion based on BMI, FFMI and weight loss	Comparison between group A given 125ml drink and group B given 200ml drink	Body weight, FFM, FM, Incremental bicycle, REE, Ergometry, SGRQ, Lung function.	Selection bias Chronology bias	20
Farooqi *et al.* (2010) [48]	Prospective Intervention 41 (21:20)	Outpatient department	Given nutrition education, then followed up at 3 and 12 months.	12-MWT, Hand-grip strength, Dietary intake	Selection bias Transfer bias	23
Gurgun *et al.* (2013) [42]	RCT 46 (28:2)	Outpatient department Inclusion based on BMI, FFMI and weight loss	Comparison of groups randomised to PRNS, PR or control	MRC, BORG, 6-MWT, SGRQ, HADS, CSA of quadricep femoris	Selection bias Bias as unblinded study	26
Planas *et al.* (2005) [39]	Randomised trial 24 (20:4)	Outpatients department Inclusion based on BMI, FFMI and weight loss	Comparison of group A and B based on additional calorie factors applied	CRDQ, Weight, FFMI, Skin fold thickness, Lung function, Energy intake	Design bias Selection bias	22
Sugawara *et al.* (2010) [41]	RCT 32 (ratio not given)	Pulmonary rehab centre	Comparison of intervention to control	Inflammation, 6-MWT, CRDQ, MRC, Energy intake	Selection bias Bias - unblinded	19
van Beers *et al.* (2019) [52]	RCT 81 (41:40)	Seven pulmonary rehab centres.FFMI below the normal range for age and sex	Extension of Van de Bool *et al.* (2017) to measure the long-term effect	Lung function, Quadricep muscle strength, DEXA, Bloods, Cost, Steps, HADS, EQ-5D	Selection bias	31
Van de Bool *et al.* (2017) [44]	RCT 81 (41:40)	Pulmonary rehabilitation centres' Low free mass index	Comparison of intervention group given drinks and control had a placebo drink.	BMI, FFMI, SKM, CET, Quadricep muscle strength, 6-MWT, Inspiratory muscle strength, Dietary intake, Steps, HADS	Study design bias Smaller sample than intended	32
Weekes, Emery and Elia, (2008) [47]	RCT 59 (30:29)	Outpatient clinic At risk of malnutrition measured by MUST	Dietary education and milk fortification in comparison to the control group.	Dietary intake, Weight, SGRQ, Townsend score, MRC	Study design bias (dropouts not accounted for). Bias – unblinded	26

Figure 1


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 60)
Additional records identified through other sources (n = 13)
Records after duplicates removed (n = 46)
Records screened (n = 46)
Records excluded (n = 16)
Full-text articles assessed for eligibility (n = 30)
Full-text articles excluded, with reasons (n = 1) Mentioned nutrition in title but examined muscle function (n=1) included participants with respiratory disease other than COPD
Studies included in qualitative synthesis (n = 0)
Studies included in quantitative synthesis (n = 28)

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16th Sept 2020

Dear Editor,

The authors declare no conflict of intrest.

Yours sincerely

Mark Williams

Professor, University of South Wales.