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Nutritional screening and nutritional support in chronic obstructive pulmonary disease (COPD)

by

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ABSTRACT
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NUTRITIONAL SCREENING AND NUTRITIONAL SUPPORT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Malnutrition is a common problem in chronic obstructive pulmonary disease (COPD) and associated with poorer prognosis. Currently controversies surround the importance of nutritional intervention and how best to nutritionally manage those identified as at risk of malnutrition. Dietary advice (DA) and oral nutritional supplements (ONS) are two of the most common first line treatments for malnutrition in COPD but the evidence base for DA is lacking and for ONS appears uncertain. To date there have been no randomised trials comparing these two treatments in COPD.

The aims of this thesis were three-fold, firstly, to establish the local prevalence of malnutrition in UK outpatients with COPD and examine the impact of malnutrition on clinical outcomes (healthcare use, mortality). Secondly, to perform a systematic review to clarify the current evidence for nutritional support in stable COPD patients and finally, to carry out a randomised trial comparing the effectiveness of a 3-moht intervention of DA versus ONS in improving quality of life (QoL) in stable outpatients with COPD.

The prevalence of malnutrition was high in outpatients with COPD (22% at risk), with a lower BMI being a strong significant independent predictor of mortality and increased emergency healthcare use. Contrary to previous reviews, the current systematic review found that nutritional support, mainly involving ONS, resulted in significant improvements in nutritional intake, body weight and anthropometry as well as several functional outcomes. For several reasons, an RCT investigating DA vs. ONS that was undertaken as part of this work was underpowered and did not find any improvements in outcomes of interest although both groups maintained weight and function possibly indicating a treatment effect. When pre- and post-intervention analysis was carried out combining both interventions (ONS + DA) significant improvements in energy and protein intakes, body weight and non-dominant handgrip strength were observed. However, with a small sample and the absence of a control group these results should be interpreted with caution.

Nutrition support is effective at treating malnutrition in COPD but the results from this thesis appear to suggest that earlier intervention is required. This highlights to importance of accurate nutritional screening and assessment in this patient group.

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Declaration of Authorship

I, **Peter Francis Collins**, declare that this thesis entitled **'Nutritional screening and nutritional support in chronic obstructive pulmonary disease (COPD)'** and the work presented in it are my own. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at the University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of other, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
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Signed:

Date: 28.12.2012

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Abbreviations

AECOPD	Acute exacerbation of COPD
BIA	Bioelectrical Impendence Analysis
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
DRM	Disease-related malnutrition
DXA	Dual-energy X-ray Absorptiometry
EI	Energy intake
EQ-5D	Euroqol 5 dimensional quality of life assessment tool
FEV_1	Forced expiratory volume in 1 second
FFM	Fat-free mass
FFMI	Fat-free mass index
FM	Fat mass
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HGS	Handgrip strength
IBW	Ideal body weight
IMD	Index of multiple deprivation
ITT	Intention-to-treat
LSOAs	Lower super output areas
MUAC	Mid-upper arm circumference
‘MUST’	‘Malnutrition Universal Screening Tool’
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
ONS	Oral nutritional supplement
PEM	Protein energy malnutrition
PE_{MAX}	Maximum expiratory muscle pressure
PI	Protein intake
PI_{MAX}	Maximal inspiratory muscle pressure
QoL	Quality of life
RCT(s)	Randomised controlled trial(s)
REE	Resting energy expenditure
S4SF	Sum of four skinfolds
SGRQ	St George’s Respiratory Questionnaire
TDA	Tailored dietary advice
TEE	Total energy expenditure
TSF	Triceps skinfold thickness
TTO	Time trade-off
UK	United Kingdom
VAS	Visual analogue scale
WMP	Whole milk powder

1.1.0 Literature Review

1.1.1 Disease-related Malnutrition

Malnutrition, or undernutrition, arises from an imbalance between nutritional intake and expenditure, which can be due to increased requirements or an inability to ingest and utilise energy, protein and nutrients. Malnutrition literally means bad nutrition, with 'mal' coming from the Greek meaning bad. Disease-related malnutrition (DRM) is common in individuals with both chronic and acute conditions as nutritional intake is often compromised. In addition to reduced intake, increased expenditure may simultaneously occur. Those with disease are likely to spend more time at rest, and resting energy expenditure (REE) has been found to be elevated in the presence of disease, particularly acute disease. Given that REE is the largest component of total daily energy expenditure (TEE) in healthy individuals and even more so in those that are inactive, the extent to which it is raised was thought to be an important consideration in the nutritional management of malnutrition. However, any increases in REE secondary to disease or illness are usually more than compensated for by a reduction in physical activity. A study in two groups of patients with chronic obstructive pulmonary disease (COPD) found comparable TEE between the two groups, despite one group having elevated REE (1), the authors found that both REE and TEE in COPD significantly correlate with fat-free mass (FFM). It appears DRM is predominantly driven by a reduced intake of energy and protein or an inability to utilise nutrition appropriately (e.g. in the face of marked inflammation) rather than increased nutritional requirements *per se*. There are several causes for reduced nutritional intake in the face of disease these include, but are not confined to, aging, pain, depression, sociological influences, disease-specific pathological changes and elevated inflammatory markers. Inflammatory cells, such as tumour necrosis factor alpha (TNF-α), C-reactive protein (CRP) and several interleukins (IL-1, IL-6 and IL-8) are associated with both reductions in energy intake and increased REE (2). These acute phase proteins and cytokines reduce appetite whilst at the same time increase demand for substrate, resulting in the release of nutrients from bodily stores (e.g. skeletal and hepatic glycolysis and gluconeogenesis of amino acids derived predominantly from skeletal muscle). Chronic wasting diseases such as COPD, cancer, hepatic

disease, and chronic renal and heart failure are all associated with these pathological changes (3).

DRM is not a problem confined to the hospital environment but has been found to be common across all echelons of society and in numerous health and social care settings, both in acute and chronic conditions, within hospital, residential and nursing home environments. A recent report by the British Association for Parenteral and Enteral Nutrition (BAPEN) has once again highlighted that the levels of malnutrition or risk of malnutrition observed in hospitals are high (28%). The fact this prevalence figure was established through screening patients shortly after admission to hospital suggests the majority of malnutrition is of community origin, with only a third of those identified as at risk of malnutrition being due to the acute effects of illness (4). It is estimated that the majority of individuals at risk of malnutrition (93%) live outside hospitals in the community, 2-3% of whom are in sheltered housing, around 5% reside in care homes and only 2% in hospitals (5). Of particular importance is the fact that 80% of those patients identified as at risk of malnutrition on admission could have been identified earlier in the community.

Patients with chronic conditions such as COPD are primarily managed within the community setting by their General Practitioner (G.P). It is estimated that COPD accounts for 1.4 million G.P consultations each year in the UK (6), up to 2 times that of angina rising to 4 times higher in those with severe respiratory disease (7). With the current economic climate within the National Health Service (NHS) there continues to be an emphasis on the ‘hospital at home’ with all, but those with the severest disease requiring intensive intervention, being managed in the community setting. However, to date nutritional screening and nutritional intervention studies have focused primarily on the acute setting yet if the increasing burden of DRM is to be addressed, interventions aimed at tackling DRM within the primary care setting appear to be where the focus should lie in future.

The treatment of malnutrition is no different to treating any other life threatening illness where early treatment is more likely to result in a successful outcome. Routine nutritional screening in the outpatient setting would be likely to lead to the earlier identification and treatment of individuals at risk of malnutrition. Physiologically, nutritional support in the community setting may be an optimum

time to intervene as outpatients are more likely to be infection free, physically active, less acutely unwell, metabolically stable and potentially more able to produce an anabolic state to best utilise any additional nutrition provided. This does raise interesting issues about where to target nutritional screening resources, research and staff in order to tackle DRM. BAPEN have suggested that at any one time, there are an estimated 3 million or more individuals at risk of malnutrition within the UK (8) whilst there are only approximately 200,000 hospital beds in the UK. This clearly indicates that malnutrition is not a problem confined to the NHS but a wider social problem. The fact there are less than 8000 registered dietitians working within the NHS, with the majority working in the acute setting, suggests there is an argument that the current structure and delivery of nutritional care in the treatment of malnutrition needs to be addressed.

BAPEN has highlighted that in order for the socio-economic burden of DRM to be tackled there needs to be greater continuation of nutritional care between the primary and secondary care settings, referred to as 'the patient journey' (9). This will involve routine nutritional screening as part of the medical management of both inpatients and outpatients and within both hospitals and G.P surgeries. With a declining length of hospital stay (average of approximately 6-7 days depending on the condition) and earlier discharge of patients from hospital into the community there is only a limited period of time in order to initiate nutritional care within the acute setting. Although research trials in outpatients have a number of challenges such trials are needed in order to inform practice if the community setting is where the focus should be.

1.1.2 Identification of disease-related malnutrition

When identifying malnutrition it is important to establish what is considered 'good' nutrition, both at an individual level and for a specific population group and what is considered 'bad' nutrition (10). This is not straightforward as physicians, dietitians, clinical nutritionists and healthcare professionals involved in the nutritional management of patients continue to disagree with the exact definition of malnutrition and what methods should be used to identify those at risk. This lack of consensus means there is presently no universally accepted definition for malnutrition and there is no one method accepted as gold standard for identifying those at risk. A definition previously suggested and widely accepted is as follows:

Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome (11).

Whilst individuals may be malnourished due to a deficiency or excess of particular nutrients leading to adverse effects (e.g. vitamin C leading to scurvy) this thesis will focus on protein-energy malnutrition (PEM) and the terms malnutrition and DRM will relate to this. However, because PEM is often a result of an impaired/inadequate intake of food it is also associated with deficiencies of many micronutrients. This thesis will also focus on the identification of PEM and its treatment.

In order to treat individuals with or at risk of PEM they must first be identified and many inconsistencies exist as to what cut-offs should be employed to diagnose malnutrition or identify those at risk of malnutrition. This will partly depend on whether nutritional screening or nutritional assessment is performed. The American Society of Parenteral and Enteral Nutrition (ASPEN) defines nutritional screening as “a process to identify an individual who is malnourished or who is at risk for malnutrition to determine if a detailed nutritional assessment is indicated”(12). Nutritional assessment may then involve biochemical analysis, examination around the adequacy of nutritional intake or body compositional assessment; It is more thorough and therefore more time consuming, may be expensive and should always be performed by a trained practitioner.

In 2005 a review identified over 70 nutritional screening tools but this did not include many locally designed tools and since the publication of the review the number is likely to have grown (13). The fact there are so many screening tools with varying components, and that there is not one agreed to be the gold standard, has meant practice has varied considerably. A recent paper reported the reliability (inter-rater agreement when using the same procedure on the same patient) and concurrent (correlation) validity (agreement between different screening procedures in the same patients) of the most commonly used screening tools (13). The authors found the inter-rater agreement for most tools is better than fair but for ‘MUST’ and the Simple Nutritional Assessment Questionnaire (SNAQ) there was near perfect agreement. However, the sensitivity of these tools to changes in nutritional status, nutritional risk and minimally important clinical differences within

the tools are yet to be established and were not what they were initially designed for. Only the Nutrition Risk Score (NRS-2002) was designed to screen and assess nutrition treatment response.

Nutritional screening and assessment tools aim to not only identify those individuals at risk of malnutrition but also those at risk of becoming malnourished. Screening tools contain various components, some include body mass index (BMI) where weight is expressed in relation to height (kg/m^2). The Mini Nutritional Assessment (MNA), the Nutritional Risk Score (NRS-2002) and the 'Malnutrition Universal Screening Tool' ('MUST') all have a BMI component. If the value is below a specified cut-off point an individual is said to be at risk of malnutrition. However, there is even disagreement as to what BMI cut-off represents underweight in patients of different ages, ethnicities and disease states. Varying BMI thresholds have been used as a universal cut-off across all age groups with some tools such as 'MUST' using a BMI < 20 kg/m^2, the NRS-2002 uses a similar cut-off of < 20.5 kg/m^2 while the MNA uses < 23 kg/m^2. While on a global population level the World Health Organization uses a cut-off of < 18.5 kg/m^2 (14). However, effective nutritional screening involves not only the identification of those malnourished but anticipates nutritional depletion therefore some argue that the BMI cut-off defining undernutrition should be raised in the elderly population and certain diseases (15). The rationale behind this is that a BMI that is optimum for health in the general population may not be the same in the presence of disease and this will be discussed in more detail in chapter 4, study 2. In addition, body compositional changes that occur with aging, namely a reduction in fat-free mass (FFM) and expansion of fat mass (FM), may further confound BMI as the sole criterion for classifying malnutrition risk. This further highlights the need for more in-depth nutritional assessment to establish what is considered a 'bad' nutritional status at a more localised level (i.e. within patients with COPD). An important consideration is that nutritional screening tools were designed for different aims, applications and processes so their ability to identify malnutrition and predict outcome will be underpinned by the population in which they were validated.
An alternative method to BMI is where an individual's weight is expressed as a percentage of their predicted ideal body weight (% IBW) (16) but this approach has the same limitations to that of BMI. Inconsistencies exist not only in which method should be used, but at what point does an individual become underweight, at risk of malnutrition or likely to be malnourished (Table 1).

Table 1 BMI categories for identifying adults at risk of chronic protein-energy malnutrition (PEM) Adapted from Stratton et al., (10).

BMI category (kg/m^2)	Weight category	Chronic PEM risk
< 18.5	Underweight	Chronic PEM probable, high risk of future complications related to DRM
18.5 – 19.9	Underweight	Chronic PEM possible, medium risk of future complications related to DRM
20.0 – 24.9	Desirable weight	Chronic PEM unlikely, low risk of future complications related to DRM
25.0 – 29.9	Overweight	Overnutrition chronic PEM very unlikely. Increased complication risk due to excess fat mass
> 30.0	Obese	Chronic excessive overnutrition, PEM extremely unlikely but obesity-related complications risk significantly increased

BMI = Body mass index; PEM = Protein-energy malnutrition.

In a 4-year prospective observational study involving 2163 elderly men and women weight loss and gain were common (17). Even in those individuals that remained weight stable small increases in FM and losses of FFM were reported. The study demonstrated that weight loss and gain tends to favour FM deposition in the elderly. For example, men lost 5.8% of their initial FFM but 10.8% of their initial FM demonstrating the body's preferential loss of fat stores. However, in those males that gained weight, they gained only 2% of their initial FFM but 17.9% of their initial FM. A characteristic of the elderly is a difficulty in regaining FFM (18). Unintentional losses in body weight and the inability to regain lost FFM may be exacerbated in the presence of elevated inflammation. This is often the case with chronic wasting diseases and is a common challenge faced during the nutritional management of these conditions. Reductions in physical activity, inadequate nutritional intake particularly protein, reduced protein synthesis, increased insulin resistance and inflammation and reduced androgenic hormones are all commonly observed with aging and disease. These changes all affect the body's ability to handle and utilise nutrition effectively and many have been previously identified as being responsible for non-response to nutritional support in COPD (19).

1.1.3 Body composition assessment techniques

The prevalence of nutritional depletion may be underestimated in certain disease states if only measurements of body weight and BMI are employed. Body composition changes are potentially accelerated in disease and can occur in individuals with a normal BMI. Therefore, assessment of FFM has been suggested to be a more sensitive measure of nutritional status. In 495 weight stable elderly males observed over 4 years a mean increase of 0.93 kg of FM and a 0.93 kg loss of FFM was found (17), demonstrating the limitations in using only weight and BMI to identify nutritional depletion. If BMI were the sole assessment criteria used to identify nutritional risk this could lead to a patient being classified as having a 'healthy' BMI with no significant weight change, but still having experienced FFM losses that are likely to impact on functional capacity and clinical outcome. For this reason, various methods to assess body composition are increasingly being used in clinical practice. These include bioelectrical impendence analysis (BIA) and dual energy x-ray absorptiometry (DXA). Despite DXA being suggested to be the most accurate way of assessing FFM, issues around practicality and cost have been raised (20).

Body composition changes in wasting conditions may occur well before any weight changes are detected (21). Depletion of FFM has been shown to contribute to impaired functional status in COPD (22) and more recently has been shown to be a more sensitive determinant of length of hospital admission than a weight loss of > 10% or a BMI < 20 kg/m^2 (23). Pichard et al., (23) using BIA found that in patients hospitalised for 1-2 days, low FFM was found in 37% however, in those hospitalised for > 12 days FFM depletion was recorded in 56% at the time of admission. Similar to a previous study by Cano et al., (21), the study by Pichard and colleagues (23) found 17% of patients to be classified as at risk according to BMI compared with 41.4% of patients having low FFM. A limitation of BIA as a nutritional assessment tool is that it does not identify those patients who are at risk of malnutrition but are not yet malnourished. Currently there are no age-specific normal ranges for FFM and cut-offs would need to be incorporated into a nutritional assessment tool that identified and quantified clinically relevant unintentional losses of FFM. Making these changes applicable across different ethnicities, age groups and disease states would be extremely complex.

In the absence of a “gold standard” for the measurement of FFM and with issues around practicality and cost, the most commonly used and pragmatic approach to nutritional assessment in the clinical setting often includes assessment of BMI. Despite the limitations discussed, BMI provides some idea of an individual’s chronic protein-energy status. Deficiencies are still possible, in terms of FFM and micronutrient status, but BMI provides a quick overall assessment and is often associated with the status of several micronutrients, nutritional state and future risk (Table 1). Whilst other forms of nutritional assessment are recognised as being extremely useful in the clinical assessment of patients, in order for nutritional screening to be done quickly, accurately and routinely, nutritional screening tools need to have practical components such as BMI. Whether BMI cut-off points need to be revised upwards for certain conditions or age groups remain to be established.

Prevalence of malnutrition

The largest challenge in addressing the problem of malnutrition is that it often goes undetected and untreated in the community, presenting at a later more advanced stage in the acute setting. This has been reported by the Nutrition Screening Weeks carried out by BAPEN (4, 24). 9336 patients on admission to hospitals/care homes were screened using the validated and most commonly used nutritional screening tool in the UK, ‘Malnutrition Universal Screening Tool’ (‘MUST’) (24). 28% (22% high risk and 6% medium risk) were at risk of malnutrition with 22% being classified as being at high risk. In accordance with the nutritional care plan linked to ‘MUST’ these patients require some form of nutritional intervention whether it be referral to a dietitian, prescription of oral nutritional supplements (ONS) or more invasive nutritional support (enteral tube feeding/parenteral nutrition). A further 6% were at medium risk requiring regular on-going monitoring, if in an acute setting the patient should be re-screened weekly and if in the community re-screening should occur every 2-3 months or at the next available opportunity. The incidence of malnutrition risk was higher if patients were admitted from another hospital or were transferred from another ward (26% from home, 34% from another hospital, 32% from another ward, and 52% from a care home) although it is hoped the increased risk observed is a disease-related progression rather than a lack of nutritional care within the hospital setting.

With the prevalence of malnutrition being strongly and independently associated with aging (4), the rapidly growing aging population has serious implications on both wider public health and the effective delivery of healthcare. Increasingly individuals are living longer in the presence of disease therefore it could be expected that the incidence of malnutrition will also increase. From an organisational level, this will have a serious impact on the NHS in terms of an increased economic and operational burden with hospitals already frequently operating at maximum capacity. Malnourished patients tend to get admitted to hospital more frequently and have protracted lengths of stay. The national BAPEN surveys highlight the need for strategies for the detection and treatment of malnutrition particularly in primary care following discharge. There is a need to grow the current evidence base for nutritional strategies outside of the hospital environment to assist in the development of standard guidelines and care pathways. This would enable patients assessed as being at risk of malnutrition in any setting, hospital, nursing home, outpatient clinic or G.P surgery, to be placed onto the appropriate care pathway that ensures they receive the most effective nutritional intervention for their needs as well regular review as necessary.

Treatment of malnutrition

Currently it remains unclear as how best to tackle the malnutrition seen in the community with tailored dietary advice (DA) delivered by a dietitian and oral nutritional supplements (ONS) being the two most common first line treatments of DRM. Both forms of treatment have a cost associated with them but ONS are increasingly being seen as an expensive treatment. There has recently been increased interest in the role of prescribing support dietitians and the ability to produce large cost savings with the implementation of nutritional screening and the reviewing of current prescriptions (25). The authors report substantial cost savings with the eradication of inappropriate prescribing and the implementation of cheaper forms of treatment however; the economic methodology used is often unclear and involves extrapolation. The substitution of ready-made liquid ONS for cheaper powdered alternatives that have not been shown to produce the same clinical results does not appear to be clinically indicated. There is an urgent need for large-scale prospective trials in the community setting demonstrating both the clinical and economic efficacy of nutritional support as there is a risk that initiating any nutritional support is seen as an unnecessary cost to the NHS.

Whilst nutritional support has been shown to result in both clinical and cost improvements, there is the issue of what the intervention should be. The current evidence base on the clinical and cost effectiveness of ONS (ready-made liquid supplements rather than powders, soups or puddings) is far greater than that of DA (10, 26, 27). A recent review suggested dietary advice with and without ONS can have favourable effects on body weight, body composition and grip strength (27) however, the number of studies are few in comparison to those involving ONS alone. Whilst a lack of evidence does not necessarily mean a lack of effectiveness and/or efficacy there is a need to establish the most clinically and cost effective first line treatment for malnutrition. Dietitians typically promote 'food first' in the treatment of DRM and this is likely due to historical reasons as well as the origins of the profession itself. Whilst ONS may be considered expensive in primary care, supplementation with ONS has been shown to result in a number of clinical benefits without negative outcomes (10). It may be the case that in ambulatory patients at home, DA may be more appropriate and efficacious but this needs to be supported by research. Comparison studies demonstrating that DA is able to produce similar improvements of a magnitude to that of ONS are lacking. Those involved with informing the nutritional care of patients have to first establish which method of nutritional support is the most appropriate at various times and in what disease states, before the focus can shift to establishing the most effective methods and processes of delivery and management.

1.1.4 Chronic Obstructive Pulmonary Disease

COPD is a progressive respiratory condition characterised clinically by dyspnoea, chronic cough and sputum production. The term COPD is an umbrella term encompassing both chronic bronchitis and emphysema with the pathology of chronic obstructive bronchitis involving obstruction of the small airways, while emphysema involves enlargement of air spaces and destruction of lung parenchyma leading to loss of lung elasticity and closure of the small airways (28). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) state COPD is a disease
characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (29).

COPD is a major global cause of chronic morbidity and mortality representing a substantial economic and social burden. It is the fourth leading cause of death in USA and Europe (30) and with future increases predicted in its prevalence it has been estimated to rise to the third highest cause of death worldwide by 2020 (31). There are an estimated 3.7 million people in the UK with COPD, but only 900,000 individuals who have received a formal diagnosis (6). In 2004, 27,487 deaths within the UK were attributed to COPD (32). Acute COPD exacerbations are one of the most common causes for hospital admissions in the UK and carry a high mortality rate. COPD accounts for 10% of all medical hospital admissions, totalling over 90,000 admissions every year (33). This results in COPD being the second highest cause of emergency hospitalisation in the UK, after coronary heart disease (33) and the direct cost of COPD to the UK healthcare system has been estimated to be between £810-£930 million per year, with the majority of the costs attributed to inpatient care (32). COPD is one of the most costly inpatient conditions that the NHS treats. Outpatients with COPD also have increased contact with their G.P in the month prior to hospital admission resulting in consultations rates up to 4 times that of angina (7). Along with direct costs to the NHS, an estimated 24 million working days per year are lost due to COPD. The incidence of COPD is closely associated with social deprivation with higher rates of COPD in more deprived communities (6). The impact of social deprivation in COPD and its relationship to malnutrition and healthcare use is explored in more detail in chapter 4, study 4. As with most chronic diseases, patients with COPD spend most of their time within the community setting. Recent data from the UK has shown 44% of patients with COPD are under the retirement age, with 24% of patients reporting to be unable to work, and a further 9% reporting that COPD seriously limited their ability to work (34). The costs to the NHS plus the substantial wider indirect socioeconomic costs of the disease have led to the overall annual cost (direct and indirect) being estimated to be between £800 million to £1.5 billion (35). Hospitalisation is the major driver of healthcare costs to the NHS, with 54% of these costs attributed to hospital admissions. Direct costs are also 5-8 times higher in those with severe COPD compared to mild and moderate disease (34).

The association between weight loss and increased mortality in COPD has been recognised since the late 20th century (36). Research into the nutritional management in COPD has increased but it is still not yet known how best to therapeutically manage the observed reductions in weight and FFM seen during

the progression of the disease. The initially slow start to research in this field may be due to a previous commonly held belief, which arguably still remains today, that losses in weight and FFM are a terminal progression of the disease and are as such inevitable and irreversible. Furthermore, it has been proposed that weight loss is actually an adaptive physiological mechanism to reduce oxygen consumption in COPD patients through reductions in body cell mass. These ideas have recently been challenged by large clinical and epidemiological studies that have shown that weight loss is not only a reversible negative prognostic factor in COPD, but also that weight gain is associated with reductions in mortality (37, 38). Interestingly the study by Schols and colleagues (37), which retrospectively looked at the survival rates of 400 moderate-severe COPD patients, showed a body mass index (BMI) < 25 kg/m^2 was the threshold below which mortality significantly increases. Lando et al., (39) observed in moderate COPD patients the best prognosis was found in normal weight or overweight patients. However, in patients with severe disease those that were overweight or obese were found to experience higher survival rates. Prescott et al., (38) had similar findings when underweight patients gained weight it was found they also went on to experience reduced mortality. In the same study overweight and obese patients who remained weight stable showed further increased survival. This relationship between body weight and survival is explored in more detail in chapter 4, study 2.

1.1.5 Mechanisms for nutritional depletion in COPD

The causes of weight loss in COPD are not fully understood but are attributed to a number of factors that contribute to both a negative energy intake and elevated energy expenditure. Although the exact mechanisms for weight loss in COPD remain to be established, there are a number of interrelating factors at play that can lead to nutritional depletion in a subset of patients (Figure 1). Nutritional depletion appears to be more common in those COPD patients with an emphysematous phenotype than those with a predominance of chronic bronchitis (40). Nutritional intake is often reduced due to the symptoms of COPD, including excess sputum production, breathlessness, fatigue, muscle wasting, recurrent infections, anorexia and meal-induced dyspnoea. The symptoms of COPD can limit not only an individual’s ability to acquire and prepare food, but also limit the quantity of the food ingested due to hyperinflation of the lungs and a flattened diaphragm leading to increased sensations of fullness and dyspeptic symptoms

(41). In semi-starvation there is an adaptive reduction in energy metabolism however, in COPD a poor nutritional intake is often accompanied by elevated low-grade systemic inflammation (2). The on-going systemic inflammation in COPD negatively affects appetite; causing anorexia, while creating a catabolic drive and loss of body cell mass. In cachectic versus non-cachectic COPD patients appetite has been found to be reduced by 45% as well as growth hormone resistance (42) and in a small sample of underweight patients with emphysema, whole body protein synthesis has also been found to been reduced (43), impairing the ability to regain lost FFM. Increased systemic inflammation is a characteristic of COPD, with elevated levels of inflammatory cells (e.g. TNF-alpha) often reported and to a level that promotes protein breakdown and suppresses protein synthesis (44). Systemic inflammation has been found to be significantly higher in smokers than ex-smokers with COPD (45, 46). These systemic problems, in addition to aging, tissue hypoxia and inactivity, lead to structural alterations and losses of FFM that can have profound effects on patient's quality of life. The wasting of body cell mass seen in COPD patients is of critical clinical importance as a loss of more than 40% is incompatible with life.

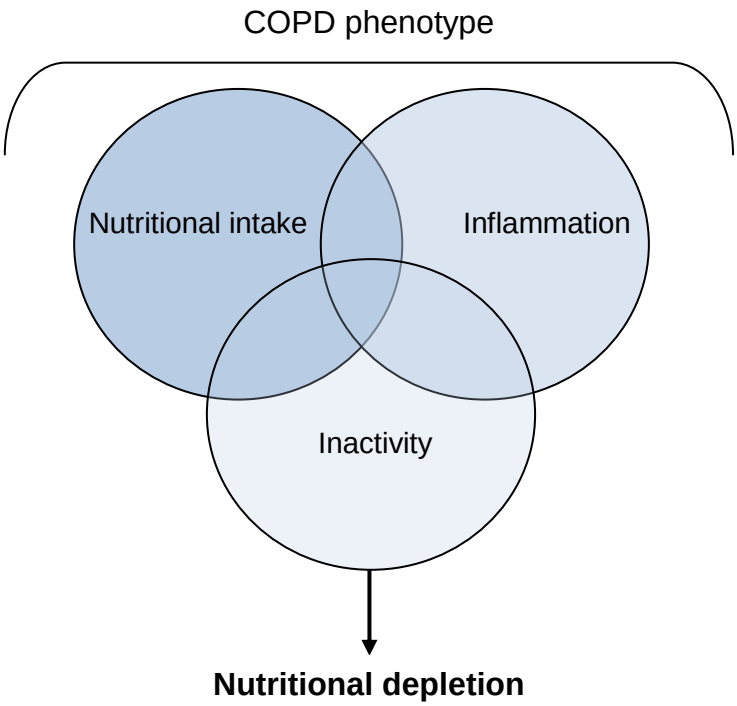


Figure 1 Aetiology of nutritional depletion in COPD (Adapted from Collins & Elia) (47)

Additional factors such as smoking status, certain medications, disease-related depression and anxiety are known to sometimes cause changes in taste and decreased appetite in COPD (48). Many patients develop psychological symptoms in addition to the physical symptoms associated with the disease. Anxiety and depression are 2-3 times more prevalent in COPD patients than the general population (49) all of which impact an individual's ability to meet their nutritional requirements. Furthermore, current smoking status is likely to have a strong influence on the adequacy of COPD patients' nutritional intake and subsequent malnutrition risk. Smokers have been shown to have lower reported intakes for vitamin C, folate, fibre and vitamin A (50) and a lower consumption of fruits and vegetables compared to non-smokers (51). A small study involving COPD patients, healthy age-matched controls and a group of elderly smokers, that did not fit the COPD diagnosis criteria, found intakes of energy, vitamins A, B1, B2, C and Calcium, Iron and Fibre to all be significantly lower in both the elderly smokers and COPD patients (52). Smoking status is closely linked to social deprivation with a higher incidence in those populations residing in areas of deprivation and those with a lower educational attainment (53). Analysis of the National Diet and Nutrition Survey revealed significant differences in vitamin C, a range of carotenoids, vitamin D and selenium intakes between the north and south regions of England and this was attributed to inequalities (54). Lower intakes of certain micronutrients, particularly antioxidants and those involved with immunity, may exacerbate lung damage and lead to increased frequency of respiratory infections. The complex associations between deprivation, smoking status and malnutrition risk in COPD will be discussed throughout chapter 4 of this thesis.

When assessing the nutritional status of COPD patients, the multi-factorial nature of DRM development and risks associated with it must be considered. It is important to be aware of the underlying mechanisms contributing to its development in order to assess the need for, and effectiveness of nutritional support. Careful assessment of the type of tissue wasting occurring though the use of various methods (bioelectrical impedance analysis, skinfold thickness, and/or mid-upper arm circumference (MUAC)) will allow a suitable strategy to be employed. At present there have been no direct comparative studies comparing the accuracy of these various methods in assessing body composition in COPD patients. Despite being more expensive, BIA is an attractive option as it negates the need for an individual skilled in taking skinfold thickness measurements

although, BIA is confounded in the presence of oedema which is a common complication in COPD.

Reductions in fat mass due to a negative energy balance, and/or losses of FFM due to an imbalance between protein synthesis and protein catabolism may occur alone or in combination. The effects of inflammation on lean body tissue leading to large losses in FFM may as well as breathlessness on exertion lead to marked and chronic physical inactivity leading to further disuse atrophy and muscle deconditioning (55). Although few nutritional intervention trials have specifically set out to increase FFM in COPD, chronic inactivity may also explain why many nutritional supplementation trials have failed to reach statistical significance with regards to the accretion of lean body mass. Any weight gain brought about through supplementation, in the absence of an anabolic stimulus, is likely to favour deposition of fat rather than lean tissue. Although Steiner and colleagues (56) found that even when nutritional intervention was delivered as part of an exercise programme in COPD outpatients, significant weight gain was only achieved in FM assessed by dual energy x-ray absorptiometry (DXA)(56). This study highlighted the difficulty in overcoming the catabolic response and achieving lean tissue weight gain. Previously, Schols et al., (57, 58) postulated that nutritional support as part of pulmonary rehabilitation with the addition of anabolic steroids may result in improved lean body mass gains. They found that nutritional support in the form of ONS (providing an additional 420 kcal/day) for 8 weeks plus intramuscular injections of anabolic steroids resulted in a mean gain in FFM of 1.4 kg (SD 2.6 kg) resulting in improved respiratory function. However, ONS alone also resulted in a mean increase in FFM of 1.1 kg (SD 2.4 kg) and significant improvements in respiratory function. This is despite the trial by Schols et al., (57, 58) providing less supplemented protein, which may be more indicative of the training content of exercise rehabilitation programmes rather than the supplement intervention (56-58).

Reduced nutritional intake can be a result of dyspnoea due to irregular breathing and arterial oxygen desaturation while eating and/or reduced functional capacity of the stomach due to hyperinflation (59, 60). In addition it has also been suggested COPD patients may also suffer from a hypoxia-related suppression of appetite (59). Since dyspnoea results in fatigue, less time may be spent eating leading to reduced energy intakes (Chapman et al., 1996 cited in Schols & Brug, (61)).

Conversely, mealtimes may be prolonged leading to alterations in food temperature, texture and palatability that may further reduce intake. Although one study has suggested dyspnoea during mealtimes is unlikely to reduce intake substantially (62).

Nutritional depletion in COPD is complex with a number of interrelated factors and mechanisms contributing to its development. The extent to which these can be addressed through nutritional support leading to improvements in nutritional status is poorly understood. However, improvements in nutritional status and weight do appear possible and result in improved outcome. The main rationale for nutritional intervention in COPD is based on the observation that weight loss is common and associated with poor outcomes. It appears that only one study has prospectively explored the effect of weight gain on survival. Schols et al., (37) reported that a weight gain of greater than 2 kg was associated with a significant improvement in survival although the sample size at 48 months, the magnitude of mortality reduction and p values were not reported. It is difficult to accept that an increase in weight after an 8-week nutritional intervention leads to improvements in survival 4 years later particularly as the group containing individuals that experienced a 2 kg weight increase did contain a number of controls. Of course this study is limited by the fact that it was a retrospective look back at the data and nutritional intervention trials with mortality as a primary endpoint would be large and costly.

It is clear there is a relationship between body weight and survival however body weight is likely to also be associated with disease progression. In addition, infective exacerbations are also associated with accelerated disease progression and mortality. In underweight patients the incidence of acute infective exacerbations requiring hospitalisation is higher than in normal weight patients (63). This raises some interesting issues as weight loss in overweight or obese patients is often advocated as part of pulmonary exercise programmes. Obesity is known to negatively affect respiratory measures such as FEV_1, even independently of smoking status (64) and weight loss is likely to lead to pulmonary function improvements (65). Paradoxically, cross-sectional epidemiological studies suggest that being overweight with COPD can also improve FEV_1 measures, implying that there is likely to be an optimum weight for respiratory function and at the same time a lower mortality risk. For the obese COPD patient with reduced FFM, weight loss may initially make it easier for them to mobilise due to decreased

whole body mass, and may reduce some of the respiratory restriction seen in obese sleep apnoeic COPD patients. However, the vast majority of research associates weight loss in COPD with increased frailty, as well as increased incidence of exacerbation, hospitalisation and mortality. There is an argument therefore that weight loss through calorie restriction alone may result in negative outcomes, leading to losses of FFM. It is likely that the best weight management strategy in the overweight or obese COPD patients involves a combination of modest calorie restriction ensuring an adequate protein intake as part of an exercise programme in which FFM is monitored. Such a multi-modal intervention would seek to provide the anabolic stimulus to help maintain FFM in a patient group where, due to pathological changes associated with the disease, it is preferentially depleted. Weight management in COPD is an area that has received very little interest and requires further research.

1.1.6 Defining malnutrition in COPD patients

Interpretation of reported malnutrition prevalence rates is often difficult as the incidence of malnutrition is not only dependant on the type and severity of any chronic disease present in the population screened but also the methods used to establish nutritional status. The wide variation in the prevalence of malnutrition in COPD patients (30-60% in inpatients and 10 - 45% in outpatients) is likely to be due partly to the different populations screened. In addition a variety of nutritional screening tools have been employed to establish the prevalence of malnutrition all with slightly different methodologies. Currently there is not one universally accepted nutritional screening tool but within the U.K, ‘MUST’ is the tool recommended by numerous healthcare professions and the department of health including the National Institute for Health and Clinical Excellence (NICE) (66).

The vast majority of nutritional screening tools will require the assessor to measure the patient’s weight. This is then expressed in relation to their height in the form of BMI or as a percentage of their ideal body weight (% IBW). In 1943 the Metropolitan Life Insurance Company in the United States introduced their standard weight for height tables for men and women (16). The values contained within these tables for weight for a specific height gradually became known as the ‘ideal’ which led to many trials reporting patients weight as a percentage of this ‘ideal’ (%IBW). When malnutrition is defined as less than 90% of ideal body weight

(equivalent to a BMI of ~19.5 kg/m^2), 20-35% of patients with COPD have been classified as underweight (22, 67).

Body composition changes occur as a natural process of aging and as mentioned includes a decrease in the proportion of FFM to FM. However, in individuals with COPD body compositional changes appear to be accelerated due to the pathophysiological changes that occur with the disease, such as increased dyspnoea and even hypoxia leading to reduced physical activity (disuse atrophy) along with elevated systemic inflammation causing breakdown and loss of lean tissue. Loss of total body mass in COPD has been mentioned already, but there is a sub-group of patients who maintain and even increase their body mass while continuing to lose FFM (22). A number of studies in COPD patients have shown that patients may present with a normal BMI but are still at nutritional risk due to clinically significant depletions in FFM. Losses of skeletal muscle mass, as a result of cachexia and disuse atrophy, are often masked by an increase in fat mass which has led some experts to predict the incidence of DRM to be higher than those reported in trials where BMI alone is used as a marker of nutritional status (68). Vermeeren et al., (68) classified nutritional depletion as a BMI ≤ 21 kg/m^2 and screened 389 outpatients across 39 centres in the Netherlands and found 12% had a BMI of < 21 kg/m^2 (68). When assessing FFM in addition to BMI the overall prevalence of nutritional depletion was reported to be 27%, with 15% of the outpatients having a normal BMI (≥ 21 kg/m^2) but a low fat free mass index, FFMI (≤ 15 females; ≤ 16 males kg/m^2). Therefore, there is a growing evidence base suggesting routine body compositional tests should be carried out in individuals with COPD. Traditionally this is done using a single-frequency bioelectrical impedance analysis (BIA) machine while the patient is in a supine position. However, in busy outpatient clinics it is unlikely staff have access or the expertise to perform this type of body compositional assessment. Recent advances in BIA technology have led to the production of weighing scales with the capability of assessing body composition; as a result it is likely that BIA will be used more frequently in clinical practice in future.

Ultimately the aim of nutritional screening is to implement appropriate nutritional support in those that need it and not to implement it in those that do not require it. In order for this to occur nutritional screening is often undertaken to produce a quantitative score that can be linked to a nutritional care plan. There are currently

no validated nutritional screening tools using FFM measures that are linked to a care pathway. The nutritional screening tool 'MUST' involves three steps in order to produce a score that is linked to a nutritional care pathway suggesting an appropriate action. The tool involves assessment of BMI as well as assessment of any recent unintentional weight loss. Finally, there is an acute disease effect score where those patients who have had, or are likely to have, more than five days with no nutritional intake are highlighted as being at future risk. The simplicity of the tool, the fact it encourages action linked with a treatment plan and that it requires no additional resources to those that would be routinely available in outpatient clinics and hospital wards make it a useful screening tool (Appendix 4). One of the main reasons why 'MUST' is used so widely within the U.K is likely due to its applicability across all healthcare settings. Routine screening using 'MUST' will allow continuity of assessment, detection of any changes in nutritional status and monitoring efficacy of treatment, thereby not only identifying those at risk but also allowing evaluation of nutritional interventions. Patients may leave hospital receiving a variety of nutritional interventions however if routine nutritional assessment and follow-up are not performed there is the risk the patient will either not receive the support for an adequate period of time or they may continue to receive it when it is no longer indicated.

1.1.7 Evidence for nutritional intervention in COPD

Evidence demonstrating that malnutrition is a modifiable risk factor in COPD appears to be scarce. This is particularly the case in the primary care setting where there is a lack of randomised controlled trials (RCTs) that include both objective and subjective clinical endpoints (69). The view that malnutrition may be irreversible in COPD has have been reinforced by several reviews (70-73). The latest Cochrane Collaboration review on nutritional support in COPD concluded that nutritional support had no significant effect despite eight of the thirteen included trials in the analysis reporting significant results in their own right. Close inspection of the methodology employed by the Cochrane author, however, shows that only cross sectional analyses were performed, i.e. only the differences between control and intervention groups at the end of intervention were analysed, and without exploring within group change, any differences induced by the nutritional intervention could potentially be masked. An updated literature search

and a more robust interrogation of the evidence for nutritional support in COPD was therefore undertaken and is described and discussed in depth in chapter 3 of this thesis.

A lack of adequately powered nutritional trials is not confided to nutritional support in COPD but when the evidence for specific nutritional interventions, such as dietary advice, are explored there appears to be a lack of evidence of effect across all conditions. Therefore both the Cochrane Collaboration reviews on dietary advice in treating malnutrition and nutritional support in COPD have highlighted a lack of effect when the available data are synthesised (26, 73). The review on dietary advice in malnutrition has recently been updated (27) but the conclusions largely remain the same. The authors of the reviews conclude there is a need for large adequately powered RCTs comparing the efficacy of various nutritional therapies commonly used to increase nutritional intake in those with DRM. Ideally the trials should include both measures of functional capacity as well as outcomes such as quality of life.

The majority of trials included in the review by Ferreira et al., (73) compared oral nutritional supplementation versus routine care, placebo, dietary counselling or anabolic steroids. It did show consistent small increases in weight, upper arm muscle circumference and forced expiratory volume in 1 second (FEV_1) but the authors state these failed to reach statistical significance. It is important to bear in mind inconsistencies in study design, inclusion and exclusion criteria, outcome measures and the varying definitions of malnutrition make synthesis and interpretation of the limited number of trial results difficult. The studies included in the analysis were graded poorly on methodological quality and data on patient focused end points, such as quality of life, were lacking. Twelve of the 13 studies included in the meta-analysis were RCTs (n = 392) and only four of the included trials involved sample sizes of more than 50 patients (56-58, 74). The trials run by Schols et al., (57, 58) and Steiner et al*.,* (56) were 8 and 7 weeks in duration and investigated the efficacy of nutritional supplementation when provided in conjunction with an exercise pulmonary rehabilitation programme. Both studies were also interested in whether supplementation resulted in gains in exercise performance and so also included patients who were not at nutritional risk, with subset analysis performed on the patients classified as nutritionally depleted. Both studies found nutritional support combined with an anabolic stimulus (exercise or

anabolic steroids) resulted in beneficial improvements (exercise capacity, weight and lean body mass) even in patients not at risk of malnutrition. However, an important point to consider is that the majority of the current evidence for nutritional support in COPD centres on these two RCTs both of which involve exercise. This is unlikely to be reflective of routine clinical practice.

1.1.8 Oral Nutritional Supplements (ONS)

ONS have been shown to improve nutritional status and lead to weight gain in COPD patients at risk of malnutrition (10). Randomised controlled trials have shown multi-nutrient energy dense (1-2 kcal/ml^{-1}) ONS significantly increased energy and protein intakes of COPD patients whilst having no affect on habitual dietary intake (57, 75). This has also been shown to be the case in trials with elderly subjects involving both short-term (6 weeks) and long-term supplementation (6 months) where no appreciable decreases in nutritional intake occurred in those receiving the ONS (76, 77). Steiner et al., (56) did report the effects of supplementation with ONS were attenuated by a reduction in food intake but the mean increase in macronutrient intake was equivalent to about 70% of the prescribed ONS. These findings are supported by a review by Stratton et al., (10) which highlighted studies that showed when ONS are prescribed in COPD patients, they lead to an increase in energy intake of 20-57% above that of food alone (78-80).

The early clinical trials investigating the effectiveness of liquid ONS reported significant increases in body weight and respiratory muscle function. However, these trials involved only 2 - 3 weeks of supplementation (81, 82). The review by Stratton et al., (10) highlighted significant improvements in functional outcome measures were most likely seen in those trials of ONS which resulted in a weight gain of > 2 kg in underweight COPD patients (79, 83). The exact causality for the improvements is difficult to establish because change in FFM was not reviewed but improvements could be driven by an improvement in intake leading to increased body weight, particularly FFM, and subsequent functional improvements. Improvements in other functional measures such as grip strength have been reported to occur prior to any changes in weight and are attributed to improved micronutrient status.

From those trials based in the community setting it was estimated that > 50% of the ONS energy provided was supplementary to food intake. Further, systematic reviews of nutritional support trials using ONS within a community setting (108 trials, n = 3747) in patients with chronic disease, including COPD, suggest that ONS can significantly increase nutritional intake whilst having no detectable suppressive effect on habitual intake (10). In order for nutritional support to be effective it has to be given for an adequate duration to optimise the appearance of clinically relevant improvements, as suggested by the numerous reviews on the topic of nutritional support (10, 26, 73). Compliance to both dietary advice and ONS supplementation are challenges faced in nutrition support. Adherence to nutritional treatment may decline during periods of prolonged supplementation and this was suggested by a study by Goris and colleagues (84) who investigated the effectiveness of ONS over 3 months. It was reported a mean intake of 95% (SD 6%) of the prescribed supplements at 1 month and a consumption of 89% (SD 14%) of the supplements at month 3. There was no difference in body weight between the intervention and control group and whilst the trial was not powered to assess compliance to treatment, any drop in compliance is likely to impact on results obtained.

A review of meta-analyses looking at the effectiveness of ONS showed consistent findings indicating reductions in mortality with ONS use versus routine care in a range of conditions (85). These benefits are seen predominantly, but are not limited to, undernourished patients. The fact that benefits may also be seen in adequately nourished patients may be the case in COPD, achieving weight gain in individuals with a BMI < 25 kg/m^2 may result in reduced mortality. However, this is yet to be confirmed with prospective nutritional intervention trials. If nutritional support is implemented early in certain conditions, particularly wasting diseases, it may be more likely to lead to clinically significant benefits than when it is implemented in more advanced stages of the condition in the presence of increased inflammation and more marked malnutrition. Creutzberg and co-workers (19) reported that COPD patients who did not respond to nutritional support were characterised by higher age, elevated systemic inflammatory markers and a lower energy intake. The authors found no difference in the energy expenditure between groups and conclude that non-response was due to relative anorexia. If nutritional support is to be successful this anorexia needs to be overcome so that total intake can be increased with little effect on habitual energy intake.

There is always a need for good quality evidence to ensure healthcare resources are allocated effectively and inform the best clinical practice. Research has shown that whilst the growth in prescription costs for ONS has slowed since 1997 from 9.5% to a 3.5% annual increase (86) the cost of prescribing ONS continues to increase at a higher rate than any other part of the drugs bill in primary care (87). The cost implications to the NHS are considerable, prescription analysis in 2003 suggested approximately £129 million was spent on ONS and enteral nutrition feeds in the community (Department of Health, 2003 cited by Stratton, (88)). It is unclear whether the increase in costs is driven by increased costs of ONS or increased usage following raised awareness of malnutrition and improved screening and detection.

1.1.9 Dietary Advice (DA)

There is a current consensus that tailored dietary advice (DA) delivered by a dietitian, involving dietary modification and fortification, is the first line treatment of malnutrition as outlined by the Manual of Dietetic Practice (89). In fact, providing DA to increase nutritional intake is a core dietetic skill but the amount of time dietitians spend delivering DA is unclear and whether it is effective in treating DRM able to provide a balanced improvement of energy, protein and micronutrients also remains to be established (26). DA is frequently delivered as a first line treatment for malnutrition often in preference to liquid ONS. ONS are often considered a secondary alternative once DA has failed, despite very little evidence to support this practice (88). Whilst the evidence is stronger for ONS compared to DA, there is an urgent need for large trials directly comparing the clinical effectiveness of both treatments. If ONS produce a range of clinical benefits, such as reduced admission rates, length of stay and mortality, it is likely the effect is mediated through improved nutrient intake and subsequent improved nutritional status. If similar improvements in nutrient intake could be achieved through DA similar clinical benefits may be found however, meta-analyses have highlighted the lack of evidence and the need for large randomised trials investigating DA (26, 27). DA underpins much of what dietitians do therefore developing the evidence base for DA has to be a global research priority for the profession in the future.

As part of DA patients are encouraged to exchange energy-poor food for energy-dense foods, increasing the frequency of meals rather than the portion size of the

meal itself. Dietitians using counselling skills are able to work with patients; family members and caregivers to devise a personalised nutritional care plan with the aim to increase the nutritional intake of the individual through these dietary changes and food fortification. A limitation of DA is that it can tend to focus on increasing the macronutrient content of the diet, although protein is particularly challenging to significantly increase in elderly patients, but may fail to increase micronutrient intake. Although it is likely benefits from nutritional support are derived from achieving a balanced increase in macro- and micronutrients, at present there is no evidence to suggest that DA plus the addition of a broad-spectrum multi-vitamin and mineral is effective.

A recent study by Weekes et al*.,* (74) demonstrated that DA and food fortification using whole milk powder (WMP) was successful in improving nutritional intake (energy and protein) leading to weight gain that persisted during follow-up suggesting a lasting behavioural change. These benefits may be due to the length of the intervention phase (6 months) and that it was fairly intensive involving 3 home visits by a dietitian. In addition some patients continued to purchase the milk powder that was used as part of the intervention themselves indicating a dietary behaviour change (90). Further research is needed into the efficacy of DA as delivered as part of routine clinical practice as outpatients are rarely seen 3 times in three months within the setting of their own home which does somewhat limit the transferability of the study's findings. In addition, there is an argument that DA tends to focus on macronutrient consumption with ensuring a consistent increase in micronutrient consumption challenging with DA alone. There is currently no evidence that micronutrient supplementation alone or in combination with DA is effective.

The study carried out by Weekes et al., (74) is one of only 12 studies comparing DA and control recently identified in the latest Cochrane review (27), and the only one involving COPD patients. The study involved outpatients outside the confines of a rehabilitation programme so there was no anabolic stimulus provided through physical activity. The study did involve a much longer intervention phase (6 months) looking at the efficacy of nutritional support delivered in the form of tailored DA delivered by a dietitian and the provision of whole milk powder (WMP) within the community setting. Nutritional supplementation resulted in significant improvements in weight of approximately 2 kg, which appears to be the threshold

at which significant demonstrable functional improvements are observed in this patient group (10). Interestingly the intervention also resulted in significant improvements in quality of life, which previous systematic reviews had highlighted as being an outcome lacking in previous trials (73). The improvements seen in weight and FFM persisted beyond the period of intervention suggesting small but lasting changes in dietary behaviour (74, 90). However, the previous reviews highlight the current lack of adequately powered trials investigating the effectiveness of both ONS and DA in the community which means currently, there are no agreed recommendations for their use (88). This applied to the management of malnutrition across all conditions in the community but is particularly the case for the use of both treatments in the management of malnutrition in COPD and indicate an urgent need for clear guidance.

As part of the intervention by Weekes et al., (74) WMP was provided to the subjects for a period of 6 months, which is currently something that is rarely seen in routine clinical practice. The cost difference between WMP and ONS in the community setting is likely to be considerable, formal economic analysis is needed adequately factoring the cost of dietetic time. An additional consideration would be whether the current structure and size of the dietetic workforce exists in order to deliver the intervention. With the majority of the dietetic workforce based within the acute setting and the high prevalence of malnutrition within the community, it is very unlikely that the either the size or the location of the dietetic workforce is sufficient to effectively address the problem. In fact due to increased economic challenges faced by many NHS trusts some areas have actually seen the number of dietetic posts reduce.

1.1.10 Novel therapeutic strategies to improve nutritional status

Anorexia is one of many factors contributing to the development of weight loss observed in COPD. The use of appetite stimulating medication in cachectic COPD patients is gaining increased interest. Megestrol Acetate (MA), which is a hormone known to stimulate appetite, has been shown substantially increase body weight in COPD outpatients (+3.2 kg) following 800 mg/day for 8 weeks (91). Although the additional weight was gained as FM, this may explain the interesting finding that the control group had a significant improvement in 6-minute walk distance, although the improvement was unlikely to be clinically relevant. The addition of

extra (‘non-functional’) body weight may have hindered improvements in exercise performance. The findings by Weisberg et al., (91) that MA resulted in expansion of FM had previously been reported in trials involving wasting conditions. The authors attribute the failure to increase FFM was likely due to the trial not taking place alongside an exercise programme. Whether MA supplementation, in combination with exercise and nutritional support, results in increased FFM remains to be established.

The use of androgenic hormones has been reported with some success when combined with exercise, which may have a further positive effect on protein anabolism (57, 58, 92-94). The trial by Schols et al., (57, 58) suggested that a combination of anabolic steroid medication and nutritional support as part of an exercise programme might lead to a greater improvement in FFM and respiratory muscle strength without any adverse side effects. However, the improvements were not significantly enhanced above that of nutritional support alone. More recently a trial has demonstrated that exercise and oral testosterone led to a range of improvements including weight, FFM, muscle strength and quality of life (92). The effects of anabolic medication appear to be dose dependent with trials reporting few side effects. However, further research is required demonstrating the safety of anabolic hormone supplementation in large groups of COPD patients before it is likely to be routinely used to treat nutritional depletion. Further exploration is also required around whether the effect of such supplementation is enhanced with nutritional support as has been suggested by Schols et al., (57) and Pison et al., (92).

Inflammation is a characteristic of COPD particularly those patients that are identified as at nutritional risk and cachectic. The majority of nutritional intervention trials have focused on improving energy and protein intakes of these patients however some patients have been found to be unresponsive to nutritional support and exercise. These non-responders where characterised as having elevated systemic inflammation which potentially prevented the accrual of body weight and FFM (19). Whether this inflammation can be reduced leading to improvements in nutritional status is an area of active research. Broekhuizen et al., (95) postulated that polyunsaturated fatty acids (PUFA) could modulate nuclear kappa B, which is known to be activated in underweight COPD patients (96), and influence inflammation. Through a double blind RCT they intervened using 9 g PUFA/day

alongside an 8-week intervention. Supplementation with PUFA significantly increased exercise performance however this could not be attributed to a reduction in inflammatory markers. Whether these results could be repeated in malnourished exercising COPD patients receiving nutritional support would be interesting.

1.1.11 Challenges to nutritional support

Severe COPD can be a disabling condition resulting in chronic immobility and reduced exercise capacity, which are likely to impact on patient's ability to fortify their food in the home. Many COPD patients may live in isolation without the support network to assist with implementing long standing dietary change. COPD can severely limit an individual's functional capacity and as such their ability to acquire, prepare and consume food limiting the effectiveness of DA and food fortification. Likewise with ONS supplementation, COPD patients may find consumption of certain sip feeds challenging due to volume and taste fatigue leading to poorer compliance. Compliance to the intervention is an important area to assess when performing a nutritional intervention trial. Acceptability and compliance to treatment often goes unreported if patients withdraw consent after randomisation to a particular treatment arm. One of only a few trials that did report on this found that in 116 malnourished elderly outpatients eligible to participate in the trial 23% declined with the most common reason cited being refusal to take ONS (97). This has important clinical implications and should therefore be a primary outcome reported in all nutritional intervention trials.

Recently, a growing challenge to nutritional support concerns economics. The costs of ONS have been mentioned but it is important to highlight ONS prescriptions currently accounts for approximately 1% of the total prescribing budget in England with malnutrition costing approximately 10% of the total healthcare budget (98). This suggests that appropriate and targeted use of ONS, although requiring investment, could lead to overall savings. Only a 1% reduction in the annual costs attributed to malnutrition could lead to a substantial return on investment. In the face of the current financial challenges faced by the NHS, critically evaluating the clinical and cost-effectiveness of treatments is more important than ever. However, it could be argued this evaluation extends to all aspects of nutritional care.

In order to come to conclusions on the clinical and cost-effectiveness of an intervention there is a need to determine whether the intervention has been implemented. If there is good compliance with the intervention but no significant improvement, it reasonable to conclude that there is a lack of efficacy. If there is no improvement in outcome in association with a poor or uncertain compliance the conclusion is more uncertain. It is possible that the treatment is potentially efficacious, but has not been taken in sufficient quantities to demonstrate efficacy. Alternatively it may lack efficacy and even if the target amount is taken it will not demonstrate improved outcomes. If no improvements in outcome are detected this is a failure of the intervention (good compliance but no significant improvement). However, if compliance to the treatment is poor and there was a failure to intervene (poor compliance to intervention) this does not necessarily mean the treatment does not work. This area is open to debate, as compliance will always be built in to the effectiveness of an intervention. If patients do not adhere to a treatment it will never be effective. Around the issue of compliance to treatment, it is not known whether there are differences in the amount of ONS consumed between primary and secondary care settings. For example, in a secondary care environment the individual may receive regular encouragement from healthcare staff and whilst in acute setting under supervision consume more of the supplement. If the individual is in isolation in the community without support compliance may decline. Conversely, out of hospital in their own environment with ready access to the ONS at any time of day and with the means to prepare (chilled, room temperature, heated) and consume the ONS in the way they wish (out of the bottle with a straw, from a cup) may improve compliance.

The increased awareness of nutrition and health status over the past decade, mostly through media coverage, has brought with it an additional challenge to nutritional intervention with regards to dietary modifications. DA often centres on patients manipulating their diet in a way that encourages regular small volumes of food that are energy dense. This often involves the fortification of foods with food items such as cream, cheese, butter, and whole milk. Dietitians have to work closely with patients as many may have negative attitudes to adding these food items as they may be seen as ‘unhealthy’. Patients may raise concerns if they are currently taking lipid-lowering medication, which is common in COPD. In this case it is important the risks of DRM and explained to the patient and through the counselling skills of the dietitian it may be possible through negotiation that the

patient agrees to alter their dietary habits. However, it does require careful consideration of the patients' personal health beliefs and clinical condition.

Any healthcare professional involved with the nutritional management of patients needs to have a holistic approach. This is particularly relevant in COPD patients where behavioural attitudes can prevent successful implementation of nutritional care. This was addressed in detail by Schols & Brug (61) who highlighted that individuals are influenced by outcome beliefs, i.e. the most likely consequence of a particular behaviour perceived by the individual. This can create barriers to nutritional intervention, as a low-calorie diet (reduced intake) is not followed by immediate sickness, with weight loss often insidious. Whereas consuming more calories in the short term may lead to abdominal discomfort due to gastric filling and postprandial dyspnoea. A patient is likely to perceive these short-term negative outcomes with greater importance on a daily basis leading to poor compliance to the intervention and limiting the success of the intervention (failure to intervene). In clinical trials, with the absence of any demonstrable change it is important to establish whether this has been driven by a failure of the intervention or a failure to intervene. It is likely ONS and DA will have different effects in terms of nutritional intake, the composition of that intake (macro- and micronutrients), dietary patterns, appetite as well as unique challenges relating to compliance, but this is an area that is yet to be studied in COPD patients.

It has been argued that the reason controversy remains around whether nutritional support is clinically effective in COPD outpatients is studies are often conducted amongst those patients with the severest of disease with a negative protein balance mediated by marked inflammation, decreased blood levels of anabolic hormones and tissue hypoxia (61). In addition the effects of nutritional support are attenuated by oral glucocorticoid treatment, which is common in COPD particularly during periods of infective exacerbation. This may explain why the few trials investigating nutritional support in acutely unwell COPD patients have failed to demonstrate a benefit with a negative nitrogen balance being highly correlated with corticosteroid therapy (75).

Recent meta-analyses, performed by Ferreira et al., (73) and Baldwin and Weekes (26), suggest a potential reason for the failure to demonstrate an effect of nutritional support is that the included trials found it difficult to significantly increase energy intake pointing towards "failure to intervene" rather than a "failure of the

intervention". Failing to intervene could simply be due to the subjects having existing severe obstructive disease with significant wasting and inflammation that may lead to poor compliance, anorexia and/or a poor response to nutritional therapy. Many severe COPD patients may find themselves in a cachectic state unable to achieve anabolism. There is evidence to suggest a sub-group of patients who suffer from chronic inflammatory conditions such as COPD respond poorly to nutritional intervention. This non-response to nutritional support is said to be multi-factorial including aging, relative anorexia, insulin resistance and an elevated systemic inflammatory response (19). Whilst the trial by Creutzberg et al., (19) involved a very small sample size (n 24) it is the first study to try to assess the aetiology of non-responders to nutritional support in COPD. Aging is associated with a reduced nutritional intake, thought to be due to reduced REE, reduced physical activity energy expenditure and reduced FFM. Interestingly, in the study by Creutzberg and colleagues (19) there was a lower dietary intake in the non-responders independent of age, REE and FFM. This suggests systemic inflammation could be exerting a significant anorexigenic effect.

1.1.12 Conclusion

Despite the huge clinical, social and economic implications of malnutrition, there remains confusion around how best to tackle the problem within certain chronic disease states. There is a lack of evidence demonstrating either the efficacy or effectiveness of DA in improving clinical or economic outcomes (26, 27, 99) whilst conversely, there is a substantial evidence base demonstrating such effects for ONS across a number of conditions (10, 100, 101).

Despite a substantial evidence base for nutritional support involving ONS, one condition where the evidence is particularly unclear is for that of COPD. COPD is one of the most costly conditions managed by the NHS and one in which malnutrition is common. Data to be presented later in this thesis will again highlight that the prevalence of malnutrition in this patient group is high (**chapter 4, study 1**) and that malnutrition is associated with poorer outcomes in terms of both survival and healthcare use (**chapter 4, study 2 and 3**) although, despite these issues, this thesis will report that COPD patients spend the majority of their time outside of the hospital environment within their own homes.

This chapter has highlighted that there is a lack of trials directly comparing nutritional interventions in the treatment of malnutrition, which include outcomes of relevance to the patient (e.g. quality of life). Data from a randomised trial presented later in this thesis (**chapter 5**) investigates the effectiveness of ONS versus DA in the treatment of malnourished COPD outpatients with the primary outcome being quality of life. The trial also addresses the areas highlighted to be lacking by previous reviews and is carried out in a setting where the majority of DRM is present.

With the focus now on evidence-based practice, the current economic climate within the NHS, the socioeconomic burden of DRM and the fact that the majority of malnutrition appears to be treatable, the work undertaken for this thesis aims to clarify the evidence base for nutritional support and improve the nutritional care that COPD patients receive.

2.0 Chapter 2 - Overview of the thesis

2.1 Aims of the thesis

The overall aims of the thesis are to review the current evidence base for nutritional support in COPD (systematic review and meta-analysis), broadly explore the problem of malnutrition in COPD and its relationship with clinical and social factors (nutritional screening study) and finally carry out a randomised trial to explore the effectiveness of two of the most commonly used nutritional interventions (ONS versus DA).

The specific objectives of this thesis are to:

- Clarify the current evidence base for nutritional support in COPD (**Chapter 3**, systematic review and meta-analysis)
- Establish the local prevalence of malnutrition in outpatients with COPD using the 'Malnutrition Universal Screening Tool', 'MUST' (**Chapter 4, study 1**).
- Establish the extent to which malnutrition risk ('MUST') and nutritional status (BMI) affect clinical outcome (**Chapter 4, study 2 and 3**) and associated with increased malnutrition risk (**Chapter 4, study 4**)
- Investigate which method of nutritional support is the most effective first line treatment for malnutrition in COPD outpatients (**Chapter 5**, Nutritional intervention - randomised trial).

2.2 Outline of the thesis

The thesis is divided into three parts. Firstly, **chapter 3** reviews the current evidence base for nutritional support in COPD focusing specifically on the current controversies in the field and justifying the need for further work. Secondly, **chapter 4** contains four studies that are presented from a 2-year longitudinal observation survey involving 424 outpatients with COPD that formed part of the recruitment process for a larger randomised trial. The four studies examine the effect of nutritional status on clinical outcome and healthcare use as well as exploring the influence of social demographics on these outcomes. Finally, the randomised trial investigating the effectiveness of two commonly used first line treatments for malnutrition in COPD is presented in **chapter 5**.

2.3 Evolution of the thesis and roles of the author in this work

The study design of the randomised trial was established prior to me commencing my PhD candidature as a result ethical approval was granted shortly before I started. The study design was conceived and agreed by Professor Marinos Elia and Dr Rebecca Stratton (PhD supervisory team). The reasoning behind agreeing the study design before I had started was the trial was very ambitious seeking to recruit 200 COPD outpatients who were at risk of malnutrition and carryout follow-up assessments for 12 months within the community. To conceptualise the study, apply for ethical approval and attempt to recruit the numbers required would simple not have been possible within the funded period of the PhD. As it turned out, I commenced my PhD candidature in September 2007 and the final recruit (number 85) was recruited on 20th May 2010 and my PhD funding ceased September 2010 demonstrating the time required to recruit malnourished outpatients with severe disease.

My role as the researcher and PhD candidate in this work was therefore as follows:

- Recruitment and management of additional recruitment sites, applying for site-specific ethical approval and identifying chief investigators at each site to oversee the recruitment of patients. Sites recruited in addition to the primary site included: Lymington, Winchester, Bournemouth and Portsmouth hospitals.

- Initiation of a programme of nutritional screening in outpatients across two hospitals as a means of identifying potential patients for recruitment into the randomised intervention trial. Carrying out training for the staff involved in performing the nutritional screening.
- Performing a literature review in the area of nutritional support in COPD and designing and carrying out a systematic review and meta-analysis of the current evidence base for nutritional intervention in COPD. Exploring in detail the current controversies surrounding previous reviews and the different analytical methods employed. Where data was difficult to extract from papers or more sophisticated interpretation of meta-analyses was required, expert advice was sought from Professor Marinos Elia (primary PhD supervisor)
- Original data collected by trained respiratory nurse specialists and respiratory healthcare assistants as part of the nutritional screening trial was synthesised, managed and analysed by me, although again where more complex statistical analysis was required around health economic modelling (Chapter 4, study 2) expert advice was sought from Professor Marinos Elia.
- All original data collected as part of the randomised trial was carried out by me and I had primary responsibility for the management and analysis of the data. Whilst I obtained detailed 24-hour dietary recalls from patients, the nutritional intake data was entered by a research assistant not associated with the trial.

Strict inclusion and exclusion criteria into the randomised trial were employed and unfortunately this led to challenges with recruitment. As later described in chapter 4 the majority of patients presenting to the primary recruitment site had severe or very severe obstructive respiratory disease. Identification of patients with severe respiratory disease, who were at risk of malnutrition but at least 4 weeks free from exacerbation was problematic. Within the time constrains of a PhD, it therefore became apparent that the trial was likely to under-recruit and to therefore be underpowered and so greater importance, than was initially intended, has been placed on the work relating to the screening cohort within this thesis. However, it should be noted that this cohort was initially intended only as a method of recruiting patients to the intervention trial and so the type of data collected on these patients was limited. It is therefore acknowledged that data on co-

morbidities, quality of life, respiratory physiology (e.g. DLCO) and body composition would have greatly enriched the data collected and would have assisted in informing my conclusions.

Whilst the randomised trial was underpowered the results are still promising and supportive of results elsewhere in the thesis (Systematic review and meta-analysis). In addition, whilst the results from the observational cohort have limitations they have highlighted new data relating to the complex interaction between social deprivation, malnutrition and clinical outcomes in COPD. The systematic review and meta-analysis findings are extremely impactful and suggest a disservice has been done to the field of nutrition in the management of COPD and it is hoped the findings of which will once again stimulate interest in the area.

3.1.0 Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis

3.1.1 Introduction

The negative impact of COPD is not confined only to the lungs and one of the earliest extra-pulmonary effects of the disease is progressive weight loss. Malnutrition is a common problem in individuals with COPD with prevalence rates as high as 60% in inpatients and 45% in outpatients reported (10). Malnourished COPD patients demonstrate greater gas trapping, lower diffusing capacity and reduced exercise performance when compared to heavier, non-malnourished patients with a similar severity of disease (102). As was highlighted in the chapter 1, observational studies have shown that if nutritional assessment includes only body weight and unintentional weight loss a subgroup of patients, with an apparently normal BMI, would not be identified as at nutritional risk despite being FFM deplete (21, 68). A cross-sectional survey by Cano et al., (21) in 300 outpatients with COPD requiring long-term oxygen therapy found 17% of patients to have a low BMI, whereas the prevalence of FFM depletion was more than two-fold higher (38%). This accelerated loss of lean tissue, which may lead to sarcopenia and cachexia, is likely to be facilitated by elevated inflammation, which is commonly observed in COPD. It is has also been suggested that inflammation in COPD is a contributory factor that limits or prevents accretion of lean tissue following nutritional support (19). Wasting of muscles not only detrimentally affects respiratory function, including reduced ability to expectorate to clear a chest infection, but it also promotes fatigability and reduces exercise tolerance and ability to work. However, it has not been possible to establish the exact causality between malnutrition and COPD as malnutrition may be the consequence of a greater respiratory disease severity leading to a compromised nutritional intake (loss of body weight) and reduced physical activity (muscle atrophy). Conversely, wasting of the muscles involved in breathing may precede severe respiratory disease. The effect of nutritional support in the management of malnourished COPD patients has also been controversial. Traditional thinking has tended to regard weight loss as an irreversible consequence of COPD, a view that has arguably been reinforced by recent meta-analyses (72, 73). Such analyses have

not only concluded that nutritional support has no significant effect on improving anthropometric measures such as weight and muscle mass, but also that it produces no demonstrable improvements in lung function and muscle strength. Several nutritional intervention studies have challenged this idea (37, 57, 58, 79, 83, 103) with the result that there remains confusion about whether there is a need to identify and treat malnutrition in COPD. For example, in its 2010 updated report on COPD, the National Institute for Health and Clinical Excellence (NICE) (6), referred to the failure of a previous meta-analysis to demonstrate significant changes in weight and other outcomes with nutritional support (73), whilst referring to a previous study which demonstrated such improvements with the use of oral nutritional supplements (ONS) (104). Despite these apparent inconsistencies the guideline recommended that ONS should be given to patients with a low BMI (< 20 kg/m^2) stating this was based on grade D evidence (lower quality) rather than the evidence from published systematic reviews and meta-analyses, and evidence from at least one RCT, which according to the NICE criteria qualify for grade A evidence (6).

On examining previous systematic reviews of nutritional support, differences in the methods of analysis were found (10, 72, 73, 105). Unlike previous reviews (10, 72, 88), the latest Cochrane Collaboration review (73) carried out only cross-sectional analysis examining the differences between control and intervention groups at the end of the intervention period but not the changes induced by either intervention or control or the impact of any baseline imbalance on the final point estimates. Treatment effect within groups as well as information on the presence of any variability between the two groups at baseline, beyond the fact that they were not significantly different, was not reported. Therefore, the current systematic review and meta-analysis aimed to carry out an updated systematic review of the literature as five years had passed since the Cochrane review. In addition, the present review aimed to carry out a more comprehensive analysis of the data in particular accounting for any baseline variability and exploring within group change for relevant outcomes. Through employing this methodology it is hoped greater clarification around the effectiveness of nutritional support in COPD will be provided.

3.1.2 Subjects and Methods

3.1.2.1 Search strategy and identification of trials

The new review was planned, conducted and reported according to published guidelines (106-108). A systematic search of the literature was conducted in July 2010 to identify RCTs investigating nutritional support in COPD. Searching electronic databases identified potentially relevant studies. The databases searched included PubMed (accessed 7th January, 2010), Web of Science (accessed 7th January, 2010) and OVID (accessed 7th January, 2010). These 3 databases were selected as they are amongst the most commonly used in systematic literature reviews and cover a variety of medical disciplines. In order to identify the largest number of trials and ensure relevant trials were not missed a broad search strategy was implemented however trials were restricted to English language citations only. The search terms and mesh headings used included: chronic obstructive pulmonary disease, COPD, emphysema, weight, depletion, diet*, nutrition*, supplement*, protein, carbohydrate, calori*, feed*, malnutrit*, nourish*, sip feed (liquid oral nutritional supplement), nutrition intervention, nutrition support. A combination of these search terms was also used to identify trials. In addition to electronic database searching, manual searching of previous reviews on nutritional support in COPD and references of identified trials was undertaken by PFC (PFC - PhD candidate).
Studies were initially screened by reading the abstract and where a study could not be excluded the full article was reviewed. The assessment of trial eligibility was done by two independent assessors (PFC and ME – PhD supervisor) with any disagreement discussed and agreed prior to inclusion.

3.1.2.2 Inclusion and exclusion criteria

Studies were deemed eligible for inclusion in the review if they conformed to the pre-determined inclusion and exclusion criteria. To investigate the overall efficacy of nutritional support (food strategies (food fortification, food snacks), dietary advice (DA), oral nutritional supplements (ONS), and enteral tube feeding (ETF)) the following inclusion criteria for trials was devised: (i) randomised trials, (ii) intervention with food strategies, DA, ONS or ETF, (iii) duration of intervention > 2

weeks, (iv) control group receiving placebo or no dietary intervention (e.g. usual care, which could include advice and encouragement to eat) and (v) stable patients with a diagnosis of COPD (not exacerbating), (vi) human studies only, (vii) English language only.

The intervention could provide either a proportion or all of the daily nutritional requirements for energy, protein and micronutrients and where feeds were used (e.g. ONS), these could be nutritionally complete or incomplete. Studies using parenteral nutrition were excluded.

3.1.2.3 Data extraction

Outcome data sought included total nutrient intake (energy and protein), body weight, upper arm anthropometry, body composition, and handgrip strength. Data were collected at baseline and at the end of the intervention phase where possible. Data were collected within data extraction tables allowing data synthesis and analysis from studies with varying populations (nourished/undernourished), intervention types (food strategies, DA, ONS, ETF) and intervention duration. Where data were not reported in the text but illustrated within a figure, the figure was expanded and the data extracted. This was done for energy intake (82, 109) and weight (80, 109). In some papers where mean values were reported without standard deviations (SD) or standard errors (SE), it was possible to calculate SD and SE using reported p values. In one study assessing handgrip strength (83), data reported in kg was considered to be unrealistic and therefore assumed to be in pounds.

3.1.2.4 Quality assessment

The quality of included studies was assessed using a commonly used scoring system (Jadad scoring system) which comprises three components addressing whether a study is described as randomized, whether the study described as double blind and were drop-outs accounted for. It then scores according to the appropriateness of randomization and blinding with the maximum possible score being 5 (110). Quality assessment of trials was performed by one researcher (PFC) and independently verified by another assessor (RJS – PhD supervisor).

3.1.2.5 Synthesis of data and statistical analysis

Following the extraction of data from included trials, where appropriate and feasible, the results of comparable outcome measures were combined and meta-analysis performed. Statistical analysis was performed using SPSS (version 16.0, Chicago, IL) and meta-analysis (random effects model) using Comprehensive Meta-analysis (Biostat Inc, NJ USA version 2). Analysis was carried out in order to explore differences between groups as well as changes within groups. The effect size was reported as difference in means and standard error. The values used for changes were as reported by the various studies only a minority of which adjusted for baseline values (56-58, 74). The correlation coefficient between baseline and end measurements was calculated (111). Any computed values that were slightly greater than 1.000 due to rounding of reported or calculated SDs, were assumed to have a value of 1.00. Where meta-analysis was not possible analysis of mean data was performed (protein and mid-arm muscle circumference).

Pre-specified sub-group analysis was performed according to type of nutritional support (oral nutritional supplements (ONS), enteral tube feeding (ETF), dietary advice (DA)) and baseline nutritional status (nourished ('non-depleted') *versus* malnourished ('depleted')). Malnutrition was considered to be present if the mean BMI was less than 20 kg/m^2 or mean ideal body weight was less than 90%. Meta-regression analysis was used to investigate whether duration or amount of intervention influenced the effect size for each outcome. The overall treatment difference was considered statistically significant if the p value was < 0.05 and forest plots were used to present effect size.

3.1.3 Results

A total of 46 studies were identified as potentially eligible from the literature search (19, 56-58, 74, 75, 79-84, 93, 95, 103, 109, 112-141) and of these 33 were excluded (Figure 2). Exclusion reasons included 4 unsuitable study design (122, 125, 137, 138), 5 non-randomized trials (19, 81, 113, 129, 136), 3 target population not suitable (75, 112, 141), 7 no control or placebo group (114, 116-119, 135, 140), 12 unsuitable intervention or review (93, 95, 115, 120, 123, 124, 126, 128, 131-134), 2 inadequate intervention duration (127, 139). A large

randomized trial comparing an intensive management program versus usual care was not included as nutritional support was provided to only a subgroup of patients where indicated in both arms (130, 142). A summary of the search process is shown in Figure 2.

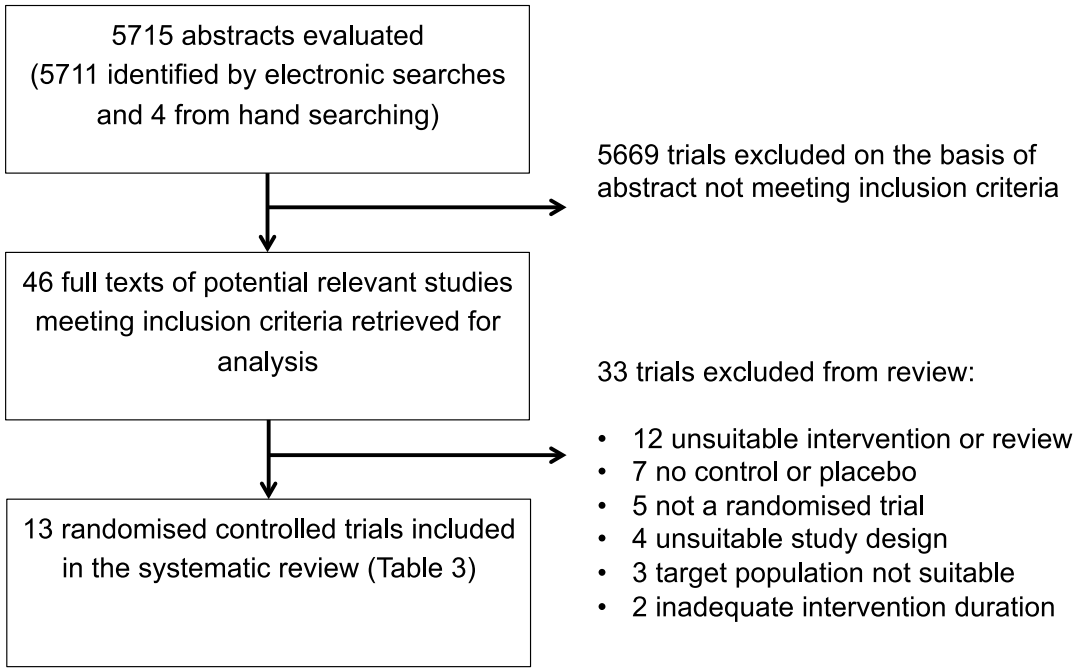


Figure 2 Study selection process.

Table 2 Outcome measures of randomised controlled trials included in the systematic review and meta-analyses.

Outcome measure	Systematic review		Meta-analysis†	
	No. studies	No. participants treatment/control	No. studies	No. participants treatment/control
Energy intake	11	195/184	5	94/97
Protein intake	5	88/92	2	53/57
Weight	13	225/214	13*	225/214
Body composition	4	115/115	0	-
Mid arm muscle circumference	7	124/125	3	53/51
Skinfold thickness	9	117/107	2	43/40
Handgrip strength	5	87/90	4	77/79
FEV_1	10	174/158	2	43/40
PI max	7	114/109	5	91/86
PE max	6	81/59	3	51/41
Walking distance	5	77/86	0	-
Quality of life	2[#]	55/70	0	-

** 8 studies if no assumptions were made in order to obtain data on dispersion (SDs).*

† Meta-analysis with measures of dispersion. ♯ Weekes et al., (74) assessed quality of life using both a generic (SF36) and a disease-specific tool (St George's Respiratory Questionnaire; SGRQ); FEV_1 = forced expiratory volume in 1 second; PI max = maximum inspiratory pressure; PE max = maximum expiratory pressure.

The review included 13 RCTs of 439 individuals with COPD randomised into either a treatment group (n = 225) or a control group (n = 214), (Table 2). Eight studies were performed completely within the outpatient setting (56, 74, 79, 80, 84, 104, 109, 121) three in inpatients (57, 58, 82) and two studies involved both outpatient and inpatient settings (83, 103). Separate analysis of the trial by Schols et al (57, 58) was performed according to nourished or malnourished patients (Table 3). Patients recruited to the trials had a diagnosis of COPD ($FEV_1/FVC < 0.70$) and were in a stable condition free from exacerbation. Patients recruited to the trials were classified as having severe COPD, range 30-40% predicted FEV_1 (FEV_1 <

50% predicted (stage III)) (29). No study provided results on acute phase proteins, or cytokines, and of the four studies reporting circulating albumin, three had normal values (80, 82, 109) and one close to the lower limit of normal (104).

The majority of trials (11, n = 189 intervention *vs*. n = 185 control) provided nutritional support by ONS (56-58, 79, 80, 83, 84, 103, 104, 109, 121), mostly liquid supplements, some of which were specifically formulated for use in patients with COPD (Percentage energy: 60% carbohydrate, 20% fat, 20% protein (Respifor ®, Nutricia Ltd) (56, 84), 28.2% carbohydrate, 55.1% fat, 16.7% protein (Pulmocare ®, Abbott)) (121). One trial used nocturnal ETF (n = 6 *vs*. n = 4) (82) and one trial used tailored dietary advice delivered by a dietitian and the provision of a milk powder supplement (n 30 *vs*. 25) (74). There were no trials of food snacks or food fortification alone. The intervention period ranged from 16 days (82) to 6 months (74), with the amount of nutritional support prescribed ranging from 355 kcal/day (121) to 1080 kcal/day (103).

The majority of studies (n = 8) (74, 79, 80, 82, 83, 103, 104, 121) were principally of malnourished ('depleted') individuals (BMI < 20 kg/m^2 or % ideal body weight < 90%). The trials by Schols et al., (57, 58) and Steiner et al., (56) included both nourished and undernourished patients as part of a rehabilitation exercise programme and performed, or allowed for, subset analysis according to nutritional status (56-58). Two other studies included both undernourished and nourished subjects, with a predominance of underweight, since in one the mean BMI was < 20 kg/m^2 (< 90% IBW) (84) and in the other, % IBW ranged from 61 -108% (109) (Table 14).

All trials (n = 13 RCT) included in the review reported weight and weight change (or it could be calculated). The next most frequently reported anthropometric measures were triceps skinfold thickness and mid arm muscle circumference. Other outcomes included energy (n = 11) and protein (n = 5) intakes and the functional measure, handgrip strength (n = 5) (Table 2).

3.1.3.1 Quality of studies

The review identified 3 studies assessed to be of high quality (≥ 4) (56, 82, 104), and ten of lesser quality (≤ 2) using the Jadad scoring system (110) (Table 3).

3.1.3.2 Publication bias

Publication bias could only be appropriately investigated using funnel plot analysis for weight, which was the only outcome to be reported in greater than 10 RCTs (Figure 3). Although 10 studies can be viewed as inadequate to produce a valid funnel plot (143), it has been previously used as a minimum threshold (144) below which the power of the test is too low to distinguish chance from real asymmetry.

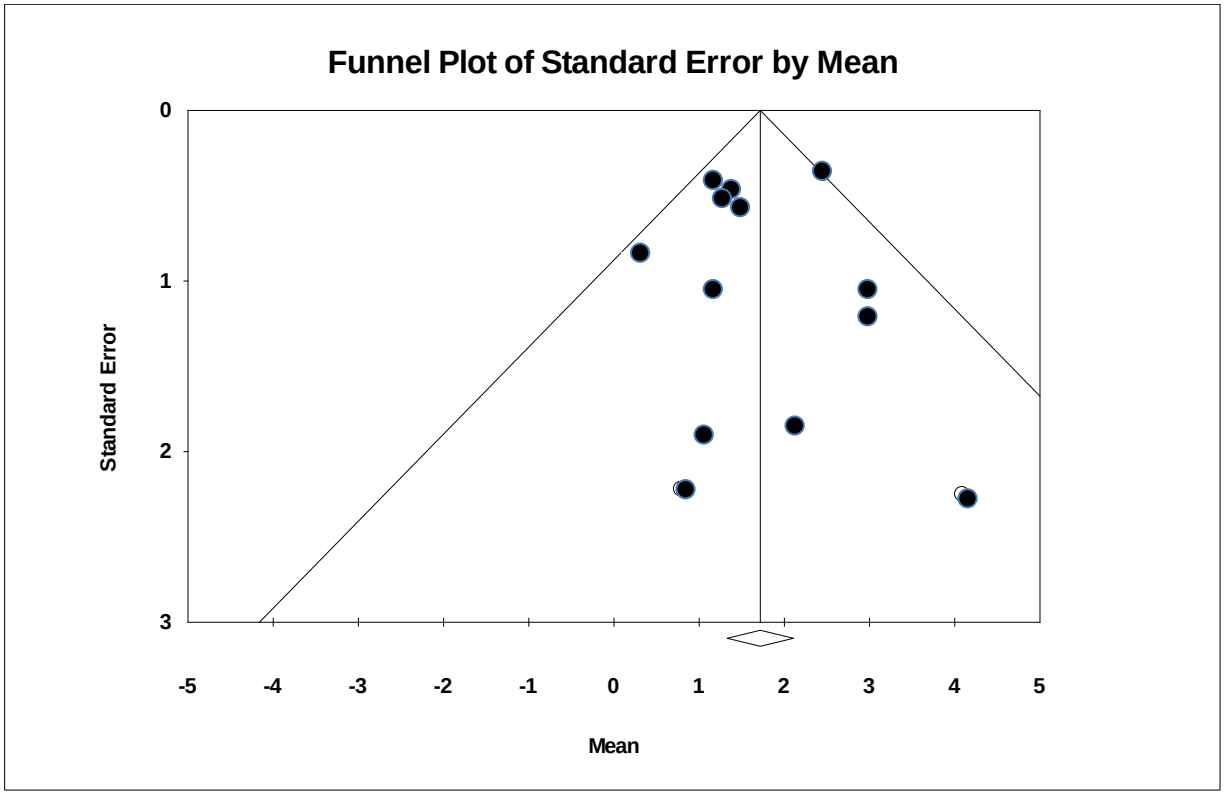


Figure 3 Funnel plot exploring publication bias for those RCTs reporting body weight (n = 13 studies)

Table 3 Summary of the randomised controlled trials included in the systematic review according to intervention.

Study	Sample size Treatment/ control	Characteristics/setting (intervention *vs.* control)	Nutritional intervention (type/prescribed amount/duration)	Control group	Outcome measures	Study quality (Jadad)†
Oral nutritional supplements						
DeLetter et al., (121)	18/17	Malnourished 82.8% IBW Outpatients	ONS (Pulmocare, 1.5kcal/ml) ONS target: 355 kcal/d 8 weeks	Usual diet	Energy, Protein, Wt, FFM, MUAC, MAMC, TSF, FEV_1, 6MWT	11000 (2)
Efthimiou et al., (79)	7/7	Malnourished 79.5 *vs*. 81.3% IBW Outpatients 60 *vs*. 64 years	ONS (Build Up, 1.13kcal/ml) ONS target: 640-1280 kcal/d Encouragement to eat (same in control group) 12 weeks	Usual diet (with encouragement)	Energy, Protein, Wt, %IBW, MAMC, TSF, HGS, FEV_1, PI max, PE max, HGS, 6MWT, sternomastoid strength, general well-being	10000 (1)
Goris et al., (84)	11/9	Nourished and malnourished* 19.8 kg/m^2 (~87% IBW) (19.6 *vs*. 20* kg/m^2) Outpatients 61 *vs*. 62 years	ONS (Respifor, 1.5kcal/ml) ONS target : 563 kcal/d Encouragement to eat (same in control group) 12 weeks	Usual diet (with encouragement)	Energy, BMI	11000 (2)
Knowles et al., (109)	13/12	Nourished and malnourished 61-108% IBW Outpatients 68 *vs*. 70 years	ONS (Sustacal, 1kcal/ml) ONS target: To increase total EI by 50%. Weekly encouragement 8 weeks	Usual diet	Energy, Wt, MAMC, TSF, FEV_1, PI max, PE max	11000 (2)
Lewis et al., (80)	10/11	Malnourished 86.3 *vs*. 84.6 % IBW Outpatients 65 *vs*. 59 years	ONS (Isocal HCN, 2kcal/ml) ONS target: 500-1000 kcal/d Encouragement 8 weeks	Usual diet	Energy, Protein, Wt, MAMC, TSF, HGS, FEV_1, PI max, PE max	10000 (1)

Otte et al., (104)	13/15	Malnourished 77 *vs*. 73% IBW outpatients 57 years	ONS (Novo, 1kcal/ml) ONS target: 400 kcal/d Encouragement 13 weeks	Placebo (blinded) (encouragement)	Wt, %IBW, MAMC, skinfold thickness (s4SF), FEV_1, 12MWT, well-being	10111 (4)
Fuenzalida et al., (103)	5/4	Malnourished inpatients and outpatients 78.5% IBW 62 years	ONS (Sustacal HC, 1kcal/ml) ONS target: Up to 1080 kcal/d 3 wks inpatient + 3 wks outpatient (6 wks total)	Usual diet	Energy, Wt, MAMA, TSF, FEV_1	10000 (1)
Rogers et al., (83)	15/12	Malnourished 78 *vs*. 79% IBW 64 years outpatients (intervention group admitted for first 4 weeks)	ONS (various, self-selected) Tailored to individual dietary habits and dietary advice ONS target: Intakes >1.7 x REE and minimum 1.5g/kg/d 15 weeks	Usual diet	Wt, %IBW, MUAC, TSF, HGS, PI max, PE max, 12MWT, breathlessness rating	10000 (1)
Schols et al., (57)	33/38	Nourished 102.4% IBW inpatient PR program (not hospital) mean age unclear	ONS (Mixture of Nutridrink, Protifar, Fantomalt,Oil; seven mixtures of different flavors; 2.1kcqa/ml) ONS target: +420 kcal/d Encouragement to eat regular meals 8 weeks	Usual diet (and encouragement with oral diet)	Energy, Wt, MAMC, FM, FFM, FEV_1, PI max, 12MWT	10001 (2)
Schols et al., (58)	39/25	Malnourished 84.1% IBW inpatient PR program (not hospital) mean age unclear	ONS (Mixture of Nutridrink, Protifar, Fantomalt,Oil; seven mixtures of different flavors; 2.1kcqa/ml). ONS target: +420 kcal/d. Encouragement to eat regular meals 8 weeks	Usual diet (and encouragement with meals)	Energy, Wt, FM, FFM, FEV_1, PI max, 12MWT	10001 (2)

Steiner et al., (56)	25/35	Nourished/ malnourished ~105% IBW (23.9 *vs*. 23.5 kg/m^2) outpatients PR programme 66 *vs*. 68 years	ONS (Respifor, 1.5kcal/ml) ONS target: +570 kcal/d 7 weeks	Placebo (blinded)	Energy, Protein, Wt, FM, FFM, HGS, ISWT, ESWT, QoL	10111 (4)
Enteral tube feeding						
Whittaker et al., (82)	6/4	malnourished 76 *vs*. 82% IBW Inpatients 71 *vs*. 64 years	Nocturnal ETF (Isocal) ETF target; Feed delivered: at least 1000 kcal/d or 1.7 x REE whichever greater Nasoduodenal / jejunal tube feeding 16 days	Placebo ETF (equivalent volume providing <100kcal/night)	Energy, Wt, TSF, FEV_1, PI max, PE max, adductor pollicis muscle function	11110 (4)
Dietary advice, dietary leaflet plus milk powder						
Weekes et al., (74)	30/25	malnourished ~88%IBW (~19.8 kg/m^2) outpatients 69 years	Tailored dietary advice (DA) + leaflet of information + milk powder DA target: 600 kcal/d 6 months	Leaflet of information	Energy, Protein, Wt, MAMC, s4SF, HGS, FEV_1, PI max, PE max, QoL	10001 (2)

- *Goris et al., (2003)(84): control group referred to as depleted however, according to UK guidelines the subjects would not be considered to be so (8); ONS = oral nutritional supplements; DA = dietary advice (education); ETF = enteral tube feeding; Wt = weight; BMI = body mass index; % IBW = percentage ideal body weight; FM = fat mass; FFM = fat free mass; FFMI = fat-free mass index; MUAC = mid-upper arm circumference; MAMC = mid-arm muscle circumference; MAMA = mid-arm muscle area; TSF = triceps skinfold; s4SF = sum of 4 skinfolds; HGS = handgrip strength; FEV1 = forced expiratory volume in 1 second; PI max = maximum inspiratory pressure; PE max = maximum expiratory pressure; 6MWT/12MWT = 6- or 12-minute walk test; ISWT = incremental shuttle walk test; ESWT = endurance shuttle walk test; QoL = quality of life; PR program = pulmonary rehabilitation program; REE = Resting energy expenditure.. †The number in parenthesis represents the overall score. The five individual scores represent scores for description and appropriateness of randomization/blinding as well as any description of withdrawals.*

3.1.3.3 Dietary intake

Data on total energy intake were available in 11 studies (56-58, 74, 79, 80, 82, 84, 103, 109, 121). When limiting analysis to those studies where nutrition was ingested orally meta-analysis was possible on 5 studies (56, 74, 80, 109, 121) (after excluding a study involving nocturnal ETF (82). There were no significant differences in daily energy intake between supplemented and control groups at baseline (mean difference 11 SE 87 kcal, p = 0.903), but at the end of nutritional treatment (56, 74, 80, 109, 121) a significant difference was found in favour of the supplemented group (diet + ONS or DA); 236.3 SE 71 kcal, p < 0.001. Information on the mean changes in energy intake was available from 6 studies although measures of variation were available in only 2 of them. In all 6 studies the mean changes in energy intake were greater in the intervention group than control group by 318 SD 157 kcal/day (p = 0.004, weighted for sample size). Similar significant results were also obtained from the five studies that involved ONS (413 SD 175 kcal/day, p = 0.006) (56, 79, 80, 109, 121). Considering only the two studies that were amenable to meta-analysis (56, 74) the change in intake was also found to significantly favour the supplemented group compared to the control group (234 SE 63 kcal, p < 0.001). Each study, one involving ONS and the other tailored dietary advice and milk powder supplementation, independently yielded significant results favouring the intervention.

Of the 13 studies, only two failed to report the prescribed nutritional intervention data in a way that could be analysed (83, 109). Meta-regression analysis revealed no association between target amount of nutrition support and any increase in weight (p = 0.90, slope < 0.0001 units). Furthermore, no relationship was found between the amount of weight gained and the duration of nutritional support (13 RCT, p = 0.936, slope < 0.004 units).

Information on mean changes in protein intake was available in 5 studies (56, 74, 79, 80, 121) (but measures of variation were available in only two of them) (56, 74). All 5 studies reported mean daily protein intakes that were greater in the supplemented than control group by 16.5 SD 10.3 g/day (p = 0.023, weighted for sample size). Similar results were also obtained in the 4 studies involving ONS (18.2 SD 7.0 g/day, p = 0.014). Considering only the two studies that were suitable for meta-analysis (56, 74) protein intake favoured the supplemented group by a

similar amount 14.8 SE 3.6 g/day, $p < 0.001$. As with energy, both studies were significant in their own right ($p < 0.001$).

3.1.3.4 Body weight

The trials of nutritional support showed a consistent increase in weight, which was significant in 7 out of 8 individual studies. However, a detailed analysis is undertaken below for comparison of conclusions from previous meta-analyses. Using information on body weight obtained from 8 studies, three sets of meta-analyses were carried out to compare control and intervention groups (Table 4). These involved baseline weight, end weight, and change in weight (56-58, 74, 82, 83, 103, 104). Figure 4 (upper) shows that baseline weight in the intervention and control groups was not statistically different ($p = 0.240$) but on average the control group was 1.217 SE 1.04 kg heavier than the treatment group. Figure 4 (middle) illustrates that after nutritional intervention the difference between control and intervention groups remained non-significant ($p = 0.506$; with individual study results on both sides of the reference line) but this time the control group was lighter than the supplemented group by 0.746 SE 1.12 kg. Figure 4 (lower) shows that the mean improvement (increase) in weight in the intervention group was greater than in the control group in all eight primary studies, and this was significant in seven of the individual studies. Not surprisingly the overall effect size of the meta-analysis was highly significant, with a mean increase in weight in favour of the intervention group of 1.83 SE 0.262 kg, $p < 0.001$. This corresponds to 3% of initial body weight.

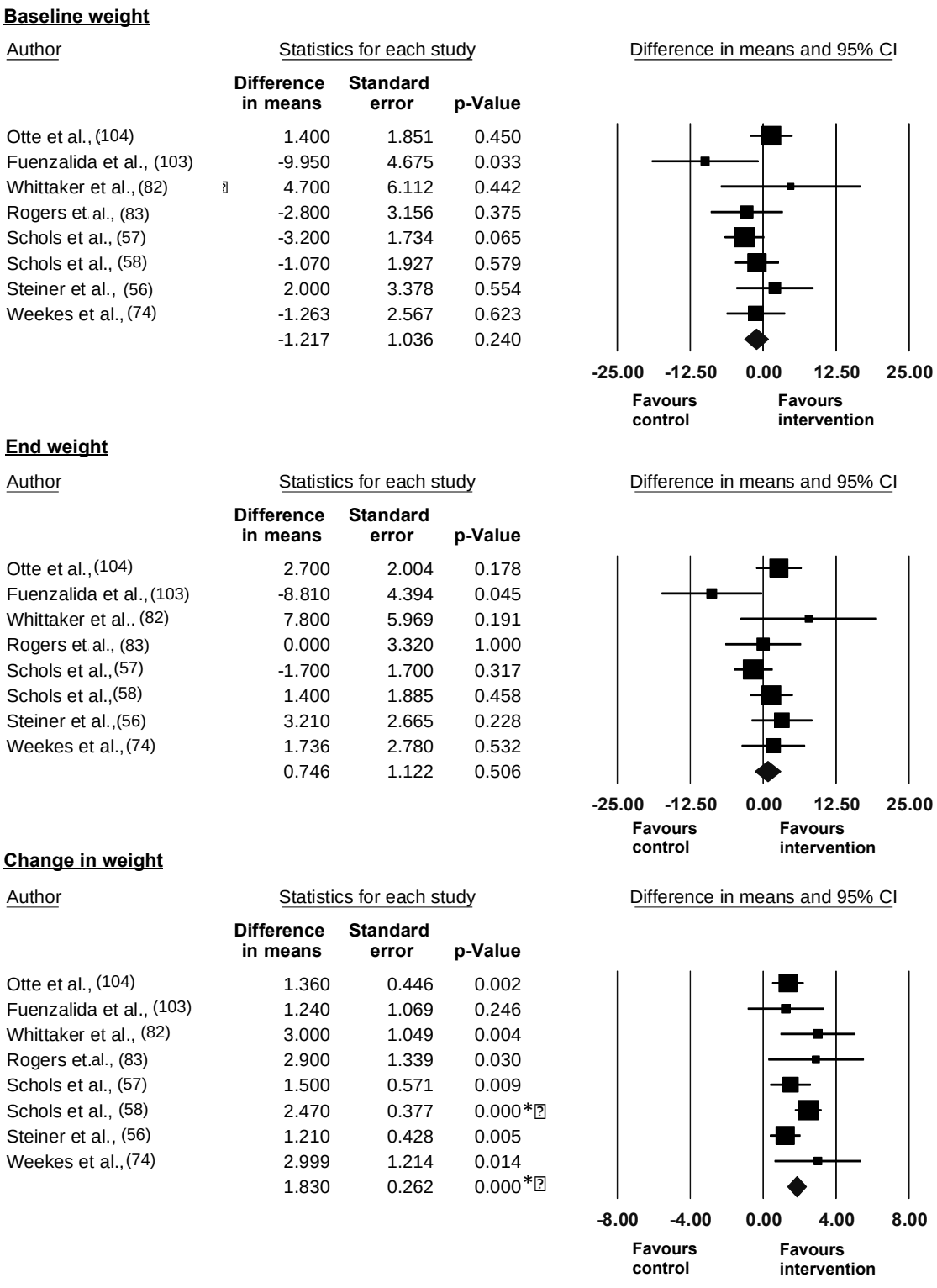


Figure 4 Forest plots for 8 studies demonstrating the difference in weight between control and intervention before (upper) and after intervention (middle) and the change in weight in kg (bottom) induced by the intervention (* = nourished ('non-depleted'), others = depleted (malnourished)). 0.000 = $p < 0.0005$.

Inspection of the Forest plots (Figure 4) also shows that the variability (indicated by the 95% confidence intervals) between the intervention and control groups,

both for the primary studies and the summary effect of all the studies combined, is much smaller for the change in weight (lower plot) than for the baseline weight (upper plot) and end weight (middle plot). Table 4 summarizes these results, and shows that not only is the overall change in weight significantly greater in the intervention than the control group (by almost 2 kg), but the observed variance at baseline and end is almost 20 times greater than the variance of the change in weight). This is due to a high correlation between pre- and post-weight in both the intervention group and the control group. For the primary studies, r ranged from 0.97 to 1.00 in the control groups and 0.82 to 1.00 in the intervention groups; and for the summary effect (meta-analysis r was 0.995 (95% CI 0.979, 0.999) for the control group, 0.997 (95% CI 0.974, 1.000) for the intervention group 0.993 (95% CI 0.947, 0.999). Simple correlation analysis of mean results (without measures of variation) obtained from the same studies also indicated a very high relationship between baseline and end weight (r = 0.993 and 0.991 for the control and intervention groups respectively and r = 0.985 for the two groups in combination).

Table 4 Summary statistics of effect size and dispersion of effect size based on 8 primary studies with data on baseline weight, end weight and change in weight

	Effect size: difference between groups (kg)†	Standard error of the difference (kg)	p value for effect size
Baseline weight (kg)	-1.217	1.070	0.240
End weight (kg)	+0.746	1.258	0.506
Change in weight (kg)	+1.830	0.068	<0.001

† Intervention group minus control group (meta-analysis, random effects model). Small discrepancies in the sum of the effect size (change in weight) are due to extraction from different data sets provided within manuscripts (Table 3 and Figure 4).

A sensitivity analysis (Figure 5) was carried out by combining the above eight studies with another five studies that lacked information on variation of weight change, in either the control or intervention groups (79, 80, 84, 109, 121). The SD of the final weight for one trial (121) was obtained from a previous review (73). For these studies a very large estimate of the SD of the change was assumed, (SD of the change corresponding to 10% of baseline weight). All 13 primary studies reported a mean weight change in favour of the intervention group (Figure 5). The

summary effect size and its significance remained similar (1.69 SE 0.30 kg, 95% CI 1.1, 2.3 kg, p < 0.001) to those obtained with the 8 primary studies with complete information (Figure 5). A similar, significant result was also noted when only studies involving ONS were analysed, 1.63 SE 0.23 kg, p < 0.001. The meta-analysis of 13 studies for weight change revealed no evidence of publication bias using funnel plots and tests such as the Begg and Mazumdar (p = 0.502) and Egger tests (p = 0.686).

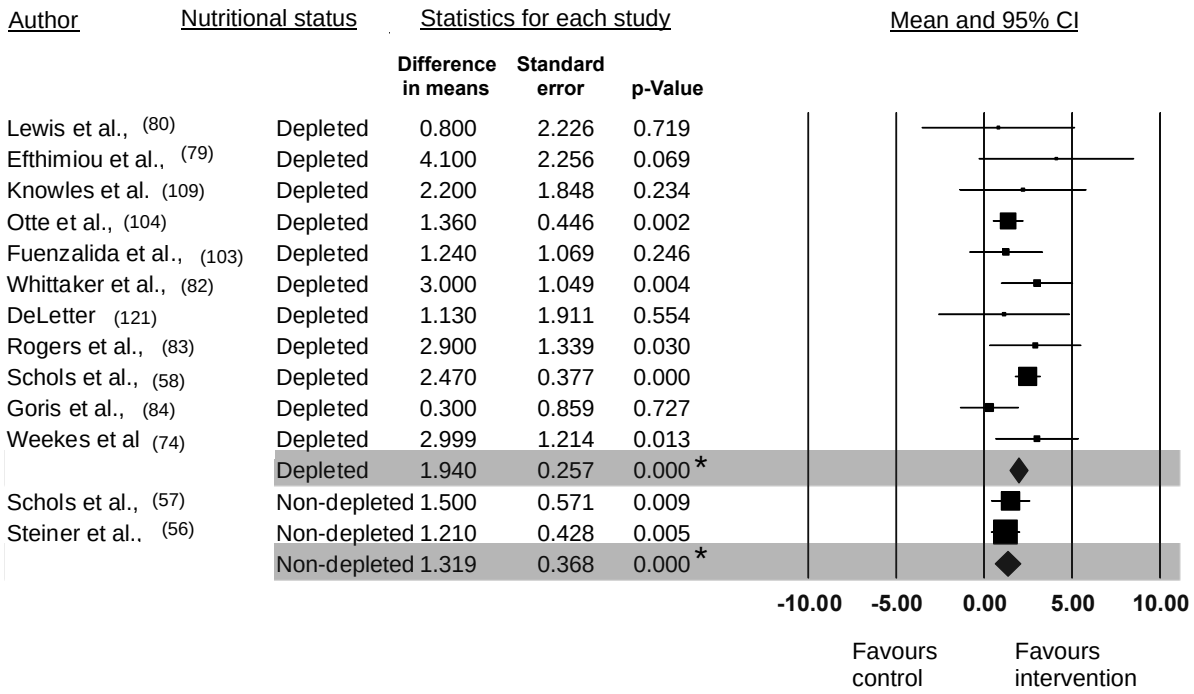


Figure 5 Meta-analysis of the influence of nutritional support on weight (kg) change for 13 studies grouped according to nutritional status (nourished = non-depleted; malnourished = depleted). 4 studies provide nutritional support as part of an exercise rehabilitation programme (56-58, 84), (* = p < 0.0005).

When the 13 primary studies were analysed according to nutritional status (studies with malnourished ('depleted') subjects versus studies that included normally nourished ('non-depleted') subjects) both groups showed a significant increase in weight in favour of the intervention group (non-depleted 1.319 SE 0.368 kg, p < 0.001 *versus* depleted 1.940 SE 0.257 kg, p < 0.001), but the difference between nourished versus malnourished groups was not significant. Undernourished subjects had a more pronounced response to nutritional support but it should be

noted that the two trials including nourished individuals were performed within an exercise rehabilitation program that may have augmented the effects of nutritional support. Meta-regression did not reveal a significant relationship between the magnitude of the weight increase, which favoured the intervention group, and the following individual covariates: %IBW at baseline (n = 13 RCTs, slope -0.021 %IBW/kg; p = 0.228), target intake from the nutritional intervention (n = 11 RCTs, slope < 0.001 kcal/kg; p = 0.847), excluding two trials which did not report the target intervention amount (10, 20) and duration of intervention (n = 13 RCTs, slope < 0.004 kg/week; p = 0.937).

3.1.3.5 Body composition

Assessment of FFM was carried out in 4 studies (56-58, 121) and although 3 out of the 4 trials showed slight improvements in fat-free mass with supplementation (0.17 - 1.0 kg; 0.7 - 2.0 % of baseline), these were not significant. All four studies used different methods to assess FFM (bioelectrical impedance (57, 58), dual energy X-ray absorptiometry (DXA)(56) and skinfold thickness (121) . Seven trials reported data on measured mid-arm muscle circumference (MAMC) (57, 74, 79, 80, 104, 109, 121), an indirect measure of FFM. In six of the seven trials, the mean change favoured the intervention group compared to the control group by a mean of 2.4% (range -1.0 - 5.5%, p = 0.045, one sample t-test when weighted for sample size). Only 3 trials were amenable to meta-analysis (74, 80, 104) and these showed an improvement in favour of the intervention group (effect size 0.296 SE 0.158 cm, p = 0.061).

Nine studies (74, 79, 80, 82, 83, 103, 104, 109, 121) used one or more skinfold thicknesses to describe changes in body fat, 7 used triceps skinfolds and 2 studies used the sum of 4 skinfold sites (S4SF) (74, 104). It was possible to calculate changes from eight studies (74, 79, 82, 83, 103, 104, 121). The mean changes in eight studies favoured nutritional support (p = 0.008 (sign test)). Two primary studies using S4SF were appropriate for meta-analysis (14, 25) both of which were significant in their own right. The test of overall effect was +4.2 SE 1.2 mm, p < 0.001.

3.1.3.6 Pulmonary function and respiratory muscle strength

Respiratory function (FEV_1) was assessed in 10 studies (57, 58, 74, 79, 80, 82, 103, 104, 109, 121), 9 of which (57, 58, 74, 79, 80, 82, 103, 104, 109, 121) provided separate information in intervention and control groups. However, the results were presented in different ways: two reported no significant differences in the change in FEV_1 over time (74, 104), 7 reported no significant change in either group over time (57, 58, 74, 79, 82, 104, 109) and two reported the mean values of FEV_1 at the start and end of the study period, but since they were virtually identical (80) or very close to each other (121) within the control and the intervention groups it can be deduced that there were no significant changes over time in either group and no significant differences between groups. Indeed, there was no evidence from any of the studies that the changes in FEV_1 or changes in other measures of respiratory function, such as FVC (74, 79, 80, 82, 104, 109), FEV_1/FVC (80, 82), TLC (79, 82, 109) and blood gases (80, 104, 109) differed between intervention and control groups. Two studies, reporting measured FEV_1 (74) and percentage predicted FEV_1 (104), were meta-analysed using standardized differences. Nutritional support was not associated with any improvement in FEV_1 (-0.213 SE 0.22 L, p = 0.335).

PI max was reported in eight studies (57, 58, 74, 79, 80, 82, 83, 109) of ONS (n 6), ETF (n 1) and dietary advice (n 1). Five of these studies (58, 74, 79, 82, 83) were amenable to meta-analysis, four of which favoured nutritional support (Figure 6). The overall summary measure obtained using random effects meta-analysis was significant in favour of nutritional support (+4.04 SE 1.86 cm H_2O, p = 0.030). The meta-analysis was undertaken assuming that the SD of the change in the control group of one of the studies (79) was the same as that of the ONS group. The latter was established from the combination of the reported mean change in PI max and a p value of 0.05 (but since the reported p value was < 0.05, the calculated value is conservative). When a sensitivity analysis was carried out assuming the SD of the change ranged from 75% to 125% of that in the ONS group, there was little change in the overall point estimate (+4.11 SE 1.83 cm H_2O, p = 0.024 and +3.98, SE 1.90 cm H_2O, p = 0.049 respectively). The associated weight change in the same five studies also favoured nutritional support (+2.17 SE 0.44 kg; p < 0.001).

One of the three studies that could not be included in the meta-analysis found a significant increase in PI max over time in the ONS group and not in the control group (109), one reported PI max to be unchanged (80) and the final study did not report the relevant data needed for inclusion in the meta-analysis (57).

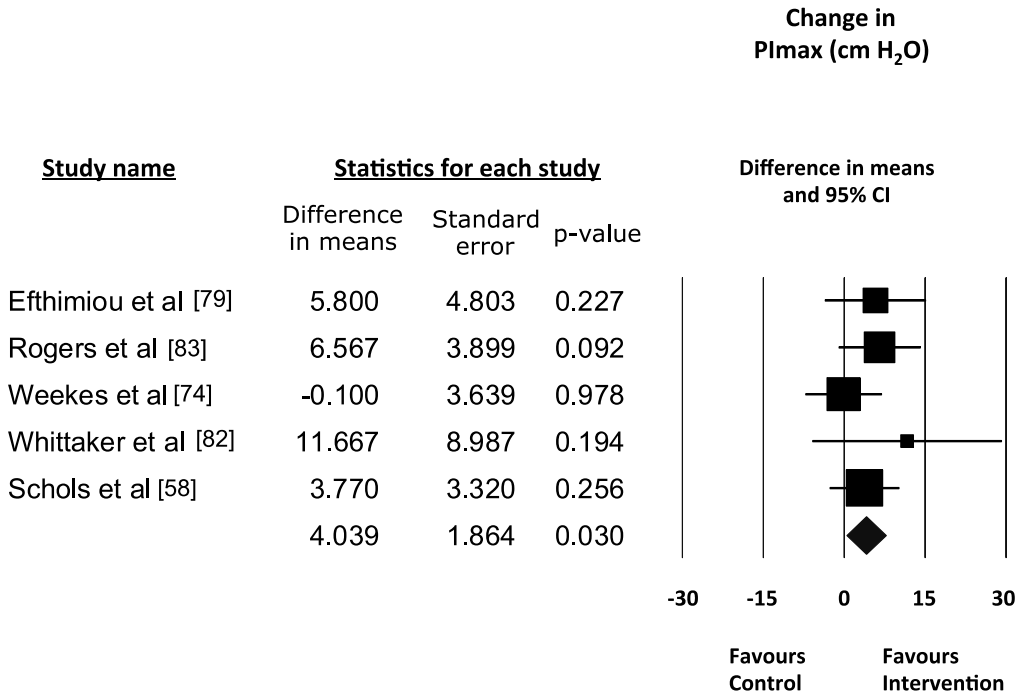


Figure 6 Meta-analysis demonstrating the effect of nutritional support on PI max (cm H_2O).

PE max was reported in six studies, 4 involving ONS (74, 79, 80, 82, 83, 109), one ETF (82) and one using dietary advice (74) but meta-analysis was only possible in four of them (74, 79, 82, 83) (Figure 7). This meta-analysis found that nutritional support significantly improved PE max in favour of the intervention group (+13.06 SE 5.81 cm H_2O, p = 0.025), with all four studies favouring the intervention group and two significant in their own right (one involving ETF (82) and the other involving ONS (83)) (Figure 7). The meta-analysis of PE max was undertaken assuming that the SD of the change in the control group of one of the studies (79) was the same as that in the ONS group. When a sensitivity analysis was carried out assuming that the SD of the change ranged from 75% to 125% of that of the ONS group there was virtually no change in the point estimate obtained by the random effects meta-analysis (+13.02, SE 5.83 cm H_2O, p = 0.026; and +13.12 SE

5.78 cm H_2O, p = 0.024 respectively) The associated weight change in the same four studies also significantly favoured the nutritional support group (+3.10 SE 0.67 kg; p < 0.001).

Of the two studies that could not be included in the meta-analysis, one reported no significant difference in measurements between groups (109) and the other no significant change within groups (80).

To assess respiratory accessory muscle strength a further study measured sternomastoid strength and fatigability and found that ONS resulted in significantly increased strength (p < 0.05) and reduced fatigability after 3 months of supplementation, while non-significant changes in the opposite direction occurred in the control group. The differences between groups returned towards baseline after cessation of treatment (79).

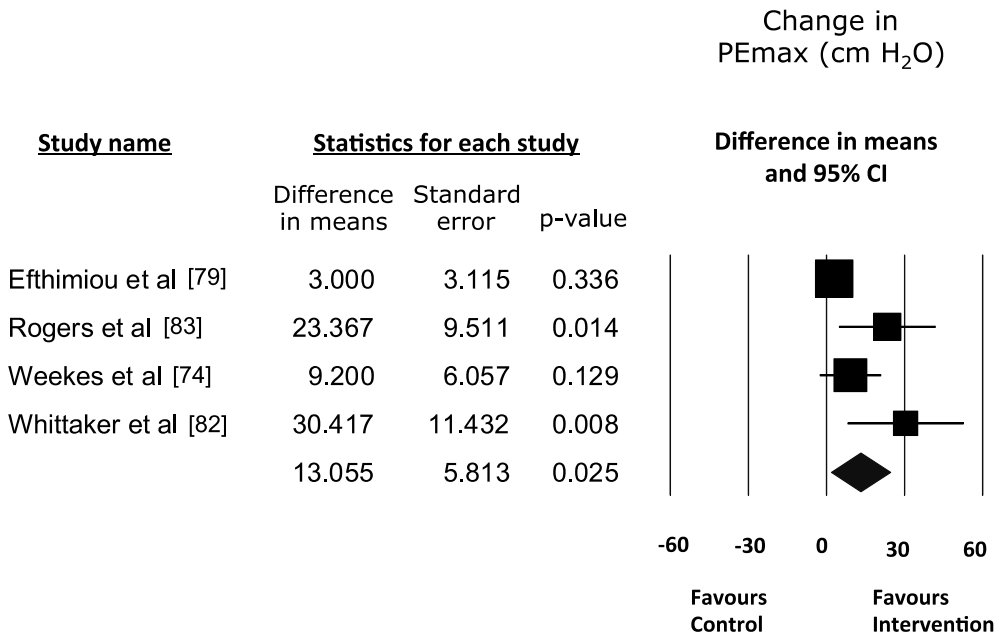


Figure 7 Meta-analysis demonstrating the effect of nutritional support on PE max (cm H_2O).

3.1.3.7 Maximum voluntary peripheral muscle strength

Five studies assessed peripheral muscle strength using handgrip strength (56, 74, 79, 80, 83), with four of the five providing nutritional support using ONS. Four studies (56, 74, 79, 83) were amenable to meta-analysis and all favoured intervention, two significantly so in their own right (79, 83) (Figure 8). The mean changes were +1.41 SE 0.66 kg, p = 0.032 (range 0.3 - 5.2 kg (1.3 - 18.5%) above baseline in favour of the intervention group). In undertaking this meta-analysis two assumptions were made: the SD of the change for the control group in the study of Efthimiou et al., (79) was the same as that for the ONS group; and the unrealistically high grip strength values reported for both intervention and control groups in the study of Rogers et al., (83) were in lbs rather than in kg. To address the latter uncertainty about the units of measurement the meta-analysis was repeated using standardized differences (overall point estimate 0.56, SE 0.22; p = 0.009, Figure 8. To address the former uncertainty, a sensitivity analysis was undertaken by altering the SD of the change by ± 25% (75% to 125%), which produced little change in the overall point estimate and the associated statistical significance of the differences between groups (using a value of 75% for the SD of the change, the overall effect size in the meta-analysis was 0.59, SE 0.23 (p = 0.010); and with 125% for the SD of the change, the effect size was 0.52, SE 0.20 (p = 0.008). Even if the sensitivity analysis involved an alteration of the SD of the change by as much as ± 50% (50% to 150%) there was little overall impact on the effect sizes and p values (effects sizes ranging from 0.48 to 0.58 and p values from 0.021 to 0.018 respectively). The associated change in body weight in the same four studies significantly favoured the intervention group (+2.06 SE 0.65 kg; p = 0.001).

Steiner et al., (56) reported that quadriceps muscle strength increased more in the supplemented than control group (+17.4 kg or ~5% vs. +3.6 kg or ~1% increase, p = 0.068) after adjustment for baseline values. When these results replaced those of HGS in the random effects meta-analysis on muscle strength, and the amalgamated results analysed using standardized differences, the point estimate remained significant (effect size 0.56, SE 0.22, p = 0.010).

A small study of ETF reported no significant differences in the changes between intervention and control groups in electrical stimulation tests involving the adductor pollicis muscle (82).

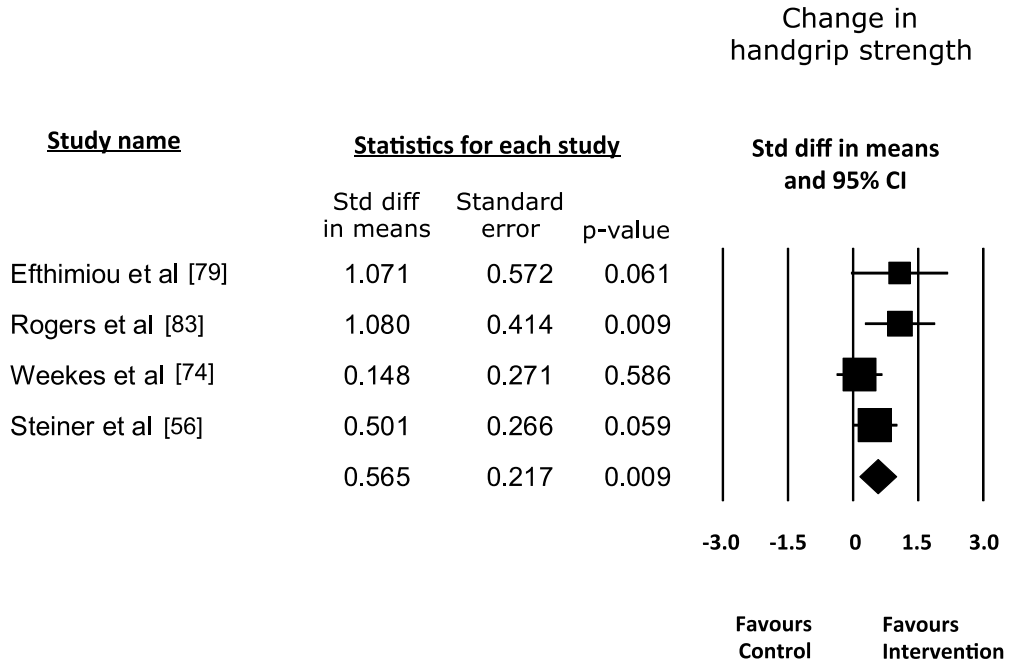


Figure 8 Forest plot for change in handgrip strength (standardised difference in means)

3.1.3.8 Walking distance and endurance during walking

Seven studies examined the influence of nutritional support on improving exercise tolerance (56-58, 79, 83, 104, 121). Four studies favoured the intervention group (56, 79, 83, 121), one favoured the control group, (104) and the remaining two studies (57, 58) did not provide the necessary information to assess which group was favoured. Meta-analysis was not performed due to the use of different methodologies, types of tests, and ways of reporting results (e.g. some reporting median values (56) and others mean values) and lack of measures of variation and/or p values for some of the within group changes (79).

Using the 6 minute walk test (6MWT), Efthimiou et al., (79) reported significant improvements in the ONS group (53 m (~+12.8%); $p < 0.05$) but not in the control group (1 m (~+1.4%) NS) and DeLetter et al., did the same (121) (+ 35.4 m (~+11.6%) *vs.* -1.2 m (~-0.4%)). Using the 12 minute walk test (12MWT) Rogers et al., (83) found that the distance walked increased significantly more in the ONS group (34 m (~7%) at 4 weeks and 143 m (~28%) at 4 months) compared to the control group (a deterioration of 42 m (-8%) at 4 weeks and 0.3 m (-0.1%) at 4 months) ($p = 0.03$ for the difference in the mean change between the two groups). Otte et al., (104) reported no significant changes in the 12 minute walking distance in either the ONS or control groups (-81 m (~-9.0%) *vs.* +50 m (~6.3%) respectively). Schols et al., (57, 58) reported an improvement in the 12-minute walking distance in subgroups of depleted (173 m, 29%) and non-depleted (147 m, 24%) patients undergoing pulmonary rehabilitation, with no significant differences between the intervention and control groups. Using the shuttle walk tests in subjects undergoing pulmonary rehabilitation, Steiner et al., (56) found that performance improved to a greater extent in the intervention (ONS) than control group with respect to endurance walk tests (mean increase in distance walked, 60.0 m *vs.* 42.6 m; ~ 29% *vs.* 19%; $p = 0.182$) and the incremental walk tests (median increase in duration, 328 seconds (~x2 baseline value *vs.* 191 seconds, ~x0.9 baseline value; $p = 0.172$), but the differences were not significant.

3.1.3.9 Quality of life and subjective measures of breathlessness

Five studies examined the effect of nutritional support on QoL, but since the results were obtained using different tools and reported in different ways, they were not subjected to meta-analysis (56, 74, 79, 83, 104). One study of dietary advice reported a significant improvement in the health component of quality of life in favour of the intervention group, using both the St George's Respiratory questionnaire and SF36 (18% and 55% improvement respectively according to the intention to treat analysis) (74). These changes were mirrored by significant differences in breathlessness. Another study reported a significant improvement in general well-being of the nutrition intervention (ONS) group (~27%) and not in the control group (~6%) (79), which was paralleled by a significant improvement in breathlessness in the intervention and not in the control group. A third study of ONS reported that a greater proportion of subjects felt their well-being had

improved as a result of the nutrition intervention compared to control (23% *vs.* 13%) and a smaller proportion felt it had deteriorated (15% *vs.* 33%), but given the small sample size (13 *vs.* 15) the differences were not statistically significant (104). This same study reported a tendency for breathlessness to improve in favour of the intervention group ($p = 0.20$). One of the two remaining studies briefly reported no significant differences in health-related quality of life assessed at enrolment or at 4 months using the Sickness Impact Scores (83), and no significant differences in breathlessness scores, which contributed to the overall QoL. The final study involving subjects undergoing exercise rehabilitation, found significant improvements in health-related quality of life, and in breathlessness (both assessed using the Self-reported Chronic Respiratory Questionnaire), in both the control and intervention groups (56), with no significant differences between them.

Other outcomes

The only study that examined activities of daily living in malnourished patients with COPD reported that the nutrition intervention group found it significantly easier to perform everyday activities compared to the control group ($p = 0.009$ in the per protocol analysis and $p = 0.06$ in the intention to treat analysis, the difference in the changes being about 18% and 11% of the baseline values respectively (74)).

Four studies reported changes in immunological tests (82, 103, 104, 109). One of these (103) found significant improvements in delayed cutaneous hypersensitivity, and total circulating lymphocyte count, without associated changes in circulating immunoglobulin concentrations, during nutritional repletion of malnourished patients with COPD. Two trials, one involving ETF (82) and one ONS (109), briefly reported that lymphocyte counts remained unchanged over the study period. Finally, a study (104) involving ONS reported no significant changes in T helper/T suppressor ratio and mitogen reaction of T lymphocytes to phytohemagglutinin. None of these three studies reported separately the changes that occurred in each group. Furthermore, none of these three studies or any of the other studies included in this systematic review measured cytokines or acute phase proteins.

3.1.4 Discussion

This systematic review with meta-analyses aimed to investigate controversies regarding the evidence base for the efficacy of nutritional support in patients with COPD. It found that nutritional support leads to improvements in nutritional intake, body weight, muscle mass (mid-arm muscle circumference) and fat mass (skinfold thickness), as well as an improvement in peripheral muscle strength (handgrip and quadriceps strength). Improvements in respiratory muscle strength, measured by inspiratory and expiratory pressures were also improved. Other functional measures reported were walking distance that although improved in six out of seven studies failed to reach statistical significance. However, only three studies were carried out as part of an exercise rehabilitation programme (56-58). In the two trials that did assess quality of life (56, 74) both reported significant improvements in favour of nutritional support using a variety of quality of life tools, two of which were disease-specific (St George's Respiratory Questionnaire, SF-36 and Self Reported Chronic Respiratory Questionnaire).

These findings are completely in contrast to those of previous reviews and meta-analyses (70, 72, 73, 126, 145) which reported no significant differences between intervention and control groups. The three previous meta-analyses (72, 73, 126) did not examine changes in dietary intake. If total dietary intake in the intervention group did not increase significantly above that of the control group it could explain why these reviews and meta-analyses reported lack of a demonstrable effect, of nutritional support on a range of outcomes. However, the current review did examine nutritional intake and found that nutritional support resulted in a significantly greater increase in both protein and energy intake (dietary intake + ONS). The magnitude of these results are similar to those of previous reviews where clinical outcomes have been improved through nutritional support in a variety of clinical conditions including COPD (10). It therefore appears that the discrepancies between the current review and previous ones are mainly due to methodological differences, two of which are clarified below.

Firstly, the current study explored the possibility that pre- and post-intervention variability can mask significant within and between group changes, even when no significant differences between groups exist at either time point. This analysis shows that the end values that are mostly unadjusted for baseline have been used

as the basis of calculations in previous meta-analyses. These values may primarily reflect those at baseline, rather than the changes induced by the intervention e.g. for body weight a non-significant difference existed between groups at baseline favouring the control group, in order for any improvements to be significant after intervention they would first have to overcome this deficit (masking the magnitude of the effect). In contrast, when the weight changes induced by the intervention were used as the basis of the calculations there was a substantial increase in precision resulting in a significant improvement in favour of nutritional support.

Secondly, unlike previous systematic reviews and meta-analysis on COPD the current review included another simpler approach to analysing randomised controlled trials (t-test and sign test), so that trials without measures of variation could be included. Whilst this approach is not as sophisticated as the standard type of meta-analysis that involves measures of variation, it provides a broader quantitative perspective of the evidence base, by considering trials that would not otherwise be included. It is also more informative and complementary to a narrative description of individual studies. The combined approach adds confidence to the conclusions of the review by supporting all the major findings of the more sophisticated meta-analyses, both with respect to statistical and substantive (clinical) significance of the effect size (energy and protein intake, weight, arm muscle circumference, and grip strength).

A different type of methodological problem concerns the four studies that measured body composition to establish fat and fat free mass, all using different techniques (skinfold, bioelectrical impedance, DXA). Currently, there are no reference values for body composition in COPD and the different methods employed in primary studies have not been adequately validated in this patient group. Although in three out of the four studies the changes favoured the intervention group, the effect was generally small (overall ~1% fat free mass or less than 1% body weight) and statistically not significant. In contrast, a more consistent methodological approach using anthropometric measurements (MAMC) to estimate muscle mass, the largest component of fat free mass, yielded significant results in favour of the intervention group. Similarly, use of the raw skinfold measurements (rather than unsubstantiated extrapolations of raw

measurements to body composition based on relationships established in healthy people) also indicated improvements in favour of the intervention group.

The statistical findings of this systematic review also need to be considered from a clinical perspective. It has previously reported that a weight gain of approximately 2 kg in COPD (similar to the magnitude of the mean weight change in favour of the intervention group observed in this review) is likely to be associated with functional and clinical benefits (10). In addition, post-hoc observational analysis of a prospective nutritional intervention trial (57) found that weight loss was reversible through nutritional support and that those depleted and non-depleted patients who gained weight (> 2 kg) experienced significantly improved survival. However, it was not clear whether the improved survival rates were adjusted for disease severity and analysis did include a number of individuals within the placebo group who gained > 2 kg (37). Although the improvements in arm muscle circumference and muscle strength observed in this study are only mild to moderate (~ 3% on average but as high as 7% in one study), in patients who have already become depleted and who have already lost a substantial amount of weight and function (which seems likely for most of the malnourished patient groups included in this meta-analysis), small changes in muscle mass might be expected to produce substantial functional or clinical benefit in those that are close to the threshold of disability. The findings of this review would suggest an increase in weigh approaching 2 kg is enough to lead to functional improvements. Of particular relevance in COPD is the improvement in the mechanics of breathing (PI max and PE max) and this may be what is partially driving the improvements in quality of life. Poor nutritional status is known to negatively affect both diaphragmatic size (146), diaphragm contractility (147) and pulmonary function (148), and interestingly in anorexia nervosa patients refeeding results in improvements in FEV_1 and diaphragm contractility (149). In the current review FEV_1 was unresponsive to nutritional support and may be a reflection of the irreversible disease pathology of COPD. Further work is needed in order to explore whether improvements in the nutritional status of COPD patients leads to improvements in the diffusing capacity of the lung although one would think this would be unlikely.

Policies and guidelines on nutritional support also need to consider the plausibility of the results and how they may be inter-related. For example, a causal pathway can be proposed, whereby nutritional interventions increase total dietary intake of

protein and energy, with resulting increases in weight and muscle mass, which in turn leads to improvements in muscle strength. The findings of this systematic review are consistent with such a pathway. They are also consistent with a variety of other functional and clinical outcomes previously mentioned (150) .

This review has identified the limitations of the current literature for nutritional support in COPD. First, the conclusions are based on a limited number of studies (n 10) that were judged to be of poor quality, with only three studies judged to be of high quality (score of 4) on the Jadad scale (0 (poorest quality), 5 (highest quality)). A limitation of the Jadad grading system is it does not account for statistical power, as a result one trial despite having a total of 10 subjects received a score of 4 (82). Second, due to lack of data in the primary papers it was not possible to examine the effect of inflammation on nutritional status and response to nutritional support, nor characterise the subjects as cachectic, according to an endorsed definition (151). Third, of the 13 primary studies included in this systematic review 11 involved ONS, one involved nocturnal enteral tube feeding and the other involved dietary advice given by a dietitian and provision of milk powder. Therefore, the current evidence is largely based on ONS and it is weak or lacking for other forms of nutritional support, such as snacks, or dietary modification/fortification. This could have clinical implications for the first line treatment of malnutrition as The British Dietetic Association currently recommends the first step to improving nutritional intake is done via ordinary foods and fortification with the use of ONS as a secondary step once the initial intervention has failed (89). Finally, of the 13 RCTs, 10 targeted malnourished patients and three targeted malnourished and non-malnourished patients (56, 57, 109) with some trials allowing for subset analysis according to nutritional status (56-58). Therefore, the evidence base for nutritional support primarily involves malnourished rather than well-nourished patients, although in those undergoing a rehabilitation programme there is an anabolic potential through increased physical exercise that may augment the effects of additional nutrition. More trials are needed before conclusions can be made on what is the optimum period of supplementation as meta-regression revealed no relationship in the current review.

This review found that nutritional support in COPD produces significant improvements in several functional outcomes including respiratory and limb

muscle strength and strengthen the argument that a casual pathway exists linking increased nutritional intake to increased body weight and function. The current meta-analyses found that for each of the tests used to document improved respiratory muscle function (PI max and PE max) and non-respiratory (handgrip/quadriceps) muscle strength there was a highly significant increase in body weight of more than 2 kg (2.1 - 3.1 kg) in favour of the nutrition intervention group. Schols et al., (37) found that both an improved inspiratory mouth pressure (PI max) and a weight gain of > 2 kg were associated with significantly improved survival, in keeping with a previous review reporting that that significant functional improvements were seen in malnourished patients receiving ONS when weight gain was > 2 kg (10). It appears this level of weight gain should be a therapeutic target in malnourished COPD patients and the current review confirms that weight gain of this magnitude is associated with functional improvements in this patient group and that malnutrition is a modifiable in COPD.

In the clinical setting increasing importance is being placed on the assessment of functional outcomes. HGS is not only a reliable marker of peripheral muscle strength it also predicts clinical outcomes (152) such as mortality, morbidity, post-operative complications and increased length of hospital stay. In the elderly a loss of grip strength often means a loss of independence. Although muscle strength is closely related to mid-arm muscle area (153), whole body protein content (154), and even body weight and BMI (155), a variety of studies suggest that changes in muscle function can occur independently of muscle mass (10). It has recently it has been suggested that muscle strength responds faster to nutritional depletion and repletion than anthropometric measures such as BMI and FFM (152), probably as a result of increased availability of energy, electrolytes and micronutrients in muscle. Therefore, the improvement in muscle strength induced by nutritional intervention in malnourished COPD patients is likely to be due to a combination of increased force generated by the available muscle and increased muscle mass, which is consistent with the increase in mid-arm muscle circumference (or area) reported in RCTs of COPD (150) and other conditions (156). Mid-arm muscle area has been found to be a better predictor of mortality than BMI in patients with COPD (157). Therefore, nutritional support leading to weight gain (> 2 kg) and increased MAMC could confer survival benefits as suggested by previous studies (37, 38).

Exercise tests in COPD have also been found to predict outcomes (158), such as mortality and post-operative complications (159, 160). This review examined the effect of nutritional support in COPD patients undertaking different types of walking and shuttle tests undertaken on a flat surface, but the reviewed studies were not amenable to meta-analysis. However, four of the five studies favoured the nutritional support group, and the only studies reporting significant improvements in performance also favoured those receiving nutritional support. While these tests have limitations (e.g. some patients still have difficulties walking faster on flat surfaces as their condition improves, but they can walk up a steeper slope) they at least assess important aspects of the patient's ability to function in ways that are relevant to everyday life (161).

The evidence base on the effect of nutritional support on immunological function is very limited, not least because none of the three studies (82, 103, 109) that assessed restricted aspects of immune function reported the results separately for the intervention and control groups. In addition, the total absence from these studies of cytokine measurements and acute phase proteins as markers of the inflammatory response highlights the need to examine immune/inflammatory-nutrition interactions. This is because the immune system not only helps prevent and aid recovery from respiratory infections, but also because it is linked to the processes involved in nutritional depletion and repletion of body tissues and their responsiveness to nutritional support (19). Whether exercise has a pro- or anti-inflammatory role in COPD is unclear (162, 163) however, a trial involving a combination of education sessions, nutritional support and low-intensity exercise in a cohort of malnourished (mean BMI 18.0 kg/m^2) patients with moderate COPD produced some very promising results (164) that included improvements in weight, peripheral and respiratory muscle strength, exercise capacity, quality of life and a reduction in inflammation (measured by IL-6, IL-8, TNF-α, high sensitive CRP levels). Whether these improvements were due to the exercise intervention, the polyunsatured fatty acid-enriched ONS or a combination of the two warrants further exploration. Similarly a sub-set analysis of the INTERCOM trial showed a 24-month intervention of dietary counselling by a dietitian, ONS and exercise rehabilitation resulted in significant improvements in weight, respiratory and peripheral muscle strength (165).

An outcome that was found to be unresponsive to nutritional support in the current review was lung function (assessed by tests such as FEV_1, FVC and blood gases), but this is likely to reflect the irreversible nature of lung pathology in COPD. It may seem surprising that the lack of an effect of nutritional support on objective tests of lung function were sometimes associated with significant improvements in subjective measures of breathlessness. However, since malnutrition has effects on the central nervous system, including modulation of the sensitivity of the respiratory centre to hypoxic stimulation (166), it is plausible that nutritional support influences the sensation of breathlessness through centrally mediated mechanisms. Interestingly, cross sectional studies of men with COPD have reported that breathlessness is inversely related to BMI independently of respiratory function tests (diffusing capacity to carbon monoxide, PaO2, P0.1/PI max) (167). Breathlessness influences quality of life, which probably explains the striking concordance between them, both within and between groups of the reviewed RCTs.

The extent to which changes in functional outcome measures reflect clinically relevant improvements in patient well-being can be difficult to establish. For example, a small change in muscle strength (which may be as little as a few percent, as in some of the reviewed studies) may go totally unnoticed in strong well-nourished subjects, but in malnourished patients who are close to the threshold of disability (168) they may be easily noticed and make the difference between being able to get up and not get up from a bed or a chair, and between being independent and dependent on others. Nevertheless, attempts have been made to establish the minimum clinically relevant changes associated with some of these tests. For example, it has been conservatively estimated that the minimum clinically important difference in 6 minute walking distance is 54 - 80 m (169), which exceeds that found in the only two nutrition intervention studies that employed the 6MWT (an improvement in favour of ONS by a mean of 47 m (79), and 37 m (121)) . However, much larger changes have been found with the 12MWT e.g. an improvement of 143 m has been attributed to ONS in the study of Rogers et al. (83). The minimum clinically important improvement in ISWT has been estimated to be 47.5 m. The minimum benefit distinguishable by patients relates to 78.7 m (170). The only reviewed COPD study that used ISWT to examine the effects of ONS during pulmonary rehabilitation (56) found improvements in walking distance in favour of the nutrition intervention group that

were less than the suggested thresholds. However, the patients were studied during pulmonary rehabilitation and the effect of ONS in combination with the other treatments showed a statistically significant overall improvement of 60 m. This study was comprised mainly of patients who were not classified as malnourished (87%). It is possible that those with malnutrition in receipt of ONS behaved differently from those randomized to control but the numbers are likely to have been small and such information was not reported. The benefits of exercise rehabilitation are well established (171), however, as alluded to by Steiner and colleagues (56), it can produce a negative energy balance which might require reversal by supplementation before an improvement in training outcomes can be demonstrated. A recent RCT of patients with chronic respiratory failure, the majority of whom had COPD, participating in an exercise rehabilitation program and classified as malnourished (BMI 21.5 SD 3.8 kg/m^2 and FFM deplete) found that nutritional support (ONS 3 x per day), education and oral testosterone undecanoate led to significant improvements in body weight, FFM, strength and function above control (92). At present it is unclear whether all malnourished COPD patients undertaking exercise training should receive additional nutritional support or indeed whether training should commence in those who are malnourished without nutritional support (164). It would appear pertinent to recommend that all COPD patients at risk of malnutrition should receive some form of nutritional support during rehabilitation and recommendations are required.

Since a cure is impossible for COPD patients, a major goal in the management of the disease is the improvement or maintenance of body function, and quality of life. This systematic review describes the types and magnitude of functional benefits that are likely to arise through nutritional support. It suggests that at least some of the adverse functional consequences of severe COPD are reversible by nutritional support. The review also suggests that whilst several of the studies were judged to be of high quality, many were of lower quality, and therefore the evidence base for the role of nutritional support in COPD needs to be strengthened.

The fact that 10 of the 13 trials included in the current review were carried out before 2000 may reflect that 2000 coincided with the publication of the first Cochrane Collaboration review, including the majority of the current evidence, concluding that nutritional support has no effect in COPD. This may have

dampened interest in the field however, it is hoped the positive findings of this review will highlight the priority to undertake further work, including an examination of the interactions that might exist between nutritional supplementation and factors such as malnutrition, inflammatory status and graded physical activity in both stable disease and those with infective exacerbations of COPD.

3.1.5 Summary

Whilst this systematic review and meta-analysis has demonstrated that nutritional support is effective at treating malnutrition, it is almost entirely based on ONS and a number of questions still remain. Firstly, there is a paucity of data investigating the effectiveness of dietetic intervention in treating malnutrition in COPD, whether the intervention is food fortification, dietary counselling or foods and snacks. Chapter 4 will explore the complex relationships between nutritional status, disease severity, social deprivation, smoking status and how they relate to clinical and economic outcomes. Dietary advice is often recommended as the first line treatment for malnutrition however; at present this clinical approach does not appear to be evidence based practice. As dietary advice and counselling underpins much of dietetic practice, there is an urgent need for RCTs demonstrating the effectiveness of dietary interventions particularly in the nutritional management of COPD. As this chapter has highlighted, the current evidence base for nutritional support in COPD is almost entirely based on ONS highlighting the need for further DA trials. The randomised trial presented in chapter 5 aims to establish which method of nutritional support is most effective at treating disease-related malnutrition in stable outpatients with COPD.

Acknowledgement:

Parts of this chapter have been published:

Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. American Journal of Clinical Nutrition. 2012; 95: 1385-1395.

In addition published abstracts are presented in Appendix 1:

Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. Clinical Nutrition. 2011, 6 (Suppl. 1): 153.

Collins PF, Stratton RJ, Elia M. Nutritional support and functional capacity in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. Clinical Nutrition. 2011, 6 (Suppl. 1): 153-154.

Collins PF, Stratton RJ and Elia M. Oral nutritional supplements in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. Thorax. 2011, 66 (Suppl. 4): A173-A174.

4.1 Study 1- Malnutrition in outpatients with COPD

4.1.1 Introduction

Traditionally, weight loss observed in COPD was considered an inevitable component of disease progression and as such an irreversible pathology however, numerous nutritional intervention trials have challenged this idea (37, 57, 74, 79, 83, 103). Schols et al., (58) found that low body weight can be reversed through appropriate nutritional therapy but there are a sub-group of patients that are less responsive to nutritional support. Today nutrition is increasingly being seen as an important adjunctive therapy in the management of COPD (6, 172) but how best to nutritionally manage individuals with the disease remains unclear.

Despite malnutrition affecting only a sub-population of COPD patients it has been shown to be an independent risk factor for a number of negative clinical sequalae. Malnutrition is associated with increased rates of infective exacerbation (173) and subsequent reductions in health-related quality of life, as measured by the St George's Respiratory Questionnaire; SGRQ (174). Patients with COPD had the highest emergency hospitalisation rate to English hospitals in 2000/2001 (175) and malnutrition has been shown to be associated with increased healthcare utilisation and mortality in those patients with severe COPD receiving long-term oxygen therapy (176). Body weight has also been found to be a significant predictor of mortality both in those with moderate (177) and severe obstructive lung disease (39). Despite a significant amount of research in the area there remains confusion as to the exact prevalence of malnutrition and malnutrition risk in COPD. Estimates vary between 30 - 60% in inpatients and 10 - 45% in outpatients depending on the method of nutritional assessment used and the disease severity of the population screened (10). This wide variation is mostly attributed to the varying methods of nutritional screening used to establish the incidence of malnutrition. Nutritional screening tools often involve varying components including an assessment of body weight (body mass index; BMI or percentage ideal body weight; %IBW), recent unintentional weight loss over the previous 3 - 6 months, likely future nutritional intake ('Malnutrition Universal Screening Tool', 'MUST' and 'Subjective Global Assessment'; 'SGA'), and the presence of neuropsychological problems ('Mini Nutritional Assessment'; 'MNA').

'MUST' is the nutritional screening tool most commonly used to screen adults in the UK and is a short scoring system which categorises a patient's risk of malnutrition and importantly directs a nutritional management response on the basis of a score of 0, 1, 2 or greater with the maximum possible score being 6 (Appendix 4). The score is calculated using BMI categories, any clinically significant unintentional weight loss over the previous 3 - 6 months and predicted starvation in the near future (likely nil by mouth for more than 5 days). 'MUST' is supported by numerous professional organisations involved in the nutritional care of patients including the British Dietetic Association, the Royal College of Nursing and its use is recommended by the National Collaborating Centre for Acute Care (66). 'MUST' has been previously shown to have 'fair-good' to 'excellent' agreement with the other commonly used screening tools, whilst being quick and easy to use across healthcare settings (178). 'MUST' has also been shown to have good predictive validity for negative clinical outcome in elderly care inpatients (179).

Despite 'MUST' being validated across both primary and secondary care and the fact that COPD patients frequently move between these two healthcare settings there have been no published studies using 'MUST' reporting the prevalence of malnutrition risk in either primary or secondary care outpatients with COPD. This is rather surprising since there is substantial evidence highlighting the independent negative effects of low BMI (39) and weight change (38) in COPD, both of which are assessed within 'MUST'.

4.1.2 Aims

The aims of the study were three-fold:

- To establish the prevalence of malnutrition risk amongst COPD patients attending respiratory outpatient clinics run across two hospitals in Hampshire, England.
- To investigate whether the level of malnutrition risk seen in outpatients with COPD differed to that of age and sex matched controls from the UK general population.
- To establish whether the prevalence of malnutrition risk was greater in those with more severe obstructive lung disease.

4.1.3 Methods

A prospective nutritional screening survey was carried out between July 2008 and May 2009 across two respiratory centres in Hampshire, a large tertiary teaching hospital (Southampton General hospital; SGH) and a smaller community hospital (Lymington New Forest hospital; LYM). Outpatients with a diagnosis of COPD attending respiratory clinics were routinely screened by the respiratory specialist nurse or respiratory healthcare assistant using the 'Malnutrition Universal Screening Tool'; 'MUST' (180) (www.bapen.org.uk). The staff performing the nutritional screening received training in order to perform the measurements and calculations correctly and to ensure accuracy of results and attempt to reduce inter- and intra-centre variability. Outpatients were weighed on class III clinical weighing scales (Seca, Germany) to the nearest 0.1 kg. Height was measured on one occasion during the baseline assessment without shoes, using a freestanding portable Leicester stadiometer to the nearest 0.1cm (Invicta Plastics Ltd, Leicester, United Kingdom). Measured weight and height were used to calculate BMI (step 1 'MUST'):

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

Percentage unplanned weight loss (step 2 'MUST') over the previous 3-6 months was calculated according to the following equation:

$$\%\ \text{weight change} = \frac{\text{previous weight} - \text{current weight}}{\text{previous weight}} \times 100$$

Although unlikely in the outpatient setting, if a patient had been or was likely to be nil by mouth for five days this was recorded (step 3 'MUST'). Following the 3-step assessment, each outpatient was categorised either as at low, medium or high risk of malnutrition according to 'MUST'. Outpatients were classified as at high risk if they had a BMI < 18.5 kg/m^2 or had experienced ≥ 10% unintentional weight loss in the previous 3 – 6 months or had a combination of a BMI between 18.5 – 19.9 kg/m^2 and had ≥ 5% unintentional weight loss over 3 - 6 months. Individuals were classified as at medium risk either because their BMI was between 18.5 - 19.9 kg/m^2 or unintentional weight loss between ≥ 5 and 9.9% (Appendix 4). Any

outpatients not classified as medium or high risk were classified as at low risk of malnutrition.

Disease severity was also recorded in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria (29). COPD severity was established from patients medical records using the most recently recorded post-bronchodilator spirometry test and the following FEV_1 predictive values: GOLD I (mild) FEV1 > 80%, GOLD II (moderate) FEV_1 ≥50% to ≤ 80%, GOLD III (severe) FEV_1 ≥ 30 % to < 50% and GOLD IV (very severe) FEV_1 < 30%. The relationship between disease severity according to GOLD stage was then related to malnutrition risk according to 'MUST' criteria (low, medium or high risk). Where possible any missing information on disease severity was retrospectively collected by the research dietitian using hospital electronic records. The BMI of the cohort was compared to data of age and sex matched controls obtained from figures within the Health Survey for England (181). Statistical analysis was performed using SPSS (version 16.0, Chicago, IL) to examine the differences in the prevalence of malnutrition risk between the two centres as well as the relationship between COPD disease-severity and malnutrition risk.

The screening cohort was performed as a means to recruit to the randomised trial (chapter 5) as such data on body composition; co-morbidities and inflammation at the time of nutritional screening were not collected.

4.1.4 Results

Prevalence of malnutrition in COPD

A total of 424 outpatients with COPD were routinely screened using 'MUST', 190 at SGH, 234 LYM; 222 males, 202 females; mean age 73 years (SD 9.9 years); mean body mass index 25.9 kg/m^2 (SD 6.4 kg/m^2) Table 5. The overall prevalence of malnutrition was 22% (95% CI 18 - 26%; 9% medium risk, 13% high risk). Two-thirds of those patients identified as at risk of malnutrition across the two centres were classified as at high risk of malnutrition. Only 6% of outpatients scored on step 2 of 'MUST' reporting 5% or more recent unintentional weight loss. The prevalence of malnutrition risk was significantly higher at the larger teaching

hospital in comparison to the smaller community hospital; 28% *versus* 17%, p = 0.04 using ANOVA (Figure 9).

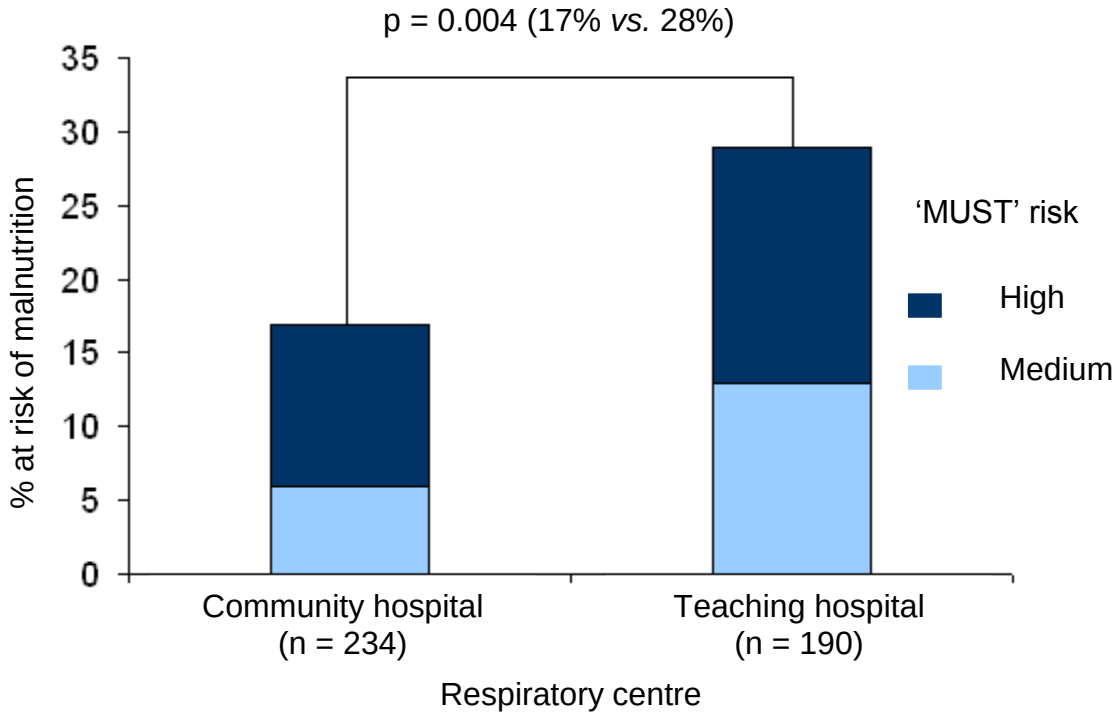


Figure 9 Prevalence of DRM across two respiratory centres in Hampshire.

Similar results were also obtained when analysing the prevalence of malnutrition risk across respiratory centres according to the three malnutrition risk classifications of 'MUST', Teaching hospital: Low 71.6%, Medium 12.6%, High 15.8% versus Community hospital: Low 83.3%, Medium 6.0%, High 10.7%; p = 0.010 χ^2.

Table 5 Characteristics and malnutrition risk of COPD outpatients attending two hospitals; Southampton General Hospital and Lymington New Forest Hospital.

	SGH (n = 190)	LYM (n = 234)	Total (n = 424)	p
Demographics				
Females (n)	93	109	202	
Males (n)	97	125	222	0.628
Age (years)	72 (42-96)	74 (40-95)	73 (40-96)	0.078
	n = 180	**n = 233**	**n = 413**	
Height (m)	1.65 (0.1)	1.66 (0.9)	1.66 (0.9)	0.208
	n = 186	**n = 234**	**n = 420**	
Weight (kg)	69.8 (20.2)	72.6 (18.1)	71.4 (19.1)	0.134
	n = 190	**n = 234**	**n = 424**	
BMI (kg/m^2)	25.4 (6.7)	26.1 (6.0)	25.8 (6.3)	0.232
'MUST' risk (Cat^3) (n (%))				
Low	136 (71%)	195 (83%)	331 (78%)	
Medium	24 (13%)	14 (6%)	38 (9%)	
High	30 (16%)	25 (11%)	55 (13%)	0.010†
'MUST' risk (Cat^2) (n (%))				
Low	136 (72%)	195 (83%)	331 (78%)	
Medium + High	54 (28%)	39 (17%)	93 (22%)	0.004†

SGH = Southampton General Hospital; LYM = Lymington New Forest Hospital; BMI = Body mass index; values for height, weight and BMI are displayed as mean (standard deviation); age is displayed as mean (range) and analysed using ANOVA; all other values are number (%); † = denotes statistical difference (p < 0.05) χ^2. MUSTCat^2 = Low and Medium + High 'MUST' scores; MUSTCat^3 = Low, Medium and High 'MUST' scores.

BMI classification in COPD

BMI classification showed 16% of patients had a BMI less than 20.0 kg/m^2 (5% BMI 18.5 – 19.9 kg/m^2 and 11% BMI < 18.5 kg/m^2). 8.2 % of outpatients were identified as at risk of malnutrition due to clinically significant unintentional weight loss of >5% over the previous 3 - 6 months with over half (4.7%) of those exceeding 10%. Of the patients screened 50% were classified as either

overweight or obese (Figure 10) however, the prevalence of overweight and obesity BMI classifications was considerably lower in the COPD outpatients compared to age and sex matched controls for males and females from the UK general population. The BMI distributions in both males and females with COPD demonstrated a significant left-skew when analysed using cumulative frequency distribution curves (Figures 11a and 11b).

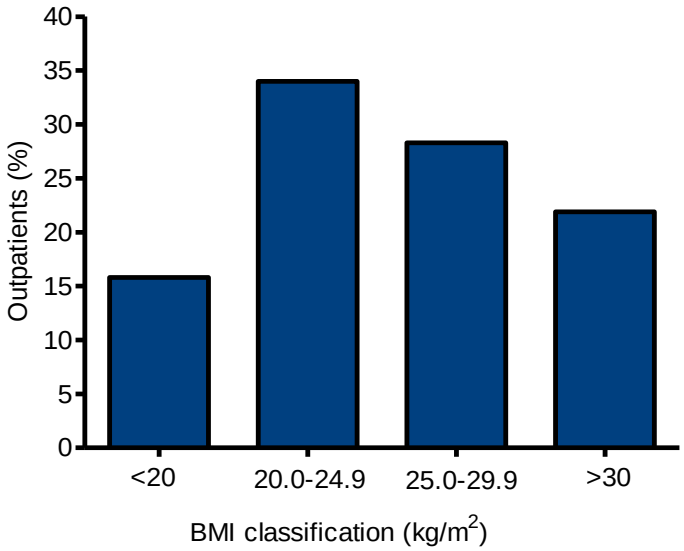


Figure 10 Body mass index classification in outpatients with COPD (n = 424).

BMI cumulative frequency distribution curves for female and male COPD outpatients were plotted against age and sex matched controls from the UK general population and analysed for significant differences using the two-sample Kolmogorov-Smirnov test (Figures 11a and 11b). BMI distributions for both males and females with the disease were significantly different to that of the general population ($p < 0.001$) with the distribution shifting towards the left indicating more patients having a lower BMI classification.

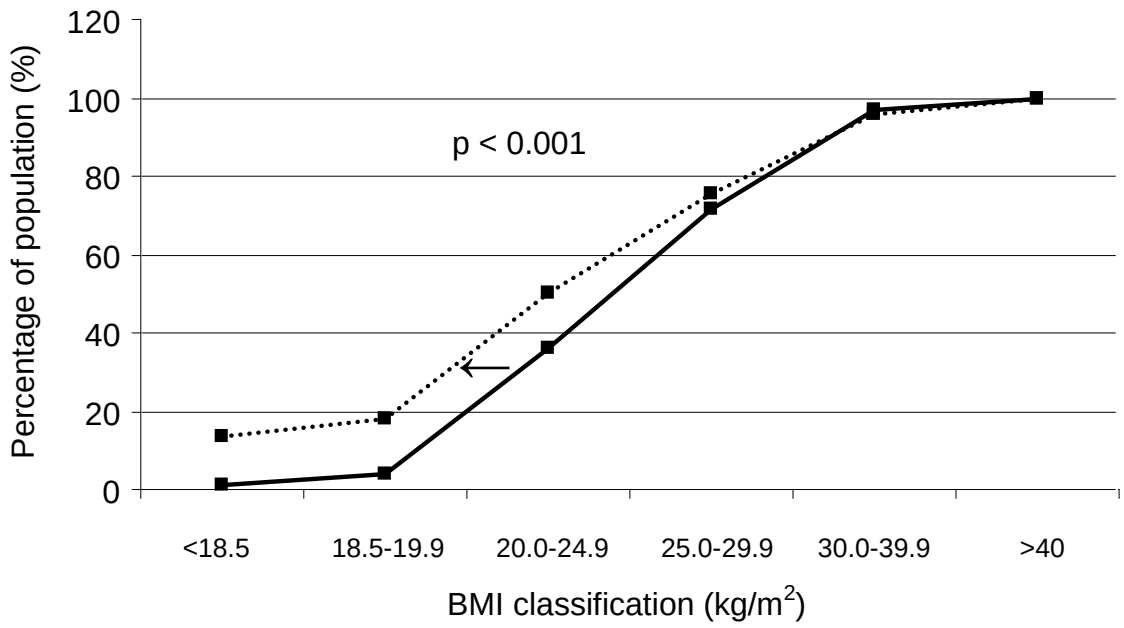
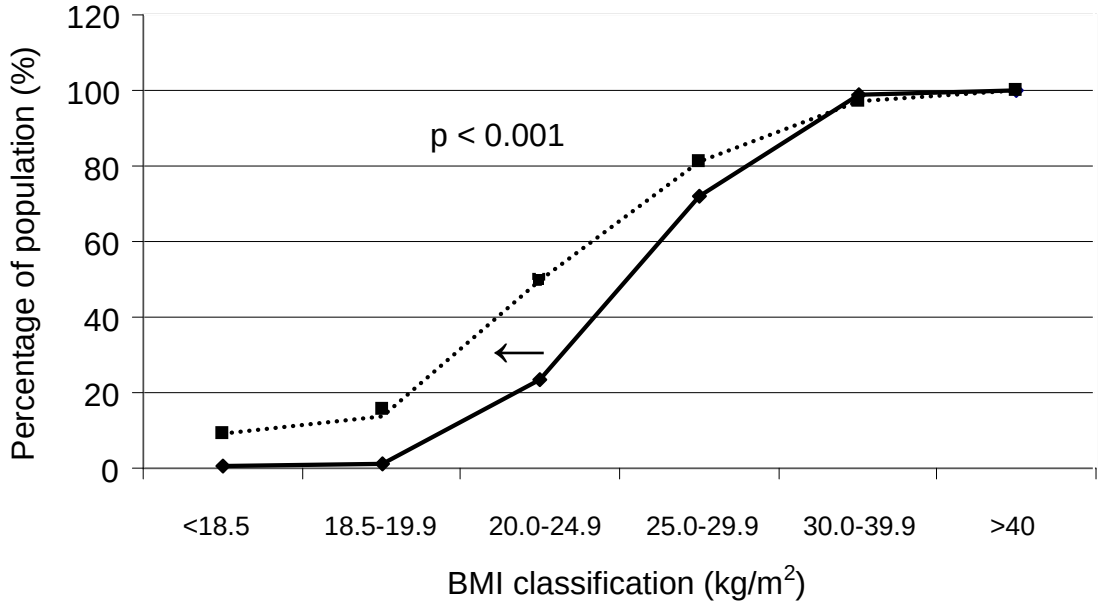


Figure 11a



Figures 11b BMI cumulative frequency distribution curve for females (a) and males (b) COPD outpatients (dashed line) *versus* age and sex matched controls from the general population (solid line); ← = possible disease-related 'drift'. Data for the general population obtained from the Health Survey for England (181).

Disease-severity and malnutrition risk

Data on disease severity were obtained for 389 (92%) of the outpatients screened according to the Global Initiative for Chronic Obstructive Lung Disease; GOLD (29), 166 at SGH, 223 at LYM, and related to malnutrition risk (Table 6). It was found the prevalence of malnutrition risk significantly increased with disease severity (χ^2 p trend < 0.001; moderate 11%, severe 17%, very severe 36%). The severity of disease seen in the patients attending each centre was not significantly different (χ^2; p = 0.450) and there were no differences in age 74 years *versus* 72 years (Table 5). Malnutrition risk was not related to age or gender but was found to be significantly higher amongst the patients attending the larger teaching hospital compared to the community hospital (p = 0.04).

Table 6 Prevalence of malnutrition risk in relation to disease severity classification according to GOLD criteria (29) (n = 389).

'MUST' risk	Low (n = 304)	Medium (n = 33)	High (n = 52)	p
Disease severity				
Moderate	88 (89%)	4 (4%)	7 (7%)	
Severe	132 (83%)	13 (8%)	14 (9%)	
Very severe	84 (64%)	16 (12%)	31 (24%)	<0.001†

Values are number of patients (% at risk of malnutrition according to disease severity); value is Linear-by-Linear Association; χ^2 p-trend. † denotes a significant relationship between disease severity and malnutrition risk.

4.1.5 Discussion

Prevalence of malnutrition in COPD

This study shows that malnutrition risk (using 'MUST') is a common problem in outpatients with COPD , with 22% being identified as being at risk. This is within the range previously reported in this patient group and setting (10 - 45%) but provides the first prevalence statistic using this particular nutritional screening tool. Two thirds of the current cohort identified as at risk of malnutrition were at high risk requiring some form of nutritional support. However, only 6% were documented as

having experienced any recent unintentional weight loss. This is surprising in this patient group and anecdotally reflects a lack of confidence in assessing percentage weight loss by respiratory nurses and healthcare assistants. Considering this and the fact that the presence of oedema was not routinely documented could mean a prevalence of 22% is actually an underestimate.

The wide range in the prevalence rates previously reported has been mainly attributed to the varying methods of nutritional assessment used (10). Currently, there is no universally accepted nutritional screening tool, which does make interpretation between studies difficult. Previous studies have used a range of cut-off points to define malnutrition risk from a BMI of less than 20 kg/m^2 to less than 90% ideal body weight (IBW) and more recently a fat free mass index (Fat free mass (FFM), kg/height, m^2) of less than 16 kg/m^2 for males and less than 15 kg/m^2 in females (182). When this criteria was used to assess functional lean mass in Dutch outpatients with moderate to severe COPD a low FFM was reported in 20% (67). In this case body composition was assessed using single frequency bioelectrical impedance analysis and FFM calculated using a disease specific equation based upon a linear relationship of FFM to height^2/resistance derived from 32 normal to underweight COPD patients using deuterium dilution as a reference method (183).

BMI classification in COPD

BMI classification in the current study showed that whilst the prevalence of those with an underweight classification was high (16%), overweight and obesity were also common in this patient group (28% and 22% respectively). These findings are slightly higher than those of a previous study that reported an obesity prevalence of 18% in 317 Dutch outpatients with COPD (184). Despite overweight and obesity being high in COPD outpatients the levels were significantly lower than that of the UK general population. One possible explanation for this drift in BMI distribution is disease-related. A subgroup of COPD patients encounter a number of functional and pathological changes that impact on their ability to achieve their nutritional requirements, as a result they drift down across BMI classifications. Although the current study is a cross sectional observational and as such a snap shot of the population, a BMI ‘drift’ towards lower values has previously been reported by Prescott et al., (38) where increased mortality was found in individuals with COPD

who lost ≥1 unit of BMI. Further increases in mortality were observed in those with a > 3 BMI unit loss and weight loss was associated with increased all-cause mortality in those both with and without COPD.

Malnutrition, co-morbidities and COPD disease-severity

Malnutrition risk was significantly related to the severity of respiratory disease, with 36% of those with very severe COPD being identified as at risk. Whereas in those outpatients with moderate COPD 11% were at risk of malnutrition. These results are not surprising as the prevalence of malnutrition risk is often associated with the severity of disease. Severe COPD is likely to impair an individual's ability to acquire, prepare and consume food substantially increasing an individual's risk and susceptibility to malnutrition. Currently the prevalence of malnutrition risk in mild COPD is relatively unknown, and with recent re-classifications of disease-severity by GOLD (29) and NICE (6) care is needed to compare FEV_1 bands rather than traditional categories. Retrospective analysis of the Copenhagen City Heart study by Landbo et al., (39) classified patients with an FEV_1 percentage predictive of >70% as mild. Mild COPD is now classified as FEV_1 > 80% predicted and an FEV_1/FVC ratio < 0.7 (6, 29). The current study was carried out in respiratory outpatient clinics held across two hospitals that were attended by patients with more advanced disease. Those individuals with a diagnosis of mild COPD are likely to be primarily managed by their G.P and it is estimated in the UK up to 2 million individuals may be undiagnosed (185). A programme of nutritional screening in general practice will be the only way to accurately establish the prevalence of malnutrition risk in mild COPD.

A limitation of the current study is that co-morbidity data was not obtained. The reason for this is that the current study was primarily initiated as a means of identifying patients that would be potentially suitable for the randomised intervention trial presented in chapter 5. It is acknowledged that having data on both co-morbidities and inflammation at the time nutritional screening was performed would have greatly enriched the data and allowed for better conclusions to be drawn. The incidence and prevalence of almost all cardiovascular outcomes observed as part of the Veterans Medical Administration study which included over 70,000 COPD patients (186) and these co-morbidities are independently associated with greater hospitalisation rates and mortality (187).

Body composition in COPD

Whilst there is a substantial amount of evidence to demonstrate negative clinical outcomes in underweight patients, the clinical course of overweight patients is less clear. Fat tissue accumulation has been shown to impair ventilatory function in adults resulting in reductions in FEV_1 and FVC that is attributed to the mechanical effects of obesity overloading the respiratory muscles (188). Being obese with COPD could also impair physical activity accelerating disuse atrophy of FFM and further accumulation of fat mass (sarcopenic obesity). However, a paradox appears to exist as increased BMI has been observed to be protective in terms of mortality rate in those with respiratory disease (39). In those with severe respiratory disease, being overweight or obese appeared to result in improved survival; this is explored in more detail in study 2 of this chapter. More research is clearly needed to determine the optimum nutritional management of those COPD patients that are overweight and obese, whilst adequately controlling for respiratory disease severity.

It has been suggested the use of body weight as a sole criterion for assessment of malnutrition risk may underestimate the prevalence of malnutrition and this is a limitation of the current study. Assessment of body composition in the current cohort of patients would have enriched the data collected, further trials exploring the complex interaction between body composition, malnutrition risk, inflammation and quality of life are required particularly investigating their influence of clinical outcomes.

Body compositional changes have been found in COPD patients attending pulmonary rehabilitation, where lean body mass deficits were found in patients with an apparently normal BMI (22). It has previously been shown that the prevalence of a low FFM can be higher than that of being underweight, in terms of BMI, due to the pathology of COPD leading to a relative sparing of fat mass and a preferential loss of FFM (21). Such an observation is somewhat dependent on the BMI and FFMI criteria used. The potential masking of FFM losses when BMI alone is used was demonstrated in the Copenhagen City Heart study which over 7 years followed-up 1898 COPD patients and found 25% of those with an apparently normal weight had a FFMI lower than the bottom 10^{th} percentile of the Danish general population (189). FFM as assessed by bioelectrical impedance could be a

useful tool in identifying those at risk, as this ‘functional’ compartment of body mass has been shown to have the largest effect on a patient’s quality of life when measured by the disease specific St George’s Respiratory Questionnaire; SGRQ (190).

Whilst assessment of FFM appears to be an effective adjunctive prognostic tool in COPD, it may not be possible to implement its use across all healthcare settings since this would require additional investment in resources and training both in the measurement and interpretation of body composition. The updated clinical guidelines on COPD from NICE (6) state BMI may be a less reliable measure of nutritional status in the elderly due to the structural and body compositional changes seen in COPD. It goes on to state that weight change, particularly if greater than 3 kg, should be noted and acted upon. The rationale for selecting a 3 kg weight change opposed to a percentage change is unclear but may be based on the observational study by Prescott et al., (38) where a 1 unit loss in BMI was equivalent to an approximate reduction in weight of 3.8 kg. In terms of providing clarity on the nutritional management of COPD patients, the updated clinical guidelines are rather disappointing and demonstrate that the nutritional management of COPD patients has advanced little in the last 6 years. The rather arbitrary cut-off of 3 kg is only based on grade D evidence that is unreferenced and is likely to be ineffective in routine clinical practice for several reasons. Firstly, depending on a patient’s initial weight a 3 kg weight change may not be clinically significant particularly if the majority of patients are classified as overweight or obese as was found in the current study. It would appear assessment of percentage weight change would be a far more sensitive measure. Secondly, the guideline does not directly recommend routine nutritional screening using a validated screening tool such as ‘MUST’ but simply signposts to a previous guideline on nutritional support in adults which does recommend the use of ‘MUST’. Identifying COPD patients at risk of malnutrition and implementing successful nutritional support is complex and challenging, but is certainly made easier with routine nutritional screening, a disappointing omission from the guideline.

In order to identify outpatients at risk of DRM in busy respiratory outpatient clinics nutritional screening has to be performed using pragmatic measurements that can be performed quickly, accurately and result in the initiation of nutritional care

where appropriate. ‘MUST’ has been shown to fulfil these requirements (178) and it has been extensively validated across both primary and secondary care settings making it particularly useful in the current patient group as they readily pass between inpatient and outpatient care settings. This is the first published survey to use the tool to assess the prevalence of malnutrition risk in outpatients with COPD (191) (Published abstract 1). To date there has been only one other study as part of a PhD thesis using a tool similar to ‘MUST’ to establish the prevalence of malnutrition risk in UK outpatients with COPD (90). 474 patients were screened of which 30% where classified as at risk of malnutrition. 24% had weight loss exceeding 5% over the previous 6 months with 11% having weight loss exceeding 10%. 18% had a BMI < 20.0 kg/m^2, half with a BMI < 18.5 kg/m^2 (90), demonstrating similar trends to the current study. A limitation of the current study and a possible explanation why the malnutrition risk levels differ between that of Weekes et al., (90) could be due to outpatients experiencing significant weight loss initially going undetected at the current site. Prior to the survey commencing routine nutritional screening and documentation of weight was not done formally at either respiratory centre which resulted in the previous weight component of the ‘MUST’ score often being incomplete if patients were unable to recall their previous weight and a previous weight was often not documented in the medical notes within the last 6 months. This would affect the validity of the results obtained and potentially underestimate the true prevalence of malnutrition risk. This could explain why Weekes et al., (90) found 24% of outpatients had lost > 5% weight over the previous 6 months compared to only a quarter of that in the current survey. Whilst another possible explanation could be due to differences within the populations screened, such as disease-severity, age and socioeconomic status, it is very unlikely that not all of the COPD outpatients that passed through the sites were assessed. Unfortunately accurate data on the unique attendances at each site during the period of screening was not available but the large teaching hospital had 1203 contacts with individuals with a diagnosis of COPD. This will have included multiple contacts for some patients as well as including those with other primary respiratory conditions (e.g. asthma, bronchiectasis) which would have been removed from analysis. Whilst some patients are likely to have been missed as part of the current cohort study, the prevalence reported is within that previously reported. Over a third of completed screening forms in the current study were removed due to it being a duplicate visit however, future studies should seek

to account for the entire target population passing through the screening site during the specified time.

A factor that may have led to an underestimation of the prevalence of malnutrition risk in both the present study, and that of Weekes et al., (90), is the fluid shifts observed in COPD. Peripheral oedema is a common complication in COPD due to disease pathology and some medication management. Unfortunately this was not assessed in the current screening survey and this may have led to higher than true weights being measured in oedematous patients. 'MUST' does make an effort to adjust for fluid disturbances but this was not done in the current study due to a limited capacity to provide the additional training required for staff across centres. Previous nutritional intervention studies have reported 36% and 54% of the patients to be receiving diuretic medication highlighting the challenge of assessing a patient's dry weight (57, 58, 90). Oedema due to right heart failure (cor-pulmonale) is common in COPD due to pulmonary hypertension. Around the time of infective exacerbations significant peripheral oedema can develop due to immobility and non-steroidal anti-inflammatory drugs causing sodium retention. Fluid retention is difficult to account for but will lead to an overestimate in individuals' weight if a correction is not attempted, and a subsequent overestimation of BMI potentially leading to misclassification by 'MUST'.

The 'MUST' report produced by BAPEN has produced guidelines for estimating dry weight in the presence of oedema. These are crude measures and clinical judgement is advised but as guidance it is estimated mild oedema contributes 2 - 3 kg of additional weight, moderate oedema 6 kg of weight with severe oedema contributing to an estimated 10 kg (192). Establishing the severity of oedema pragmatically in outpatients does involve a subjective assessment so it is open to interpretation error. This can be reduced if standardised weight estimates, as those recommended by BAPEN, are routinely used to predict a patient's dry weight and staff performing the assessment are suitably trained in nutritional assessment. Training and monitoring is vitally important as inaccurate assessment could ultimately determine whether or not an individual receives nutritional treatment.

4.1.6 Conclusion

Whilst assessment of nutritional status is challenging in patients with COPD, it is clear community based malnutrition is a common problem with the majority of patients being at high risk and in accordance with 'MUST' require some form of nutritional intervention. The current trial is the first to report malnutrition risk using 'MUST' in this patient group and it is hoped other respiratory centres will implement 'MUST' allowing regional comparisons in the future. The difference in the prevalence of malnutrition risk between the respiratory centres highlights why confusion remains as to the exact prevalence of malnutrition risk in this patient group. One potential cause could be differences in deprivation between the two centres as the community hospital was located in what is deemed to be a more affluent area and this is explored in detail in study 4. The current study found that one in five COPD outpatients to be at risk of malnutrition and it was hypothesised that it would be this group of patients that would go on to experience poorer clinical outcome and present a greater operational and economic burden to the NHS. These issues are explored further in studies 2 and 3, which follow.

4.2 Study 2 - Malnutrition risk and mortality in COPD

4.2.1 Introduction

COPD is a leading cause of morbidity and mortality worldwide with an estimated 210 million affected individuals. Globally COPD is attributed to the deaths of approximately 3 million people each year (14). An estimated 3 million people in the UK are thought to have COPD causing 30,000 deaths per year (6), carrying one of the highest mortality rates of any disease seen in UK patients (175). Malnutrition is a common problem in COPD with 22% of outpatients found to be at risk (study 1, published abstract 1, Appendix 2) (191). Loss of body cell mass and nutritional depletion is a common and serious problem in COPD therefore identifying those patients who have lost weight, or at risk of losing weight, is essential to ensure prompt targeted nutritional intervention. Routine nutritional screening for malnutrition risk should be a central component of the medical management of both inpatients and outpatients with the disease. Disappointingly, recent national guidelines for the management of COPD patients across both primary and secondary care failed to recommend the practice of routine nutritional screening in COPD, the rationale behind this omission is unclear but it may relate to the fact there is a paucity of evidence linking formal nutritional screening to outcomes in COPD (6).

There are a number of nutritional screening tools currently being used including, Subjective Global Assessment; SGA (193), Mini-Nutritional Assessment; MNA (194), Nutrition Risk Screening-2002; NRS-2002 (195) and ‘Malnutrition Universal Screening Tool’; ‘MUST’ (180). Currently there is no one screening tool considered to be the gold standard with numerous tools being used in a variety of healthcare settings and occasionally within the same setting. This lack of consensus with regards to screening does make interpretation of results problematic. The same patient may be screened using one method as an outpatient and re-screened using a different method on admission to hospital. Despite ‘MUST’ being the most commonly used nutritional screening tool across both primary and secondary healthcare settings in the UK, and the fact that COPD patients are high service users across both settings, there has been no studies to date investigating the efficacy of ‘MUST’ in predicting poor clinical outcome in outpatients. This is rather

surprising considering the applicability of ‘MUST’ to this patient group as alluded to within study 1. Previous research investigating survival rates post admission in 522 geriatric patients found that BMI was an independent predictor of 1-year mortality, with the lowest survival seen in those patients with a BMI < 20 kg/m^2 (196). Similar results were found when patients were routinely screening for malnutrition risk using ‘MUST’, which again was found to predict negative clinical outcomes in elderly care inpatients (179). The fact that COPD patients readily move between primary and secondary care highlights the need for an effective nutritional screening tool to be able to map the patient ‘journey’ across settings allowing accurate longitudinal interpretation of an individual’s nutritional status.

It is well established that BMI is an independent predictor of mortality in COPD with a clear relationship between decreasing BMI and increasing mortality (38, 39, 177). A low BMI has been shown to be associated with increased COPD related mortality in 220,000 relatively lean (mean BMI 21.7 kg/m^2) Chinese men (197), whilst weight loss has also been found to be an independent risk factor for all-cause mortality in COPD (38). Both a low BMI and weight loss independently predictor poor clinical outcome in COPD both of which are assessed by ‘MUST’ suggesting it would be a particularly effective tool at predicting outcome in COPD.

4.2.2 Aim

The aim of the study was to investigate whether routine nutritional screening, using ‘MUST’, performed in outpatients with COPD was able to predict clinical outcome in terms of survival (at 1 and 2 years of follow-up).

4.2.3 Methods

The current study used the same cohort of COPD outpatients that were routinely screened using ‘MUST’ between July 2008 and May 2009 as part of study 4.1. Electronic hospital records were accessed for each COPD outpatient across the two respiratory centres. Data were collected at 1 year and 2 years after the date screened using ‘MUST’ and it was documented whether the patient had died both within 12 and 24 months of screening and the date of death recorded. Mortality rates were then compared to malnutrition risk according to ‘MUST’ (low risk versus

medium + high risk) using binary logistic regression analysis. Data on the date of death were used to assess survival rates according to malnutrition risk and adjusted for potential confounders using Cox-regression survival analysis.

Ad hoc analysis was performed investigating the influence of disease-severity on mortality rates classified according to BMI classification. The theory of the 'obesity paradox' where patients classified as overweight or obese demonstrate improved survival was also explored.

4.2.4 Results

Mortality at 1-year was significantly related to BMI classification (underweight 20.9%, normal weight 14.6%, overweight 5.0%, obese 4.3%, $p < 0.001$ χ^2 p trend) (Figure 12). When the American Thoracic Society and European Thoracic Society (198) cut-off of < 21 kg/m^2 defining underweight in those over 50 years was employed, mortality in the underweight group was 23.5% compared to 11.5% in the normal weight with the mortality rates in the overweight and obese remaining the same ($p < 0.001$, χ^2 p trend).

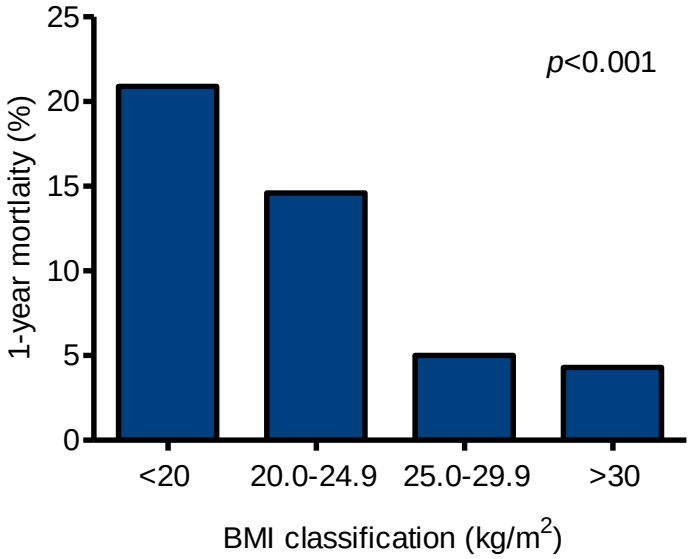


Figure 12 1-year mortality rates according to BMI classification. χ^2 p-trend analysis.

Malnutrition risk assessed using 'MUST' was found to be a significant predictor of 1-year mortality rates (19% medium + high risk *versus* 8% low risk for 'MUST'; OR 2.71 95% CI 1.419 - 5.181; p = 0.002) in outpatients with COPD. Analysis

according to each of the three 'MUST' categories found both medium and high risk to have twice the mortality rate at 1-year than low risk category (Low risk: 8.2%, medium risk: 21.1%, high risk: 18.2%; p = 0.007 χ^2). 'MUST' was found to have a similar predictive capacity was found for long-term mortality (2-years) when using binary logistic regression analysis (42% medium + high risk versus 22% low risk for 'MUST', OR 2.57 95% CI 1.58 - 4.19, p < 0.001) (Figure 13). Despite malnutrition risk being three-fold greater in those with severe disease (moderate 11%, severe 17%, very severe 36%; χ^2 p trend < 0.001), malnutrition risk remained a significant predictor of 1-year mortality even after adjustment for age, disease severity and deprivation (p = 0.042; OR 2.1, 95% CI 1.013 - 4.482) (Figure 14).

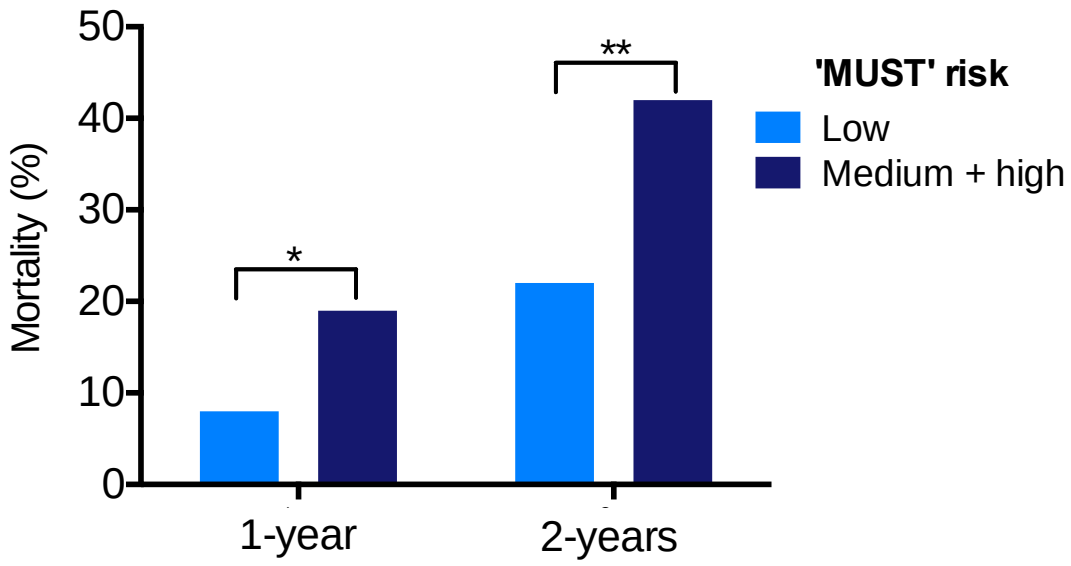


Figure 13 Mortality at 1 and 2 years according to malnutrition risk assessed using 'MUST' (low risk versus medium + high risk) adjusted for age, deprivation and COPD disease-severity using binary logistic regression analysis. * - p = 0.002; **- p < 0.001. (8% *vs*. 19% at 1 year and 22% *vs.* 42% at 2 years).

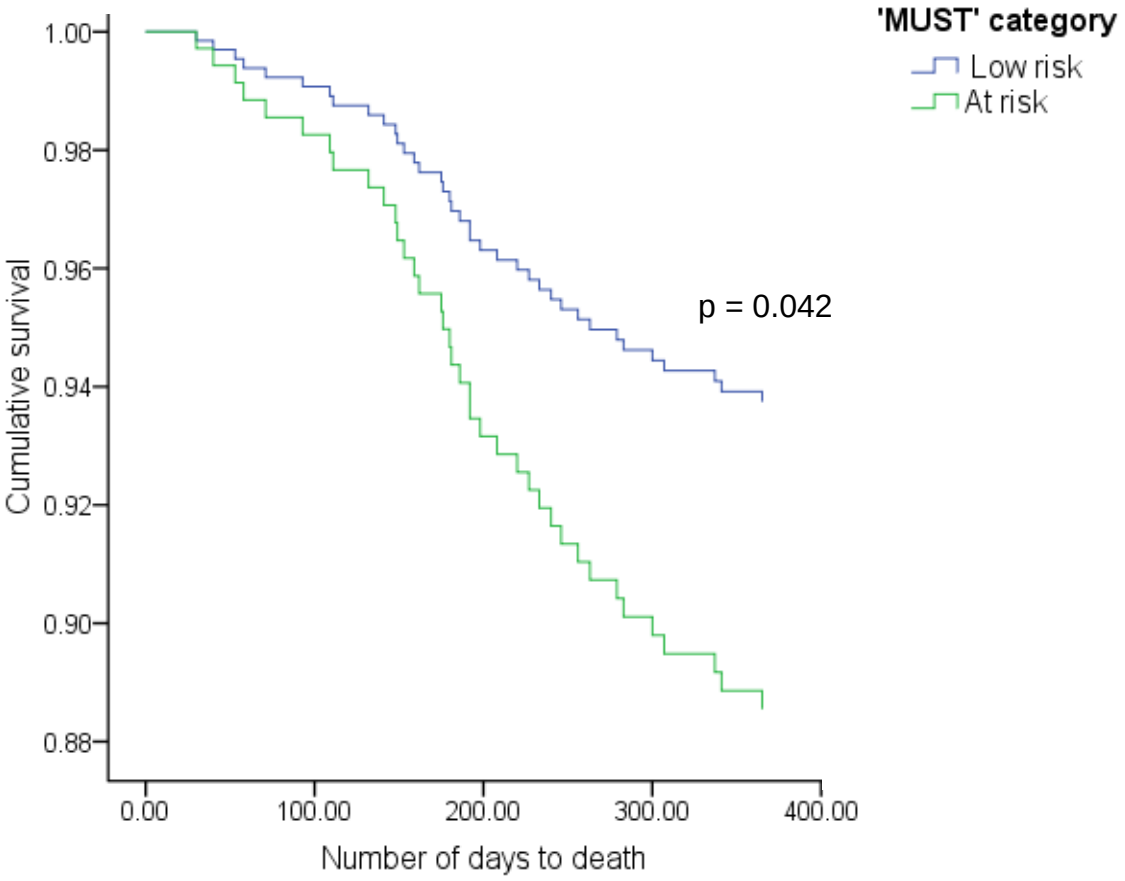


Figure 14 Cox-regression survival plot illustrating the relationship between malnutrition risk (medium + high risk) and the number of deaths within 1 year of screening in 389 outpatients with COPD. (Adjusted for age, deprivation and disease-severity).

Cox-regression survival plots demonstrated that those outpatients classified as being at risk of malnutrition (medium + high risk 'MUST' category) had significantly reduced 1-year survival rates when compared to those patients not at risk (Figure 14). Along with 'MUST', age (OR 1.064, B 0.062 SE 0.019, p = 0.001), IMD score (OR 1.042, B 0.041 SE 0.014, p = 0.002) and COPD disease-severity (OR 1.811, B 0.594 SE 0.253, p = 0.019) were all significant independent predictors of mortality at 1-year. Assessment of BMI showed that overweight or obese outpatients had the lowest mortality rates. Outpatients with a BMI classification within what is recommended as the optimum range for health in the general population demonstrated similar poor survival to those individuals with a BMI < 20 kg/m^2 (Figure 15). The significant discrepancies in survival rates and BMI classification remained significant at 2 years (Figure 16).

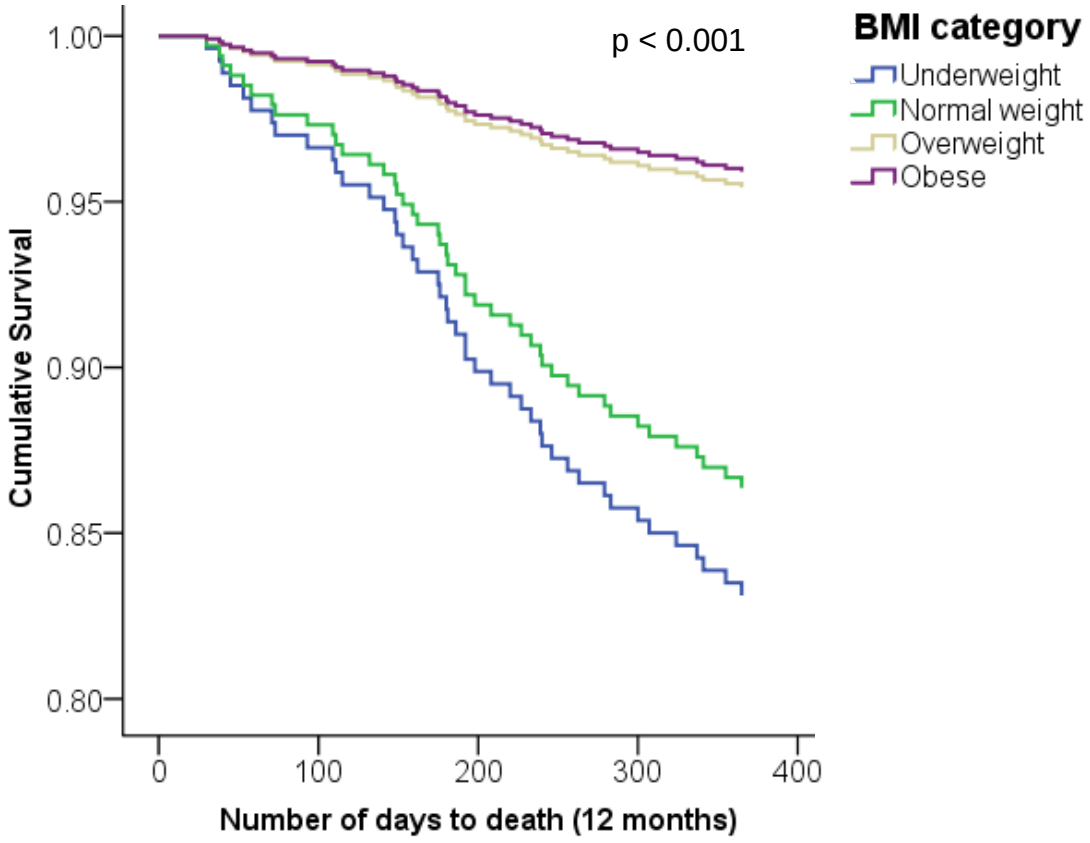


Figure 15 Cox-regression plot illustrating the relationship between BMI classification and the proportion of outpatients with COPD surviving at 12 months of screening (n = 424). Values adjusted for age, gender, deprivation and disease-severity.

The relationship between increased BMI and reduced mortality rate at 1 year was most prominent in those outpatients with very severe and severe respiratory disease in comparison to those with moderate disease (Figure 17). Figure 17 illustrates that those patients with moderate or severe disease overweight or obesity resulted in reduced mortality however, in those with very severe disease obesity was associated with the best survival rate.

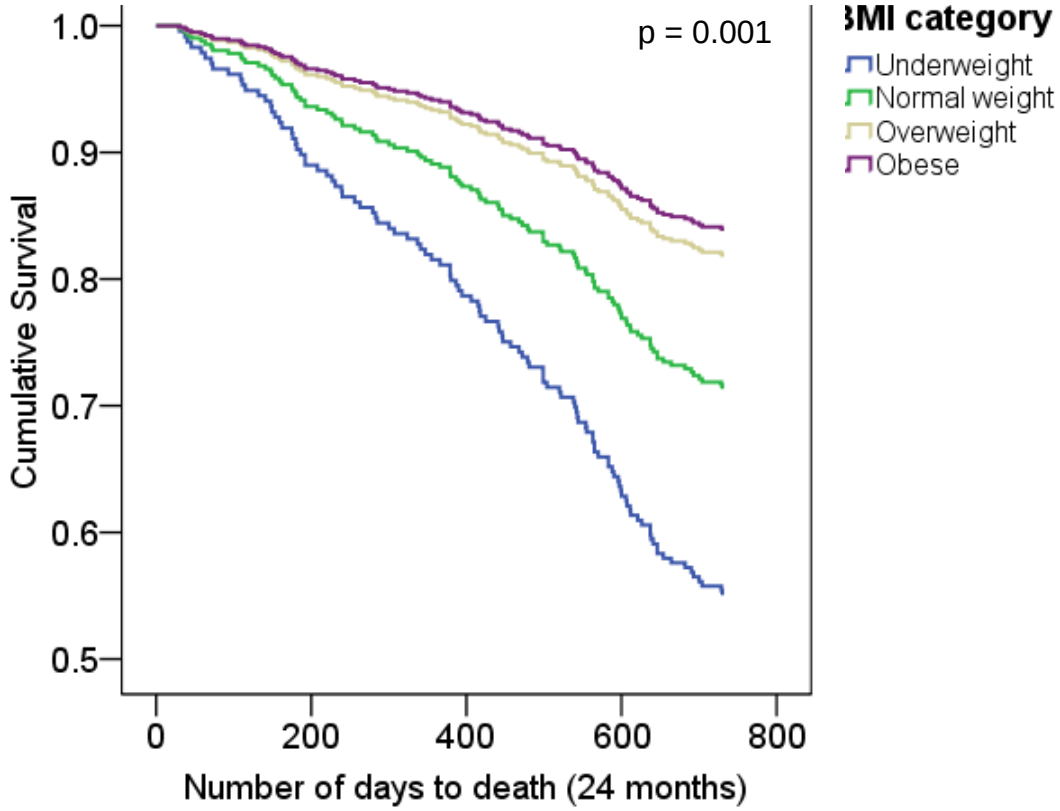


Figure 16 Cox-regression plot illustrating the relationship between BMI classification and the proportion of outpatients with COPD surviving after 24 months of screening (n = 420). Values adjusted for age, deprivation and disease-severity. 4 patients were lost to follow-up.

In addition to BMI being an independent predictor of 2-year mortality after adjusting for age, deprivation and COPD disease-severity, 'MUST' was also able to predict poor outcome at 2 years ($p < 0.001$, Cox-regression analysis). At 24-months age (OR 1.053, B 0.051 SE 0.012, $p < 0.001$), COPD disease-severity (OR 1.755, B 0.562 SE 0.152, $p < 0.001$) and deprivation (OR 1.025, B 0.025 SE 0.009, $p = 0.006$) all remained significant independent risk factors for mortality.

Mortality was found to be significantly higher at the larger teaching hospital at 1-year (14% SGH *vs.* 8% LYM, $p = 0.030$ χ^2) but this was not the case 2 years after screening (31% SGH *vs.* 23% LYM, $p = 0.081$ χ^2). Similar results were also obtained when those individuals participating in the randomised nutritional intervention trial were excluded (1 year: SGH 13% *vs*. LYM 6%, $p = 0.020$; 2-years: SGH 28% *vs*. LYM 22%, $p = 0.077$ χ^2).

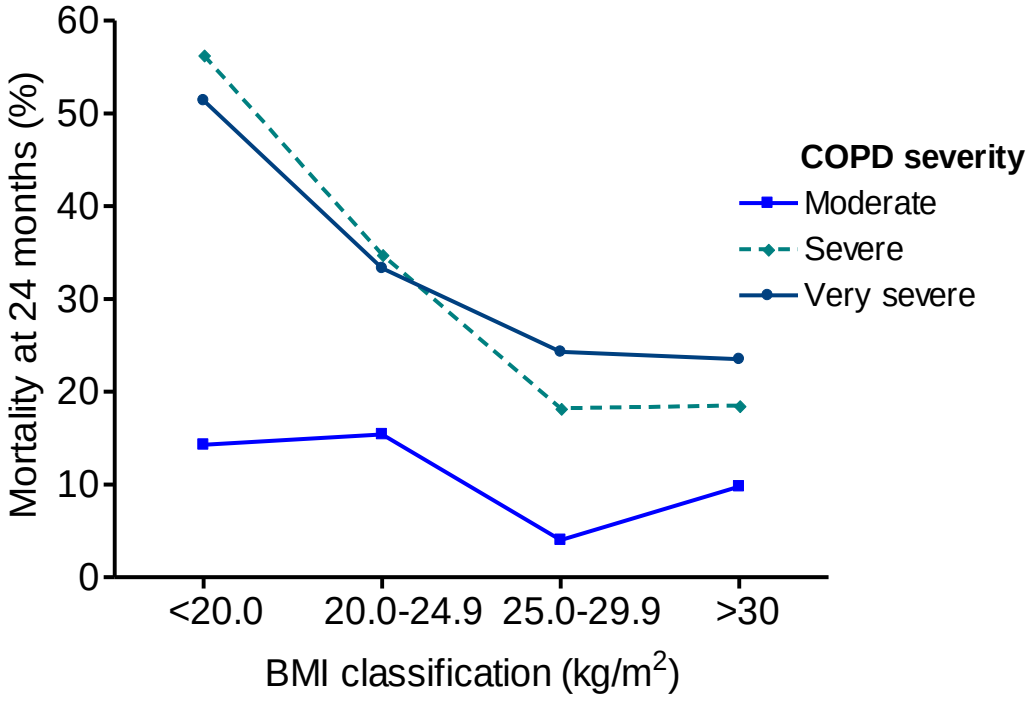


Figure 17 2-year mortality according to disease-severity (29) and BMI classification. χ^2 moderate p = 0.580; severe p = 0.013; very severe p = 0.064.

4.2.5 Discussion

This study shows that malnutrition risk assessed using 'MUST' is able to predict 1-year mortality in outpatients with COPD. These findings are in line with a substantial body of evidence demonstrating the potential protective effect of elevated body mass during times of disease, particularly in chronic wasting conditions such as COPD. One such study in COPD patients found BMI to be a significant predictor for 1-year survival even when adjusted for age, gender, FEV_1 and PaO_2 (176). Similar to the current study, the overall lowest mortality rate was seen in obese patients. There is no clear pathological mechanism why obesity would confer better survival rates in those with severe COPD. One possible explanation may lie in the fact that FFM has be found to be a more sensitive predictor of mortality than BMI in COPD patients (182, 189) and obesity is associated with increased absolute levels of lean body mass which may be protective. Indeed, obese patients have increased energy reserves that may be protective during periods of acute illness and reduced nutritional intake. This may also explain why those outpatients classified as normal weight, and as such low risk using 'MUST', went on to experience mortality rates similar to those classified

as underweight. In absolute terms normal weight patients are likely to have reduced FFM in comparison to overweight or obese individuals with the same severity of disease (199). Simply mobilising as an obese individual will lead to the accrual of increased muscle mass driven by an elevated mechanical load and it may be this body compositional compartment that is exerting the protective effect. This has been suggested by Vestbo et al., (189) and is supported by the finding that mid-arm muscle area is a more sensitive predictor of mortality in COPD than BMI (157). The exact pathophysiology of the obesity paradox needs to be established as it remains unclear whether elevated fat mass or muscle mass is providing the survival advantage seen in COPD.

Large epidemiological observation studies have consistently found reduced and elevated body weight to be associated with certain diseases. BMI and mortality are often described to have a U-shaped relationship, where those individuals who are underweight or overweight/obese show increased all cause mortality. A large observational study in 7735 British men aged 40 - 59 demonstrated this U-shaped relationship and found the highest mortality was amongst those men who had a BMI < 20 kg/m^2 or greater than or equal to 28 kg/m^2. The authors note that the highest mortality was seen in the very lean (< 20 kg/m^2), followed by the lean (20 - 22 kg/m^2) but the mortality was largely due to non-cardiovascular diseases, particularly lung cancer and respiratory disease again illustrating the impact of chronic wasting conditions on body weight and mortality (200).

Malnutrition assessed using BIA in COPD patients during acute respiratory failure following an acute exacerbation was associated with decreased active cell mass and increased intensive care unit mortality (201). A low BMI has also been shown to be an independent predictor of 6-month mortality following acute exacerbation of COPD (63). It is difficult to establish definitive causality of a reduced BMI and increased mortality in COPD. It is known that increased severity of disease is associated with reduced BMI however, malnutrition is known to compromise respiratory function (reverse causality) through weakening the muscles involved with breathing (202). Malnutrition risk and disease-severity are both independently associated with increased mortality whilst being associated with one another.

The current findings are similar to previous studies that showed an obesity paradox existing in COPD and those patients with very severe disease classified

as being obese had the lowest mortality rate (39). It can be argued that BMI classifications for the general population are not suitable in the chronically ill elderly and those with chronic wasting conditions. In COPD this relationship has been referred to as reversed epidemiology (203) and has been reported in a number of conditions including chronic kidney disease (204). The argument for amended BMI cut-offs for the elderly is supported by findings in Swedish elderly in their eighties where those aging with little morbidity had BMI values between 26 and 27 kg/m^2 (Björkelund et al., 1997 cited by Flodin et al., (196)). A recent collaborative meta-analysis investigating BMI and cause-specific mortality in 900,000 adults (Prospective Studies Collaboration, 2009) found mortality related to COPD to be strongly associated with reduced BMI. Between the BMI range 15 - 25 kg/m^2, for each 5 kg/m^2 reduction in BMI there was a four-fold increase in the risk of mortality. The observations of reverse epidemiology appear to be limited to wasting diseases as mortality rates in cardiovascular diseases increased with BMI.

From epidemiological evidence it is clear that care is needed when assessing malnutrition risk and nutritional status in conditions such as COPD due to body compositional changes seen with the disease. Indeed many of the changes seen are similar to those observed in elderly sarcopenic patients but in the case of COPD these FFM losses appear to be accelerated. If BMI is used alone there is a risk that a sub-group of patients will be classified as low risk of malnutrition but go on to experience similar poor clinical outcomes and increased healthcare use to that of an individuals with a BMI < 20 kg/m^2. FFM has been linked to outcomes other than mortality, in COPD patients undergoing lung volume reduction surgery, higher post-operative complications were found in those individuals who have a low FFM (205). Vestbo and colleagues (189) found that 13% of the COPD patients they screened using BIA had a normal BMI but a low FFMI. In fact more of the patients identified as lean tissue deplete had a normal BMI than a low BMI. Although a low BMI was classified as < 18.5 kg/m^2, again highlighting the varying cut-off values used in nutritional assessment trials.

One of the strengths for the current study is that effort was made to adjust for factors that are known to influence survival in COPD (disease-severity, age and social deprivation). This is the first study to demonstrate the long-term predictive validity of ‘MUST’ in COPD patients. Should routine nutritional screening be a future recommendation made by NICE (6) these results suggest that ‘MUST’

would be a valid tool appropriate to recommend. There are however, limitations to the current study firstly the assessment of FFM was not performed which meant the influence of body composition on survival could not be accounted for. Absolute FFM could have been preserved and even increased in the overweight and obese outpatients that may have exerted a protective effect. Secondly, it remains to be established whether disease-severity was adequately controlled for and the survival discrepancies seen between BMI classifications are not driven by differences in respiratory function particularly diffusing capacity. Abnormal diffusing capacity has been found to be significantly associated with BMI with underweight COPD patients having significantly poorer diffusing capacity than overweight and obese patients despite having similar COPD severity classifications according to FEV_1 (206). The changes observed in the current study could be simply a reflection of the historical phenotypical description of the 'blue bloater' and the pink puffer'. Emphysematous patients may have represented a higher proportion of the underweight/normal weight BMI classification and the chronic bronchitis patients comprising the overweight/obese classification. A number of difference sub-groups of patients exist under the umbrella term of COPD that could contribute to a different nutritional status and outcome.

4.2.6 Conclusion

This is the first study to show that 'MUST' is able to predict mortality risk in COPD patients and as such is simple and effective tool in identifying those patients at risk. The finding is not surprising considering 'MUST' assesses BMI and weight loss, which are known to be independent risk factors for poor clinical outcome in COPD. Currently there are no screening tools that include the formal assessment of FFM and whilst it is acknowledged assessment of BMI may not be as sensitive a predictor of mortality than assessment of FFM, it is a cheap, quick and pragmatic assessment suitable across all healthcare settings.

The current findings support a large body of evidence highlighting the observation of the obesity paradox in COPD and this raises questions about when and how to nutritionally intervene in this patient group. Further research is needed in order to understand the mechanisms behind the protective effect of an increased body mass in the presence of disease. Studies reporting the obesity paradox in COPD, the current study included, have failed to adequately adjust for respiratory function

often only adjusting for COPD disease-severity (FEV_1 % predicted). Future studies should aim to explore the paradox adjusting for the diffusive capacity of the lung and accounting for the differing phenotypes contained within COPD.

What influence malnutrition risk and the obesity paradox has on the clinical course of COPD patients in terms of hospital admission rate and length of stay is less clear. Study 3 explores this issue in more detail.

4.3 Study 3 - Malnutrition and healthcare utilisation in COPD

4.3.1 Introduction

Malnutrition is an under-recognised and under-treated problem within the UK, the British Association of Parenteral and Enteral Nutrition (BAPEN) have produced numerous publications highlighting the scale and cost of malnutrition to the UK (4, 24). The latest report estimates that in 2007 public expenditure on disease-related malnutrition in the UK was in excess of £13 billion per annum (8). The report highlights that certain societal trends will continue to lead to increases in the economic burden of malnutrition and specifically mention increases in the prevalence of chronic obstructive pulmonary disease (COPD). The economic burden of COPD to the UK economy is huge, in 2000/2001 the direct cost to the National Health Service (NHS) was estimated to be £491,652,000 and £982,000,000 when indirect costs were included (NICE, CG101(6)). More than half of these costs are directly attributed to the provision of in-hospital care. Emergency hospital admissions to UK hospitals have been rising for several years producing a significant economic and operational burden to the NHS and making COPD one of the most costly conditions managed by health services (175).

It is clear societal trends are only likely to influence the levels of malnutrition seen in future. Aging plays a huge role with individuals living longer in the presence of disease however, another societal trend which is arguably increasing, concerns inequalities in health and social deprivation. As the difference between areas of low and high deprivation continue to grow certain areas are likely to see the prevalence of malnutrition rise. A previous study highlighted the link between deprivation and malnutrition risk in elderly care inpatients (207). It was found those patients admitted to hospital and classified as at risk of malnutrition were more likely to reside in deprived areas as well as more likely to die during admission. The largest and arguably the most influential population trend over the last century, and one particularly relevant to the levels of malnutrition seen in COPD, is that of the ageing population. It is established that there is an age-related decline in pulmonary function even in the absence of a smoking history which suggests the prevalence of COPD is likely to rise beyond the estimated 3 million suffers

currently in the UK (185). Malnutrition has previously been shown to be a common problem in COPD with 22% of outpatients classified as at risk (Published abstract 2, Appendix 1, Chapter 4, study 1) (191). It is suggested the prevalence of malnutrition risk to be higher in hospitalised COPD patients and there is also likely to be some geographical variation. In the absence of a universally accepted nutritional screening tool it is impossible to establish the exact prevalence of those at risk of malnutrition in COPD but it is feasible that over 200,000 individuals with a formal diagnosis of COPD are at risk of malnutrition. If one were to take the 3 million individuals in the UK estimated to have COPD and assume a prevalence of malnutrition of 10% (lowest reported in outpatients) it is possible there are over 300,000 malnourished individuals with COPD at any one time. This not only has serious implications for the detection and management of respiratory disease and malnutrition risk but also the burden on health and social care as well as wider society. As was highlighted in Study 2, the interaction between malnutrition risk and COPD is complex with causality difficult to ascertain. Early identification and intervention both in terms of malnutrition risk and the disease itself may improve outcome and abate disease progression.

Malnutrition has an adverse impact on every organ in the body including the lungs. Malnutrition risk in COPD is associated with increased healthcare utilisation in terms increased inpatient care, which suggested that those individuals identified as at risk of malnutrition present a substantial economic burden to the NHS. A previous study in COPD patients receiving long-term oxygen therapy (LTOT) found that nutritional status, in terms of BMI, was a significant independent predictor of both duration and rate of hospitalisation. In patients with a BMI < 20 kg/m^2 the mean annual time spent in hospital was 29.6 ± 40.4 days *vs.* 17.5 ± 30.1 days in obese patients; > 30 kg/m^2 (176). The exact association between BMI, malnutrition risk and subsequent healthcare use in COPD outpatients has not been explored. Whilst ‘MUST’ has been shown to be valid at predicting mortality in COPD, the ability of the tool to predict healthcare use has not been explored.

4.3.2 Aims

The aims of the study were to assess the extent to which malnutrition risk, assessed by ‘MUST’, was related to poor clinical outcome. Outcomes assess were

hospitalisation rates, the nature of the admission (emergency or elective), and the subsequent length of hospital stay and patient mortality. In addition the effect of any participation in pulmonary rehabilitation programmes on mortality and healthcare use was also explored.

4.3.3 Methods

Healthcare use for each of the 424 outpatients routinely screening using 'MUST' as part of study 4.1 was collected retrospectively 1 year after the date of screening. Healthcare use was recorded from the electronic hospital records for each of the two hospitals (Southampton General Hospital and New Forest Hospital, Lymington). Admission and discharge dates allowed the calculation of length of hospital stay, the type of admission (emergency or elective) and whether the admission was ended due to death of the patient were also collected. Outpatient clinic attendances, home visits by a specialist respiratory nurse, and participation in a pulmonary rehabilitation programme were also recorded. 1-year healthcare use was then related to malnutrition risk as assessed by 'MUST' (low risk *vs.* medium + high risk).

As the exact details surrounding admissions were not recorded, healthcare costs were calculated using Department of Health bed stay costs (2007) and combining the values attributed to COPD (e.g. emergency admission/ventilated or emergency admission/ambulatory) to produce overall mean costs per day for emergency and elective admissions. This allowed estimated costs to be attributed to admissions for the purpose of interpretation.

4.3.4 Results

Disease-severity was not associated with increased outpatient appointments during 12 months ($p = 0.313$) and this remained non-significant when adjusted for age, malnutrition risk and deprivation using multivariate analysis ($p = 0.213$). 1-year healthcare utilisation, in terms of emergency and elective hospital admission rate, subsequent length of hospital stay and outpatient appointment attendance, was not related to 'MUST' classification. Total mean length of hospital stay (emergency + elective) in 1 year was 7.7 (SD 18) days per patient. There was

a trend for higher emergency admissions in the malnourished group along with a higher rate of mortality during admission however; neither reached statistical significance (Table 10 and 11). Despite the prevalence of malnutrition risk being found to be significantly higher at the larger teaching hospital (17% *vs.* 28%, p = 0.004 (study 1)), 1-year healthcare use costs (cost per patient per year) did not differ significantly between the two hospitals (£1599 SD £2579 versus £1820 SD £2199, p = 0.340 ANOVA). In fact the cost tended to be higher at the smaller hospital.

Table 7 1-year healthcare use according to COPD disease-severity classification (29) (n = 389)

COPD disease-severity	**Moderate**	**Severe**	**Very severe**	**p**
Total # ELEC Adms/patient	0.28 (0.67)	0.29 (0.81)	0.24 (0.71)	0.818
Total ELEC LOS/patient (d)	0.67 (3.5)	1.81 (11.0)	0.76 (7.54)	0.371
Total # EM Adms/patient	0.59 (1.0)	1.04 (1.72)	1.21 (2.8)	0.062
Total EM LOS/patient (d)	1.95 (4.34)	7.82 (19.6)	7.94 (15.6)	0.005*

Values mean (SD) using ANOVA analysis; # = number; ELEC = elective; Adms = admissions; EM = emergency.

When healthcare use was explored according to COPD disease-severity the only significant relationship was for the category looking at the duration of emergency admissions (Table 7). A significant trend existed with the length of stay increasing with COPD severity. However, whilst total 1-year healthcare costs tended to be higher in those with severe disease this failed to reach statistical significance (Table 8).

Table 8 Total 1-year healthcare costs according to COPD disease-severity (n = 389)

COPD disease-severity	n	Cost per patient per year (£)	p
Moderate	99	1342 (1533)	
Severe	159	1858 (2249)	
Very severe	131	1908 (2980)	0.149

Values are mean (SD), ANOVA analysis.

When analysis of healthcare use was restricted to only those patients within the cohort that had at least one admission during the 12-month follow-up period no significant trends emerged (Table 9).

Table 9 Total 1-year healthcare costs for admitted patients according to COPD disease-severity (n = 207)

COPD disease-severity	n	Cost per patient per year (£)	p
Moderate	45	2490 (1615)	
Severe	90	2913 (2510)	
Very severe	72	3070 (3615)	0.545

Values are mean (SD), ANOVA analysis including only those patients that had been admitted to hospital (emergency or elective).

No association was found between 'MUST' risk category and annual healthcare use (Table 10). Analysis of each component of healthcare costs and total costs did not significantly differ between risk categories where compared across two (low *vs*. medium + high) or all three categories (low *vs*. medium *vs*. high). Similar results were also obtained when analysis was confined only to those patients that had at least one admission.

Table 10 1-year healthcare use according to 'MUST' category

Annual healthcare use	'MUST' Low risk (n = 331)	'MUST' Medium + High risk (n = 93)	p
Number of EM admissions	0.58 ± 1.16	0.74 ± 2.2	0.353*
Total EM LOS (days)	4.9 ± 13.5	4.9 ± 12.1	0.994*
Number of ELEC admissions	0.25 ± 0.7	0.32 ± 0.9	0.416*
Total ELEC LOS (days)	0.9 ± 7.3	1.7 ± 7.1	0.331*
Number of outpatient appointments	3.7 ± 2.8	3.5 ± 3.1	0.459*
Death ending hospital admission (%)	5%	9%	0.165†

*Values reported as mean ± SD per patient with the exception of mortality (% of group); EM = emergency; ELEC = elective; LOS = length of stay; † = χ^2 test; * = ANOVA.*

Following the findings presented in the previous study demonstrating that BMI classification was a more sensitive predictor of mortality than 'MUST' risk, analysis of healthcare use and mortality was carried out where 'MUST' risk was reclassified. Outpatients at low risk were divided into low risk with a normal BMI or low risk and overweight or obese (Table 11). Outpatients identified as at low risk according to 'MUST' but who had a normal BMI classification went on to experience a higher rate of emergency hospitalisation than either the overweight/obese low risk group and even the medium and high risk 'MUST' group. However, when total healthcare costs were analysed according to the three 'MUST' categories no relationship was found (low risk £1651 SD 1926; medium risk £1729 SD 2765; high risk £2141 SD 4013; p = 0.367 ANOVA).

Table 11 Healthcare use and mortality and its relationship to 'MUST' risk and BMI classification (n = 424)

Annual healthcare use	'MUST' Low risk (normal) (n = 121)	'MUST' Low risk (overweight/obese) (n = 210)	'MUST' Medium + High risk (n = 93)	p
Number of EM admissions	1.0 ± 1.58	0.3 ± 0.72	0.74 ± 2.2	<0.001*
Total EM LOS (days)	9.8 ± 20.0	2.2 ± 6.1	4.9 ± 12.1	<0.001*
Number of ELEC admissions	0.19 ± 0.6	0.29 ± 0.79	0.32 ± 0.9	0.386*
Total ELEC LOS (days)	0.4 ± 1.9	1.2 ± 9.0	1.7 ± 7.1	0.412*
Number of outpatient appointments	4.1 ± 3.2	3.5 ± 2.6	3.5 ± 3.1	0.137*
Death ending hospital admission (%)	7%	3%	9%	0.114†

*Values are mean per patient ± SD except mortality (% of group); EM = emergency; ELEC = elective; LOS = length of stay; † = χ^2 test; * = ANOVA.*

Study 2 highlighted that while 'MUST' risk independently predicted 1-year mortality it appeared that BMI classification may be a more sensitive predictor. Post-hoc analysis was performed exploring the amount of healthcare use according to BMI classification recorded as part of 'MUST' (Table 11).

Table 12 Annual secondary care healthcare use according to BMI classification (n = 424)

BMI category (kg/m^2)	<20 (n = 67)	20 - 24.9 (n = 144)	25 - 29.9 (n = 120)	>30 (n = 93)	p
No. EM admissions per patient	1.5 (3.7)	1.2 (1.7)	0.74 (1.4)	0.71 (1.1)	0.001*
EM LOS (days per patient)	6.5 (12.8)	9.6 (19.3)	5.3 (17.3)	3.6 (9.0)	0.034*
No. ELEC admissions per patient	0.33 (0.75)	0.22 (0.71)	0.20 (0.67)	0.39 (0.90)	0.216
ELEC LOS (days per patient)	1.94 (7.9)	0.59 (2.6)	0.48 (3.2)	2.1 (13.0)	0.240
OPA per patient	3.4 (2.5)	4.1 (3.4)	3.4 (2.6)	3.5 (2.6)	0.163

*No. = number; EM = emergency; ELEC = elective; LOS = length of stay; OPA = outpatient appointments; Values are reported as mean ± SD; p values for ANOVA; * = statistically significant (p < 0.05).*

In terms of elective hospital admission rates and length of hospital stay a 'U-shaped' trend was observed, where those patients with an underweight or obese classification experienced higher admission rates and a longer duration of admission (Table 12).

Pulmonary rehabilitation

Of the 424 outpatients 14.2% (n = 60) participated in outpatient pulmonary rehabilitation programmes (PR) at some point during 12 months after initial nutritional screening. 15% of those patients with a low 'MUST' score participated compared to 11% of those assessed as being at risk of malnutrition, medium + high risk (χ^2 p = 0.287). A higher number of patients at high risk of malnutrition participated in PR than at medium risk (14% *vs*. 5%; χ^2 p = 0.139) suggesting malnutrition risk does not represent a barrier to participation. However, whether patients completed the full rehabilitation programme was not assessed. It was

found that those patients that participated in PR had significantly lower mortality rate at 1-year than those that did not attend (2% *vs.* 12%; χ^2 p = 0.015). Although disease-severity was independent predictor of 1-year mortality using binary logistic regression (p = 0.033), disease-severity was not related to whether a patient attended PR, with the highest attendance being in those with very severe disease (45% very severe, 33% severe, 12% moderate).

In terms of healthcare use, outpatients that participated in PR were found to have significantly higher emergency hospitalisation rates (PR: 1.5 SD 4.2 emergency admissions per patient/year *vs*. No PR: 0.91 SD 1.36; ANOVA p = 0.037, in those that did not participate). Although subsequent length of hospital stay (PR: 5.27 SD 15.7 days versus No PR: 6.82 SD 16.2 days; ANOVA p = 0.488) and overall cost associated with the admission (PR: £974 SD £3578 *vs*. No PR: £735 SD 1316; ANOVA p = 0.343) did not differ between groups. The overall difference in healthcare costs at 1-year were predominantly due to increased outpatient contact in the patients attending PR (PR: £1068 SD £536 *vs*. No PR: £341 SD £270; ANOVA p < 0.001). Overall total healthcare costs at 1-year were significantly higher in those outpatients that attended PR (PR: £1545 SD £1904 *vs*. No PR: £2794 SD £4101; ANOVA p < 0.001).

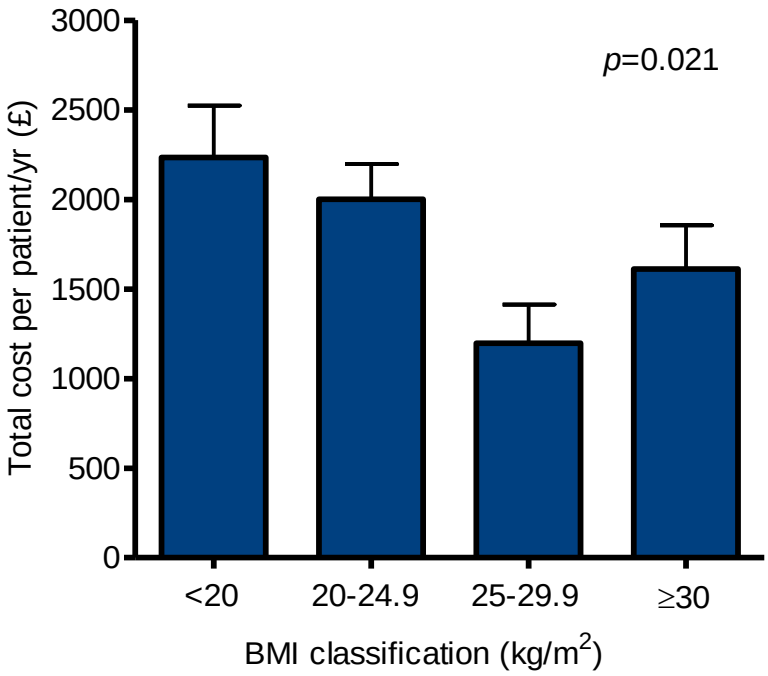


Figure 18 Annual healthcare use (secondary care) cost per patient per year (£) according to BMI classification, values mean (SE) adjusted for age, gender and disease-severity using univariate analysis (n = 389).

Figure 18 illustrates the annual secondary care healthcare use costs per patient according to BMI classification. There was a significant curvilinear relationship between BMI classification and 1-year healthcare use costs both before and after adjustment for age, gender and disease-severity (p = 0.017 and p = 0.021; ANOVA and univariate analysis (quadratic equation)). Within a year of screening outpatients classified as underweight presented the largest financial burden to the NHS costing £2235 (SD 288) per patient. Individuals who were normal weight (20 - 24.9 kg/m^2) cost £2001 (SD 197) per patient per year compared to obese outpatients costing £1612 (SD 244). Similar total 1-year healthcare costs were found using unadjusted values (underweight £2293 SD 3940; normal weight £1988 SE 2270; overweight £1187 SD 1426; obese £1670 SD 1913; ANOVA p = 0.014).

Outpatients with the lowest total annual secondary care healthcare use were classified as overweight, costing per patient £1197 (SD 217). Due to the BMI distribution of the cohort, in absolute annual costs in the current cohort this equated to a cost of £288,144 (SD £19,296) in the normal weight patients due to having the largest sample size (34% of cohort; n = 144). After the normal weight category, the obese category was the second most costly at £149,916 (SD

£22,692) closely followed by the underweight group despite having the smallest number of patients (16% of cohort; n = 67) at £149,745 (SD £19,296). Despite 28% of the cohort being overweight it was this group of patients who again had the lowest absolute 1-year healthcare costs at £143,640 (SD £26,040). Whilst underweight individuals used the most emergency healthcare, obese patients used a similar amount of elective healthcare (Table 12). This combined with the larger proportion of obese to underweight individuals in the current cohort meant the difference in absolute costs was less.

Table 13 Total 1-year cost per patient

BMI category (kg/m^2)	< 20 (n = 67)	20-24.9 (n = 144)	25-29.9 (n = 120)	≥ 30 (n = 93)	p
Cost (£) EM Adm/yr	1096 (3187)	1140 (1858)	404 (856)	428 (944)	0.001
Cost (£) ELEC Adm/yr	576 (1309)	377 (1247)	351 (1172)	679 (1573)	0.216
Cost (£) OPA/yr	436 (441)	460 (408)	413 (394)	464 (409)	0.767

EM = emergency; ELEC = elective; Adm = admission; yr = year. Values are mean (SD).

When total 1-year costs for emergency and elective admissions taking into account duration of stay were analysed, a significant trend existed for the emergency admissions with overweight and obese patients having a much shorter duration of stay (Table 12) and as such a significantly reduced cost; p = 0.001 (Table 13). There was no relationship between BMI classification and the cost of 1-year elective or outpatient appointments.

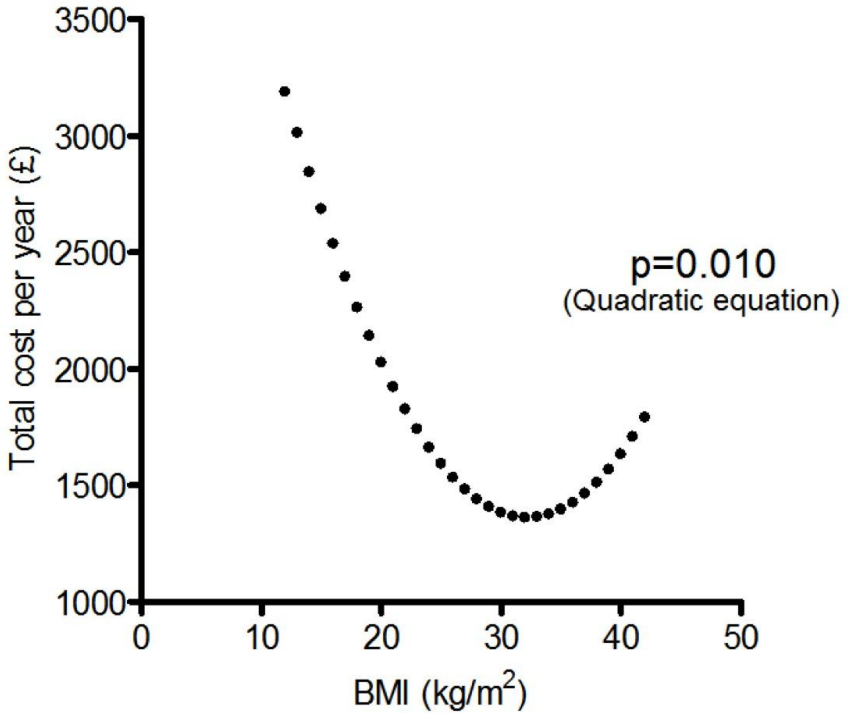


Figure 19 Healthcare use and BMI model. Total secondary healthcare use (emergency admissions, elective admissions, outpatient appointments) per patient per year according to BMI, adjusted according to age, gender and disease-severity using univariate analysis.

Post-hoc analysis using one-way ANOVA examining quadratic trends found there to be a significant U-shaped association between BMI classification and elective admission rate and length of stay (p quadratic trend = 0.010). Total healthcare use costs were adjusted according to BMI, age, gender and disease-severity using univariate analysis (Figure 19). The predicted costs according to the model suggest the lowest annual healthcare use costs are in those individuals with a BMI of approximately 32 kg/m^2. As BMI exceeds this level the total secondary care healthcare use costs begin to rise. It is clear those individuals with a BMI of less than 20 kg/m^2 incur the largest costs.

Outpatients classified as normal weight represented the largest financial burden to the NHS costing £4372 (SD 677) per patient. Individuals with a BMI < 20 kg/m^2 cost £3278 (SD 728) per patient per year compared to obese outpatients costing £2199 (SD 633). Outpatients within the overweight category experienced the lowest 1-year costs per patient of £1360 (SD 260).

In terms of absolute 1-year costs in the current cohort this equated to a cost of £629, 568 (SD £97, 488) in the normal weight patients due to having the largest sample size. After the normal weight category, the underweight category was the second most costly at £219, 626 (SD £48, 776), closely followed by obese individuals costing £204, 507 (SD £58, 869). Whilst the underweight individuals used the most emergency healthcare, obese patients tended to use more elective healthcare. This combined with the larger proportion of obese than underweight individuals in the current cohort meant the difference in absolute costs was less.

4.3.5 Discussion

Despite malnutrition risk identified using 'MUST' being found to be an independent predictor of 1-year mortality (study 2); this study found that malnutrition risk was not associated with increased healthcare utilisation and subsequent costs both when analysing the whole cohort and only those that experienced at least one admission. As malnutrition is often attributed to increased hospitalisation rates and protracted lengths of admission the current finding is somewhat surprising but could be due to several reasons: firstly, the previous study highlighted that patients at risk of malnutrition according to 'MUST' were significantly more likely to die sooner in the year thus reducing the time with which to use healthcare. In addition, malnourished individuals admitted to hospital had a tendency for a higher mortality therefore curtailing their admission, as this has been demonstrated in a larger UK sample of hospitalised COPD patients by Steer et al., (208). This may partly explain the finding that normal weight patients assessed to be at low risk of malnutrition were found to have higher healthcare use that those at high risk of malnutrition. As has been illustrated earlier in this chapter, normal weight patients at low risk of malnutrition go on to have poor clinical outcomes that could also be attributed to body compositional changes (reduced FFM), which is more prevalent within the lower BMI categories. Despite 'MUST' being found to be a poorer predictor of healthcare use than BMI in outpatients, it is important to note 'MUST' was not designed to predict outcomes such as mortality but establish the need for nutritional support. Predicting clinical outcomes using nutritional screening tools is common but as Elia and Stratton (209) recently highlighted, most were not designed for this purpose. Whereas BMI is often used to predict an individual's future risk as well as establish whether they are underweight or overweight.

Therefore if mortality and healthcare use are outcomes of interest BMI may be a more appropriate measure. BMI is included in the BODE index which involves the assessment of BMI, airflow obstruction, dyspnea and exercise capacity. The BODE index has been found to be a better predictor of hospitalisations than its components alone (210).

This study found no difference in the annual healthcare costs between the two centres despite the risk of malnutrition being found to be significantly higher at the larger hospital (chapter 4, study 1). In fact costs per patient tended to be lower at the larger hospital, which could be due to a number of factors. Firstly, the larger hospital had a supported discharge scheme where those patients frequently admitted for AECOPD are identified early and discharged home under daily supervision for a period of time. Secondly, mortality was significantly higher at 1-year amongst the patients attending the larger hospital (study 2). Although caution is needed when interpreting the costs associated with admissions as it was not possible to assess the care patients received whilst admitted which would impact on overall costs.

It was observed that outpatients that participated in pulmonary rehabilitation (PR) had significantly lower mortality rates at 1-year than those that did not attend although this could simply be a reflection of those with the more stable respiratory disease being able to attend. It is difficult to establish the exact causality as disease-severity was an independent predictor of mortality but was not related to whether a patient attended PR, with the highest attendance being in those with very severe disease. Exercise rehabilitation is now recommended as a key therapy for the management of COPD patients underpinned by the highest quality evidence (171). Whilst the current findings support the findings of others that participation in exercise programmes appear to improve survival in this group of patients (211), in the absence of data on co-morbidities firm conclusions cannot be drawn. This reduced mortality could partly explain the current finding that increased healthcare costs were associated with pulmonary rehabilitation attendance which is in contrast to previous findings (212). The relationship between malnutrition risk, co-morbidities and disease-severity, PR referral, uptake and completion warrants further exploration involving a much larger sample than the one obtained.

An obesity paradox, where individuals appear to have improved survival despite having an elevated BMI, has previously been described in chronic wasting conditions such as COPD (213). This paradox was demonstrated in the current cohort of outpatients, where increased body mass appeared to be protective in terms of mortality (214). Post-hoc analysis was performed investigating whether BMI classification were associated with healthcare use in addition to the improved survival. A significant inverse relationship between BMI and 1-year emergency healthcare use (admission rate and length of hospital stay) was found with overweight and obese outpatients less likely to require emergency hospitalisation and experienced shorter durations of hospital admission. Whilst these findings corroborate those of others, it is acknowledged adequate adjustment of co-morbidities would have greatly informed the analysis.

Although 'MUST' was initially designed and validated as tool for identifying the need for nutritional support, the findings of this study suggest that whilst 'MUST' had predictive validity and is able to independently predictor mortality (Study 2) it is less sensitive at identifying outpatients with COPD who are likely to be high healthcare users. This may be unique to the outpatient setting as in a cohort of 606 COPD patients hospitalised for an acute exacerbation of COPD (AECOPD), a high 'MUST' score for BMI (< 18.5 kg/m^2) predicted inpatient mortality, OR 2.5, 95% CI 1.27 - 4.91, p = 0.008 (208). The authors also found that weight loss (> 10%) predicted early readmission (within 28 days) OR 3.90 95% CI 2.09 - 7.28, p < 0.001. A high 'MUST' score was the only measurement that significantly predicted both inpatient mortality and early readmission (208). However, in the current study the heterogeneity of COPD patients contained within the low risk category of 'MUST' appears to weaken its predictive validity in identifying those groups of patients most likely to go on to experience increase emergency healthcare use. Assessment of patients according to four BMI classifications may be less likely to miss patients that are FFM deplete than 'MUST' however both are limited in this regard. The fact patients with an apparently low risk for malnutrition and a normal BMI went on to do so poorly both in terms of hospitalisation rate, length of stay and whether their admission was ended through mortality is in need of further investigation. As BMI is a component of 'MUST' exploration around whether the tool could be modified for use in the COPD population improving its sensitivity and specificity. One possible option could be to consider raising the BMI cut-off threshold to the < 21 kg/m^2 currently specified by both the American and

European Thoracic Societies (198). Such a move would seek to identify those patients that are at nutritional risk who would be likely to respond to nutritional support. Chapter 3 highlighted there is evidence that patients considered nourished benefit from nutritional support when administered alongside an exercise rehabilitation programme, although this is based on only two studies (56, 57). Further studies are required in order to justify new BMI cut-offs for defining nutritional depletion in COPD both in terms of predicting clinical outcome as well as likely responsiveness to any nutritional support. Currently 'MUST' is the only nutritional screening tool which has been shown to be useful in identifying both COPD inpatients and outpatients that require nutritional support but also are likely to go on to experience poor clinical outcomes. Yet there does appear to be a group of COPD patients that are missed by current nutrition screening strategies that go on to experience similar poor outcomes but that would have likely responded to nutritional support.

The current study only assessed HCU in the secondary care setting with hospitalisation and outpatient appointments, HCU within the primary care setting in terms of medication use and GP clinic attendance was not monitored. To date no studies have been carried out specifically assessing the prevalence of malnutrition in COPD patients within the general practice setting. This study found that the total mean length of hospital stay (emergency + elective) per patients in a year to be 7.7 days which means COPD patients spend the majority of their time outside of hospital (98%). There is a significant burden associated with COPD across both primary and secondary care with G.P consultation rates for COPD said to be twice that of angina, rising to four times in those with severe COPD (7).

The findings of the current study support those of Challieux et al., (176) who observed a similar paradox but in a much larger sample size (n = 3138) in COPD patients receiving LTOT between 1984 and 1993. The authors found the highest healthcare use in terms of admission rate and length of hospital stay (LOS) were seen in those individuals with a BMI less than 19 kg/m^2 with the lowest in those with a BMI greater than 30 kg/m^2. Using multivariate analysis BMI was found to be the biggest predictor of 1-year healthcare use. Patients with a BMI < 20 kg/m^2 were hospitalised a mean of 1.27 (SD 1.28) times per year with a mean LOS of 29.6 (SD 40.4) days compared to those classified as obese with 1.02 (SD 1.17) times per year and a mean LOS of 17.5 (SD 30.1) days. The exact mechanisms

behind what is driving the obesity paradox in COPD are poorly understood with no studies setting out to specifically address the area. In order to accurately assess the causality, adequate adjustment for inflammation, malnutrition risk, body composition, respiratory function and co-morbidities would all have to be accounted for. Arguably these issues should be address within pharmaceutical trials to appropriately phenotype the population studied.

The economic burden of COPD is significant and it was found that 1-year healthcare use was related to BMI classification with those patients with a BMI 25 - 29.9 kg/m^2 being associated with the lowest annual healthcare costs attributed to emergency admissions. In the current cohort the majority of patients (34%) were classified as GOLD stage 4 (very severe disease) (29), and it is estimated the direct cost to manage these patients is £3100 per year compared to GOLD stages 3 (£945) and 2 (£280). Similar cost trends according to disease severity are seen in the management of acute exacerbations with those patients with very severe disease costing up to 16 times more per episode (NICE, CG101, (6)). The current observational study used an overall estimated cost for an emergency or elective admission due to COPD in order to carry out an economic analysis. When the total HCU costs (emergency + elective) were modelled adjusting for covariates, there was a significant ('reverse-J shaped') trend where costs rose considerably below a BMI of 25 kg/m2. Whilst total secondary care costs were associated with a BMI of 31 – 32 kg/m2, costs did begin to rise as BMI exceeded 35 kg/m2. Whilst emergency healthcare use and as a result costs were associated with those with a lower BMI, obese individuals tended to have more elective admissions and particularly prolonged lengths of admission, some four times longer than overweight individuals.

4.3.6 Conclusion

In addition to BMI being a significant predictor of mortality as demonstrated in study 2, it is also associated with emergency hospitalisation rates and duration of hospital admission. Whilst nutritional screening tools such as 'MUST' are able to predict poor outcomes it is important to consider whether this was the purpose for which the tool was initially designed. Although BMI was able to predict healthcare use and mortality, patients with an apparently normal BMI still went on to experience poor outcomes The most likely reason for this is due to negative body

compositional change, namely the loss of FFM, that are known to commonly occur in COPD and which are likely to go undetected in a sub-group of patients if only simple nutritional screening and calculation of BMI are used. This was illustrated in the current study where individuals with a low ‘MUST’ risk and a normal BMI still went on to experience poor outcomes. The possible inclusion of an indirect assessment of muscle mass (e.g. mid-arm muscle circumference) or body compositional assessment using technology such as BIA may assist in identifying those patients that are FFM deplete and likely to go on to use increased amounts of healthcare.

4.4 Study 4 - Influence of deprivation on malnutrition risk and clinical outcome

4.4.1 Introduction

National and international policies aim to abolish the health inequalities associated with deprivation however, the health gradient between affluent individuals and communities compared to those more deprived remains considerable and may even be growing. Often the terms poverty, deprivation and social exclusion are used interchangeably however, Peter Townsend in 1979 writing on poverty in the United Kingdom defines poverty as:

'individuals, families and groups can be said to be in poverty if they lack the resources to obtain the types of diet, participate in activities and have the living conditions and amenities which are customary, or at least widely encouraged or approved in the society to which they belong' (215)

Townsend suggests people are said to be deprived if they lack the resources to escape deprivation in terms of diet, clothing, housing, household facilities (fuel and environmental), as well as educational, working and social conditions (216). The most deprived areas in England tend to be in the North in the conurbations of Manchester, Liverpool and Newcastle and also in the large metropolitan areas of Yorkshire and the West Midlands (217). Overall the South East is less deprived than any other region despite having some pockets of deprivation in large urban areas such as Southampton and Portsmouth.

There has been interest in how social inequalities impact on health for over a century however interest has increased over the last three decades. The increased interest in how deprivation influenced health and mortality is due to the publication of the 'Black Report' by the British government, which essentially found that large differences in mortality and morbidity existed, favouring the higher social classes and these differences were not being addressed by health and social care at the time (218). Such a finding is not approved in modern societies where inequalities are trying to be eradicated. However, a report a decade after the Black Report on inequalities suggested that social class differences in mortality were

continuing to widen and improvements in the assessment of deprivation were showing even greater differentials in terms of mortality (219). The inequity in the distribution of income, and as such wealth, suggests further widening in mortality rates in the future. Whilst there has been a substantial amount of research investigating the influence deprivation has on the incidence of coronary heart disease and the prevalence of smoking, there is currently very little evidence linking deprivation to malnutrition risk. Although a previous study did demonstrate such a link in a heterogeneous group of elderly care inpatients (207). In the study by Stratton and Elia (207) deprivation was assessed using the index of multiple deprivation (IMD) and it was shown to be a significant independent predictor of inpatient mortality in a mixed cohort of patients (medical, surgical, elderly care, trauma and orthopaedic). In the survey patients classified as at risk of malnutrition using 'MUST' (medium + high risk) were admitted from significantly more deprived areas in comparison to those individuals classified as at low risk. Deprivation assessed using a variety of methods (education, income and other indices of social class), has been shown to be associated with increased levels of mortality in a number of chronic diseases. It has been suggested that the socioeconomic gradient in chronic obstructive pulmonary disease (COPD) is as great, if not greater, than any other disease (220). Mortality from COPD in England is more likely in urban and deprived areas particularly in the north of the country and social-inequalities have been shown to be associated with increased rates of respiratory infections requiring hospitalisation (221). Increased mortality due to social inequalities is evident in the fact that males aged 20-64 years employed in unskilled manual occupations are 14 times more likely to die from COPD than those in professional occupations (NICE, CG101 (6)). Therefore deprivation is both associated with both the incidence and outcome of COPD.

Secondary analysis of the National Diet and Nutrition Survey (1998) found geographical inequalities exist in the prevalence of protein-energy malnutrition as well as deficiencies in several nutrients (vitamin C, vitamin D and Selenium) across elderly individuals in England (54). The authors report a north-south divide in malnutrition risk prevalence rates, with malnutrition risk found to be 73% higher in the northern region of England (the north, north-west, Yorkshire and Humberside) compared to southern regions (London, south-east and south-west). The prevalence of malnutrition risk in central regions (East Midlands, West Midlands and East Anglia) was also found to be 58% higher in comparison to the

south, raising issues of both health inequality and localised resource due to the cost implications associated with malnutrition risk. During 2000/2001 there were 2,895,234 patients admitted as an emergency to hospitals across England (175). The authors assessed the subsequent healthcare use of these patients over three years after the initial admission and found that deprivation assessed using the index of multiple deprivation (IMD) was associated with increased emergency hospital admission rate. This linear relationship between deprivation and emergency admission rate continued in each year of follow-up. Surprisingly there was a negative linear relationship between deprivation and death rate within 1, 2 and 3 years. Within this large data set it was found that 48,821 individuals were admitted as an emergency in 2000/2001 due to COPD, one of the highest admission rates for any condition. 27% of these individuals became high impact service users, which the authors define as patients who have an emergency admission who then go on to have a further 2 emergency admissions within 12 months. The subsequent admission rates were the highest for any disease in the following 2 years and second only to diabetes in the third year of follow-up (175) demonstrating the considerable economic burden COPD has on the NHS. What was not investigated and not adjusted for by Bottle and colleagues was the influence of malnutrition risk and it remains unclear what is the main driving force behind the increased healthcare use.

It is well established that malnutrition is associated with increased healthcare use in terms of hospital admissions, subsequent length of stay and outpatient appointments (10). Study 3 demonstrated that in COPD the relationship between malnutrition risk and healthcare use is more complicated and this is likely to be associated with the ‘obesity paradox’. Whilst ‘MUST’ did not predict 1-year healthcare use it did predict 1-year mortality and it appears healthcare use was related more to an individual’s BMI. However, it is not clear to what extent deprivation is independently associated with the malnutrition risk seen in COPD patients. It is also unclear whether the social deprivation experienced by COPD patients is independently associated with increased healthcare use.

4.4.2 Aims

The aims of the study were to firstly establish whether malnutrition risk is associated with deprivation. Secondly, explore the relationship between COPD disease-severity and deprivation and whether deprivation is associated with increased 1-year healthcare utilisation and mortality.

4.4.3 Methods

This study included the same cohort of 424 COPD outpatients that were routinely screened for malnutrition risk (detailed methods of assessment using 'MUST' are described in study 4.1). To assess the influence of deprivation on malnutrition risk, each patient's postcode was recorded on the date of nutritional screening and this was used to establish each individuals deprivation risk according to the index of multiple deprivation; IMD (217). The IMD established according to each geographical location of each patient's home address (postcode or Lower Layer Super Output Area; LSOA) allowed estimation of deprivation at the small area level. The IMD aims to establish the deprivation experienced by individuals living within that local area. IMD is a complex matrix including several components such as employment, income, health and education deprivation as well as barriers to housing and crime (Table 14). The higher the IMD score, the greater the level of deprivation said to be experienced by the individuals living within that postal address (217). Deprivation data was related to each individual's malnutrition risk according to 'MUST' (180). It was then investigated whether certain components of the overall IMD score were more related to malnutrition risk than others. Secondly, it was established whether the levels of deprivation experienced by patients was related to 1-year healthcare use in terms of emergency and elective hospital admissions, length of hospital stay and secondary care outpatient appointment attendance. Finally, the relationship between 1-year mortality and deprivation was examined to see whether those patients residing in deprived areas experienced poorer outcome.

Table 14 Outcome measures assessed within deprivation domains (adapted from Nobel et al., (217))

Deprivation domain	Purpose of the domain
Income	Capture proportions of the population experiencing income deprivation in the area (LSOA). Indicators include for example: income support households, job seekers allowance, working tax credit households.
Employment	Employment deprivation due to involuntary exclusion of the working-age population from the world of work. Includes: job seekers allowance, incapacity benefit, disablement allowance.
Health & disability	Identifies areas with relatively high premature mortality, morbidity (reduced health-related quality of life, increased disability). Includes: years of potential life lost, comparative illness and disability ratio and mood and anxiety disorders. [This domain does not measure aspects of behaviour/environment that may predict health].
Education skills & Training	Measures deprivation in educational attainment, skills and training for the whole population in the local area. Includes: average test scores (key stages), proportion of non-advanced education beyond the age of 16 and 18.
Barriers to housing	Assesses geographical and wider barriers to housing. Including: affordability, household overcrowding, and homelessness.
Crime	Measure local area crime rates in terms of burglary, theft, criminal damage and violence.
Living environment	Aims to identify deprivation in both the indoor and outdoor environment. Indoors includes: social and private housing in poor condition and houses without central heating. Outdoors includes: air quality and road traffic accidents.

4.4.4 Results

Deprivation data were obtained on each of the 424 outpatients according to their postcode or LSOA. The mean population per SOA was 1552 (SD 213), mean IMD for the cohort was 15.9 (SD 11.1), IMD scores ranged from 1.88 to 57.05, with the higher the IMD score reflecting a higher overall level of deprivation. Outpatients that died within 1-year of screening were significantly more likely to reside within a deprived postcode than those in less deprived areas (mean IMD for those surviving compared to those deceased 19.7 *vs*. 15.4, p = 0.023, OR 1.03, 95% CI 1.00 - 1.06). Deprivation remained a significant independent risk factor for mortality even when adjusted for age, gender, malnutrition risk and disease severity using binary logistic regression (p = 0.008, OR (per unit increase of IMD) 1.04, 95% CI 1.04 - 1.07). Deprivation was not associated with increased disease-severity (p = 0.906) or body mass index, kg/m^2 (p = 0.921) using ANOVA analysis.

It was found that those outpatients identified as being at risk of malnutrition (medium and high according to 'MUST') in study 1 were significantly more likely to reside in a deprived area than those at low risk of malnutrition (IMD 18.3 *vs*. 15.2; p = 0.018; OR (per unit increase of IMD) 1.024, 95% CI 1.004 - 1.044). Deprivation remained a significant independent risk factor for malnutrition even when adjusted for age, gender and disease-severity using binary logistic regression (p = 0.044; OR 1.023, 95% CI 1.001 - 1.045).

Table 15 The index of multiple deprivation (IMD), IMD domains and their relationship to malnutrition risk (medium + high risk) in COPD. Analysis using ANOVA (n = 424 outpatients) values are mean (SD)

Deprivation domains	'MUST' risk		p
	(Low risk) (n = 93)	(Medium + High risk) (n = 331)	
Overall IMD	15.2 (10.9)	18.3 (11.4)	0.018
Income	0.21 (1.5)	0.14 (0.1)	0.664
Employment	0.075 (0.036)	0.083 (0.037)	0.060
Health deprivation & disability	-0.478 (0.72)	-0.217 (0.69)	0.002
Education skills & training	19.9 (16.7)	117.8 (648.1)	0.006
Barriers to housing	33.4 (258.2)	59.1 (258.0)	0.398
Crime	-0.20 (0.76)	0.027 (0.72)	0.010
Living environment	13.5 (10.8)	17.5 (12.5)	0.003

Malnutrition risk was not only significantly associated with increased overall deprivation (IMD score) but also with several of the deprivation domains, such as health and disability, education skills and training, crime and living environment (Table 15). The results suggest several components to having a direct impact on an individual's nutritional intake and as such malnutrition risk (Table 16).

Table 16 The relationship between malnutrition risk (medium + high risk) and components of the index of multiple deprivation (IMD), values adjusted for age, gender and disease-severity using binary logistic regression (n = 389 outpatients).

Deprivation domains (score)	Odds ratio (95% CI)	p
Overall IMD	1.023 (1.001-1.045)	0.045*
Income	0.921 (0.612-1.388)	0.695
Employment	258.5 (0.351-190,217)	0.099
Health deprivation & disability	1.643 (1.151-2.346)	0.006**
Education skills & training	1.010 (0.955-1.024)	0.186
Barriers to housing	1.000 (1.000-1.001)	0.307
Crime	1.531 (1.087-2.155)	0.015*
Living environment	1.025 (1.003-1.047)	0.024*

* = $p < 0.05$; ** = $p < 0.001$.

There are 32,482 LSOAs in England with the rank of 1 given to the most deprived LSOA and the rank of 32,482 given to the least deprived. The mean LSOA for the cohort of patients was 19,576 (SD 8289) however there was a significant difference in the level of deprivation between the two respiratory centres. Patients attending outpatient clinics at the larger teaching hospital (Southampton General Hospital) resided in significantly more deprived areas than those patients attending the smaller community hospital (Lymington New Forest Hospital) when assessed using the overall IMD score (21.3 ± 12.4 *vs.* 11.6 ± 7.4; $p < 0.001$) and LSOA rank (15,510 ± 8137 *vs.* 22,877 ± 6827; $p < 0.001$) using ANOVA. None of the LSOAs covered by the two respiratory centres ranked in the 100 worst SOAs in England which tended to be in the north of England and demonstrates the fact that Hampshire overall is an area with low levels of deprivation.

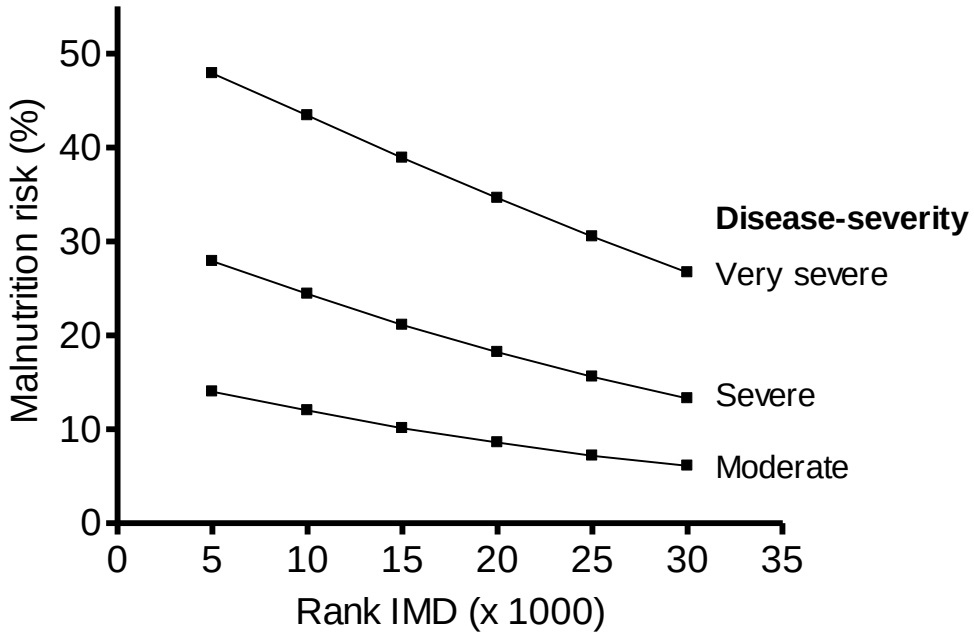


Figure 20 Malnutrition risk (medium + high risk) in relation to rank deprivation (IMD) according to disease severity analysed using binary logistic regression adjusting for age, gender, disease-severity (GOLD criteria (29)) and Rank deprivation (IMD). The higher the Rank IMD the lower the deprivation. Disease-severity ($p < 0.001$) was positively associated with the prevalence of malnutrition risk whilst the rank IMD ($p = 0.019$) was negatively associated with malnutrition seen in COPD outpatients.

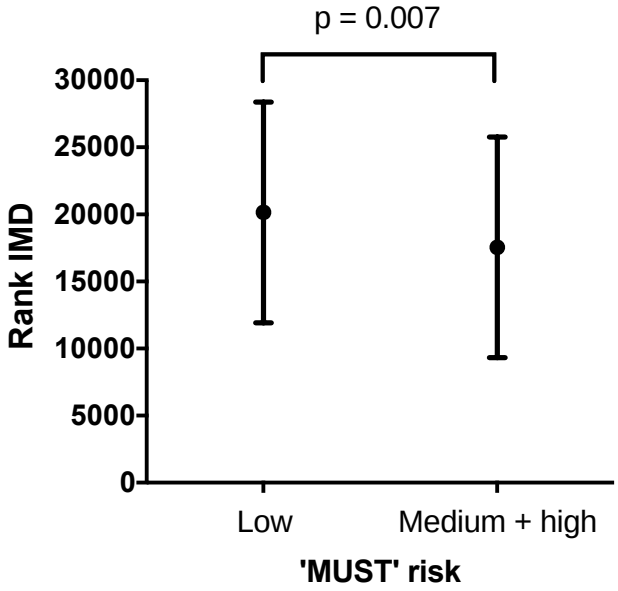


Figure 21 Malnutrition risk according to 'MUST' and deprivation (rank IMD)

Individuals identified as at risk of malnutrition were significantly more likely to reside in more deprived areas (low: 20,147 SD 8233 versus medium + high risk: 17,454 SD 8214; p = 0.007 ANOVA analysis) however, although the dispersion was wide as illustrated by Figure 21 above. Conversely, no relationship was found between COPD disease-severity and deprivation (Figure 22).

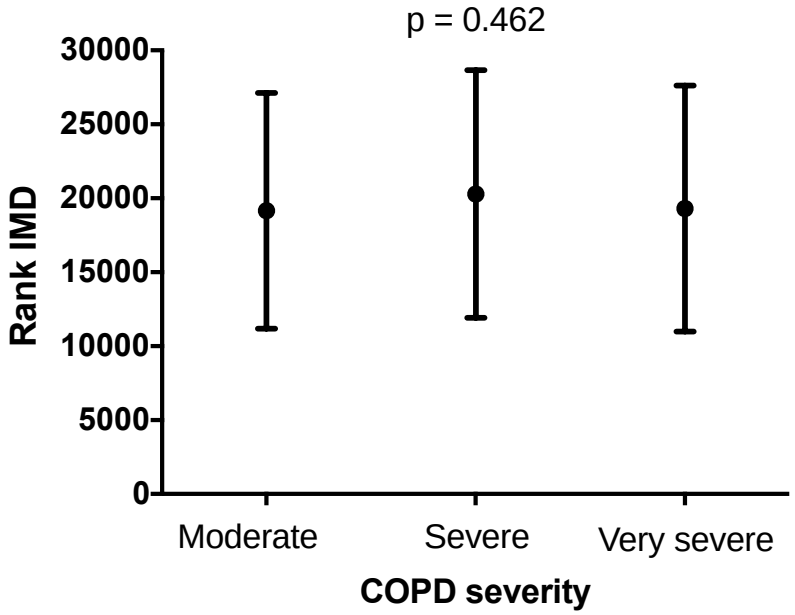


Figure 22 Deprivation (rank IMD) according to COPD disease classification (29)

Cox-regression analysis investigating the effect of Rank IMD quartiles on 1-year mortality adjusting for age, COPD disease-severity, 'MUST' risk and BMI (Figure

23). After adjustment only those individuals residing in the bottom quartile had an independent significantly increased mortality (> 75% as the comparator: < 2 5% p = 0.025; 25 - 50% p = 0.092; 50 - 75% p = 0.639; overall p = 0.091). BMI (p = 0.002) and age (p = 0.007) remained significant independent predictors of mortality at 1-year, with a lower BMI and a higher age associated with an increase in mortality. COPD disease-severity (p = 0.074) and 'MUST' (p = 0.168) were not independent risk factors after adjustment.

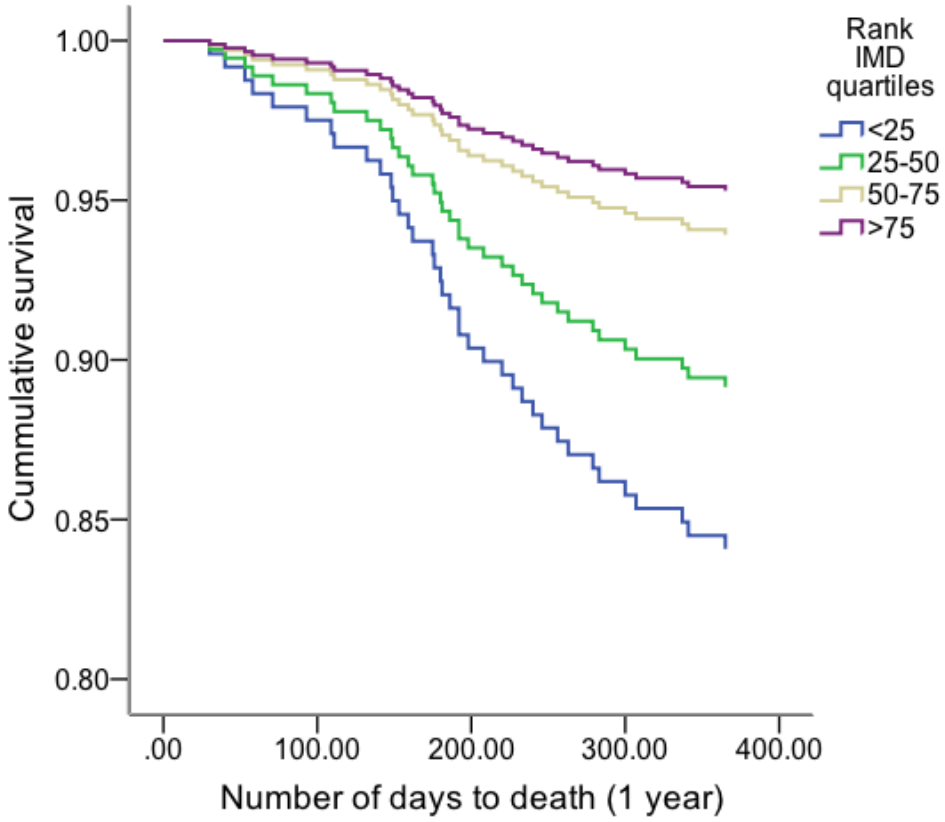


Figure 23 1-year mortality according to Rank IMD quartiles adjusted for age, COPD disease-severity, 'MUST' and BMI.

Pulmonary Rehabilitation

There was a significant difference in deprivation between those patients that attended PR and those that did not with those individuals tending to reside in less deprived areas being more likely to attend an exercise programme (PR: rank IMD 22,694 SD 7057 *vs*. No PR: 19,062 SD 8373; ANOVA p = 0.002). Attendance at PR programmes between the two centres was markedly different with 2% of those

patients attending the larger teaching hospital participating in PR compared to 24% of the smaller community hospital (χ^2 $p < 0.001$).

Table 17 The influence of deprivation on 1-year healthcare use

1-year healthcare use (n = 424)	β-coefficient *	p
Number of emergency hospital admissions (n)	0.24	<0.001
Emergency length of hospital stay (days)	1.5	0.015
Number of elective hospital admissions (n)	0	0.842
Elective admission length of hospital stay (days)	1.2	0.001
Secondary care outpatient appointments (n)	-4.1	0.002

*Adjusted using univariate analysis for age, gender, malnutrition risk ('MUST' risk) and disease-severity using multivariate analysis. * = β-coefficient illustrates the unit increase per patient in the cohort per 10-unit increase in IMD (mean IMD 15.9 SD 11.1).*

Deprivation was found to be associated with increased 1-year secondary healthcare use and this remained significant even when adjusted for age, disease-severity and malnutrition risk using multivariate analysis (Table 17). Cost analysis revealed that for every unit increase in IMD there was an average annual cost increase of £107 (Table 18).

Table 18 Influence of deprivation on annual secondary care healthcare costs.

1-year cost analysis	β-coefficient *	p
Lower Quartile cost per patient	£78 (23.4)	< 0.001
Average cost per patient	£107 (29.2)	0.001
Upper Quartile cost per patient	£118 (32.4)	< 0.001

*Adjusted using univariate analysis for age, disease-severity and BMI using multivariate analysis. * = β-coefficient illustrates the unit (£) increase per patient in the cohort per year per unit increase in IMD score (mean IMD score 15.9 SD 11.1).*

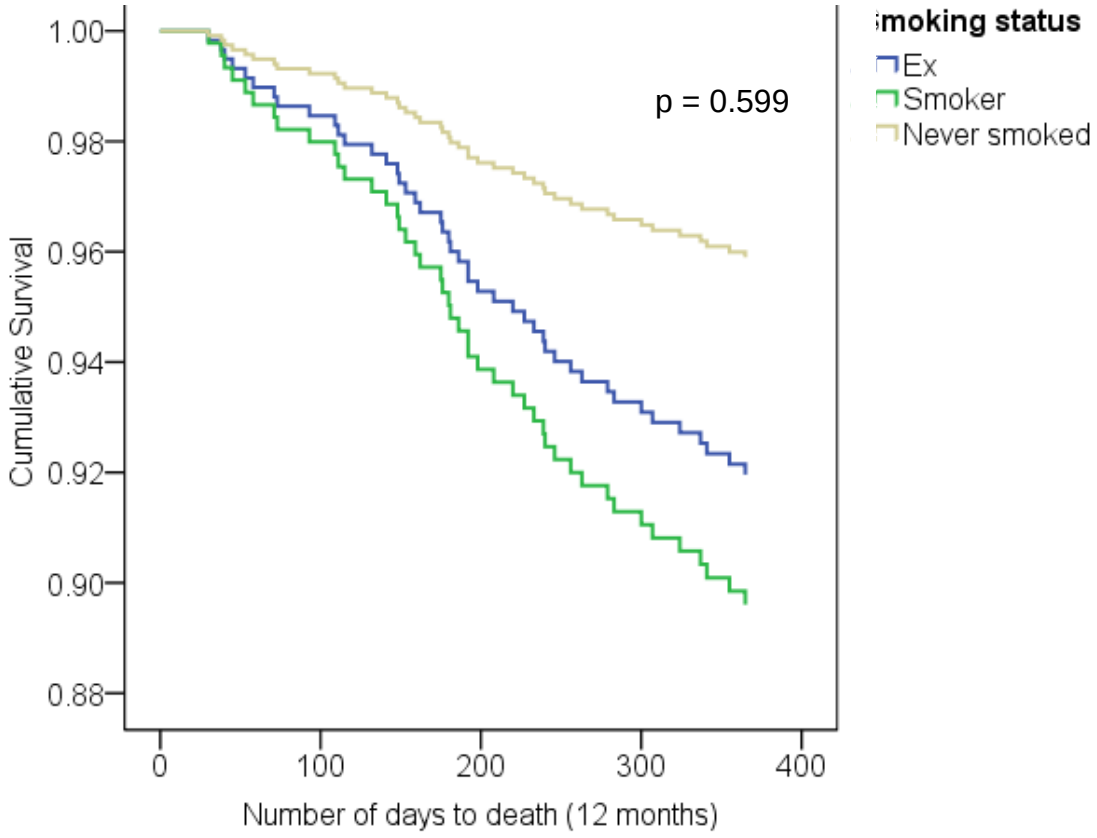


Figure 24 Smoking status and 1-year survival adjusted for BMI, deprivation, age, gender and COPD disease-severity using cox-regression (n = 419)

Data on smoking status were collected on 419 outpatients, 4.3% of outpatients were documented as having never smoked, 77.1% of outpatients were recorded as ex-smokers and 18.6% were current smokers. Malnutrition risk was found to be significantly higher in current smokers compared to ex-smokers; 32.1% *vs*. 19% χ^2

p = 0.011. Smoking status was also found to be significantly associated with deprivation, with outpatients classified as ex-smokers and never smokers residing in significantly less deprived areas than current smokers (Ex-smokers IMD 15.0 SD 10.4; never smoked 11.64 SD 10.2; current smoker 20.4 SD12.9; χ^2 p trend < 0.001). Current smokers had poorer 1-year survival than ex-smokers (Figure 24) but this was not significant. Only BMI classification (OR 0.562, 95% CI 0.407 to 0.775; p < 0.001) and age (OR 1.043, 95% CI 1.009 to 1.078; p = 0.012) remained significant predictors of 1-year mortality with cox-regression analysis. However, when using binary logistic regression, malnutrition risk, deprivation, age and disease-severity were all significantly associated with 1-year mortality but smoking status was not.

At 2 years, four of the cohort was lost to follow-up but smoking status at the time of screening remained a poor predictor of long-term survival (p = 0.489) (Figure 25). There were significant differences in age between the groups (ex-smokers 74 SD 10 years, smokers 67 SD 10 years; non-smokers 73 SD 8 years; p < 0.001 one-way ANOVA). After a 2-year follow-up period, BMI (OR 0.638, 95% CI 0.524 to 0.777; p < 0.001), age (OR 1.040, 95% CI 1.019 to 1.062; p < 0.001) and deprivation (IMD score OR 1.018, 95% CI 1.001 to 1.035; p = 0.038) all remained significant independent predictors of mortality.

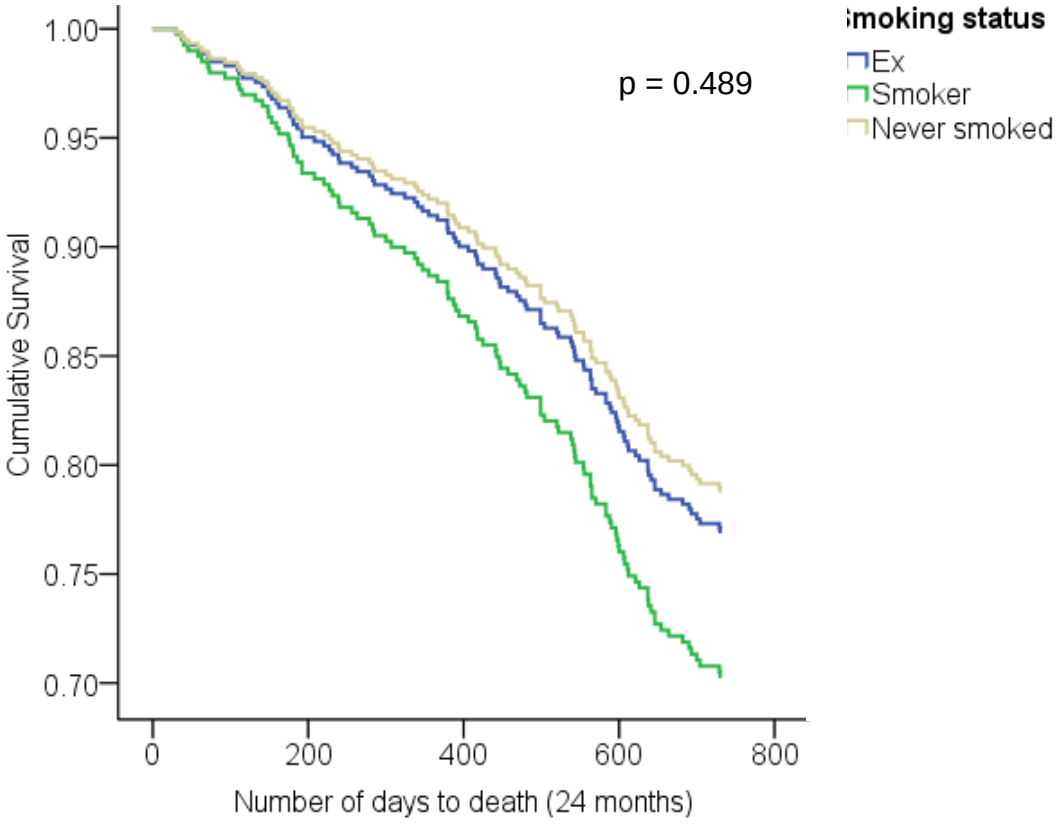


Figure 25 Smoking status and 2-year survival adjusted for BMI, deprivation, age, gender and COPD disease-severity using cox-regression (n = 415)

4.4.5 Sub-group analysis

The screening study identified 93 of 424 outpatients as at risk of malnutrition, 27 (29%) of the 93 identified as at risk of malnutrition were enrolled into the nutritional intervention trial. The exact reasons for enrolment failure is unclear, some of the 66 patients not enrolled would have already been receiving nutritional support and others may have gone on to receive nutritional support during the period of observation. Others may have declined to participate or were prevented from participating due to meeting the exclusion criteria, this is acknowledged as a limitation in interpreting the findings of the observational study. Despite the limitation of a small sample size of 93 it was felt appropriate to explore whether enrolment into the randomised trial presented later in chapter 5 had any influence on outcomes such as mortality and health care use.

The table below (Table 19) described the differences between the outpatients identified as at risk of malnutrition that were enrolled into the randomised trial compared to those that were unable to be unrolled.

Table 19 Comparison of those outpatients identified as at risk of malnutrition that were enrolled into the randomised trial versus those that were not included.

Enrolled to the randomised trial	**Enrolled (n = 27)**	**Not enrolled (n = 66)**	**P**
Characteristics			
Gender (Female: Male)	14:13	37:29	0.711†
Age (years)	74.5 (9.2)	72.3 (11.7)	0.402
BMI (kg/m^2)	17.9 (1.9)	19.0 (3.2)	0.120
COPD disease-severity			
Moderate (%)	3.7	17.2	
Severe (%)	29.6	32.8	
Very severe (%)	66.7	50.0	0.166†
Mortality			
Mortality at 12 months (%)	29.6	15.2	0.109†
Mortality at 24 months (%)	55.6	36.9	0.100†
Healthcare use			
Total LOS EM + ELEC (d)	11.8 (8.0)	6.5 (13.5)	0.132
Costs			
Total 1-year outpatient appointment costs (£)	491 (498)	398 (439)	0.371
Total 1-year healthcare use costs: EM (£)	1843 (4847)	547 (954)	0.039*
Total 1-year healthcare use costs: EM + ELEC (£)	2652 (3545)	1695 (2444)	0.240

Mean SD; analysis using one-way ANOVA; † = χ^2; * = $p < 0.05$; EM – emergency; ELEC – elective; LOS – length of stay.

4.4.6 Discussion

This study found that deprivation is an independent risk factor for malnutrition in outpatients with COPD. Deprivation was associated with increased 1-year healthcare utilisation and poorer clinical outcome with those outpatients residing in the lowest Rank IMD quartile having significantly higher mortality rates. This was significant even after adjusting for covariates and clear trends were seen when the cohort was split into quartiles according to the location of their residence, with those in the highest quartile (least deprived) having the lowest mortality rate although the overall trend failed to reach significance. Outpatients residing in deprived areas experienced significantly higher rates of emergency hospital admission along with a significantly longer length of emergency hospital stay. Interestingly whilst deprivation was not significantly related to the number of elective admissions, deprivation was associated with a significantly longer length of hospital stay during those admissions. A possible explanation for this is that deprivation has previously been found to be an independent risk factor for malnutrition that has subsequently been shown to be associated with increased length of hospital admission in a number of conditions (10). Malnourished patients with COPD will present to the hospital for their elective admission nutritionally compromised. Depending on the treatment they were to receive they would be at increased risk of post-operative complications and experience delayed time to discharge (10).

The current findings are slightly different to those of Stratton and Elia (207) where deprivation was independently associated with both malnutrition risk and inpatient mortality and malnutrition risk was the significant driving force behind increased length of hospital admission. Smoking status has previously been reported to be associated with a more rapid decline in weight with aging (222) and the current study found that malnutrition risk was significantly related to smoking status. Those outpatients that were documented as being current smokers tended to reside in significantly more deprived areas than those outpatients that had stopped smoking or were classified as having never smoked. Interestingly smoking status was not associated with 1- or 2-year mortality when adjusted for age, disease-severity and malnutrition risk. However, a serious limitation to this analysis is the likely changeable nature of smoking status in this group of patients and the lack of co-morbidity data. Within 2 years ex-smokers may have become smokers again

and smokers may have stopped making interpretation difficult. However, the small number of patients classified as never smokers still went on to have high mortality rates suggesting that is it unlikely smokers who stopped would have survival above this level. Survival in this cohort of patients appears to be influenced prominently by age, disease-severity, malnutrition risk and social deprivation. When the interaction between malnutrition risk, deprivation according to Rank IMD and disease-severity were modelled, there were significant relationships between malnutrition prevalence, disease-severity and deprivation. Although no relationship between deprivation and COPD disease-severity was found.

IMD is multi-faceted and includes several domains that contribute to the overall deprivation score. IMD was chosen as it is widely used and has been shown to have good agreement with other commonly used deprivation tools. In the current study malnutrition risk was significantly and independently associated with increased overall deprivation scores, indicating high deprivation. Several domains of IMD were found to be significantly associated with malnutrition risk including, health and disability, education skills and training, crime and living environment. Many of these components can directly impact on an individual's nutritional status. Both the health and disability and disability and psychological issues domains are likely to negatively impact on a person's nutritional intake if high. Poor health and disability is likely to impair a person's ability to acquire, prepare and consume a nutritionally balanced diet predisposing to increased risk of malnutrition. Deprivation in education may limit compliance to medication therapy and possibly their ability to identify a declining clinical condition and seeking healthcare advice, which may partly explain the finding of reduced secondary care outpatient attendance. Additionally, individuals from deprived backgrounds may be less demanding of healthcare professionals resulting in different treatment pathways.

The indices of deprivation are a useful tool for identifying those patients at risk of deprivation. Although deprivation is difficult to assess the IMD goes some way to measure deprivation across England but nation specific IMD data is also available for Scotland and Wales. This data can be used to target high-risk patient groups, especially those likely to require additional support and avoid admission to hospital as a result of the intervention. Whilst targeted interventions may save considerable amounts of money, it would be logistically challenging as pockets of deprivation are likely to exist all over a region and would required varying investment across

England. Several cities in the U.K. experience extremes of high and low levels of deprivation for example, Solihull contains 133 lower super output areas (LSOAs) of which 7% of the LSOAs are in the most deprived 10% in England but 27% are in the least deprived 10% of LSOAs. Conversely, in Bradford almost 30% of the LSOAs are in the most deprived 10% whilst over 6% are in the least deprived (217). The authors of the indices of multiple deprivation highlight that caution is needed when interpreting IMD data as it does not measure an individual's deprivation *per se* but the deprivation an individual is likely to encounter while residing in a specific geographical location (postcode). Not every individual residing within a LSOA can be said to be deprived, for example, within the 6496 LSOAs that are amongst the 20% most deprived in England, approximately 37% of older people residing within these postcodes are likely to be income deprived. The 2009 IMD scores are however more sensitive at a local level than previous IMD measures where larger geographical regions were used.

In the current study the mean number of emergency admissions was 0.62 (SD 1.5) per patient with a mean length of stay of 4.9 (SD 13.3) days. Deprivation was a significant independent predictor for 1-year healthcare utilisation even when adjusted for using multivariate analysis. Conversely, deprivation was linked to reduced secondary care outpatient appointment attendance, and whilst deprivation had no effect on the rate of elective hospital admissions it was associated with increased length of elective hospital stay. Deprivation was not associated with increased disease severity, as classified by the GOLD criteria ($p = 0.580$).

Whilst these local results are the first to highlight the negative implications of deprivation in COPD patients, and the fact IMD may be a useful tool in highlighting high-risk patient groups, care should be taken in extrapolating them into other areas with widely different patterns of deprivation. In 2007 the British Lung Foundation produced the document 'Invisible lives' documenting areas of the UK where COPD was most prevalent (185). It is striking that those regions with the highest number of individuals of COPD and the regions with the highest proportion of COPD patients at risk of admission tend to be in the more deprived northern and central regions. Interestingly the report lists the primary care trusts (PCTs) in the UK that face the lowest challenge from COPD in terms of numbers and admission rates. Hampshire and Dorset are reported to be the PCTs facing the

least challenge from COPD, ranked third and fourth from the bottom with only Devon and Surrey below them.

Further investigation is warranted around pulmonary rehabilitation (PR) and deprivation as this study found that those patients that attended PR were significantly more likely to reside in less deprived areas. This is due to a higher percentage of outpatients attending the community hospital, which served a more affluent population, participating in PR. These reasons for this disparity is most likely due to local funding restrictions but needs further investigation when taken with the findings from the previous study that PR was associated with increased healthcare use.

Deprivation is a complicated and multifaceted health issue and there are wider implications not only in terms of presentation to healthcare professionals, but also in terms of smoking cessation, compliance to medications and compliance nutritional interventions. Deprivation can limit access to healthcare and nutrition as an individual may have reduced ability to acquire foods, access to transport to the shops and ability to purchase certain foods. Several of the IMD domains are likely to have influence on forming an individual's health beliefs and perceptions of benefit. Deprivation is an extremely complex area but one which clearly has significant negative effects on clinical outcome. The relationship between deprivation, poor nutritional status and ill health is extremely complex as demonstrated by the secondary analysis of the English NDNS data carried on by Elia and Stratton (54), which showed that the geographical differences in prevalence of malnutrition risk remained significant even when after controlling for socio-economic factors.

The nutritional screening cohort was initiated to assist with the recruitment to the randomised intervention trial (chapter 5), as such 27 (29%) of the 424 outpatients went on to enrol. To remove 27 of the 93 outpatients at risk of malnutrition from analyses would have significantly reduced the power of the results preventing any meaningful analysis being performed. Therefore, in order to establish whether participating in the intervention trial altered the clinical course of those patients a sub-group analysis was carried out. With the exception of emergency healthcare use costs being higher in the enrolled patients, no additional significant differences were observed between those malnourished patients that entered the trial and

those malnourished patients that did not. In fact the patients that enrolled onto the trial tended to experience poor clinical outcomes.

The findings of the current study and those of study 3 highlight the complex relationship between malnutrition risk, deprivation and healthcare use and mortality. COPD patients represent a group that experience high levels of both malnutrition risk and deprivation, both are likely to drive one another and results in COPD patients experiencing increased mortality and presenting a significant economic burden to the NHS. Strategies are needed to tackle the disease-related malnutrition common in COPD but assessment of deprivation may allow for more targeted interventions in those high risk patients likely to lose further weight and use high levels of healthcare.

4.4.7 Conclusion

This is the first study using IMD to show that deprivation is independently associated with an increased prevalence of malnutrition risk as well as increased 1-year mortality in outpatients with COPD. Deprivation is associated with increased economic costs driven by increased emergency hospitalisation rates and increased length of both emergency and elective hospital stay. The reasons why those outpatients from deprived areas attended significantly fewer secondary care outpatient appointments warrant further investigation. Deprivation should be a consideration in the targeted medical management of COPD patients, taking into account the social variations seen and what components of deprivation may effect successful management.

4.5 Summary of chapter

To summarise thus far, study 1 demonstrated that the prevalence of malnutrition risk is high in COPD outpatients but is variable across respiratory centres highlighting the need for routine nutritional screening in order to ensure the prompt identification of those at nutritional risk. Study 2 highlighted the negative clinical sequelae associated with disease-related malnutrition whilst alluding to the large body of observational evidence suggesting that a higher body mass in COPD is associated with better clinical outcomes. This observation has been referred to as the 'obesity paradox' and was again observed in the current cohort. Currently, no nutritional screening tool is recommended in COPD and whilst the evidence from the current has demonstrated that 'MUST' is a valid tool in this patient group; identifying those at risk of malnutrition and predicting mortality, it is less sensitive than BMI alone. Further work is needed in order to establish whether increasing the BMI threshold (e.g. from < 18.5 kg/m^2 and < 20 kg/m^2 to < 21 kg/m^2 and < 23 kg/m^2) used to identify those at risk is able to improve the identification of those COPD patients likely to do poorly as well as those likely to respond to nutritional support.

Both study 3 and 4 highlight the complex relationship between deprivation, smoking status and malnutrition. Malnutrition has significant associations with both deprivation and smoking status. Consideration of these risk factors could allow for the identification of high-risk groups and more effective allocation of resources and targeted interventions.

Despite malnutrition being a common problem in COPD and associated with a number of negative outcomes, there remains confusion around the need to formally identify those at nutritional risk and in the value of nutritional support in COPD. The following chapter aims to compare two of the most common first line interventions for the nutritional management of COPD in order to establish if one, both or neither are effective at treating malnutrition.

5.0 Nutritional support in COPD: a randomised trial

5.1.0 Introduction

Malnutrition is a considerable problem not only to acutely unwell patients with COPD but also to a substantial proportion of outpatients with the disease (**Chapter 4, Study 1**). This highlights the need for routine nutritional screening to be performed across all healthcare settings. **Chapter 4** (**Study 4 and 3**) illustrated that screening performed using a validated tool is effective at identifying those patients at risk and likely to go on and have a poorer prognosis. Despite the prevalence of malnutrition in COPD often being higher in hospitalised patients with the disease (10), the majority of malnutrition in this patient group is found in the community. The systematic review and meta-analysis in **chapter 3** illustrated that in stable COPD if malnutrition is detected it is treatable resulting in a number of clinical and function improvements. However, the overall evidence base for nutritional strategies in COPD is lacking as it is almost entirely based on ONS with only one trial including dietary advice and food fortification in outpatients (74) and one using nocturnal enteral tube feeding in inpatients (82). Despite this all three methods of nutritional support are frequently used as part of routine clinical care to provide nutrition to this group of patients. Probably the most important gap in the current evidence base is the complete lack of comparative studies. Despite ONS and DA being the most commonly used first line treatments for malnutrition to date there have been no direct comparison trials.

The latest review undertaken as part of this thesis investigating the effectiveness of nutritional support in COPD included 13 studies, only eight of which were carried out in entirely in the community setting (150). If the outpatient setting is where the majority of malnutrition lies there is a clear need for more trials investigating the effectiveness of nutritional strategies in improving outcomes in this care environment. Previous reviews have highlighted that patient specific outcomes, such as quality of life, are lacking in previous nutritional intervention trials (73). The trial by Weekes et al., (74) found that dietary advice and the provision of whole milk powder did lead to significant improvements in nutritional intake, body weight as well as quality of life. However, this was only the second trial to specifically look at the influence of nutritional support on quality of life. The

previous trial by Steiner et al., (56) was carried out as part of an exercise rehabilitation programme where significant improvements in quality of life were found in both the intervention and placebo group, suggesting the improvements were driven by the exercise programme rather than the nutritional intervention. Therefore, there is a need for further exploration around whether improved nutritional status in COPD results in improved quality of life for the patient.

Individuals with COPD that are identified as requiring nutritional support are often given ONS and/or DA as a first line treatment for malnutrition. Currently the recommendations made by the National Collaboration Centre for Acute Care for nutritional support in adults and COPD state that individuals with a BMI < 20 kg/m^2 should be given ONS (66, 223) and this is supported by nutritional organisations such as the European Society for Clinical Nutrition and Metabolism, ESPEN (172). Despite this, current nutritional management strategies for patients with COPD at risk of malnutrition are extremely variable and in some instances non-existent. This is likely to be partly driven by the current controversies surrounding the efficacy of nutritional support in COPD, which were described in **chapter 3**. Nutritional practice is also likely to vary due to there being no recommendation for routine nutritional screening within the latest NICE guideline for the management of COPD in primary and secondary care (6). The guideline also states ONS be prescribed to those patients with a BMI < 20 kg/m^2 but go on to state this is based on a lower grade of evidence. Further research is required not only demonstrating the effectiveness of nutritional support in COPD but the magnitude of the effects, whether they are of a magnitude to be of clinical relevance and if any improvements persist beyond the period of intervention.

In order for malnourished patients to receive prompt nutritional support formal screening has to occur. **Chapter 4** illustrated that nutritional screening highlights a high number of patients that require nutritional support (two thirds of those identified as at risk requiring some form of nutritional treatment). In addition, nutritional screening tools such as ‘MUST’ are valid in this patient group and are able to predict poor outcomes (**Chapter 4, Study 2 and 3**). These findings have been reproduced in a larger cohort of COPD inpatients hospitalised for an infective exacerbation of COPD (208), highlighting that nutritional screening is important across all health care settings. Guidelines for the clinical management of COPD

patients should include a recommendation for nutritional screening as part of routine care and follow-up.

Whilst there is a need for clearer recommendations for the identification of malnutrition in COPD, the next step is clearer guidance around initiating nutritional support and by what method. The evidence base for the effectiveness of ONS in COPD is robust but for other nutritional strategies is lacking. Dietary advice and food fortification is often used as the first line treatment for malnutrition across a number of conditions (89), this includes COPD despite no evidence supporting the practice beyond intuition. The trial by Weekes et al., (74) did intervene with tailored advice from a dietitian but also provided milk powder to the outpatients for 6 months. This intervention resulted in a number of significant improvements previously mentioned, most notably significant and prolonged improvements in quality of life, an outcome highlighted to be lacking from previous review. However, the provision of milk powder to patients without charge as part of the trial is currently not routine clinical practice in the NHS, which does impact on the applicability of the findings. In addition, there were also supply issues so without established supply and delivery systems to the NHS and then onto the patient this form of intervention is not routinely available. The setting up and management of such systems would also have an inherent cost to them that would have to be accounted for. The trial did illustrate that simply providing patients with literature encouraging food fortification and the consumption of energy dense foods had no effect and patients went on to lose substantial amounts of weight throughout the trial. This, despite the patients knowing they were taking part in a research trial investigating malnutrition and that they would be monitored throughout. A number of issues are raised from the findings of the study by Weekes et al, (74) firstly, simply handing out diet sheets without tailoring the advice to the individual and communicating with their immediate support network appears futile. Secondly, if patients at risk of malnutrition do not have prompt access to a dietitian or an individual trained in nutritional counselling, who can tailor advice either with or without the provision of milk powder, seemingly the only option remaining would be the prescription of ONS.

There is a need for more trials across the outpatient setting that are reflective of current clinical practice. No trial has sought to directly compare the two most common first line nutritional interventions used in COPD, ONS and DA. It is

intuitive that in individuals with a chronic wasting disease at risk of malnutrition such as COPD, the provision of DA from a dietitian will assist in attenuating further nutritional deterioration and eventually encourage repletion. However, very few trials have sought to demonstrate this. Such a lack of evidence supporting DA is surprising since the importance of good nutrition during times of illness and disease have long been known. Hippocrates (5th Century BC) wrote 'Let thy food be thy medicine, thy medicine be thy food' and 'a slender diet is always dangerous in chronic diseases, and also in acute diseases, where it is not requisite'. Despite the lack of evidence for DA, it is a core skill that dietitians are trained in. With the current economic climate and the fact that the NHS has a finite amount of resources to manage a population that are living longer in the presence of disease, it is more important than ever that medical interventions are underpinned by quality research. Healthcare commissioners will require a high-grade of evidence of effect before they are willing to finance new services whether that is a formal nutritional screening and ONS prescribing pathway or a community dietetic service. In an increasingly competitive environment, there is an urgent need for dietitians to demonstrate clinical and cost effectiveness through randomised controlled trials (RCTs).

5.1.1 Aims

Therefore the aim of this randomised, prospective, parallel, open-labelled trial was to investigate whether tailored dietary advice (DA) delivered by a dietitian would result in improvements in quality of life and a number of secondary outcomes, above that of ready-made multi-nutrient oral nutritional supplements (ONS) as a first line treatment for malnutrition in outpatients with COPD. In addition to investigating the effectiveness of the nutritional treatments, the trial also aimed to explore the effect of treatment cessation and whether any improvements persisted beyond the period of intervention.

5.1.2 Protocol

This randomised trial involved randomly allocating outpatients with a diagnosis of COPD to receive a 12-week intervention of either ONS or DA. Measurements were taken at baseline and during the intervention phase (weeks 6 and 12) to

explore the effect of the intervention. In addition, to investigate the effect of treatment cessation and whether any improvements were lost on stopping the intervention patients were assessed at weeks 26 and 52. The primary outcome measure of the trial was health-related quality of life (QoL). Increasing importance is being placed on intervention trials being for patient benefit and previous reviews have recommended that QoL be a primary outcome in future intervention trials. Patients QoL, or perceived QoL, may change even in the absence of any substantial changes in weight. The review in chapter 3 illustrated that QoL does appear to be susceptible to change following nutritional support therefore this outcome was selected.

5.1.3 Methods

1. Using the 'Malnutrition Universal Screening Tool', 'MUST' (180), recruit 200 outpatients with a diagnosis of COPD at risk of malnutrition and randomly assign them to receive either intervention A (ONS) or intervention B (DA).

2. To provide the two groups with their designated intervention for three months. For group A this involved the provision of multi-nutrient ONS tailored to the patients preferences but with no additional dietary or dietetic intervention. Group B received DA on two occasions and supportive literature for 12 weeks, in the form of a diet booklet encouraging food fortification and relevant dietary modifications.

3. To compare outcomes between and within groups from baseline through to week 12 (end of intervention), week 26 and week 52 (follow-up).

5.1.4 Outcome measures

The primary clinical outcome measure was health-related quality of life with a range of secondary outcome measures included to detect any clinical and/or functional changes.

1. Health-related quality of life was assessed using both disease specific (St George's Respiratory Questionnaire; SGRQ) and general quality of life assessment tools (Euroqol; EQ-5D) (Appendices 6 and 7).

2. Nutritional intake (24-hour dietary recall).
3. Body weight and body composition (body mass index, skin fold thickness)
4. Objective measures of functional capacity (skeletal and respiratory muscle strength using a portable handgrip dynamometer and a micro-spirometer).
5. Subjective measurements of functional capacity (MRC dyspnoea score and activities of daily living; ADL).

5.1.5 Recruitment

Outpatients were recruited between November 2007 and May 2010 from five respiratory centres across Hampshire and Dorset; Southampton General Hospital (SGH), Lymington New Forest Hospital (LYM), Royal County Hospital Winchester (WINCH), Royal Bournemouth and Christchurch Hospital (RBH) and Queen Alexandra Hospital, Portsmouth (QAH). Patients were recruited mainly through routine nutritional screening performed by trained respiratory nurses or specialist respiratory healthcare assistants performed at SGH and LYM. Patients attending respiratory outpatient appointments were weighed using electronic clinical weighing scales (Seca or Hanson HCL700) and height was measured using a freestanding Leicester stadiometer in accordance with the 'MUST' explanatory guidelines (192). Investigation into whether the patient had experienced any recent unintentional weight loss was done though patient recall, accessing the medical notes or reviewing previously completed 'MUST' assessment forms. Any patient assessed in clinic to have a 'MUST' score of greater than or equal to 1 was referred to the trial.

In addition to the routine nutritional screening implemented across all respiratory outpatient clinics at SGH and LYM, ad hoc screening and informal referral of those patients that reported recent weight loss or appeared thin occurred from RBH, WINCH and QAH. Any patients that were referred to the trial were interviewed and screened by the research dietitian in order to establish eligibility according to the inclusion and exclusion criteria and obtain written informed consent.

5.1.6 Inclusion criteria

1. Male or female
2. Age > 18 years
3. At risk of malnutrition (Medium or high risk of malnutrition using ‘Malnutrition Universal Screening Tool’, ‘MUST’ score ≥ 1 (Appendix 4)
4. Competent to provide written informed consent and able to answer questions
5. Able to achieve nutrition requirements orally
6. Willingness to participate in the trial and to follow trial protocol
7. Forced expiratory volume in 1 second < 80% predicted and forced expiratory volume in 1 second divided by forced vital capacity < 0.7 (FEV_1/FVC)

5.1.7 Exclusion criteria

1. Requirement for tube or parenteral nutrition
2. Receiving current, or within the last 4 weeks, oral nutritional supplementation
3. Palliative care
4. Chronic renal disease requiring dialysis
5. Liver failure
6. Participation in other research trials
7. Bronchiectasis
8. Already under the care of a dietitian

Patients that achieved the inclusion criteria were provided with a participant information sheet (PIS) outlining the aims and objectives of the study and the requirements for participation. Outpatients discussed the PIS with the research dietitian to ensure informed consent was obtained prior to randomisation to either treatment group.

5.2.0 Randomisation

Patients were randomised to either treatment group A (ONS) or treatment group B (DA) at the start of the baseline assessment visit. Randomisation was completed through the generation of random number tables using Microsoft Office Excel. Randomisation was stratified according to malnutrition risk in accordance with 'MUST' (medium risk versus high risk). 200 opaque envelopes, 100 for medium risk and 100 high risk, were then filled with stickers stating to which group the individual should be randomly assigned. Randomisation took place at the start of every baseline assessment visit after nutritional assessment of the individual. It was documented if the individual withdrew consent due to the treatment arm they were randomised to.
Due to the structure of the trial and the nature of the intervention it was not possible to perform a blinded trial.

5.2.1 Group A – Oral nutritional supplements (ONS)

For those patients that were assigned to receive ONS for the 12-week period, the rationale and the potential benefits of the ONS were explained at the end of the first assessment visit. It was explained to the subject that ONS would be provided for *ad libitum* consumption with the target being to achieve an additional nutritional intake of 600 kcal above that of their habitual daily intake (usually two ONS, 2 x 200ml). Initially a starter pack was left with the patient containing a variety of types and flavours of ONS (Appendix 3). The pack also contained a menu card allowing the subject to indicate their preferences. Subjects were advised to initially commence taking the ONS one per day for the first week, thus allowing the ONS to be easily incorporated into their habitual diet with minimal affect on their dietary food intake. Subjects were only supplied with ONS and received no additional dietary advice or supportive literature. Contact was made with the subject after a week in order to establish ONS preferences and whether the subject would be happy to gradually increase their intake to twice daily. Initially ONS were delivered to subjects weekly however, after 6 weeks deliveries were performed every fortnight. Fortnightly deliveries were sometimes initiated earlier if the subject remained on the same ONS and had a routine where they consumed the same number each day. ONS delivery visits lasted approximately 10 minutes during

which time the number of ONS the subject reported to have consumed was recorded and any unwanted ONS removed in order to prevent them being discarded and going unaccounted. Whilst subjects were encouraged to consume the ONS as they were able, up to two supplements per day, any further increases were done under the agreement of the research dietitian and this was closely monitored.

5.2.2 Group B – Dietary advice (DA)

Patients randomised to DA were given nutritional counselling by the research dietitian (Peter Collins) at the end of the baseline assessment visit. This enabled the dietitian to informally assess the subject's 24-hour dietary recall and to tailor the dietary advice around the individuals preferred foods. Dietary advice was tailored around the individual's social and economic situation. Similar to the ONS group, the rationale for the intervention was explained to the subject and the potential benefits of compliance highlighted. As well as dietary counselling, literature designed with the help of the department of Nutrition and Dietetics at Southampton General hospital, was provided in the form of an A5 colour leaflet entitled 'Build yourself up' (Appendix 2).
Where possible DA involved the subjects' family and/or carers and if this was not possible during the visit the subject was recommended to show the leaflet to members of their support network in the hope that it would aid compliance to dietary change and assistance with acquiring and preparing food. Subjects and family were advised to contact the research dietitian if they had any questions or difficulties in implementing any dietary changes at any point during the 12-week intervention period. Any additional contact made by subjects or family members was documented.

After discussion around the dietary leaflet, the research dietitian agreed with the subject what two or three achievable dietary changes they felt they could implement and maintain over the 6 weeks between assessment visits. This could include switching from semi-skimmed milk to whole milk, purchasing skimmed milk powder and fortifying their food, or additional fortification using increased amounts of sugar, butter and sauces in and on their food. Whilst subjects were encouraged to increase the frequency with which they ate throughout the day it was highlighted

that the aim was to also snack between meals and not to simply increase portion sizes as this would likely to lead to meal-induced dyspnoea and discomfort due to abdominal distension. Instead, subjects were advised to have regular small portion sizes with the emphasis on the energy density of the food aided by food fortification rather than the quantity of food they ate at each meal.

A common discussion with subjects and their family members was the impact of what appeared to be a seemingly unhealthy diet on their co-morbidities. Some patients were receiving lipid-lowering medication and had previously been advised to reduce their intake of many of the foods now being recommended. These issues were discussed with the research dietitian and any concerns taken into account.
During the week 6 assessment the 24-hour dietary recall was discussed to establish whether any changes had been made. Any difficulties in making changes were discussed with alternatives being given and successful dietary modifications praised and reinforced. If a subject had successfully implemented changes it was discussed whether they felt able to make one or two additional changes using the dietary leaflet.

5.2.3 Intervention phase

Both interventions lasted for a period of twelve weeks, with a follow-up period of three to nine months in order to examine the effects of cessation. Interventions were reinforced during the 6-week assessment where the rationale for the study was again explained and any questions or difficulties discussed. DA was reinforced and additional dietary modifications discussed after informal assessment of the 24-hour dietary recall. If the DA leaflet had been lost a replacement was provided, all supportive literature was collected at the end of the week-12 assessment.

5.2.4 Compliance

It was explained to patients that there was no pressure on them to take the ONS and any unwanted ONS would be collected by the research dietitian. The importance of establishing the amount of ONS consumed was highlighted and

stock checks were completed at each delivery. Compliance to treatment was also assessed through 24-hour dietary recalls that were analysed using the nutritional analysis software WISP (Tinuviel, Anglesey, UK). All dietary intake data was analysed by a research assistant not directly involved with the trial. Any ONS consumed were documented as part of the dietary recall taken by the research dietitian. Visual analogue scales (VAS) were used in both treatment arms to assess the patient's appetite, fullness and desire to eat over the previous 24-hour period.

5.3.0 Assessment visits

Assessment involved three home visits over a period of twelve weeks. In order to minimise inter-researcher error, all assessment visits were performed by the same research dietitian (Table 20). Assessment visits lasted between 45 minutes and 90 minutes depending on the condition of the patient and levels of breathless. Patients with severe COPD requiring long term oxygen therapy (LTOT) sometimes required breaks during the assessment in order to continue to verbally answer the questions.

Table 20 Clinical, functional and health-related quality of life measurements taken at each visit

Assessment	Baseline	Week 6	Week 12	Week 26	Week 52
Clinical / Functional					
Quality of life	X	X	X	X	X
MRC dyspnoea score	X	X	X	X	X
Micro spirometry	X	X	X	X	X
Handgrip strength	X	X	X	X	X
Activities of daily living	X	X	X	X	X
Nutritional status					
Weight	X	X	X	X	X
Body mass index	X	X	X	X	X
'MUST'	X		X	X	X
MUAC	X	X	X	X	X
Skinfold thickness	X	X	X	X	X
Nutritional intake					
Food and total intake	X	X	X	X	X
Appetite	X	X	X	X	X
ONS intake*		X	X	X*	X*

*HCP = healthcare professional; 'MUST' = completion of the 'Malnutrition Universal Screening Tool'; MUAC = Mid-arm muscle circumference; * = if randomised to ONS group or subsequently prescribed them as part of routine care during the trial period.*

5.3.1 Health-related quality of life

Health-related quality of life was assessed using the self-administered EQ-5D tool produced by the Euroqol group (224) (Appendix 7). Patients answered five questions relating to their health and completed the assessment tool by rating their current health on a vertical 20 cm visual analogue scale from 0 to 100 (EQ VAS). Patients marked on the scale where they rated their health between 0 ('worst imaginable health state' representing death) and 100 ('best imaginable health state' representing perfect health). Initially EQ-5D was designed to complement other health outcome measures but it can be used as a stand-alone measure. The EQ-5D was chosen as it is cognitively simple, quick to complete and has been validated across a number of long term health conditions including COPD where it has been found to be both valid and reliable (225). In addition to the VAS scores, a TTO score (time trade-off) was calculated using the EQ-5D value sets and UK specific equations (224).

Health-related quality of life (QoL) was also assessed using the disease specific questionnaire; St George's Respiratory Questionnaire; SGRQ (226). SGRQ (Appendix 6) has been previously been used to measure the functional consequences of being underweight as well as the depletion of FFM seen in COPD (74, 190). The weighted component of the tool consists of scores divided into four sections, activity, impacts, symptoms and a total score. Scores for the SGRQ range from 0 (perfect health) to 100 (worst possible health), an increase in score indicates a deterioration in perceived health status whilst a decrease represents an improvement. A change in score of 4 points is considered the minimally importance difference (MID), demonstrating a meaningful treatment effect and of relevance to the patient themselves.

5.3.2 Nutritional status, body composition and malnutrition risk

Nutritional status and body composition was assessed at each of the five assessment visits (Table 15). Weight was measured without shoes, in light clothing, using portable, clinical battery powered scales (Hanson) to the nearest 0.1 kg. All anthropometric measurements were carried out by the same research dietitian in accordance with the nutritional screening guidelines outlined within the

'MUST' explanatory booklet produced by the British Association of Parenteral and Enteral Nutrition; BAPEN (192). Please refer to chapter 4, study 1 and appendix 4 for detailed methods.

If oedema was present this was corrected for in accordance to 'MUST' prior to randomisation to treatment. A subject's dry weight was estimated in the presence of detectable oedema using the standard corrections of a 3 kg reduction of weight in the presence of mild pedal oedema, 6 kg reduction in moderate oedema and 10 kg in severe oedema when detected in both feet and in the lower legs. These corrections suggested by BAPEN are estimates and the research dietitian did employ clinical judgement before establishing a final weight and subsequent 'MUST' score. Where oedema was present and corrections had been used to calculate estimated dry weight and it remained unclear whether a patient was eligible on BMI, mid upper arm circumference (MUAC) was used as secondary method. If BMI was normal, in the presence of oedema, but MUAC was less than < 23.5 cm the subject was deemed likely to have a BMI of < 20 kg/m^2 and was considered eligible to participate in the trial.

Height was measured on one occasion during the baseline assessment without shoes, using a freestanding portable Leicester stadiometer to the nearest 0.1 cm (Invicta Plastics Ltd, Leicester, United Kingdom).

Body mass index (BMI) was calculated using the following equation: subjects weight (kg) divided by the subject's height in meters (m) squared.

$$BMI = \text{weight (kg)} \div \text{height } (m^2)$$

Weight, height and BMI were components used to complete the nutritional screening tool. Malnutrition risk was established using 'MUST' (Appendix 3) at baseline for the purpose of randomisation to treatment group and then again at the week 12 assessment. The aim was to reproduce assessment time points similar to those that occur clinically. MUAC was also measured at each assessment visit with all upper arm anthropometry performed on the subjects left side in accordance to 'MUST' guidelines (192). Bicep and triceps skinfold thickness was measured using skinfold calipers (Harpenden skinfold callipers, Baty International,

United Kingdom). All measures were repeated three times with an average value calculated. Mid upper arm circumference (MUAC), bicep and triceps skinfold thicknesses (TSF) were measured on the non-dominant side of the body. The following equation was used to calculate mid-arm muscle circumference (MAMC) (227):

$$MAMC\ (cm) = MAC\ (cm) – (0.314 \times TSF\ (cm))$$

5.3.3 Calibration of assessment equipment

Due to the trial being community based all equipment was transported to patient's homes. Monitoring of trial equipment was performed at least every 4 months to ensure continued precision and accuracy. Calibration was carried out across three similar sets of scales and handgrip dynamometers of the same manufacturer. If any large discrepancies were detected the equipment was sent back to the manufacturer for recalibration. Calibration of the portable micro-spirometer was also performed every 6 months using a 3-litre Micro Medical syringe.

5.3.4 Functional assessment

1. **Medical research council (MRC) dyspnoea scale**

The MRC dyspnoea scale (Appendix 5) was used as a subjective measurement of functional status. Scoring ranges from 0 to 5, with 0 representing the statement 'breathlessness does not limit physical activity in any way' up to 5, which is 'I am too breathless to leave the house'. Therefore, an increase in score represents deterioration in a patient's perceived breathlessness.

2. Activities of daily living (ADL) questionnaire (Barthel's Index)

The Bartels index is an instrument widely used to measure the functional capacity of an individual in performing ten basic activities in daily life. The tool consists of 10 questions establishing how easy the patient finds performing a variety of activities individuals would encounter on a daily basis, such as walking up stairs, bathing and toilet use and results in an overall score ranging from 0 to 20. The lower the total score the more incapacitated the individual is in terms of daily activities.

3. Handgrip dynamometry

Handgrip strength was measured on a portable electronic hand-held dynamometer (Department of Medical Physics, Queens Medical Centre, Nottingham, U.K) with measurements taken at each of the assessment visits. 3 measurements were taken in each hand with the subject in a seated position and an average reading taken.

4. Microspirometry

Spirometry was measured using a handheld microspirometer (Micro Medical Ltd, U.K) that was regularly calibrated using a 3-litre syringe in the pulmonary function laboratory at Southampton General Hospital. Spirometry was performed at the end of each assessment visit, where possible individuals performed three maximal exhalations with an average reading taken. The pulmonary function test was the last assessment measure performed as it often left the patient breathless making any further data collection difficult.

The test was performed with subjects in a seated position and involved taking a maximal inhalation then a maximal exhalation through the spirometer. This measured the subjects forced expiratory volume in 1 second (FEV_1) as well as their forced expiratory volume (FVC), i.e. the amount of air they can exhale in 1 second and the amount they can exhale in total. FEV_1 is a recommended pulmonary function measure in COPD patients as it is a reproducible and objective measurement with well defined normal ranges that allowing for the effects of age,

race and gender (7). FEV_1 and FVC were then to calculate disease severity according to the GOLD criteria with an FEV_1/FVC ratio of < 70% is indicative of airways obstruction (29). The serial measurements collected on each patient over the course of the trial investigated firstly, whether disease progression from moderate to severe through to very severe could be slowed and secondly, whether any improvements would be seen with nutritional support.

5.4.0 Ethical approval

Ethical approval was obtained from Southampton and South West Hampshire Research Ethics Committee A (07/Q1702/70) and Southampton University Hospitals NHS Trust ethics committee (ELIA002) on 31/07/2007. ClinicalTrials.gov identifier: NCT00538200.

5.5.0 Statistical analysis

The target sample size was 100 in each treatment arm in order to achieve the statistical power to detect differences in the primary (e.g. quality of life) and secondary (e.g. handgrip strength, weight) outcomes. Due to recruitment difficulties power calculations were also done for 50 and 40 in each treatment arm in order to establish whether meaningful differences could be obtained adding additional recruitment sites. This was calculated using SamplePower 2 aiming for 80% power determined by SPSS version 20.0 (SPSS Inc, Chicago, Illinois, USA) and statistical significance set at $p < 0.05$. For 40 versus 40, a difference in SGRQ total score of 3.79 SD 6 (4 = minimally important clinical difference) between the two groups was required to achieve 80% power.
A significant number of patients had withdrawn from the trial at the end of the intervention and considerably more by the end of the 1-year study period. Excluding these patients from statistical analysis may bias results and hamper interpretation it was therefore decide to perform two types of statistical analysis:

Per protocol analysis

All patients that completed the trial until the end of the intervention were included for analysis. Tests included one-way analysis of variance (ANOVA) as well as one-

way analysis of covariance (ANCOVA) adjusting for baseline measurements and age, 'MUST' category and baseline FEV_1 percentage predicted. This method of adjustment was standardised for all ANCOVA analyses. Within-group changes were explored using paired t-test analysis. For all tests, $p < 0.05$ was considered statistically significant and all tests were two tailed. All analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, Illinois, USA).

Intention-to-treat analysis (ITT)

In order to perform intention to treat analysis, imputed values were used for those subjects that had withdrawn before the end of the intervention phase (week 12). The imputation model was designed and calculated in SPSS (version 20, Chicago, IL) using age, 'MUST' category, and baseline percentage predicted FEV_1 as predictors. Imputed variables included the primary outcomes: EQ-5D domains (mobility, self-care, usual activities, pain and discomfort, anxiety and depression), SGRQ domains (symptoms, activity, impact and total) and activities of daily living (total score). Secondary outcomes included nutritional intake (energy and protein), body weight and handgrip strength. Analysis was performed between the two intervention groups using unadjusted (ANOVA) and adjusted (ANCOVA) values.

5.6.0 RESULTS

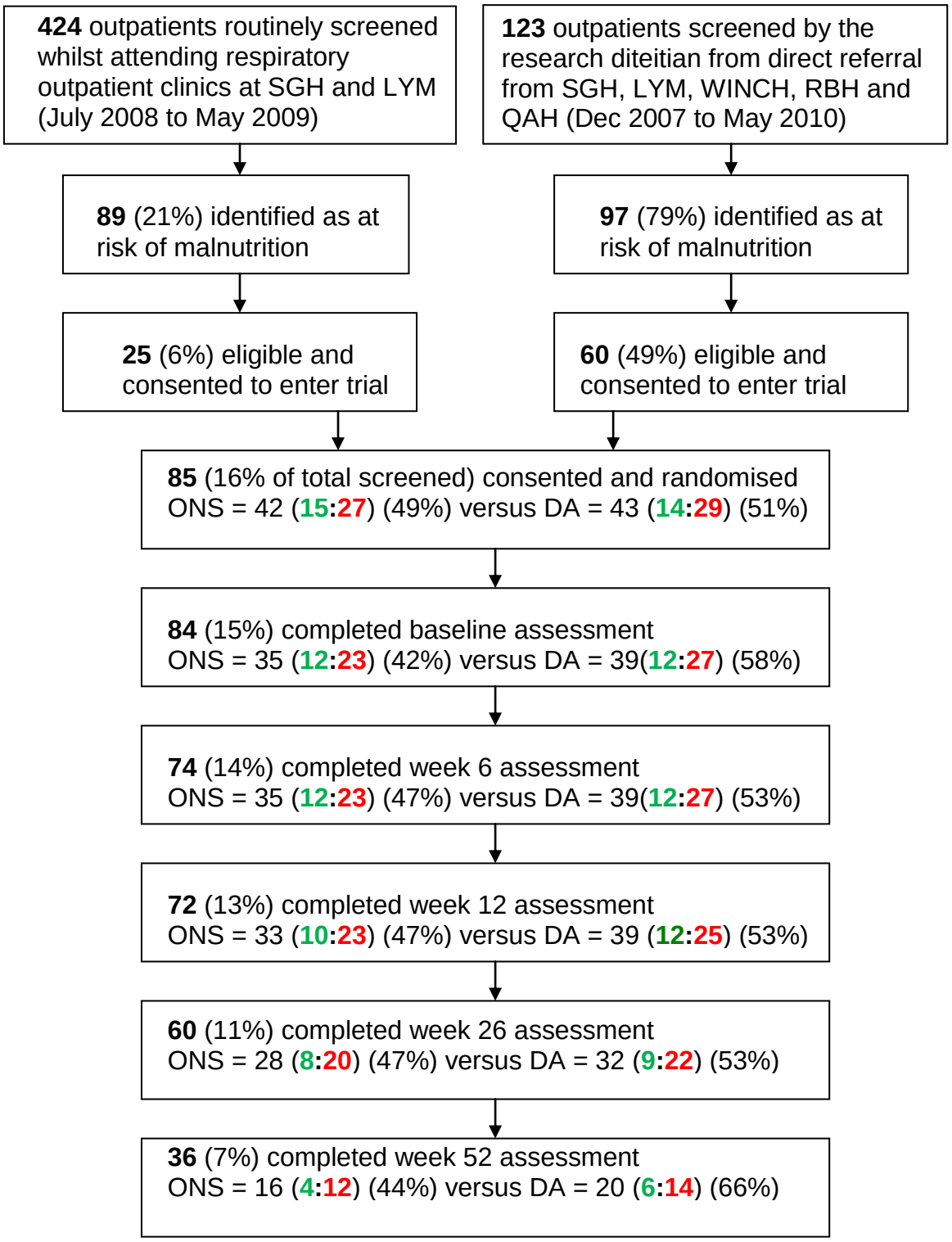


Figure 26 Trial screening, recruitment and completion schematic (End Sept 2009) SGH = Southampton General Hospital; LYM = Lymington New Forest Hospital; WINCH = Royal county hospital Winchester; RBH = Royal Bournemouth Hospital. **X** = Medium 'MUST' risk; **green** = Medium 'MUST' risk; **red** = High 'MUST' risk.

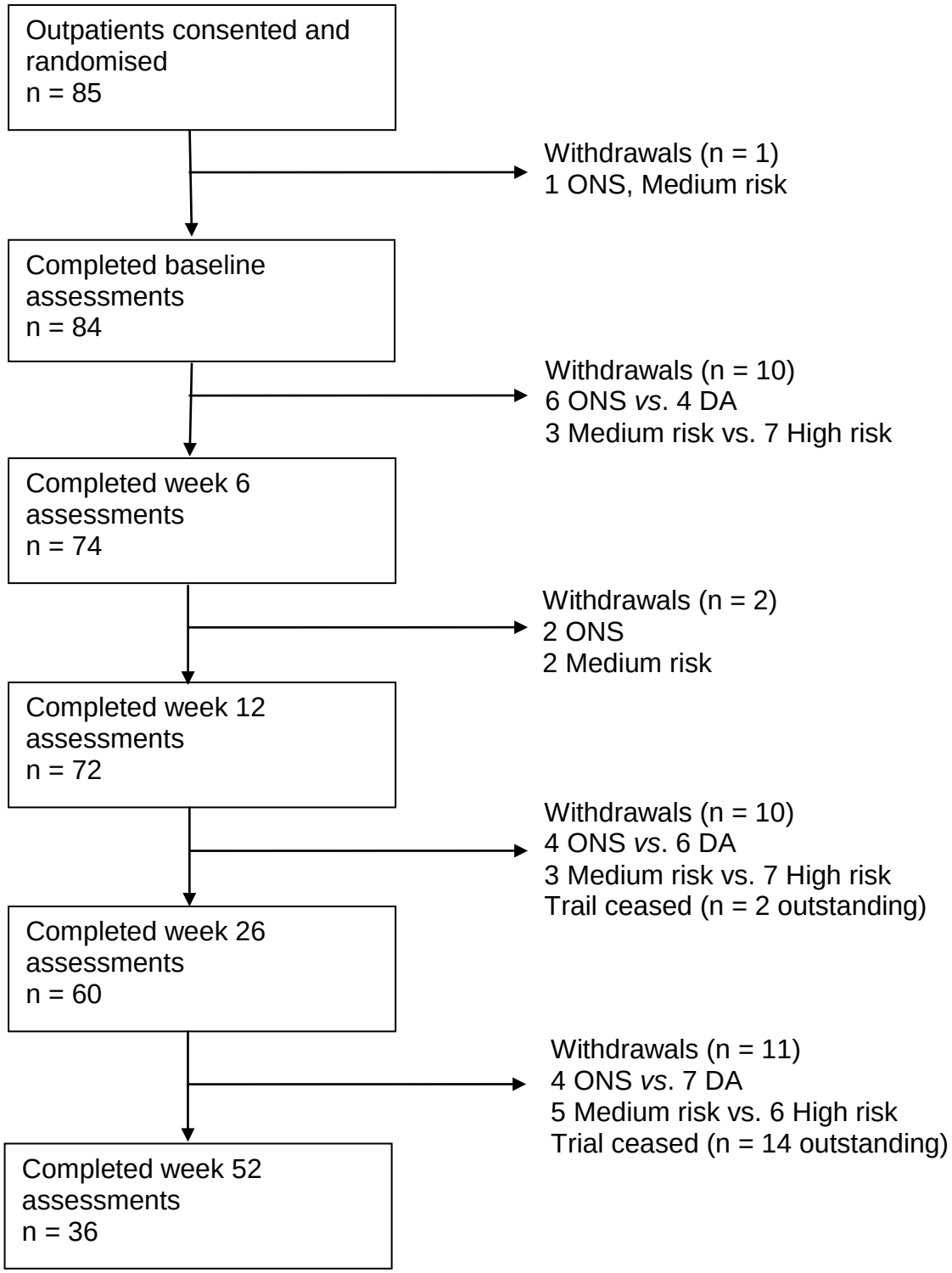


Figure 27 Trial overview illustrating progression up to the end of the trial (August 2010) and subject withdrawal points. Withdrawals are shown as subject's number, treatment arm randomised too and 'MUST' risk on entry to the trial. DA = dietary advice; ONS = oral nutritional supplements; n = 16 patients lost to follow-up due to trial ceasing.

Table 21 Baseline characteristics of the DA and ONS patient groups (n = 84)

Characteristics	ONS (n = 41)	DA (n = 43)	All (n = 84)	p
Gender				
Female	11 (42%)	16 (50%)	27	
Male	15 (58%)	16 (50%)	31	0.56*
Age (years)	73 (47-88)	72 (47-90)	73 (SD 9.8)	0.84†
Smoking status				
Ex-smoker	17 (65%)	24 (75%)	41 (71%)	
Smoker	9 (35%)	8 (25%)	17 (29%)	
Non-smoker	0	0	0	0.36*
Pack years	43.8 (22.3)	43.0 (23.5)	43.4 (22.8)	0.88*
COPD severity	(n 39)	(n 39)	(n 78)	
FEV_1 % predicted	33 (13%)	35 (15%)	36 (14%)	0.72*
Social circumstances	(n 41)	(n 43)	(n 84)	
Lives with partner/family	25 (45%)	30 (55%)	55 (65%)	
Lives alone	16 (55%)	13 (45%)	29 (35%)	0.39*
Carer/support with ADL	8 (31%)	5 (16%)	13 (22%)	0.17*
Employment status				
Retired	37 (88%)	36 (81%)	73 (86%)	
Working	3 (4%)	3 (9.5%)	4 (7%)	
Sick leave from work	2 (8%)	3 (9.5%)	5 (7%)	0.68†
Social deprivation				
IMD score	57.78 (21.9)	53.5 (25.6)	56.6 (23.9)	0.23
IMD Rank	19417 (7117)	17371 (8320)	18382 (7771)	

*Values are mean (% number of patients); Age is mean (range); Total sample age is mean (standard deviation); statistical significance = $p < 0.05$. † = X^2; * = ANOVA. ADL = activities of daily living; IMD = Index of Multiple Deprivation.*

Table 22 Baseline body composition and upper arm anthropometry

Characteristics	ONS (n = 41)	DA (n = 43)	p
Body composition			
Weight (kg)	48.8 (7.2)	50.8 (6.8)	0.21
Estimated dry weight (kg)	48.3 (7.6)	49.6 (6.9)	0.41
Height (m)	1.63 (0.1)	1.66 (0.1)	0.15
BMI (kg/m^2)	18.4 (2.1)	18.4 (1.4)	0.89
Estimated dry BMI (kg/m^2)	18.2 (2.1)	18.0 (1.3)	0.72
Oedema present	4 (15%)	5 (16%)	0.75
Mild oedema	8	2	
Moderate oedema	0	4	
Severe oedema	0	2	0.02†
'MUST' category			
Medium	14	14	
High	27	29	0.76
Upper arm anthropometry			
Unadjusted values			
MUAC (cm)	21.6 (2.2)	22.8 (2.1)	0.02†
Mid-arm muscle area (cm^2)	27.2 (8.1)	30.9 (8.9)	0.05
Biceps SKF (mm)	3.2 (1.1)	3.9 (1.5)	0.02†
Triceps SKF (mm)	6.0 (2.4)	7.5 (3.0)	0.02†
Adjusted values for weight and gender			
MUAC (cm)	21.6 (2.2)	22.8 (2.1)	0.04†
Mid-arm muscle area (cm^2)	27.2 (8.1)	30.9 (8.9)	0.05†
Biceps SKF (mm)	3.2 (1.1)	3.9 (1.5)	0.03†
Triceps SKF (mm)	6.2 (2.4)	7.5 (3.0)	0.05†

MUAC = Mid-arm muscle circumference; SKF = Skinfold thickness; Values are displayed as mean (standard deviation); † = denotes a statistically significant difference between the two groups at baseline. p values are for ANOVA between groups. Univariate analysis performed adjusting for weight and gender.

Table 23 Characteristics of outpatients that withdrew prior to the end of intervention

Group	Gender (M/F)	Age (yrs)	BMI (kg/m^2)	COPD severity	'MUST' category	Reason
ONS	M	83	19.0	Very severe	Medium	Bowel Ca
ONS	F	65	16.5	Very severe	High	Withdrew consent
DA	M	87	18.6	Moderate	Medium	Reduced capacity
ONS	F	67	14.1	Very severe	High	Withdrew consent
DA	M	76	20.5	Severe	Medium	Depression
DA	M	58	18.4	Very severe	High	Deterioration
ONS	M	86	19.2	Severe	Medium	RIP
ONS	F	88	16.8	Severe	High	Withdrew consent
DA	F	74	16.0	-	High	Withdrew consent
ONS	F	64	18.4	Severe	High	Withdrew consent
ONS	F	64	20.8	Severe	Medium	G.P advice
ONS	F	79	22.8	Severe	Medium	Withdrew consent
ONS	M	68	18.5	-	Medium	Withdrew consent
Mean		75.0	18.9			

ONS = oral nutritional supplements; DA = dietary advice; M = male; F = female

Figures 19 and 20 provide an overview of recruitment, allocation, completion and withdrawal rates reported according to the CONSORT statement (228). Baseline assessments were completed in 84 outpatients (Table 22) however, by the end of the intervention phase of the trial (week 12) 13 outpatients (15%) had withdrawn from the study (Table 23). At the end of the 12-week intervention there was a tendency for outpatients to withdraw from the ONS group (ONS 19% (n = 8) *vs.* 11% (n = 4) DA; χ^2 p = 0.286) and be classified as medium risk according to 'MUST' (21% medium (n = 6) *vs.* 12% high risk (n = 6); χ^2 p = 0.237). At week 12 the withdrawal rate was 27% with 16 subjects lost to follow-up due to the trial ceasing. Those patients that failed to complete the intervention phase of the trial reported to be significantly more breathless (p = 0.036) and had activities of daily living that were significantly impaired (p = 0.001) compared to those that completed the intervention (Table 24).

Table 24 Baseline characteristics of outpatients that completed the study (week 12) with outpatients that withdrew

Characteristics	Completed (n = 72)	Withdrew (n = 13)	p
Age (years)	72.6 (9.6)	74.6 (9.7)	0.507
Social deprivation (Rank IMD)	18,490 (8,081)	17,783 (5,991)	0.765
Smoking pack years	42.8 (19.3)	57.2 (46.5)	0.103
Body composition			
Weight (kg)	50.0 (7.0)	49.8 (8.0)	0.941
Est. dry weight (kg)	49.2 (7.0)	48.7 (9.3)	0.815
Body Mass Index (kg/m^2)	18.3 (1.6)	18.9 (2.1)	0.240
Est. dry BMI (kg/m^2)	18.0 (1.7)	18.4 (2.3)	0.452
Mid-upper arm circumference (cm)	22.1 (2.2)	22.8 (2.3)	0.342
Triceps skinfold thickness (mm)	6.7 (2.8)	7.4 (2.8)	0.426
Respiratory function			
FEV_1 (% predicted)	34.6 (12.2)	36.8 (14.5)	0.629
Quality of life & functional capacity			
Barthel's Index (ADL)	18.9 (1.4)	17.2 (1.8)	0.001*
Euroqol TTO	0.55 (0.28)	0.49 (0.29)	0.547
Quality of life VAS (0-10 cm)	55.4 (17.9)	52.9 (19.4)	0.547
SGRQ total score	55.2 (18.2)	52.9 (19.4)	0.657
MRC dyspneoa scale (0-5)	3.3 (1.1)	4.0 (0.7)	0.036*
Dietary intake			
Energy intake (kcal/day)	1544 (575)	1574 (550)	0.893
Protein intake (g/day)	50.5 (20.2)	51.6 (17.2)	0.891

*Values are mean (SD) for all variables (ANOVA); Rank IMD = rank index of multiple deprivation (0 = most deprived, 32,482 = least deprived); Barthel's Index: maximum score is 20 indicating an individual is fully independent with activities of daily living (ADL); VAS = visual analogue scale; SGRQ = St George's Respiratory Questionnaire (0 = best health and 100 = worst health); MRC = medical research council dyspneoa scale (0 = breathing does not limit physical activity to 5 = too breathless to leave the house); * = $p < 0.05$.*

5.6.1 Per protocol analysis: Primary outcome measure

Per protocol analysis was performed on all of those patients that completed baseline assessment and at least one additional assessment during the intervention. Analysis was carried out using both unadjusted values (paired t-test and ANOVA) and adjusted values (ANCOVA), adjusting for a standardised set of covariates specified earlier in this chapter (Section 5.5.0).

Quality of life

Analysis of quality of life data for those patients that completed the trial was performed before and after adjusting for covariates. For simplicity and to standardise the analysis, a set of covariates that were likely to influence quality of life and the changes in quality of life induced by the intervention were agreed (age, 'MUST' category, baseline FEV_1 % predicted).

EQ-5D

Table 25 Baseline EQ-5D and TTO values

	ONS (n = 31)	DA (n = 36)	p
Mobility	1.81 ± 0.072	1.78 ± 0.070	0.778
Self-care	1.35 ± 0.087	1.61 ± 0.107	0.075
Usual activities	2.03 ± 0.098	2.06 ± 0.097	0.867
Pain/discomfort	1.65 ± 0.099	1.67 ± 0.098	0.878
Anxiety/ depression	1.61 ± 0.100	1.78 ± 0.106	0.268
VAS	56.5 ± 2.9	55.6 ± 3.3	0.895
TTO	0.60 ± 0.041	0.52 ±0.052	0.266

Values are mean ± SE; p values for ANOVA; higher domain values = worse self-reported health status; VAS (visual analogue scale) = self-rated health state (higher value = better self rated health; 0 – 100); TTO (time trade-off) = score out of 1 (1 year, better value). Per protocol analysis performed on those patients that completed the intervention phase of the trial (week 12) and had full covariate data (age, baseline values, 'MUST', FEV_1 % predicted).

Analysis of EQ-5D domains and calculated TTO at baseline using ANOVA tests revealed no differences between the two intervention groups (Table 25). Analysis was limited to only those patients that completed the intervention phase of the trial

(week 12) and provided full data for covariate analysis. This allowed analysis using paired t-tests across each data point. Adjusting for baseline values as well as covariates that might influence quality of life (age, 'MUST' category and baseline FEV_1% predicted) using ANCOVA tests, there remained no differences in EQ-5D domains and TTO between the two interventions at the end of the intervention (Table 26).

Table 26 Week 12 EQ-5D domains and TTO values

	Adjusted baseline	**ONS (n = 31)**	**DA (n = 36)**	**Difference**	**p**
Mobility	1.79	1.82 ± 0.066	1.77 ± 0.062	+0.05 ± 0.092	0.618
Self-care	1.49	1.54 ± 0.079	1.59 ± 0.073	-0.05 ± 0.111	0.677
Usual activities	2.04	1.98 ± 0.089	1.85 ± 0.082	+0.13 ± 0.123	0.307
Pain / discomfort	1.66	1.84 ± 0.089	1.64 ± 0.082	+0.20 ± 0.123	0.109
Anxiety / depression	1.70	1.58 ± 0.096	1.52 ± 0.089	+0.06 ± 0.134	0.637
VAS	56.2	54.4 ± 2.62	58.4 ± 2.43	-4.0 ± 3.62	0.274
TTO	0.554	0.557 ± 0.040	0.605 ± 0.037	-0.048 ± 0.055	0.379

Values are adjusted means (SE); Difference = difference in values between ONS and DA (ONS – DA); p values for ANCOVA analysis between the two groups adjusting for baseline values, age, 'MUST' category and baseline FEV_1 % predicted; higher domain values = worse self-reported health status; VAS (visual analogue scale) = self-rated health state (higher value = better self-rated health; 0 – 100); TTO (time trade-off = score out of 1 (1 = 1 year, better value).

No differences were found between the interventions when the within group changes were explored, p values for the difference in EQ-5D domains and the TTO ranged from p = 0.108 to p = 0.570 using ANOVA tests. In examining the effect of treatment cessation (wash-out), ANCOVA analysis found no difference

between groups at week 26 (adjusted baseline TTO = 0.58; ONS (n = 26) 0.56 SE 0.04 *vs*. DA (n = 29) 0.60 SE 0.04; p = 0.425).

Table 27 Baseline St George's Respiratory Questionnaire (SGRQ) scores

	n	ONS	n	DA	p
Symptoms	29	61.7 ± 3.9	27	56.1 ± 5.6	0.409
Activity	29	76.7 ± 3.9	27	71.4 ± 4.4	0.374
Impact	28	44.7 ± 3.1	27	40.4 ± 4.0	0.386
Total	28	57.4 ± 3.1	27	52.7 ± 3.9	0.340

Values are mean (SE); p values for ANOVA analysis between the two groups; SGRQ scores = lower scores indicate better self-rated health state. Per protocol analysis, baseline scores are for those patients that completed the intervention phase of the trial (week 12) and had full covariate data (baseline measures, age, 'MUST' category, baseline FEV_1 % predicted).

St George's Respiratory Questionnaire (SGRQ)

At baseline subjects randomised to receive ONS tended to have poorer health indicated by higher scores for each of the SGRQ domains (Table 27) however, the groups did not significantly differ.

At the end of the intervention phase of the trial (week 12) analysis using ANCOVA tests, no differences in SGRQ domains between the two groups were observed (Table 28). Analysis of the change within each group induced by the intervention also found no difference between treatments, with p values ranging from 0.325 to 0.935 using ANOVA tests for each of the components. Importantly no domains, within either group, experienced a 4-point change although there was more than a 4-point difference between the two groups at baseline (Table 27). Patients randomised to ONS scored poorer at baseline for each of the 3 SGRQ domains, with differences greater than 4-points for each.

As was done with the TTO data, analysis was also carried out at week 26 to examine the effect of treatment cessation on total SGRQ score (adjusted baseline = 55.2; ONS (n = 24) 56.7 SE 25 *vs*. DA (n = 22) 53.8 SE 2.6; p = 0.408, ANCOVA test). The ONS group had slightly deteriorated at week 26 and the DA group experienced a non-significant improvement. Both the change within each treatment arm as well as the difference between groups did not differ.

Table 28 Mean adjusted SGRQ scores at week 12 (end of intervention phase)

	Adjusted baseline	ONS	DA	Difference	p
Symptoms	59.0	63.2 ± 3.5	54.7 ± 3.6	+8.5 ± 5.2	0.105
Activity	74.1	75.4 ± 2.0	72.2 ± 2.1	+3.2 ± 3.0	0.288
Impact	42.6	41.5 ± 1.9	42.4 ± 2.0	-0.890 ± 2.8	0.753
Total	55.1	55.2 ± 1.7	53.7 ± 1.7	+1.54 ±2.14	0.532

Values are adjusted mean (SE); Difference = difference in values between ONS and DA (ONS – DA); p values for ANCOVA analysis between the two groups adjusting for baseline values, age, 'MUST' category, baseline FEV_1 % predicted).

Paired analysis (paired t-test) of total SGRQ scores produced similar non-significant results (p range 0.172 - 0.762) to the more sophisticated analysis of covariance.

Nutritional intake

Energy intake

Data on energy and protein intake were not collected on two patients. However, data were available for 70 patients at each of the time points throughout the intervention phase allowing for unadjusted paired analysis (paired t-test). Total energy intake was significantly improved in the ONS group (food + ONS) at week 6 (+283 SE 95 kcal/day; p = 0.005). This increase was accompanied by a non-significant decrease in the energy obtained from food (ONS (food) -138 SE 101, p = 0.181), which remained at this level throughout the intervention phase. Whilst total energy intake remained elevated above baseline in the ONS group at week 12 it was not significant ((ONS + food) +243 SE 125, p = 0.061). Although favouring ONS, at no point during the intervention period did total energy intake significantly differ between the two interventions (week 6, p = 0.117 and week 12, p = 0.684, ANOVA).

Table 29 Change in energy intake within the ONS group (paired t-test analysis)

Oral Nutritional Supplements					
n	Baseline	**Week 6 (food)**	Δ kcal	95% CI Δ	p
	1521 (516)	1397 (397)	-124 (566)	-319 to +70	0.203
35		**Week 6 (ONS)**			
	1521 (516)	1823 (440)	+302 (537)	+117 to +486	0.002*
		Week 12 (food)			
	1520 (522)	1381 (527)	-139 (643)	-367 to +89	0.224
33		**Week 12 (ONS)**			
	1520 (522)	1762 (569)	+243 (718)	-12 to +497	0.061
		Week 26 (food)			
28	1566 (526)	1671 (537)	+105 (606)	-130 to +340	0.367
		Week 52 (food)			
15	1554 (624)	1588 (500)	+34 (674)	-407 to +339	0.848

(food) = estimated daily energy intake from food alone; (ONS) = estimated daily energy intake from ONS plus food, i.e. total energy intake; Δ = change in intake from baseline.

When assessing only the energy intake derived from food alone using ANOVA tests, significant differences between the two groups were seen at both week 6 (p = 0.039) and week 12 (p = 0.008) both favouring the DA group. Energy intake derived from food reduced in the ONS group by 8% at week 6 and 9% at week 12 however, overall there was a 20% and 16% increase overall. Total energy intake in the DA group increased at both week 6 (+63 SE 103, p = 0.504) and at week 12 (+157 SE 104, p = 0.139) however, neither reached significance. Similar results were also obtained using adjusted values where energy derived from food alone remained significantly higher in the DA group than the ONS group at week 12 (ONS: 1369 SE 91 kcal/d *vs*. DA: 1714 SE 85 kcal/d; difference -345 SE 126 kcal/d; p = 0.008, ANCOVA). However, total energy intake was similar in both groups at week 12 (ONS: 1746 SE 95 kcal/d *vs*. DA: 1713 SE 90 kcal/d; difference 33 SE 132 kcal/d; p = 0.802, ANCOVA) with intakes returning to baseline values on the stopping supplementation.

As an approximation, to assess whether patients were achieving their daily nutritional requirements, intakes of energy and protein were compared to the

dietary reference values for healthy individuals aged between 65 to 74 years, with a physical activity level of 1.4 (229). A value of 2100 kcal/day was selected as it fell between the 2330 kcal/day recommendation for males and 1,900 kcal/day for females. At baseline both ONS and DA groups were consuming substantially less than the recommended estimated average requirement (EAR) for energy (72% of EAR in ONS *vs*. 74% of EAR in DA). The highest intakes achieved during the trial were 1823 SD 440 kcal/day (87% EAR) at week 12 in the ONS group and 1830 SD 627 kcal/day (87% EAR) at week 52 in the DA group. When energy requirements were calculated on a kcal/kg basis (35 kcal/kg/d for weight maintenance and 40 kcal/kg/d to aim for weight gain), a mean baseline weight of approximately 50 kg would result in estimated daily requirements for energy of 1750 kcal/day (maintenance) and 2000 kcal/day (for weight gain). With nutritional intervention, both groups achieved the levels of energy intake required in order to remain weight stable but neither treatment produced mean intakes to the level required in order to promote weight gain.

Table 30 Change in energy intake in DA group (paired t-test analysis)

Dietary Advice					
n	Baseline	**Week 6**	Δ kcal	95% CI Δ	p
38	1565 (625)	1613 (530)	+48 (623)	-157 to +253	0.640
		Week 12			
37	1554 (629)	1711 (483)	+157 6327)	-54 to +368	0.139
		Week 26			
29	1568 (618)	1815 (508)	+247 (592)	+22 to +473	0.032*
		Week 52			
19	1627 (655)	1830 (627)	+202 (716)	-548 to +143	0.234

Δ = change in intake from baseline.

In order to examine the effect of treatment cessation, analysis was also performed at week 26 and week 52 allowing for a 3-month and 9-month washout period after the intervention. Paired analysis was performed at each of the four time points comparing the change in intake from baseline (Tables 29 and 30). Patients in the ONS group had a significantly elevated intake at week 6 (p = 0.002, paired t-test) and week 12 (p = 0.012, paired t-test) but this was not continued after

supplementation. Energy intake from food did reduce slightly but this was not significant and did not affect the overall improvement in energy intake (Table 29). Intakes in the DA group improved but these only reached significance at week 26 (p = 0.032, paired t-test). The wide dispersion (95% CI of the change) within both ONS and DA groups illustrated that individuals within both group were able to substantially increase their energy intake. In the DA group there was a trend for the improvement to persist beyond the period of intervention unfortunately the sample size was substantially reduced at 1-year affecting the power of the analysis.

Table 31 Comparison of total daily energy intakes between ONS and DA groups during intervention (end week 12) and follow-up (week 52)

Energy (kcal/d)	**N**	**Adjusted baseline**	**Week 6**	**Week 12**	**Week 26**	**Week 52**
ONS	13	1596	1814 (156)	1683 (182)	1779 (164)	1443 (168)
DA	17		1551 (135)	1775 (157)	1968 (141)	1852 (145)
Difference			+264 (217)	-92 (253)	-189 (228)	-409 (233)
p value			0.236	0.718	0.414	0.091

Values mean (SE); adjusted for baseline energy intake (kcal/day), age, 'MUST' category, FEV_1 % predicted using ANCOVA analysis; p values for the difference between ONS and DA at each time point; Difference = difference in values between ONS and DA (ONS – DA).

In the DA group a similar non-significant improvement in energy intake was observed during the intervention phase. However, energy intake continued to increase after intervention to an intake significantly above baseline (+247 SE 110 kcal/day, p = 0.032). This resulted in a mean daily intake of 1815 SE 94 kcal/day, 86% of EAR, the level achieved at week 6 in the ONS group. When including only those patients that provided data at each of the five data points as well as full covariate data, no differences were found between the two interventions using ANCOVA tests (Table 31).

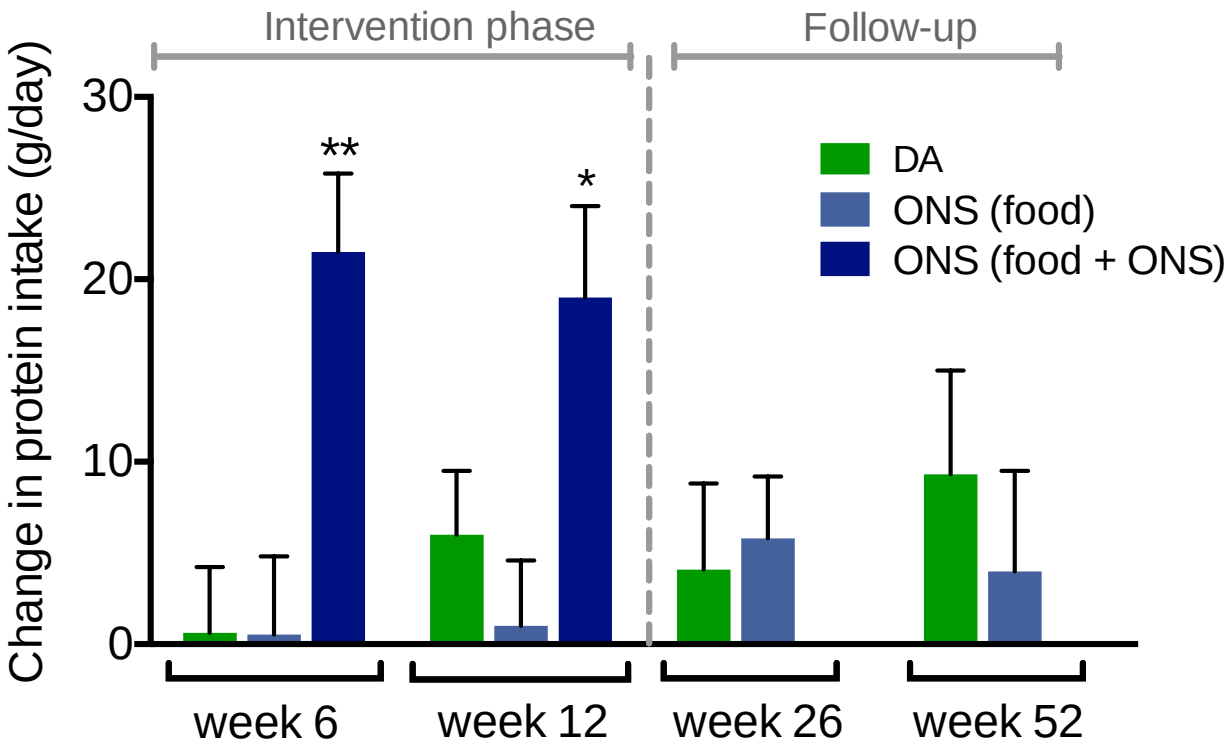


Figure 28 Comparison of the change in protein intake during the intervention and follow-up phase between ONS and DA. Values are mean change (SEM) with statistical comparison between groups, week 6: ONS (n 35) *vs*. DA (n 38); week 12: ONS (n 33) *vs*. DA (n 37); week 26: ONS (n 28) *vs*. DA (n 29); week 52: ONS (n 19) *vs*. DA (n 15), ** = p = 0.001 Difference between change in protein intake DA *vs*. ONS (food + ONS): * = p = 0.033 ANOVA.

Protein intake was significantly increased in the ONS group above that of DA at both week 6 (ONS +21.5 SEM 4.3 g/d *vs*. DA +0.52 SEM 4.3 g/d, p = 0.001 ANOVA) and week 12 (ONS +19.0 SEM 5.0 g/d *vs*. DA +1.0 SEM 3.6 g/d, p = 0.033 ANOVA) (Figure 28). However no differences between the two groups were observed on ceasing supplementation (week 26: ONS +5.8 SEM 3.4 g/d *vs*. DA +4.1 SEM 4.7 g/d, p = 0.722; week 52: ONS +4.0 SEM 5.5 g/d *vs*. DA +9.3 SEM 5.7 g/d, p = 0.513 ANOVA).

Similar results were also obtained when analysis was performed on only those patients that completed the trial, protein intake was found to be significantly improved in the ONS group with intakes at week 6 and week 12 substantially raised above baseline intakes (+22.1 SE 4.6 g/day; p < 0.001 (week 6) and +19.0

SE 5.0 g/day; p = 0.001 (week 12) unadjusted paired t-test). Total protein intakes were also significantly higher in the ONS group compared to the DA group throughout the intervention phase (week 6: ONS 71.5 SD 24.4 g/d *vs*. DA 51.7 SD 18.6 g/day, p < 0.001; week 12: ONS 68.4 SD 25.6 g/d *vs*. DA 57.0 SD 16.0, p = 0.025 ANOVA). Assuming an RNI for protein of 53 g/day (229), outpatients in the ONS group consumed 135% of the RNI for protein at week 6 and 129% at week 12. This was compared to 98% at week 6 and 108% at week 12 in the DA group.

On ceasing supplementation the total daily protein intake in the ONS group significantly fell towards the intake at baseline (-12.9 SE 5.2 g/day; p = 0.019, paired t-test), however this was slightly compensated for by an increase in dietary protein to 55.2 SE 3.7 g/day; p = 0.096. The ONS group achieved a protein intake above the RNI throughout the intervention and at week 26. The DA group achieved the RNI from week 12 onwards. When protein intakes were adjusted for, with the exception of week 6, there were no differences in daily protein intake between the two groups (Table 32).

Table 32 Total daily protein intakes between ONS and DA groups during intervention (end week 12) and follow-up (week 52) per protocol analysis.

Protein (g/d)	**n**	**Adjusted baseline**	**Week 6**	**Week 12**	**Week 26**	**Week 52**
ONS	13	50.6	75.9 (6.4)	65.3 (6.4)	56.6 (5.1)	52.5 (5.5)
DA	17		48.9 (5.5)	58.6 (5.5)	57.0 (4.4)	60.4 (4.8)
Difference			+27.0 (9.0)	+6.7 (9.0)	-0.4 (7.1)	-7.9 (7.7)
p value			0.006*	0.467	0.952	0.316

*Values mean (SE); adjusted for baseline protein intake (g/day), age, 'MUST' category, FEV_1 % predicted using ANCOVA analysis; p values for the difference between ONS and DA at each time point; * = difference calculated ONS - DA.*

Appetite VAS

In exploring patient's appetite, fullness and desire to eat on VAS (0 - 10cm), appetite scores were significantly improved from baseline in ONS group at week 12 (3.5 SD 2.2 *vs*. 4.4 SD 2.3; difference +0.9 SD 2.1; p = 0.016, paired t-test). Appetite scores in the DA group had a similar improvement although this was not significant (3.7 SD 2.4 *vs*. 4.6 SD 2.2; difference +0.8 SD 2.6; p = 0.055). Desire to eat remained unchanged within both treatment groups and fullness score were unchanged at week 12 in the DA group. There was a tendency for an increase in fullness scores in the ONS group at week 12 although this was not significantly increased above baseline (5.4 SD 2.5 *vs*. 6.3 SD 2.0; difference +0.9 SD 3.0; p = 0.1, paired t-test).

Secondary outcomes

A number of secondary outcomes were also assessed at baseline (Table 33) and at week 12 after adjusting for the predefined covariates (Table 34). At baseline significant difference in upper arm anthropometry were observed between the two groups. When comparing the baseline means between groups using ANOVA analysis, the DA group had a significantly larger mid-upper arm circumference (MUAC) (p = 0.020) and triceps skinfold thickness (TSF) (p = 0.010).

When assessing the same outcomes at week 12 (end of the intervention) using ANCOVA analysis adjusting for covariates, there were no significant differences between the two groups, with the exception of protein intake (Table 34). At the end of the intervention phase protein intake was significantly higher in the ONS group compared to the DA group (p = 0.027).

Table 33 Baseline characteristics for patients that completed to week 12 (end of intervention phase)

	n	ONS	n	DA	P
Energy (kcal/d)	31	1514 ± 92	36	1553 ± 104	0.785
Protein (kcal/d)	31	49.4 ± 3.0	36	50.9 ± 3.9	0.774
Weight (kg)	31	49.5 ± 1.3	36	50.7 ± 1.2	0.479
BMI (kg/m^2)	31	18.3 ± 0.4	36	18.3 ± 0.2	0.976
HGS left (kg)	31	17.0 ± 1.1	36	16.5 ± 1.2	0.760
HGS right (kg)	30	19.2 ± 1.3	36	19.0 ± 1.4	0.923
MUAC (cm)	31	21.4 ± 0.4	36	22.7 ± 0.4	0.020*
TSF (mm)	31	5.7 ± 0.4	36	7.5 ± 0.5	0.010*
MAMC (cm)	31	19.6 ± 0.4	36	20.3 ± 0.3	0.160

Values are mean (SE); *p values for ANOVA analysis between the two groups; BMI = body mass index; HGS = handgrip strength; MUAC = mid upper-arm circumference; TSF = triceps skinfold thickness; MAMC = mid-arm muscle circumference.*

Table 34 Difference in mean values between ONS and DA at week 12 (end of intervention phase) adjusted for baseline covariates

	Adjusted baseline	n	ONS	n	DA	Difference	p
Energy (kcal/d)	1528	31	1746 ± 95	35	1713 ± 90	+33 ± 132	0.802
Protein (g/d)	50.1	31	68.1 ± 3.6	35	56.6 ± 3.4	+11.5 ± 5.10	0.027*
Weight (kg)	50.2	31	50.8 ± 0.32	36	50.4 ± 0.30	+0.4 ± 0.40	0.423
BMI (kg/m^2)	18.3	31	18.6 ± 0.13	36	18.5 ± 0.12	+0.1 ± 0.18	0.650
HGS left (kg)	16.8	31	17.7 ± 0.64	36	17.6 ± 0.60	+0.1 ± 0.90	0.895
HGS right (kg)	19.3	30	20.1 ± 0.62	35	19.9 ± 0.62	+0.2 ± 0.93	0.796
MUAC (cm)	22.1	31	22.0 ± 0.20	36	21.9 ± 0.20	+0.1 ± 0.30	0.668
TSF (mm)	6.67	31	6.58 ± 0.21	36	6.7 ± 0.20	-0.1 ± 0.30	0.775
MAMC (cm)	20.0	31	19.9 ± 0.18	36	19.8 ± 0.17	+0.1 ± 0.25	0.589

Values are adjusted means ± SE; Difference = difference in values between ONS and DA (ONS – DA); p values for ANCOVA analysis between the two groups adjusting for baseline values, age, 'MUST' category, baseline FEV_1 % predicted); BMI = body mass index; HGS = handgrip strength; MUAC = mid upper-arm circumference; TSF = triceps skinfold thickness; MAMC = mid-arm muscle circumference.

Whole cohort analysis

No differences were detected between the ONS and DA intervention arms either during the intervention or follow-up. Both interventions were associated with

maintenance of body weight, function and quality of life. As both treatment arms were underpowered, paired t-test analysis combining both groups was performed. In 72 outpatients intervention with either ONS or DA was associated with a significant improvement in body weight (+0.46 SE kg, p = 0.026) with body weight increasing from 49.97 SD 7.0 to 50.43 SD 7.1 kg at week 12, BMI +0.2 SD 0.67 kg/m^2 (p = 0.014) These improvements were associated with a significant increase at week 12 in both energy (+198 SD 670 kcal/d, p = 0.016) and protein intakes (+12.1 SD 25.7 g/d, p < 0.001) above that of baseline values. In addition to energy, protein and body weight improvements, left handgrip strength was also significantly improved after 12 weeks (+0.94 SD 3.69 kg, p = 0.033) and the improvement persisted to week 26 (+0.71 SD 4.2, p = 0.187) although a reduction in sample size of 12 due to withdrawals reduced the statistical power. No differences were seen in right HGS, which were always significantly higher than left HGS thought-out the trial (baseline: right HGS 18.8 SD 7.5 kg vs. left HGS 16.5 SD 6.7 kg, difference 2.2 SD 2.8 kg, p < 0.001) reflective of the predominance of right handed patients. No improvements were observed in the quality of life measures.

5.6.2 Intention to treat analysis with imputed data

Intention to treat analysis was performed on recruited patients up until the end of the intervention phase (week 12). Missing data points did not exceed 10% of the variable so imputed values were entered using the modelling described previous.

Quality of life

EQ-5D

There were no differences between the two groups using the imputed values for TTO and EQ-5D domains at the end of the intervention period. Unadjusted values for TTO ITT analysis were ONS: 0.52 SE 0.048 versus DA: 0.55 SE 0.047; difference 0.032 SE 0.067; p = 0.629.
Examination of the EQ-5D self-rated health state score revealed no difference between either treatment groups using pooled means (VAS 0 - 100 cm). ONS: 53.2 SE 3.3 cm *vs*. DA: 57.7 SE 2.9 cm; difference 4.5 SE 4.6 cm; p = 0.335, ANOVA).

Time-trade off (TTO)

Similar results were also obtained using adjusted values with pooled means for TTO, ONS 0.50 *vs*. DA 0.57 (difference 0.07 SE 0.06; p = 0.280, ANCOVA).

SGRQ

The differences in SGRQ total score at week 12 between the two groups did not significantly differ (pooled means: ONS 58.8 *vs*. DA: 55.4; difference 3.4 SE 3.3; p = 0.318). These findings were similar for the unadjusted analysis (pooled means ONS: 58.8 SE 2.9 *vs*. DA: 55.4 SE 2.8; difference 3.5 SE 4.0, p = 0.388) and support the findings using the per protocol analysis.

Nutritional intake

Energy intake

ITT analysis for energy intake at the end of intervention (week 12) supported the results obtained with the earlier per protocol analysis. Pooled means did not differ between the ONS and DA groups (ONS: 1810 SE 112 kcal/day *vs*. DA: 1698 SE 99 kcal/day; difference 112 SE 169 kcal/day; pool p value = 0.519, ANOVA). A similar difference between groups was found when adjusting for covariates (ONS: 1797 kcal/day *vs*. DA: 1710 kcal/day; difference 87 SE 160 kcal/day, pooled p value = 0.590, ANCOVA).

Protein intake

Protein intakes at the end of the intervention period significantly favoured the ONS group over those receiving DA using ITT pooled mean values (ONS: 72.0 SE 5.2 d/day *vs*. DA: 56.5 SE 3.8 d/day; difference 15.5 SE 6.3 g/day; pooled p value = 0.017, ANOVA). Similar results were obtained using adjusted pooled means (ONS: 71.5 *vs*. DA: 57.0 g/day; difference 14.5 SE 6.2 g/day; pooled p value = 0.023).

The results obtained using imputed values for energy and protein are similar to the paired analyses performed according to per protocol analysis.

Secondary outcomes (Intention to treat analysis)

Using imputed values and adjusting for standardised covariates used in previous analyses (age, 'MUST' category, FEV_1 % predicted) as well as the baseline variable, no differences where found between ONS and DA at week 12 for body weight (ONS: 49.5 SE 1.1 kg *vs*. DA: 51.1 SE 1.1 kg; difference 1.6 SE 1.6 kg, pooled p value = 0.319 unadjusted (adjusted difference 0.1 SE 0.45 kg; pooled p value = 0.850)) and MUAC (ONS: 21.6 SE 0.4 *vs*. DA: 22.4 SE 0.3 cm; difference -0.89 SE 0.52 cm, pooled p value = 0.092 unadjusted (adjusted difference 0.1 SE 0.36 cm, pooled p value = 0.873)).

Functional

Handgrip Strength

Unadjusted values for both left and right handgrip strength were not significantly different between the two groups at the end of intervention using ANOVA tests. Left HGS pooled means; ONS: 18.0 SE 1.2 kg *vs*. DA: 17.0 SE 1.1 kg; difference 1.0 SE 1.6 kg; p = 0.527. Right HGS pooled means; ONS: 19.7 SE 1.3 kg *vs*. DA: 19.7 SE 1.2 kg; difference 0.0 SE 1.7 kg; p = 0.995. Adjusted values also did not differ (Left HGS difference 0.1 SE 0.86 kg, p = 0.914 and Right HGS difference 0.0 SE 0.88 kg, p = 0.980).

Activities of Daily Living

At the end of the intervention the total activities of daily living (ADL) score did not significantly differ between ONS and DA groups (pooled values: ONS 19.1 *vs*. 18.7; difference 0.40 SE 0.37; p = 0.320). Similar findings were also found when unadjusted values were examined (ANOVA). When the change in ADL score was assessed (week 12 ADL - baseline ADL) no significant differences between the two groups existed (ONS -0.40 SE 0.32 *vs*. DA -0.12 SE 0.20; pooled p value 0.280).

Summary of quality of life data (primary outcome)

Using both a generic (EQ-5D) and a disease specific assessment tool (SGRQ) to measure quality of life, no differences were detected between the ONS and DA group. Both the overall score for both assessment tools, in addition to the components within each tool, did not significantly differ at the end of the intervention. Results were similar when using both adjusted and unadjusted values according to per protocol analysis and intention to treat. A minimally important clinical difference in the SGRQ score is a 4-point change and neither group experienced a change of that magnitude.

Summary of nutritional intake data

ONS were effective at increasing total daily energy intake during the intervention phase. However, this was only significantly higher than baseline at week 6 as intake dropped slightly at week 12. DA resulted in a slight increase in energy intake at each of the assessment points during the intervention and continued to increase reaching statistical significance at week 26. Conversely, on ceasing supplementation the energy intake in the ONS group reduced back towards the basal value. Interesting, on initiating supplementation there did appear to be a compensatory drop in energy intake from food.

In addition to being effective at increasing energy intake, ONS were extremely effective at increasing protein intake. Patients in the ONS group significantly increased their total protein intakes above baseline throughout the intervention phase. However similarly to energy intake, on ceasing supplementation protein intake dropped towards the baseline intake. DA had no effect on protein intake throughout the study period demonstrating the challenge of improving protein intakes through food fortification. As with energy intake differences between groups were only seen at week 6.

5.7.0 Discussion

This study was the first in COPD patients to directly compare the effectiveness of two of the most common first line treatments for malnutrition, ONS and DA, it was unusual in that rather than comparing ONS or DA against control both

interventions were compared against each other. In addition the primary outcome measure was patient's quality of life, an outcome highlighted as lacking in previous reviews. As well as exploring the effectiveness of the two nutritional interventions, the trial also examined the effect of cessation of treatment, despite being such an important outcome this is one often lacking in many nutritional intervention trials. When quality of life was assessed using both generic and disease-specific assessment tools no significant differences in quality of life occurred either within or between the two treatment groups. In addition when the whole cohort was analysed no differences in quality of life were found. A possible reason for this is that neither group gained enough weight to translate into quality of life improvements when analysed alone and whilst the cohort combined (ONS + DA groups) gained a significant amount of weight this was only a quarter of the amount that tends to be associated with subsequent functional improvements. A previous review has suggested a weight gain of > 2 kg is required before functional improvements are realised and it is likely that these improvements assist in driving quality of life improvements (10). Despite ONS significantly increasing energy and protein intakes above baseline values there did appear to be a degree of suppression of energy intake from food of approximately 10% despite an overall increase in intake of around 16-20%. Therefore this slight reduction in intake did not prevent improvements in nutritional intake being achieved however, whether dietary counselling to maximise oral intake of energy would be able to prevent any decline and maximise the effectiveness of ONS in COPD patients remains to be established. Limitations of the current trial are that it did not assess inflammation, body composition or contain a control group. Due to participants within the trial covering a reasonably large geographical area, the burden on participants as well as transport and storage, the measurement of blood biochemistry was not performed. Whilst assessment of body composition was desirable in order to accurately assess patients using a portable BIA device would require the individual to be in the supine position. It was decided not to include this assessment as it was thought it would prolong the duration of the assessment visits, which again place an extra burden on the participant and the anthropometry measures would allow for some exploration of body compositional changes.

Ideally the current trial would have included a control group however, it was felt to randomise patients identified as at risk of malnutrition to no treatment would be unethical. Patients could have been randomised to routine care however; both of

the two main recruitment centres had poor or no access to a dietitian. In addition there could be an argument for the inclusion of a fourth arm where patients received a combination of nutritional strategies (ONS + DA), maximising both oral intake and the effectiveness of any ONS consumed, but this was not feasible within the confines of a PhD research project. To perform such a trial is likely to require a multi-centre trial over a considerable period of time in order to achieve an adequate sample size. As described in the methods, the target sample size in the current study was 100 outpatients in each arm to achieve 80% power. However, a number of challenges to recruitment were encountered: firstly the recruitment of COPD patients at risk of malnutrition but 4 weeks post infective exacerbation was difficult during winter months when infections peaked. Secondly, the stringent inclusion and exclusion criteria meant patients with a diagnosis of bronchiectasis were not eligible to participate. In addition a number of patients simply declined to take part due to the length of the study. In order to achieve the sample sized obtained, required the recruitment of several respiratory centres covering a large area of Hampshire and Dorset. Despite assessment visits being carried out within the patient's residence at their convenience retention to the study was difficult with 15% of patients withdrawing before the end of the intervention phase. Whilst one patient passed away and one received a diagnosis of cancer, the most common reason for withdrawal was a request to leave the trial and a withdrawal of consent. Many patients cited a number of reasons but most centred around fatigue in that the visits could be quite long when allowing for periods of rest due to breathlessness (up to 90 minutes) and many patients citing their days were short enough, rising late, the time taken to wash and dress, prepare and consume food and take medications at regular periods throughout the day. Some individuals found the demands of the study quite arduous. Therefore in order to achieve the target sample size accounting for refusal to participate and withdrawals would have required additional sites or a prolonged trial duration, neither of which were feasible in the current trial. In the current trial there was a tendency for a higher withdrawal rate from the ONS arm, which almost reached statistical significance, the reason for this is not fully understood. It may be due to the fact that the ONS were accounted for at each visit providing a clearer indication of compliance than self reported dietary modifications. It is feasible this added as an extra pressure within a trial setting causing those patients who were not compliant to withdraw. This of course is a challenge faced in all research, as by definition those remaining are likely to be more compliant enhancing the treatment effect of any results

obtained. As part of the enrolment process to the current study this effect was explained to both groups and that poor compliance did not necessitate exit from the trial.

Baseline energy intakes of the outpatients recruited were very low but nutritional support was associated with significant increases during the intervention phase within the ONS group and at week 26 in the DA group. Whilst it took longer for the DA group to significantly increase their energy intake, it did remain elevated suggestive of some degree of behaviour change which supports the finding of Weekes et al., (74). Intakes within the ONS group returned to baseline values on ceasing supplementation. The levels of energy intake achieved in both groups appeared to only match that required for weight maintenance, which might explain why neither group of patients lost or gained weight. Although as a whole the cohort did significantly gain weight, which is likely to be indicative of the relatively low overall energy requirements in this population. It is difficult to assess the effectiveness of the interventions alone in the absence of a control group but it appears that ONS are effective whilst they are administered but for long term sustained improvements in dietary intake DA and counselling may be required in addition to ONS. This is now a research priority in the clinical management of disease-related malnutrition.

The current intervention involved a cohort of patients with a lower mean BMI (18.4 kg/m^2) than any of the previous trials included in the meta-analysis within chapter 3. In a cohort of patients already at high risk of malnutrition with severe respiratory disease, it may be that both interventions were effective at preventing further deterioration. The trial mentioned by Weekes et al., involving UK COPD outpatients (74) included a cohort of patients with a similar severity of COPD according to FEV_1 percentage predicted but with an initial mean BMI of 19.9 kg/m^2. The baseline total daily energy intake of that cohort was also more than 400 kcal/day higher (1974 SE 57 kcal/day) than the current intervention groups (ONS: 1520 SE 91 kcal/day and DA: 1554 SE 103 kcal/day). Interestingly the study by Weekes et al (74) did involve a control group that went on to lose 2.0 kg of body weight. Examination of the control groups of those RCTs involving depleted patients included in chapter 3, seven out of eleven control groups went on to lose weight although this was not significant. Had either ONS or DA been compared to

a control group receiving no intervention with a similar BMI and disease-severity, significant differences may have been observed.

In the current study, protein intake was significantly increased with ONS supplementation both above baseline and above the intake achieved by the DA group. However, protein intakes did drop towards the end of the intervention phase and on stopping ONS intakes dropped back towards baseline. The study did demonstrate that ONS are extremely effective at increasing protein intake but that this is only during the period of supplementation. It also illustrated the challenges of increasing protein intake through DA alone. Dietary counselling and food fortification tend to focus on increasing total daily energy intake, which inevitably results in individuals increasing their consumption of energy dense (fat-rich) foods. Whilst consumption of protein rich foods is also promoted the effectiveness of a diet specifically aiming to substantially increase total protein intakes is yet to be carried out in COPD patients. The effect of a high-protein diet in COPD patients has not been explored and there may be issues around the satiety levels associated with protein that may need to be considered. During the intervention phase of the current trial protein intake was significantly increased in the ONS group however this was accompanied with a reduction in energy intake from food and was associated with an increase in fullness reported by the patients. Neither of these changes was significant but in order to achieve prolonged increases in both energy and protein intakes these outcomes warrant further investigation.

Chapter 3 reviewed the current evidence base for nutritional support in COPD and despite recommendations that ONS be provided alongside exercise rehabilitation (6, 172), only 4 trials explored the effectiveness of ONS alongside such a programme (56-58, 84). One trial involved predominantly nourished patients (56) with another including only nourished patients (58). Two of the studies used ONS specifically designed for exercising COPD patients (56, 84), with the other two using a standard ONS. The exact content of the exercise programmes was unclear and it remains to be seen whether high protein ONS in combination with targeted exercise rehabilitation (resistance training) is able to increase FFM in COPD patients. The heterogeneity of the current evidence base for nutritional support in exercise rehabilitation makes interpretation difficult but findings from the meta-analysis in chapter 3 suggest a role for nutritional support beyond simply

treating malnutrition (150). Previous studies exploring the effectiveness of ONS in acutely unwell COPD patients have had limited success in improving function (141, 230). In the face of elevated inflammation and immobility nutritional support may be effective at attenuating losses but repletion is likely to only occur during recovery. Indeed there may be windows of opportunity to maximise the effectiveness of nutritional support, such as utilising high protein ONS in exercising COPD patients free from exacerbation and not at risk of malnutrition. Such an approach may lead to substantial increases in FFM and subsequent improvements in respiratory muscle strength and peripheral muscle strength. One would assume such improvements would drive improved quality of life and potentially have a positive impact on an individual's susceptibility to infection. Such a proactive approach would have to be demonstrated within large adequately powered RCTs with clear clinical and economic end points.

The examination of several secondary outcomes (upper arm anthropometry and handgrip strength) in the current trial found no improvements with nutritional intervention, although combined analysis revealed a significant improvement in non-dominant HGS. This finding supports that of the meta-analysis where a significant increase in energy and protein intake and improvements in body weight were associated with improved grip strength (150). It may be that improved dominant grip strength was not observed, as the increase in body weight was not sufficient enough to translate to improved function. As was discuss earlier in this thesis, in nutritionally deplete individuals significant improvements may be observed quickly even in the absence of any changes in body weight and composition. Of importance is the fact that despite weight gain below 2 kg patients there was still a significant increase in strength which could be as a result of improved nutritional status and available energy substrate that changes in body mass and composition.

The current cohort of patients appeared to be extremely sedentary with many rarely leaving their homes unfortunately no formal analysis of daily physical activity levels was performed. The fact that neither group lost weight despite relatively low energy intakes suggests the patient's activity levels were considerably impaired by their illness. Assessment of habitual activity levels would have provided useful additional information. In addition assessment of baseline body composition and inflammatory status would have been useful in order to establish the prevalence of

sarcopenia or cachexia. This would have aided in the interpretation of the current findings as a previous study in COPD patients characterised non-responders to nutritional therapy as having elevated inflammatory markers (19). Being a cohort of COPD patients at high risk of malnutrition, it is very likely many of the individuals would have met the criteria for diagnosis of cachexia (151, 231). If many of the patients were cachectic this may partially explain why improvements in body weight and function were not found. However, maintaining baseline measurements in the scenario may actually represent a successful therapeutic intervention.

The current trial is one of only a few studies that have reported on the effects of cessation of ONS (79, 109). Similar to the current findings, in those trials that did examine the effects of stopping ONS, nutritional intake decreased towards the baseline intake. If ONS alone are provided, arguably this is to be expected, as no supportive dietary behaviour change will have occurred. This demonstrates that the stopping of ONS in clinical practice should only be done when the treatment goal is achieved and a period of monitoring should be undertaken to examine the effecting of ceasing nutritional support. An additional consideration is the difference in cost between the two interventions, whilst the current study did not examine costs associated with treatment this should be a consideration in future trials. Issues around not only the cost of intervention but also the applicability in routine practice should be explored. As was discussed in chapter 1, currently there is unlikely to be enough dietitians available to provide individualised dietary counselling to all of those patients with COPD at risk of malnutrition. More evidence demonstrating the both the clinical and cost effectiveness of DA is required to provide a stronger argument to service commissioners for increased dietetic posts in the outpatient setting.

Considering the findings of the review presented in chapter 3, the demonstration of the ‘obesity paradox’ in chapter 4 and the findings of the current randomised trial, it does appear that in order for nutritional support to result in significant improvements in body weight and function earlier intervention is required. Prompt identification and the initiation of nutritional support in those individuals with clinically relevant weight loss (5%) and/or a BMI < 20 kg/m^2 appear to be key thresholds. On the current evidence available, the recommendation by NICE for the nutritional management of COPD patients that those with a BMI < 20 kg/m^2 be

prescribed ONS appears sound and is supported by grade A evidence (meta-analysis) (150). In addition, ideally patients will also be reviewed by a dietitian to maximise oral intake and tailor ONS prescriptions to the preferences of the patient. Further research is required in order to establish how best to nutritionally intervene in those COPD patients that are already at high risk of malnutrition and considerably underweight (BMI < 18.5 kg/m^2). In these patients a multi-modal approach may be required where patients receive ONS, dietetic counselling and participate in exercise rehabilitation, further trials are needed in order to explore this further.

5.8.0 Conclusion

In outpatients with stable COPD that are already considerably underweight (BMI < 18.5 kg/m^2) nutritional intervention with ONS or DA does not lead to improvements in body weight, anthropometry, handgrip strength or quality of life. However, both groups maintained their baseline measurements which, considering their clinical condition, may reflect a positive treatment effect. Had either intervention been compared against a control group significant differences may have occurred. It is likely earlier intervention is required in order to achieve the increases in weight and function reported in other trials and it may be that in those with a BMI < 18.5 kg/m^2 combined nutritional therapies (ONS + DA) may be required in order to achieve elevated nutritional intakes for sufficient time. Further research is needed in order to explore the effectiveness of multi-modal approaches to nutritional support and whether improvements can be enhanced with exercise programmes.

Malnutrition is a modifiable risk factor in COPD and establishing when and how to intervene in COPD should be a research priority in the future. There is a need to undertake further work to understand which patients are most likely to respond to nutritional support and the interaction between nutritional support, malnutrition, elevated inflammation and graded physical activity. There are likely to be windows of opportunity where nutritional support is most effective. The task now is to identify them and the most effective nutritional interventions.

6.0 Chapter 6 Summary of thesis and future directions

This thesis has confirmed that malnutrition is common in outpatients with COPD and has shown that it is associated with increased healthcare use and poorer prognosis (**chapter 4**). The observational cohort studies found that whilst nutritional screening using 'MUST' was able to highlight those patients at risk of malnutrition that were likely to go on to have poorer survival, it was actually not as sensitive as BMI alone. The majority of patients within the current cohort were within what would normally be considered a healthy BMI category (20 – 25 kg/m^2), yet individuals within this group went on to have similar poor survival and increased healthcare use as those classified as underweight (< 20 kg/m^2). It was hypothesised within this thesis that this phenomenon could be partly driven FFM depletion that is going undetected and which may be partially preserved in the overweight and obese explaining this apparent paradox. In addition the separation between the underweight/normal weight and overweight/obese could be due to the heterogeneity underneath the umbrella term of COPD. It is feasible that the two distinct clinical courses could merely be representing the traditional 'pink puffer' and 'blue bloater' phenotypes. Further work is needed in order to establish the nutritional phenotypes that exist within COPD and how they are related to respiratory function, inflammation and co-morbidities.

It is clear from the findings of this thesis that current strategies used to identify nutritional risk in COPD patients are inadequate. Whilst BMI is possible a more sensitive measure than 'MUST' in identifying poor clinical outcomes in COPD, it is a static measure and does not assess the presence of any unintentional weight changes. Whether the predictive validity of 'MUST' can be improved by raising the BMI cut-offs at which an individual is identified as at risk of malnutrition warrants further work. Nutritional screening tools will all be limited by their ability to accurately assess FFM and whilst technologies such as BIA allow for the estimation of FFM, there are currently no reference values for the COPD population making comparison difficult. General FFMI cut-offs (≤ 15 kg/m^2 for females and ≤ 16 kg/m^2 for males) incorporated into a nutritional assessment tool alongside measures of BMI and recent unintentional weight loss are likely to have higher sensitivity and specificity but whether the performance of this additional measure and the requirement for specialist equipment is acceptable to clinicians is yet to be established. Yet whilst incorporation of BIA into assessment tools will

assist in identifying those with body compositional changes, there will continue to be questions around how best to treat an individual identified as FFM deplete. These are questions that need to be addressed within future trials.

Whilst malnutrition risk is significantly associated with disease-severity, adjusted analysis revealed that it is an independent predictor of malnutrition and not merely due to increase respiratory impairment. This is supported by the finding that whilst COPD disease severity cannot be reversed malnutrition is modifiable through nutritional support resulting in a number of clinical and functional improvements (**chapter 3**). This thesis provides new interpretation, of what could be considered to be relatively old data, highlighting limitations in the methodology of previous review which resulted in incorrect conclusions that nutritional support is ineffective in COPD. It is hoped that these new findings will reignite interest in the field and lead to a strengthening of the evidence base allowing nutritional management to be embedded within clinical guidelines and underpinned by the highest quality evidence.

The randomised trial (**chapter 5**) found that intervention using ONS and DA to be associated with maintenance of body weight, function and quality of life. Unfortunately, difficulties with recruitment resulted in an underpowered trial. A similar intervention trial involving DA in UK outpatients with COPD reported a large amount of weight loss in the control group (74) so weight maintenance in such a cohort of underweight individuals with severe respiratory disease may represent a treatment effect. However, in the absence of a control group it is not possible to establish if the clinical course of these patients would have been different had they received no intervention. When analysis of the whole cohort was performed (ONS + DA), the trial did indicate that despite the presence of considerable nutritional depletion and severe respiratory disease these patients were still able to demonstrate significant improvements in intake (energy and protein), body weight and function (non-dominant grip strength). Ideally these results would be confirmed in a larger sample and compared against a group receiving usual care.

In clinical practice, dietitians tend to provide ONS in combination with dietary counselling encouraging food fortification. However, formal trials investigating the effectiveness of a combined approach are lacking. In the current trial outpatients

were either randomised to receive either ONS or DA delivered by a dietitian, potentially two additional treatment arms could be added to include a group receiving usual care, as well as a group receiving a combination of both ONS and DA. This would require the recruitment of a large cohort of patients most likely as part of a multi-centre trial. The current evidence base for nutritional support in COPD appears to suggest that intervention in the form of ONS is effective in stable COPD patients with a BMI > 18.5 kg/m^2. However, in those individuals with a BMI < 18.5 kg/m^2 it appears that a multi-modal approach may be required. Although energy intake from food was not significantly reduced during the period of supplementation, maximisation of oral intake through dietary counselling is only likely to be beneficial. This has to be confirmed with larger intervention trials but a prudent recommendation based on the current evidence would be to prescribe ONS in all COPD patients with a BMI < 20 kg/m^2, this would be in agreement with the recommendations made by organisations such as the National Institute for Health and Clinical Excellence (NICE, CG32, 2006) and European Society for Clinical Nutrition and Metabolism (ESPEN) (Anker et al., 2006). However, in those individuals with a BMI < 18.5 kg/m^2, in addition to ONS the patient should be referred to a dietitian in order to maximise oral intake and hopefully instil lasting dietary behaviour change.

COPD is a complex heterogeneous disease with many different phenotypes and subgroups now identified. Whilst these differences are gradually being better understood through large multi-centre observational studies such as the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) (232), more work should be done to better understand the nutritional phenotypes under the umbrella term of COPD and the interaction between nutritional status, COPD, inflammation, exacerbations and the response to treatments. Nutritional characterisation should form part of pharmaceutical research in the field and this will require going beyond simple characterisation according to BMI and FFMI.

The issue of when to nutritionally intervene in COPD is not straightforward and will always require a degree of clinical judgement. Chapter 4 described the complex interaction between smoking status, deprivation, malnutrition risk and BMI. The confirmation that an obesity paradox exists in outpatients with COPD highlights the

need to for further work in order to understand both when to intervene for weight gain but also weight loss. There does appear to be a role for the early initiation of targeted nutrition beyond the treatment of malnutrition with increases in weight being associated with a spectrum of improvements. However, weight loss in COPD appears to be only associated with negative outcomes. Until those factors that are protective in the overweight and obese are identified, weight loss in this patient group should be initiated with caution. Calorie restriction alone will reduce fat mass but some degree of FFM loss is inevitable unless the programme of weight loss is undertaken as part of an exercise programme although such studies are yet to be carried out particularly assessing body compositional changes.

Whilst the effectiveness of nutritional support in stable individuals with COPD appears robust, it is hoped the findings of this thesis will lead to a growth in the evidence base. Chapter 3 highlighted the limited number of trials, particularly those considered to be of high quality, and that the over half of the sample size for all of those RCTs included came from two trials (56), one of which was split into two for interpretation purposes (57, 58). The majority of these trials involved nourished exercising patients. However, with the majority of COPD patients not enrolled in a formal exercise programme and the aim of nutritional support primarily being the treatment of malnutrition, there is a need for further work investigating the effectiveness of nutritional interventions in stable outpatients outside the confides of rehabilitation programmes. The findings of the whole cohort and that of the trial by Weekes et al., suggest such interventions are likely to be effective yet they have to be large enough to allow for formal economic analysis (e.g. cost per quality adjusted life year analysis) and focusing on those outcomes that are difficult to measure (healthcare use (primary and secondary care) and mortality).

An area of the evidence base that requires a great deal of work is the effectiveness of nutritional support in the acute setting during infective exacerbations of COPD. Whilst ONS are high in energy and protein and contain micronutrients to various levels, to assume one supplement is as effective across all disease states is naive. Whether specific nutritional agents can influence the inflammatory response and/or body compositional changes that occur in COPD warrants further exploration. Specific amino acids such as Glutamine and Leucine

may have enhanced roles or requirements during acute inflammation. In addition n-3 fatty acids may have a potential immunomodulatory role as suggested in other acute respiratory illnesses (233, 234). Beta-hydroxy beta-methylbutyrate (HMB), a derivative of the amino acid Leucine, has been suggested to have anti-inflammatory and anti-catabolic effects in wasting diseases (235). Although in advanced cancer cachexia the findings have been less promising (236), the use of HMB enriched high protein high energy ONS and enteral feeds certainly warrants exploration.

It is hoped this thesis will go some way to addressing the current controversy surrounding nutritional support in COPD. Nutrition should be an integral component and imbedded into the clinical management of patients with COPD and as such guidelines should recommend the formal detection and treatment of malnutrition. Dietitians have to promote their role and the contribution they can make to the respiratory multi-disciplinary team as have physiotherapists have in the past. As the complex interaction between nutritional depletion and repletion, systemic inflammation and graded physical activity becomes unravelled, it is likely that nutritional support can be tailored to the individual and their clinical condition at that time. These windows of opportunity to enhance treatment through nutrition will differ from the stable COPD outpatient, to the acutely exacerbating inpatient, through to those engaged in an exercise programme. Therefore in the coming years it is likely that the role of nutrition in chronic respiratory disease will have moved from ignorance and merely supportive care to targeted intervention resulting in large and clinically relevant functional improvements that have health consequences and impact on patient's quality of life.

'Now this is not the end. It is not even the beginning of the end. But it is, perhaps the end of the beginning' Sir Winston Churchill (1942).

6.1 References

1. Baarends EM, Schols AM, Pannemans DL, Westerterp KR, Wouters EF. Total free living energy expenditure in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997, 155 (2): 549-54.
2. Nguyen LT, Bedu M, Caillaud D, Beaufrère B, Beaujon B, Vasson M-P, et al., Increased resting energy expenditure is related to plasmaTNF-α concentration in stable COPD patients. Clinical Nutrition 1999,18 (5): 269-74.
3. Sobotka S, Allison SP, Ljungqvist O, Meier RF, Pertkiewics M, Soeters PB. Basics in Clinical Nutrition. Prague: Galen; 2011.
4. Russell C, Elia M. Nutrition screening survey in the UK in 2008. Hospitals, care homes and mental health units. British Association of Parenteral and Enteral Nutrition (BAPEN). Redditch: BAPEN; 2009.
5. Russell CA, Elia M. Malnutrition in the UK: where does it begin? Proc Nutr Soc. 2010, 69 (4): 465-9.
6. National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre, 2010. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English
7. British Thoracic Society. COPD Guidelines. Thorax, 1997, S1-S32.
8. Elia M, Russell CA. Combating Malnutrition: Recommendations for Action. British Association of Parenteral and Enteral Nutrition (BAPEN). Redditch: BAPEN, 2008.
9. Howard P, Jonkers-Schuitema C, Furniss L, Kyle U, Muehlebach S, Odlund-Olin A, et al. Managing the patient journey through enteral nutritional care. Clinical Nutrition. 2006, 25 (2): 187-95.
10. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence based approach to treatment. Oxford: CABI Publishing (CABI International); 2003.
11. Elia M. Guidelines for Detection and Management of Malnutrition. Malnutrition Advisory Group (MAG), Standing Committee of BAPEN. British Assoiation of Parenteral and Enteral Nutrition (BAPEN). Maidenhead, 2000.
12. American Society of Parenteral and Enteral Nutrition (A.S.P.E.N) Board of Directors and Standards Committee: Teitelbaum D, Guenter P, Howell WH, Kochevar ME, Roth J, Seidner DL. Definitions of terms, style, and conventions in A.S.P.E.N guidelines and standards. Nutrition in Clinical Practice. 2005, 20: 281-285.
13. Elia M, Stratton RJ. Considerations for screening tool selection and role of predictive and concurrent validity. Curr Opin Clin Nutr Metab Care. 2011, 14 (5): 425-33.
14. World Health Organization (WHO). Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization, 2000. p. 1-253.
15. Beck AM, Ovesen L. At which body mass index and degree of weight loss should hospitalized elderly patients be considered at nutritional risk? Clinical Nutrition. 1998, 17 (5): 195-8.
16. Metropolitan Life Insurance Company. Metropolitan Life Insurance Company: New weight standards for men and women, Statistical Bulletin, 1959. p. 1-4.
17. Newman AB, Lee SL, Visser M, Goodpaster BH, Kritchevsky SB, Tylavsky FA, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. Am J Clin Nutr. 2005, 82 (4): 872-8.

18. Hebuterne X, Bermon S, Schneider SM. Ageing and muscle: the effects of malnutrition, re-nutrition, and physical exercise. Curr Opin Clin Nutr Metab Care. 2001, 4 (4): 295-300.
19. Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000, 161 (3 Pt 1): 745-52.
20. Steiner MC, Barton RL, Singh SJ, Morgan MD. Bedside methods versus dual energy X-ray absorptiometry for body composition measurement in COPD. Eur Respir J. 2002, 19 (4): 626-31.
21. Cano NJ, Roth H, Court-Ortune I, Cynober L, Gerard-Boncompain M, Cuvelier A, et al. Nutritional depletion in patients on long-term oxygen therapy and/or home mechanical ventilation. Eur Respir J. 2002, 20 (1): 30-7.
22. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis. 1993, 147 (5): 1151-6.
23. Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. Am J Clin Nutr. 2004, 79 (4): 613-8.
24. Russell CA, Elia M. Nutrition Screening Survey in the UK in 2007. British Association of Parental and Enteral Nutrition (BAPEN). Redditch: BAPEN; 2008.
25. Skinner RA, Smith JC. Dietitian management of oral nutritional supplement prescribing is cost effective and improves quality of care. Proc Nutr Soc. 2008, 67: E120.
26. Baldwin C, Weekes CE. Dietary advice for illness-related malnutrition in adults. Cochrane database of systematic reviews. 2008, (1): CD002008.
27. Baldwin C, Weekes CE. Dietary advice with or without oral nutritional supplements for disease-related malnutrition in adults. Cochrane database of systematic reviews. 2011, 9: CD002008.
28. Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med. 2000, 343 (4): 269-80.
29. Global Initative for Chronic Obstructive Lung Disease (GOLD). A pocket guide to COPD diagnosis, management, and prevention. 2010.
30. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2007, 4 (7): 502-6.
31. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). Respiration. 2001, 68 (1): 4-19.
32. British Thoracic Society. The Burden of Lung Disease, 2nd Edition. London, 2006 [cited 2011 August 2011]; Available from: http://www.brit-thoracic.org.uk
33. Price LC, Lowe D, Hosker HS, Anstey K, Pearson MG, Roberts CM. UK National COPD Audit 2003: Impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. Thorax. 2006, 61 (10): 837-42.
34. Britton M. The burden of COPD in the U.K: results from the Confronting COPD survey. Respiratory Medicine. 2003, 97 Suppl C:S71-9.
35. Halpin DM. Health economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006, 3 (3): 227-33.
36. Vandenbergh E, Van de Woestijne KP, Gyselen A. Weight changes in the terminal stages of chronic obstructive pulmonary disease. Relation to respiratory function and prognosis. Am Rev Respir Dis. 1967, 95 (4): 556-66.

37. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998, 157 (6 Pt 1): 1791-7.
38. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. Eur Respir J. 2002, 20 (3): 539-44.
39. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med.1999, 160 (6): 1856-61.
40. Engelen MP, Schols AM, Lamers RJ, Wouters EF. Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. Clinical Nutrition.1999, 18 (5): 275-80.
41. Gronberg AM, Slinde F, Engstrom CP, Hulthen L, Larsson S. Dietary problems in patients with severe chronic obstructive pulmonary disease. J Hum Nutr Diet. 2005, 18 (6): 445-52.
42. Koehler F, Doehner W, Hoernig S, Witt C, Anker SD, John M. Anorexia in chronic obstructive pulmonary disease--association to cachexia and hormonal derangement. Int J Cardiol. 2007, 25; 119 (1): 83-9.
43. Morrison WL, Gibson JN, Scrimgeour C, Rennie MJ. Muscle wasting in emphysema. Clin Sci (Lond). 1988, 75 (4): 415-20.
44. Li YP, Schwartz RJ, Waddell ID, Holloway BR, Reid MB. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. Faseb J. 1998, 12 (10): 871-80.
45. Pelegrino NR, Tanni SE, Amaral RA, Angeleli AY, Correa C, Godoy I. Effects of Active Smoking on Airway and Systemic Inflammation Profiles in Patients with Chronic Obstructive Pulmonary Disease. Am J Med Sci. 2012, ePrint.
46. Serapinas D, Narbekovas A, Juskevicius J, Sakalauskas R. Systemic inflammation in COPD in relation to smoking status. Multidiscip Respir Med. 2011, 6 (4): 214-9.
47. Collins PF, Elia M. Clinical Nutrition. Editors: Ljungqvist O, Stratton RJ, Elia M, Lanham-New S. Wiley-Blackwell; 2012.
48. Chapman KM, Winter LC. using nutrition to prevent respiratory decline. Geriatrics. 1996; 51 (12): 37-42.
49. Kunik ME, Roundy K, Veazey C, Souchek J, Richardson P, Wray NP, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. CHEST. 2005; 127 (4): 1205-11.
50. Subar AF, Harlan LC, Mattson ME. Food and nutrient intake differences between smokers and non-smokers in the US. Am J Public Health. 1990, 80 (11): 1323-9.
51. Palaniappan U, Jacobs Starkey L, O'Loughlin J, Gray-Donald K. Fruit and vegetable consumption is lower and saturated fat intake is higher among Canadians reporting smoking. J Nutr. 2001, 131 (7): 1952-8.
52. Obase Y, Mouri K, Shimizu H, Ohue Y, Kobashi Y, Kawahara K, et al. Nutritional deficits in elderly smokers with respiratory symptoms that do not fulfill the criteria for COPD. International Journal of Chronic Obstructive Pulmonary Disease. 2011; 6: 679-83.
53. Shohaimi S, Luben R, Wareham N, Day N, Bingham S, Welch A, et al. Residential area deprivation predicts smoking habit independently of individual educational level and occupational social class. A cross sectional study in the Norfolk cohort of the European Investigation into Cancer (EPIC-Norfolk). J Epidemiol Community Health. 2003, 57 (4): 270-6.

54. Elia M, Stratton RJ. Geographical inequalities in nutrient status and risk of malnutrition among English people aged 65 y and older. Nutrition. 2005, 21 (11-12): 1100-6.
55. Bernard S, LeBlanc P, Whittom F, Carrier G, Jobin J, Belleau R, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998, 158 (2): 629-34.
56. Steiner MC, Barton RL, Singh SJ, Morgan MD. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. Thorax. 2003, 58 (9): 745-51.
57. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med. 1995, 152 (4 Pt 1): 1268-74. [*Nourished patients*]
58. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med. 1995a; 152 (4 Pt 1): 1268-74. [*Malnourished patients*]
59. Congleton J. The pulmonary cachexia syndrome: aspects of energy balance. Proc Nutr Soc. 1999, 58 (2): 321-8.
60. Schols A, Mostert R, Cobben N, Soeters P, Wouters E. Transcutaneous oxygen saturation and carbon dioxide tension during meals in patients with chronic obstructive pulmonary disease. CHEST. 1991, 100 (5): 1287-92.
61. Schols AMWJ, Brug J. Efficacy of nutritional intervention in chronic obstructive pulmonary disease. Eur Respir Mono. 2003; 24: 142-52.
62. Gray-Donald K, Carrey Z, Martin JG. Postprandial dyspnea and malnutrition in patients with chronic obstructive pulmonary disease. Clinical and investigative medicine Medecine clinique et experimentale. 1998, 21 (3): 135-41.
63. Connors AF, Jr., Dawson NV, Thomas C, Harrell FE, Jr., Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med. 1996, 154 (4 Pt 1): 959-67.
64. Steele RM, Finucane FM, Griffin SJ, Wareham NJ, Ekelund U. Obesity Is Associated With Altered Lung Function Independently of Physical Activity and Fitness. Obesity. 2009; 17 (3): 578-84.
65. Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. CHEST. 2004, 125 (6): 2046-52.
66. National Institute for Health and Clinical Excellence. Nutrition support in adults: Oral nutrition support, enteral tube feeding and parenteral nutrition. 2006.
67. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. Eur Respir J. 1994, 7 (10): 1793-7.
68. Vermeeren MA, Creutzberg EC, Schols AM, Postma DS, Pieters WR, Roldaan AC, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med. 2006, 100 (8): 1349-55.
69. van Binsbergen JJ, Delaney BC, van Weel C. Nutrition in primary care: scope and relevance of output from the Cochrane Collaboration. Am J Clin Nutr. 2003, 77 (4 Suppl): 1083S-8S.
70. Ferreira I. Up date nutritional support for patients with COPD. Respiratory Medicine. 2008 (Update 4): 127-31.
71. Ferreira I, Brooks D, Lacasse Y, Goldstein R. Nutritional intervention in COPD: a systematic overview. CHEST. 2001, 119 (2): 353-63.

72. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. CHEST. 2000, 117 (3): 672-8.
73. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS, White J. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005 (2): CD000998.
74. Weekes CE, Emery PW, Elia M. Dietary counselling and food fortification in stable COPD: a randomised trial. Thorax. 2009, 64 (4): 326-31.
75. Saudny-Unterberger H, Martin JG, Gray-Donald K. Impact of nutritional support on functional status during an acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997, 156 (3 Pt 1): 794-9.
76. Turic A, Gordon KL, Craig LD, Ataya DG, Voss AC. Nutrition supplementation enables elderly residents of long-term-care facilities to meet or exceed RDAs without displacing energy or nutrient intakes from meals. J Am Diet Assoc. 1998, 98 (12): 1457-9.
77. Wouters-Wesseling W, Van Hooijdonk C, Wagenaar L, Bindels J, de Groot L, Van Staveren W. The effect of a liquid nutrition supplement on body composition and physical functioning in elderly people. Clinical Nutrition. 2003, 22 (4): 371-7.
78. Norregaard O, Tottrup A, Saaek A, Hessov I. Effects of oral nutritional supplements to adults with chronic obstructive pulmonary disease. Clinical and Research Physiology. 1987; 23: 388s.
79. Efthimiou J, Fleming J, Gomes C, Spiro SG. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1988, 137 (5): 1075-82.
80. Lewis MI, Belman MJ, Dorr-Uyemura L. Nutritional supplementation in ambulatory patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1987, 135 (5): 1062-8.
81. Wilson DO, Rogers RM, Sanders MH, Pennock BE, Reilly JJ. Nutritional intervention in malnourished patients with emphysema. Am Rev Respir Dis. 1986, 134 (4): 672-7.
82. Whittaker JS, Ryan CF, Buckley PA, Road JD. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. Am Rev Respir Dis. 1990, 142 (2): 283-8.
83. Rogers RM, Donahoe M, Costantino J. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. A randomized control study. Am Rev Respir Dis. 1992, 146 (6): 1511-7.
84. Goris AH, Vermeeren MA, Wouters EF, Schols AM, Westerterp KR. Energy balance in depleted ambulatory patients with chronic obstructive pulmonary disease: the effect of physical activity and oral nutritional supplementation. Br J Nutr. 2003, 89 (5): 725-31.
85. Stratton RJ, Elia M. A review of reviews: A new look at the evidence for oral nutritional supplements in clinical practice. Clinical Nutrition. 2007; 2 (1): 5-23.
86. Stratton RJ, Elia M. Are oral nutritional supplements of benefit to patients in the community? Findings from a systematic review. Curr Opin Clin Nutr Metab Care. 2000; 3 (11): 311-5.
87. McCombie L. Sip feed prescribing in prmary care: an audit of current practice in Greater Glasgow Health Board, Glasgow, UK. J Hum Nutr Diet. 1999; 12 (3): 201-12.
88. Stratton RJ. Should food or supplements be used in the community for the treatment of disease-related malnutrition? Proc Nutr Soc. 2005; 64: 325-33.
89. Thomas B. Malnual of Dietetic Practice. Third Edition. London: Blackwell; 2003.

90. Weekes CE. An evaluation of dietetic strategies in the management of chronic obstructive pulmonary disease; nutrition screening, tailored dietary advice and food fortification. London: King's College, University of London; 2005. [*PhD thesis*]
91. Weisberg J, Wanger J, Olson J, Streit B, Fogarty C, Martin T, et al. Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. CHEST. 2002, 121 (4): 1070-8.
92. Pison CM, Cano NJ, Cherion C, Caron F, Court-Fortune I, Antonini MT, et al. Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial. Thorax. 2011, 66 (11): 953-60.
93. Ferreira IM, Verreschi IT, Nery LE, Goldstein RS, Zamel N, Brooks D, et al. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. CHEST. 1998, 114 (1): 19-28.
94. Creutzberg EC, Wouters EF, Mostert R, Pluymers RJ, Schols AM. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. CHEST. 2003, 124 (5): 1733-42.
95. Broekhuizen R, Wouters EF, Creutzberg EC, Weling-Scheepers CA, Schols AM. Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. Thorax. 2005, 60 (5): 376-82.
96. Agusti A, Morla M, Sauleda J, Saus C, Busquets X. NF-kappaB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. Thorax. 2004, 59 (6): 483-7.
97. Payette H, Boutier V, Coulombe C, Gray-Donald K. Benefits of Nutritional Supplementation in Free-living, Frail, Undernourished Elderly People. Journal of the American Dietetic Association. 2002; 102 (8): 1088-95.
98. Stratton RJ, Elia M. Encouraging appropriate, evidence-based use of oral nutritional supplements. Proc Nutr Soc. 2010; 69: 477-87.
99. Baldwin C, Parsons T, Logan S. Dietary advice for illness-related malnutrition in adults. Cochrane database of systematic reviews. 2001 (2): CD002008.
100. Stratton RJ, Elia M. The skeleton in the closet: malnutrition in the community Encouraging appropriate, evidence-based use of oral nutritional supplements. Proc Nut Soc. 2010; 69: 477-87.
101. Russell CA. The impact of malnutrition on healthcare costs and economic considerations for the use of oral nutritional supplements. Clinical Nutrition. 2007; 2 (1): 25-32.
102. Ezzell L, Jensen GL. Malnutrition in chronic obstructive pulmonary disease. Am J Clin Nutr. 2000, 72 (6): 1415-6.
103. Fuenzalida CE, Petty TL, Jones ML, Jarrett S, Harbeck RJ, Terry RW, et al. The immune response to short-term nutritional intervention in advanced chronic obstructive pulmonary disease. Am Rev Respir Dis. 1990, 142 (1): 49-56.
104. Otte KE, Ahlburg P, D'Amore F, Stellfeld M. Nutritional repletion in malnourished patients with emphysema. J Parenter Enteral Nutr. 1989, 13 (2): 152-6.
105. Stratton RJ and Elia M. A critical, systematic analysis of the use of oral nutritional supplements in the community. Clinical Nutrition. 1999; 18 (2): 29-84.
106. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999, 27; 354 (9193): 1896-900.
107. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 The Cochrane Collaboration; 2009.

108. Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. University of York; 2009.
109. Knowles JB, Fairbarn MS, Wiggs BJ, Chan-Yan C, Pardy RL. Dietary supplementation and respiratory muscle performance in patients with COPD. CHEST. 1988, 93 (5): 977-83.
110. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996, 17 (1): 1-12.
111. Borenstein M, Hedges LV, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons Ltd; 2009.
112. Adams G. Effect of nasogastric feedings on arterial oxygen tension in patients with symptomatic chronic obstructive pulmonary disease. Heart Lung. 1988 Sep;17(5):594.
113. Aguilaniu B, Goldstein-Shapses S, Pajon A, Levy P, Sarrot F, Leverve X, et al. Muscle protein degradation in severely malnourished patients with chronic obstructive pulmonary disease subject to short-term total parenteral nutrition. J Parenter Enteral Nutr. 1992, 16 (3): 248-54.
114. Akrabawi SS, Mobarhan S, Stoltz RR, Ferguson PW. Gastric emptying, pulmonary function, gas exchange, and respiratory quotient after feeding a moderate versus high fat enteral formula meal in chronic obstructive pulmonary disease patients. Nutrition. 1996, 12 (4): 260-5.
115. Baldi S, Aquilani R, Pinna GD, Poggi P, De Martini A, Bruschi C. Fat-free mass change after nutritional rehabilitation in weight losing COPD: role of insulin, C-reactive protein and tissue hypoxia. Int J Chron Obstruct Pulmon Dis. 2010; 5: 29-39.
116. Borum ML, Lynn J, Zhong Z, Roth K, Connors AF, Jr., Desbiens NA, et al. The effect of nutritional supplementation on survival in seriously ill hospitalized adults: an evaluation of the SUPPORT data. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. J Am Geriatr Soc. 2000, 48 (5 Suppl): S33-8.
117. Broekhuizen R, Creutzberg EC, Weling-Scheepers CA, Wouters EF, Schols AM. Optimizing oral nutritional drink supplementation in patients with chronic obstructive pulmonary disease. Br J Nutr. 2005, 93 (6): 965-71.
118. Cai B, Zhu Y, Ma Y, Xu Z, Zao Y, Wang J, et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. Nutrition. 2003, 19 (3): 229-32.
119. Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. Nutrition. 2003, 19 (2): 120-7.
120. Deacon SJ, Vincent EE, Greenhaff PL, Fox J, Steiner MC, Singh SJ, et al. Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008, 178 (3): 233-9.
121. DeLetter M. A nutritional intervention for persons with chronic airflow limitation. University of Kentucky; 1991. [*PhD Thesis*]
122. Dore MF, Laaban JP, Orvoen-Frija E, Kouchakji B, Joubert M, Rochemaure J. Role of the thermic effect of food in malnutrition of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997, 155 (5): 1535-40.
123. Efthimiou J, Mounsey PJ, Benson DN, Madgwick R, Coles SJ, Benson MK. Effect of carbohydrate rich versus fat rich loads on gas exchange and walking performance in patients with chronic obstructive lung disease. Thorax. 1992, 47 (6): 451-6.

124. Faager G, Soderlund K, Skold CM, Rundgren S, Tollback A, Jakobsson P. Creatine supplementation and physical training in patients with COPD: a double blind, placebo-controlled study. Int J Chron Obstruct Pulmon Dis. 2006, 1 (4): 445-53.
125. Felbinger TW, Suchner U. Nutrition for the malnourished patient with chronic obstructive pulmonary disease: more is better! Nutrition. 2003, 19 (5): 471-2.
126. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional supplementation in stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2000 (3): CD000998.
127. Forli L, Pedersen JI, Bjortuft O, Vatn M, Boe J. Dietary support to underweight patients with end-stage pulmonary disease assessed for lung transplantation. Respiration. 2001, 68 (1): 51-7.
128. Fuld JP, Kilduff LP, Neder JA, Pitsiladis Y, Lean ME, Ward SA, et al. Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax. 2005, 60 (7): 531-7.
129. Grigorakos L, Sotiriou E, Markou N, Stratouli S, Boutzouka E, Philntisis G, et al. Combined nutritional support in patients with chronic obstructive pulmonary disease (COPD), under mechanical ventilation (MV). Hepatogastroenterology. 2009, 56 (96): 1612-4.
130. Hoogendoorn M, van Wetering CR, Schols AM, Rutten-van Molken MP. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? Eur Respir J. 2010, 35 (1): 79-87.
131. Iovinelli G, Marinangeli F, Ciccone A, Ciccozzi A, Leonardis M, Paladini A, et al. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs medium chain triglycerides. Minerva Anestesiol. 2007, 73 (1-2): 65-76.
132. Kubo H, Honda N, Tsuji F, Iwanaga T, Muraki M, Tohda Y. Effects of dietary supplements on the Fischer ratio before and after pulmonary rehabilitation. Asia Pac J Clin Nutr. 2006, 15 (4): 551-5.
133. Laviolette L, Lands LC, Dauletbaev N, Saey D, Milot J, Provencher S, et al. Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study. J Med Food. 2010, 13 (3): 589-98.
134. Marchesani F, Valerio G, Dardes N, Viglianti B, Sanguinetti CM. Effect of intravenous fructose 1,6-diphosphate administration in malnourished chronic obstructive pulmonary disease patients with chronic respiratory failure. Respiration. 2000, 67 (2): 177-82.
135. Planas M, Alvarez J, Garcia-Peris PA, de la Cuerda C, de Lucas P, Castella M, et al. Nutritional support and quality of life in stable chronic obstructive pulmonary disease (COPD) patients. Clin Nutr. 2005, 24 (3): 433-41.
136. Slinde F, Gronberg AM, Engstrom CR, Rossander-Hulthen L, Larsson S. Individual dietary intervention in patients with COPD during multidisciplinary rehabilitation. Respir Med. 2002, 96 (5): 330-6.
137. Vargas M, Puig A, de la Maza M, Morales P, Vargas D, Bunout B, et al. [Patients with chronic airflow limitation: effects of the inspiratory muscle training with threshold load valve, built with appropriate technology, associated to nutritional support]. Rev Med Chil. 1995, 123 (10): 1225-34.
138. Vermeeren MA, Wouters EF, Nelissen LH, van Lier A, Hofman Z, Schols AM. Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease. Am J Clin Nutr. 2001, 73 (2): 295-301.

139. Angelillo VA, Bedi S, Durfee D, Dahl J, Patterson AJ, O'Donohue WJ, Jr. Effects of low and high carbohydrate feedings in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. Ann Intern Med. 1985, 103 (6 Pt 1): 883-5.
140. Slinde F, Gronberg AM, Engstrom CR, Rossander-Hulthen L, Larsson S. Individual dietary intervention in patients with COPD during multidisciplinary rehabilitation. Respiratory Medicine. 2002, 96 (5): 330-6.
141. Vermeeren MA, Wouters EF, Geraerts-Keeris AJ, Schols AM. Nutritional support in patients with chronic obstructive pulmonary disease during hospitalization for an acute exacerbation; a randomized controlled feasibility trial. Clinical Nutrition. 2004, 23 (5): 1184-92.
142. Hiemstra PS, van Wetering S, Stolk J. Neutrophil serine proteinases and defensins in chronic obstructive pulmonary disease: effects on pulmonary epithelium. Eur Respir J. 1998, 12 (5): 1200-8.
143. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001, 20 (4): 641-54.
144. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. Brit Med J. 2006, 333 (7568): 597-600.
145. Ferreira I. Up date nutritional support for patients with COPD. Respiratory Medicine. 2008 (update 4): 127-31.
146. Arora NS, Rochester DF. Effect of body weight and muscularity on human diaphragm muscle mass, thickness, and area. Journal of applied physiology: respiratory, environmental and exercise physiology. 1982, 52 (1): 64-70.
147. Lewis MI, Sieck GC, Fournier M, Belman MJ. Effect of nutritional deprivation on diaphragm contractility and muscle fiber size. Journal of applied physiology. 1986, 60 (2): 596-603.
148. Gonzalez-Moro JM, De Miguel-Diez J, Paz-Gonzalez L, Buendia-Garcia MJ, Santacruz-Siminiani A, De Lucas-Ramos P. Abnormalities of the respiratory function and control of ventilation in patients with anorexia nervosa. Respiration; international review of thoracic diseases. 2003, 70 (5): 490-5.
149. Murciano D, Rigaud D, Pingleton S, Armengaud MH, Melchior JC, Aubier M. Diaphragmatic function in severely malnourished patients with anorexia nervosa. Effects of renutrition. American journal of respiratory and critical care medicine.1994, 150 (6 Pt 1): 1569-74.
150. Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Clin Nutr. 2012, 95 (6): 1385-1395.
151. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clinical Nutrition. 2008 Dec;27(6):793-9.
152. Norman K, Stobaus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clinical Nutrition. 2011 Apr;30(2):135-42.
153. Hornby ST, Nunes QM, Hillman TE, Stanga Z, Neal KR, Rowlands BJ, et al. Relationships between structural and functional measures of nutritional status in a normally nourished population. Clinical Nutrition. 2005;24(3):421-6.
154. Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. The American journal of clinical nutrition. [Research Support, Non-U.S. Gov't]. 2007 May;85(5):1257-66.
155. Budziareck MB, Pureza Duarte RR, Barbosa-Silva MC. Reference values and determinants for handgrip strength in healthy subjects. Clinical Nutrition. [Research Support, Non-U.S. Gov't]. 2008 Jun;27(3):357-62.

156. Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev. 2012 Apr;11(2):278-96.
157. Soler-Cataluna JJ, Sanchez-Sanchez L, Martinez-Garcia MA, Sanchez PR, Salcedo E, Navarro M. Mid-arm muscle area is a better predictor of mortality than body mass index in COPD. CHEST 2005, 128 (4): 2108-15.
158. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. American Journal of Respiratory and Critical Care Medicine. 2003, 167 (4): 544-9.
159. Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Annals of internal medicine. 2001, 135 (10): 847-57.
160. Datta D, Lahiri B. Preoperative evaluation of patients undergoing lung resection surgery. CHEST. 2003, 123 (6): 2096-103.
161. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. CHEST. 2005, 128 (4): 2025-34.
162. Koechlin C, Couillard A, Cristol JP, Chanez P, Hayot M, Le Gallais D, et al. Does systemic inflammation trigger local exercise-induced oxidative stress in COPD? Eur Respir J. 2004, 23: 538-44.
163. Garrod R, Ansley P, Canavan J, Jewell A. Exercise and the inflammatory response in chronic obstructive pulmonary disease (COPD)--Does training confer anti-inflammatory properties in COPD? Med Hypotheses. 2007, 68 (2): 291-8.
164. Sugawara K, Takahashi H, Kasai C, Kiyokawa N, Watanabe T, Fujii S, et al. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. Respiratory Medicine. 2010, 104 (12): 1883-9.
165. van Wetering CR, Hoogendoorn M, Broekhuizen R, Geraerts-Keeris GJW, De Munck D, Rutten-van Molken MPMH, et al. Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. Journal of the American Directors Association. 2010; 11 (3): 179-87.
166. Doekel RC, Jr., Zwillich CW, Scoggin CH, Kryger M, Weil JV. Clinical semi-starvation: depression of hypoxic ventilatory response. N Engl J Med. 1976, 12; 295 (7): 358-61.
167. de Torres JP, Casanova C, Montejo de Garcini A, Aguirre-Jaime A, Celli BR. Gender and respiratory factors associated with dyspnea in chronic obstructive pulmonary disease. Respir Res. 2007; 8: 18.
168. World Health Organization (WHO). Active Aging: a Policy Framework. Madrid, Spain, 2002.
169. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005, 2 (1): 125-9.
170. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008, 63 (9): 775-7.
171. Lacasse Y, Goldstein R, Lasserson T, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrance Database of Systematic Reviews. 2006; 18 (4): CD003793.
172. Anker SD, John M, Pedersen PU, Raguso C, Cicoira M, Dardai E, et al. ESPEN Guidelines on Enteral Nutrition: Cardiology and pulmonology. Clinical Nutrition. 2006, 25 (2): 311-8.

173. Hallin R, Koivisto-Hursti UK, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). Respir Med. 2006, 100 (3): 561-7.
174. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998, 157 (5 Pt 1): 1418-22.
175. Bottle A, Aylin P, Majeed A. Identifying patients at high risk of emergency hospital admissions: a logistic regression analysis. J R Soc Med. 2006, 99 (8): 406-14.
176. Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. CHEST. 2003, 123 (5): 1460-6.
177. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body Weight in Chronic Obstructive Pulmonary Disease: The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am J Respir Crit Care Med. 1989; 139 (6): 1435-8.
178. Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. Brit J Nutr. 2004, 92 (5): 799-808.
179. Stratton RJ, King CL, Stroud MA, Jackson AA, Elia M. 'Malnutrition Universal Screening Tool' predicts mortality and length of hospital stay in acutely ill elderly. Brit J Nutr. 2006, 95 (2): 325-30.
180. Elia Me. The 'MUST' Report: Nutritional Screening for Adults - a multidisciplinary responsibility. Malnutrition Action Group (MAG). British Association of Parenteral and Enteral Nutrition (BAPEN): Redditch.; 2003.
181. Craig R, Shelton NE. Health Survey for England 2007. London: The Information Centre; 2009.
182. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr. 2005, 82 (1): 53-9.
183. Schols AM, Wouters EF, Soeters PB, Westerterp KR. Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. Am J Clin Nutr. 1991, 53 (2): 421-4.
184. Steuten LM, Creutzberg EC, Vrijhoef HJ, Wouters EF. COPD as a multicomponent disease: inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. Prim Care Respir J. 2006, 15 (2): 84-91.
185. Foundation BL. Invisible Lives: Chronoc Obstructive Pulmonary Disease (COPD) - finding the missing millions. London, 2007.
186. Mapel DW, Dedrick D, Davis K. Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991-1999. COPD. 2005, 2 (1): 35-41.
187. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J. 2008, 32 (4): 962-9.
188. Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function: the normative aging study. CHEST. 1997, 111 (4): 891-8.
189. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med. 2006, 173 (1): 79-83.

190. Shoup R, Dalsky G, Warner S, Davies M, Connors M, Khan M, et al., Body composition and health-related quality of life in patients with obstructive airways disease. Eur Respir J. 1997, 10 (7): 1576-80.
191. Collins PF, Stratton RJ, Kurukulaaratchy R, Warwick H, Cawood AL, Elia M. Prevalence of malnutrition in outpatients with chronic obstructive pulmonary disease. Proc Nutri Soc. 2010; 69 (OCE2): E147.
192. Todorovic V, Russell C, Stratton R, Ward J, Elia M. The 'MUST' Explanatory Booklet. Redditch: BAPEN; 2003.
193. Detsky AS, Baker JP, O'Rourke K, Johnston N, Whitwell J, Mendelson RA, et al. Predicting nutrition-associated complications for patients undergoing gastrointestinal surgery. Journal of Parenteral and Enteral Nutrition. 1987, 11 (5): 440-6.
194. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev. 1996, 54 (1 Pt 2): S59-65.
195. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clinical Nutrition. 2003; 22 (4): 415-21.
196. Flodin L, Svensson S, Cederholm T. Body mass index as a predictor of 1 year mortality in geriatric patients. Clinical Nutrition. 2000, 19 (2): 121-5.
197. Yang L, Zhou M, Smith M, Yang G, Peto R, Wang J, et al. Body mass index and chronic obstructive pulmonary disease-related mortality: a nationally representative prospective study of 220,000 men in China. Int J Epidemiol. 2010, 39 (4): 1027-36.
198. American Thoracic Society/ European Respiratory Society. Standards for the diagnosis and management of patients with COPD. ATS/ERS, 2004. Available from: http://www.thoracic.org/clinical/copd-guidelines/index.php
199. Sabino PG, Silva BM, Brunetto AF. Nutritional status is related to fat-free mass, exercise capacity and inspiratory strength in severe chronic obstructive pulmonary disease patients. Clinics (Sao Paulo). 2010, 65 (6): 599-605.
200. Wannamethee G, Shaper AG. Body weight and mortality in middle aged British men: impact of smoking. Brit Med J.1989, 299 (6714): 1497-502.
201. Faisy C, Rabbat A, Kouchakji B, Laaban JP. Bioelectrical impedance analysis in estimating nutritional status and outcome of patients with chronic obstructive pulmonary disease and acute respiratory failure. Intensive Care Med. 2000, 26 (5): 518-25.
202. Schols AM, Wouters EF. Nutritional abnormalities and supplementation in chronic obstructive pulmonary disease. Clin Chest Med. 2000, 21 (4): 753-62.
203. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, Kovesdy CP, Younessi H, Anker SD, et al. Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care. 2007, 10 (4): 433-42.
204. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. Am J Kidney Dis. 2007, 49 (5): 581-91.
205. Nezu K, Yoshikawa M, Yoneda T, Kushibe K, Kawaguchi T, Yasukawa M, et al. The change in body compsotion after bilateral lung volume reduction surgery for underweight patients with severe emphysema. Lung. 2000, 178 (6): 381-9.
206. Sahebjami H, Doers JT, Render ML, Bond TL. Anthropometric and pulmonary function test profiles of outpatients with stable chronic obstructive pulmonary disease. Am J Med. 1993, 94 (5): 469-74.
207. Stratton RJ, Elia M. Deprivation linked to malnutrition risk and mortality in hospital. Brit J Nutri. 2006, 96 (5): 870-6.

208. Steer J, Norman E, Gibson GJ, Bourke SC. Comparison of indices of nutritional status in prediction of in-hospital mortality and early readmission of patients with acute exacerbations of COPD. Thorax, 2010; 65: A127.
209. Elia M, Stratton RJ. An analytic appraisal of nutrition screening tools supported by original data with particular reference to age. Nutrition. 2012, 28 (5): 477-94.
210. Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. CHEST. 2005, 128 (6): 3810-6.
211. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005, 172 (1): 19-38.
212. Rubí M, Renom F, Ramis F, Medinas M, Centeno MJ, Górriz M, et al. Effectiveness of pulmonary rehabilitation in reducing health resources use in chronic obstructive pulmonary disease. Archives of Physical Medicine and Rehabilitation. 2010, 91 (3): 364-8.
213. Franssen FM, O'Donnell DE, Goossens GH, Blaak EE, Schols AM. Obesity and the lung: 5. Obesity and COPD. Thorax. 2008, 63 (12): 1110-7.
214. Collins PF, Elia M, Smith TR, Kurukulaaratchy R, Cawood AL, Stratton RJ. The impact of malnutrition on hospitalisation and mortality in outpatients with chronic obstructive pulmonary disease. Proc Nutri Soc. 2010, 69 (OCE2): E148.
215. Townsend P. Poverty in the United Kingdom: Penguin; 1979.
216. Townsend P. Deprivation. Journal of Social Policy. 1987; 16 (2): 125-46.
217. Noble M, McLennan D, Wilkinson K, Whitworth A, Barnes H, Dibden C. The English Indices of Deprivation 2007. UK national Statistics: Neighbourhood and Communites. London, 2008.
218. Black DC. Inequalities in health. London: Penguin; 1980.
219. Smith GD, Bartley M, Blane D. The Black Report on socioeconomic inequalities in health 10 years on. Brit Med J. 1990, 301: 373-7.
220. Prescott E, Vestbo J. Socioeconomic status and chronic obstructive pulmonary disease. Thorax. 1999, 54 (8): 737-41.
221. Hawker JI, Olowokure B, Sufi F, Weinberg J, Gill N, Wilson RC. Social deprivation and hospital admission for respiratory infection: an ecological study. Respiratory Medicine. 2003, 97 (11): 1219-24.
222. Rasmussen F, Tynelius P, Kark M. Importance of smoking habits for longitudinal and age-matched changes in body mass index: a cohort study of Swedish men and women. Prev Med. 2003, 37 (1): 1-9.
223. National Clinical Guideline Centre. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. National Institute for Health and Clinical Excellence. London, 2006.
224. Szende A, Oppe M, Devlin N. EQ-5D value sets: inventry, comparative review and user guide. Dordrecht, The Netherlands: Springer; 2007.
225. Pickard AS, Wilke C, Jung E, Patel S, Stavem K, Lee TA. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respiratory Medicine. 2008, 102 (4): 519-36.
226. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respiratory Medicine. 1991, 85 Suppl B: 25-31.
227. Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. Am J Clin Nutr. 1982, 36 (4): 680-90.
228. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of Internal Medicine. 2010, 152 (11): 726-32.

229. Department of Health. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Committee on Medical Aspects of Food Policy. London: TSO; 1991.
230. Saudny-Unterberger H, Martin JG, Gray-Donald K. Impact of nutritional support on functional status during an acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997, 156 (3 Pt 1): 794-9.
231. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clinical Nutrition. 2010 Apr;29(2):154-9.
232. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010, 11: 122.
233. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. Journal of Parenteral and Enteral Nutrition. 2008, 32 (6): 596-605.
234. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006, 34 (4): 1033-8.
235. Aversa Z, Bonetto A, Costelli P, Minero VG, Penna F, Baccino FM, et al. beta-hydroxy-beta-methylbutyrate (HMB) attenuates muscle and body weight loss in experimental cancer cachexia. Int J Oncol. 2011, 38 (3): 713-20.
236. Berk L, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, et al. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). Support Care Cancer. 2008,16 (10): 1179-88.

7.0 Appendices

Appendix 1 Publication and published abstracts

Publication 1 - Collins PF, Stratton RJ, Elia M (2012). Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *American Journal of Clinical Nutrition* (In press).

Background: The efficacy of nutritional support in the management of malnutrition in chronic obstructive pulmonary disease (COPD) is controversial. Previous meta-analyses, based only on cross-sectional analysis at the end of intervention trials, found no evidence of improved outcomes.

Objectives: To conduct a meta-analysis of randomized controlled trials (RCTs) to clarify the efficacy of nutritional support in improving intake, anthropometry and grip strength in stable COPD.

Design: Literature databases were searched to identify RCTs comparing nutritional support versus control in stable COPD.

Results: Thirteen RCTs (n 439) of nutritional support (dietary advice (1 RCT)), oral nutritional supplements (11 RCTs), and enteral tube feeding (1 RCT) versus control were identified. Analysis of the changes induced by nutrition support, as well as those obtained only at the end of the intervention, revealed significantly greater increases in mean total protein and energy intake with nutritional support by 14.8 g and 236 kcal per day. Meta-analyses also demonstrated greater improvements in favor of nutrition support, in grip strength (5.3%, $p<0.050$, 4 studies (n 156)), and body weight (1.94 SE 0.26 kg, $p<0.001$; 11 studies, n 308) which could not be demonstrated by analysis of values at the end of the intervention, largely due to bias associated with baseline imbalance between groups.

Conclusion: Nutritional support, mainly in the form of oral nutritional supplements, improves total intake, anthropometry and grip strength. Previous conclusions based only on analysis of cross-sectional measurements at the end of the intervention period may have masked the changes induced by the intervention.

Abstract 1 Proceedings of the Nutrition Society (2010) 69 (OCE2): E147.
Malnutrition Matters, Joint BAPEN and Nutrition Society Meeting, Cardiff, Wales, 13-14 October 2009.

Prevalence of malnutrition in outpatients with chronic obstructive pulmonary disease. By P.F. COLLINS[1], R.J. STRATTON[1], R. KURUKULAARATCHY[2], H. WARWICK[3], A.L. CAWOOD[14] and M. ELIA[1], *[1]Institute of Human Nutrition, School of Medicine, University of Southampton, [2]Department of Respiratory Medicine, [3]Department of Nutrition & Dietetics, Southampton University Hospital NHS Trust, Southampton, SO16 6YD [4]Medical Affairs, Nutricia, Wiltshire, BA14 0XQ*

Disease-related malnutrition is common in patients with chronic obstructive pulmonary disease (COPD) and is associated with increased hospitalisation and increased mortality (Collins *et al*; 2009). Despite this there remains confusion as to the exact prevalence of malnutrition in COPD outpatients, with estimates between 10-45% depending on the method of nutritional assessment used (Stratton *et al*; 2003). Using the 'Malnutrition Universal Screening Tool' 'MUST' (Elia; 2003), this survey aimed to establish the local prevalence of malnutrition in outpatients with COPD.

A prospective nutritional screening survey was carried out between July 2008 and May 2009 at a large teaching hospital (Southampton General Hospital; SGH) and a smaller community hospital within Hampshire (Lymington New Forest Hospital; LYM). 425 outpatients with COPD were routinely screened with 'MUST'; 190 at SGH, 235 at LYM; 223 males, 202 females; mean age 73 (SD 9.9) years; mean body mass index 25.9 (SD 6.4) kg/m^2. Disease severity (NICE; 2004) was obtained for 246 patients and related to malnutrition risk.

Overall prevalence of malnutrition was 21% (95% CI 17-25%; 7% medium risk, 14% high risk) and this was two- fold greater in those with severe disease compared to those with mild and moderate disease (mild 13%, moderate 12%, severe 26%; χ^2 P=0.027). Age and gender were not significantly related to malnutrition risk, however the prevalence was significantly higher at the larger teaching hospital (26% vs. 17%, P=0.020).

Malnutrition is common in COPD outpatients with an overall prevalence of 21% within the study population, the majority of which were at high risk requiring nutritional treatment. The overall prevalence of malnutrition significantly increased with disease severity. This is the first published survey to use 'MUST' in outpatients with COPD.

Collins PF, Elia M, Smith TR, Kuruklaaratchy R, Cawood AL, Stratton RJ, (2009) abstract submitted to the BAPEN conference 2009.
Elia M (Editor) (2003) The 'MUST' report. BAPEN, Redditch (www.bapen.org.uk).
National Institute for Clinical Excellence (2004) Clinical Guideline 12.
Stratton RJ, Green CJ & Elia M (2003) Disease-related malnutrition: an evidence based approach to treatment, CABI publishing Oxford.
Acknowledgement: funded by an unrestricted educational grant from Nutricia.

Abstract 2 Proceedings of the Nutrition Society (2010) 69 (OCE2): E148.
Malnutrition Matters, Joint BAPEN and Nutrition Society Meeting, Cardiff, Wales, 13-14 October 2009.

The impact of malnutrition on hospitalisation and mortality in outpatients with chronic obstructive pulmonary disease. By P.F. COLLINS[1], M. ELIA[1], T.R. SMITH[2], R. KURUKULAARATCHY[3], A.L. CAWOOD[14] and R.J. STRATTON[1], *[1]Institute of Human Nutrition, University of Southampton, [2]Gastroenterology, Royal Bournemouth Hospital, BH7 7DW, [3]Respiratory Medicine, Southampton University Hospital NHS Trust, Southampton, SO16 6YD [4] Medical Affairs, Nutricia, Wiltshire, BA14 0XQ.*

Chronic obstructive pulmonary disease (COPD) is both a common and costly condition to the NHS (Britton; 2003) and a recent survey suggests malnutrition could be present in one fifth of outpatients with COPD (Collins *et al*; 2009). This survey aimed to assess the extent to which malnutrition is related to poor clinical outcome (hospitalization and mortality) in this patient group. Using the 'Malnutrition Universal Screening Tool', 'MUST', (Elia; 2003) 205 COPD outpatients (mean age 73 (SD 9.6) years; mean body mass index 25.3 (SD 5.9) kg/m^2) were screened for malnutrition with subsequent healthcare use and mortality data prospectively collected 6 months post-screen.

	'MUST' Low risk (n =156)	*'MUST'* Medium + High risk (n = 49)	*P*
No. of EM and ELEC admissions per patient in 6 mo	0.65 $\pm$ 1.1	1.10 $\pm$ 2.0	0.043*
No. of EM admissions per patient in 6 mo	0.48 $\pm$ 0.9	0.92 $\pm$ 1.8	0.023*
EM and ELEC LOS per patient in 6 mo (days)	4.2 $\pm$ 14.0	6.3 $\pm$ 14.0	0.354†
EM LOS per patient in 6 mo (days)	3.3 $\pm$ 10.4	5.7 $\pm$ 13.3	0.185†
6 mo mortality rate (%)	5.8	16.3	0.023*

EM = emergency; ELEC = elective; LOS= length of stay; * = χ^2 test; † = t test.

Outpatients at risk of malnutrition had almost twice the number of hospital admissions and were three fold more likely to die within six months than those not at risk (risk ratio 2.83; CI 95%, 1.15-6.94; P=0.023) (Table 1). The impact of malnutrition on admission rate and mortality remained significant even when adjusted for age.

This survey shows that malnutrition in COPD outpatients is associated with increased hospitalisation and mortality rates.

Britton M (2003) *Respiratory Medicine* 97: S71-S79.
Collins PF, Stratton RJ, Kurukulaaratchy R, Warwick H, Cawood AL & Elia M (2009) abstract submitted to the BAPEN conference 2009.
Elia M (Editor) (2003) The 'MUST' report. BAPEN, Redditch (www.bapen.org.uk).
Acknowledgement: funded by an unrestricted educational grant from Nutricia.

Abstract 3 Clinical Nutrition (2010), volume 5 (Suppl. 2): 17.
32nd ESPEN Congress, Nice, France, 5-8 September 2010.

'MUST' predicts 1-year survival in outpatients with chronic obstructive pulmonary disease. By P.F. COLLINS[1], R.J. STRATTON[1], R. KURUKULAARATCHY[2], H. WARWICK[3], A.L. CAWOOD[4] and M. ELIA[1], *[1]Institute of Human Nutrition, University of Southampton, [2]Respiratory Medicine, [3]Nutrition & Dietetics, Southampton University Hospital NHS Trust, Southampton, SO16 6YD [4] Medical Affairs, Nutricia, Wiltshire, BA14 0XQ.*

Rationale: The 'Malnutrition Universal Screening Tool', 'MUST' (Elia; 2003) is currently the most commonly used nutritional screening tool in the U.K. and is validated for use across healthcare care settings. However, there are no published studies investigating the validity of 'MUST' in predicting outcomes in patients with chronic obstructive pulmonary disease (COPD). This study aimed to investigate the effect of malnutrition risk using 'MUST' (medium + high risk) on 1-year survival in a cohort of COPD outpatients.
Methods: 425 outpatients with a diagnosis of COPD were routinely screened using 'MUST' between July 2008 and May 2009; 223 males, 202 females; mean age 73 (SD 9.9) years; mean body mass index 25.9 (SD 6.4) kg/m^2. Disease severity was also recorded according to the GOLD criteria (2009). Mortality rates were collected 12 months after screening with 'MUST.
Results: Overall prevalence of malnutrition was 21% (95% CI 17-25%; 7% medium risk, 14% high risk). Using binary logistic regression malnutrition risk was found to be a significant predictor of 1-year mortality rates (19% medium + high risk vs. 8% low risk for 'MUST'; OR 2.711 95% CI 1.419-5.181; *P*=0.003). Malnutrition risk was three-fold greater in those with very severe disease than moderate and severe disease (moderate 11%, severe 17%, very severe 36%; χ^2 *P*=<0.001). However, malnutrition risk remained an independent predictor for 1-year mortality even after adjustment for age, disease severity and deprivation (*P*=0.046; OR 2.1 95% CI 1.013-4.482). Similar results were also found using Cox Regression analysis (*P*=0.002 and *P*=0.023). Gender had no significant effect on mortality.
Conclusion: This study shows that malnutrition risk, measured by 'MUST', independently predicts 1-year mortality in COPD outpatients.
References: Elia M (Editor) (2003) The 'MUST' report. BAPEN, Redditch (www.bapen.org.uk). GOLD (2009) www.goldcopd.com

Abstract 4 Clinical Nutrition (2010), volume 5 (Suppl. 2): 165.
32nd ESPEN Congress, Nice, France, 5-8 September 2010.

The influence of deprivation on malnutrition risk in outpatients with chronic obstructive pulmonary disease. By P.F. COLLINS[1], M. ELIA[1], R. KURUKULAARATCHY[2], T.R. SMITH[3], A.L. CAWOOD[4] and R.J. STRATTON[1], *[1]Institute of Human Nutrition, University of Southampton, [2]Respiratory Medicine, [3]Gastroenterology, Southampton University Hospital NHS Trust, Southampton, SO16 6YD, [4]Medical Affairs, Nutricia, Wiltshire, BA14 0XQ.*

Rationale: National and international policies aim to abolish health inequalities associated with deprivation. There is little information linking deprivation to malnutrition risk, although one study demonstrated such a link in a heterogeneous group of inpatients (Stratton & Elia; 2006). This study aimed to establish whether malnutrition was influenced by the level of deprivation in patients with chronic obstructive pulmonary disease (COPD) attending outpatient clinics.
Methods: 425 outpatients with COPD were routinely screened for malnutrition using the 'Malnutrition Universal Screening Tool', 'MUST' (Elia; 2003), between July and May 2009; 202 males, 188 females; mean age 73 (SD 9.9) years; mean body mass index 25.8 (SD 6.4) kg/m^2. The index of multiple deprivation (IMD) was established according to the geographical location of the patient's address (postcode). IMD includes employment, income, health and education deprivation. The higher the IMD score the greater the deprivation (Noble *et al*; 2008). Disease severity data was assessed using GOLD criteria (2009).
Results: Those at risk of malnutrition (medium + high risk; 21%) were significantly more likely to be deprived compared to those at low risk of malnutrition (IMD 18.3 *vs*. 15.2; *P*=0.018; OR (per unit increase of IMD) 1.024, 95% CI 1.004-1.044). Deprivation remained a significant independent risk factor for malnutrition even when adjusted for age, gender and disease severity using binary logistic regression (*P*=0.044; OR 1.023, 95% CI 1.001-1.045).
Conclusion: Deprivation is a risk factor for malnutrition in COPD outpatients and should be considered as part of their nutritional management.

References: Stratton & Elia (2006) Br J Nutr; 96: 870-876. Elia M (Ed.) (2003) The 'MUST' report. BAPEN, Redditch (www.bapen.org.uk), Noble M *et al* (2008) The English indices of deprivation 2007 (www.communities.gov.uk), GOLD (2009) www.goldcopd.com

Abstract 5 Thorax (2010), Volume 65 (Suppl. IV): A74-A75.
*British Thoracic Society Winter Meeting, London, 1-3 December 2010***.**

Deprivation is an independent predictor of 1-year mortality in outpatients with chronic obstructive pulmonary disease. By P.F. COLLINS[1], R.J. STRATTON[1], R. KURUKULAARATCHY[2], and M. ELIA[1], *[1]Institute of Human Nutrition, School of Medicine, University of Southampton, [2]Respiratory Medicine, Southampton University Hospital NHS Trust, Southampton, SO16 6YD*

Deprivation is linked to increased incidence in a number of chronic diseases but its relationship to chronic obstructive pulmonary disease (COPD) is uncertain despite suggestions that the socioeconomic gradient seen in COPD is as great, if not greater, than any other disease (Prescott & Vestbo; 1999). There is also a need to take into account the confounding effects of malnutrition which have been shown to be independently linked to increased mortality (Collins et al., 2010). The current study investigated the influence of social deprivation on 1-year survival rates in COPD outpatients, independently of malnutrition.

424 outpatients with COPD were routinely screened for malnutrition risk using the 'Malnutrition Universal Screening Tool'; 'MUST' (Elia; 2003), between July and May 2009; 222 males and 202 females; mean age 73 (SD 9.9) years; body mass index 25.8 (SD 6.3) kg/m^2. Each individual's deprivation was calculated using the index of multiple deprivation (IMD) which was established according to the geographical location of each patient's address (postcode). IMD includes a number of indicators covering economic, housing and social issues (e.g. health, education and employment) into a single deprivation score (Nobel *et al*., 2008). The lower the IMD score, the lower an individual's deprivation. The IMD was assigned to each outpatient at the time of screening and related to1-year mortality from the date screened.

Outpatients who died within 1-year of screening were significantly more likely to reside within a deprived postcode (IMD 19.7 $\pm$ SD 13.1 *vs*. 15.4 $\pm$ SD 10.7; OR 1.03, 95% CI 1.00 – 1.06; p=0.023) than those that did not die. Deprivation remained a significant independent risk factor for 1-year mortality even when adjusted for malnutrition as well as age, gender and disease severity (binary logistic regression; OR 1.04, 95% CI 1.04 – 1.07; p=0.008). Deprivation was not associated with disease-severity (p=0.906) or body mass index, kg/m^2 (p=0.921) using ANOVA.

This is the first study to show that deprivation, assessed using IMD, is associated with increased 1-year mortality in outpatients with COPD independently of malnutrition, age and disease severity. Deprivation should be considered in the targeted management of these patients.

Prescott & Vestbo (1999) Thorax; 54:737-741, Collins P.F *et al*., (2010) Clinical Nutrition, abstract (*In Press*) , Elia M (Ed.) (2003) The 'MUST' report. BAPEN, Redditch (www.bapen.org.uk), Nobel *et al*., (2008) The English indices of deprivation 2007 (www.communities.gov.uk)

Acknowledgement: funded by an unrestricted educational grant from Nutricia.

Abstract 6 Thorax (2010), Volume 65 (Suppl. IV): A140.
British Thoracic Society Winter Meeting, London, 1-3 December 2010.

Deprivation is associated with increased healthcare utilisation in patients with chronic obstructive pulmonary disease. By P.F. COLLINS[1], R.J. STRATTON[1], R. KURUKULAARATCHY[2], and M. ELIA[1], *[1]Institute of Human Nutrition, School of Medicine, University of Southampton, [2]Respiratory Medicine, Southampton University Hospital NHS Trust, Southampton, SO16 6YD*

Deprivation assessed using the index of multiple deprivation (IMD) has been shown to be an independent risk factor for 1-year mortality in outpatients with chronic obstructive pulmonary disease; COPD (Collins *et al*., 2010). IMD combines a number of economic and social issues (e.g. health, education, employment) into one overall deprivation score, the higher the score the higher an individual's deprivation. Whilst malnutrition in COPD has been linked to increased healthcare use it is not clear if deprivation is also independently associated. This study aimed to investigate the influence of deprivation on 1-year healthcare utilisation in outpatients with COPD.

IMD was established in 424 outpatients with COPD according to the geographical location for each patient's address (postcode) and related to their healthcare use in the year post-date screened (Nobel *et al*., 2008). Patients were routinely screened in outpatient clinics for malnutrition using the 'Malnutrition Universal Screening Tool', 'MUST' (Elia; 2003); mean age 73 (SD 9.9) years; body mass index 25.8 (SD 6.3) kg/m^2 with healthcare use collected 1 year from screening.

1-year healthcare use (n=424)	Mean (SD)	β-coefficient*	*p*
No. of emergency hospital admissions	0.62 (1.5)	0.31	0.001
Emergency length of hospital stay (days)	4.9 (13.2)	2.4	0.001
No. of elective hospital admissions	0.27 (0.75)	0	0.842
Elective admission length of hospital stay (days)	1.1 (7.2)	1.2	0.001
No. of secondary care outpatient appointments	3.7 (2.9)	-0.41	0.002

**=increase in resource use per 10 unit increase in IMD. Adjusted using univariate analysis for age, gender, malnutrition risk ('MUST' risk) and disease-severity using multivariate analysis. Per patient in the cohort.*

Deprivation assessed using IMD (mean 15.9; SD 11.1) was found to be a significant predictor for the frequency and duration of emergency hospital admissions as well as the duration of elective hospital admission. Deprivation was also linked to reduced secondary care outpatient appointment attendance but not an increase in failure to attend and deprivation was not associated with increased disease severity, as classified by the GOLD criteria (p=0.580).

COPD outpatients residing in more deprived areas experience increased hospitalisation rates but decreased outpatient appointment attendance. The underlying reason behind this disparity in healthcare use requires further investigation.

Collins P.F. *et al*., (2010) Clinical Nutrition, abstract (*In Press*); Stratton R.J. *et al*., (2003) Disease-related malnutrition, CABI publishing; Elia M (Ed.) (2003) The 'MUST' report. BAPEN, Redditch (www.bapen.org.uk); Nobel *et al*., (2008) The English indices of deprivation 2007 (www.communities.gov.uk). Acknowledgement: funded by an unrestricted educational grant from Nutricia.

Abstract 7 Thorax (2010), Volume 65 (Suppl. IV): A74.
*British Thoracic Society Winter Meeting, London, 1-3 December 2010***.**

The 'Obesity Paradox' in chronic obstructive pulmonary disease. By P.F. COLLINS[1], R.J. STRATTON[1], R. KURUKULAARATCHY[2] and M. ELIA[1], *[1]Institute of Human Nutrition, University of Southampton, [2]Respiratory Medicine, Southampton University Hospital NHS Trust, Southampton, SO16 6YD*

Poor nutritional status in chronic obstructive pulmonary disease (COPD) is associated with increased mortality independently of disease-severity (Collins *et al*., 2010). Epidemiological studies have suggested a protective role of obesity against mortality in COPD (Vestbo *et al*., 2006) which is contrary to data from the general population where obesity is associated with decreased life expectancy. This relationship has been referred to as the 'obesity paradox' and has been demonstrated in a number of chronic wasting conditions (Kalantar-Zadeh *et al*., 2007).

This study investigated the existence of the obesity paradox in outpatients with COPD by examining the effect of body mass index (BMI) on 1-year healthcare use and clinical outcome in terms of hospital admission rates, length of hospital stay, outpatient appointments and mortality. BMI was assessed in 424 outpatients with COPD, with measurements performed by specialist respiratory nurses during outpatient clinics. 1-year healthcare use was retrospectively collected from the date of BMI measurement.

BMI category (kg/m^2)	<20 (n = 67)	20 - 24.9 (n = 144)	25 - 29.9 (n = 120)	>30 (n = 93)	*p*
No. EM admissions per patient	1.5 (3.7)	1.2 (1.7)	0.74 (1.4)	0.71 (1.1)	0.001*
EM LOS (days per patient)	6.5 (12.8)	9.6 (19.3)	5.3 (17.3)	3.6 (9.0)	0.034*
No. ELEC admissions per patient	0.33 (0.75)	0.22 (0.71)	0.20 (0.67)	0.39 (0.90)	0.216*
ELEC LOS (days per patient)	1.94 (7.9)	0.59 (2.6)	0.48 (3.2)	2.1 (13.0)	0.240*
OPA per patient	3.4 (2.5)	4.1 (3.4)	3.4 (2.6)	3.5 (2.6)	0.163*
1-year mortality (%)	21	15	5	4	<0.001†

*No. = number; EM = emergency; ELEC = elective; LOS = length of stay; OPA = outpatient appointments; * = ANOVA; † = χ^2 p-trend. Values are mean ± SD.*

Patients classified as overweight (25.0-29.9 kg/m^2) or obese (>30 kg/m^2) experienced significantly fewer emergency hospital admissions, as well as a reduced length of hospital stay, in comparison to normal weight (20.0-24.9 kg/m^2) or underweight (<20 kg/m^2) outpatients. There was a significant negative trend between BMI classification and mortality.

This study supports the existence of the 'obesity paradox' in COPD, not only in relation to reduced 1-year mortality rates but also in terms of reduced emergency hospital admissions and reduced length of hospital stay.

Collins PF *et al*., (2010) Clinical Nutrition, abstract (OP040), 5 (S2):17; Kalantar-Zadeh K *et al*., (2007) Curr Opin Clin Nutr Metab Care; 10: 433-442; Vestbo J *et al*., (2006) Am J Respir Crit Care Med; 173: 79-83.Acknowledgement: funded by an unrestricted educational grant from Nutricia

Abstract 8 Journal of Human Nutrition & Dietetics (2011) 24 (4): 382-383.
British Dietetic Association Annual Conference: London UK 9th-11th May 2011.

The influence of smoking status on malnutrition risk and 1-year mortality in outpatients with chronic obstructive pulmonary disease.

PF Collins, RJ Stratton and M Elia. Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, Hampshire SO16 6YD.

Introduction Smoking status in outpatients with chronic obstructive pulmonary disease (COPD) has been associated with a low body mass index and reduced mid-arm muscle circumference (Cochrane & Afolabi, 2004). Individuals with COPD identified as malnourished have also been found to be twice as likely to die within 1 year compared to non-malnourished patients (Collins *et al*., 2010). Whilst malnutrition is both preventable and treatable it is not clear what influence current smoking status, another modifiable risk factor has on malnutrition risk. The current study aimed to establish the influence of smoking status on malnutrition risk and 1-year mortality in outpatients with COPD.
Methods: A prospective nutritional screening survey was carried out between July 2008 and May 2009 at a large teaching hospital (Southampton General Hospital) and a smaller community hospital within Hampshire (Lymington New Forest Hospital). 424 outpatients with a diagnosis of COPD were routinely screened using the 'Malnutrition Universal Screening Tool', 'MUST' (Elia, 2003); 222 males, 202 females; mean age 73 (SD 9.9) years; mean body mass index 25.9 (SD 6.4) kg/m^2. Smoking status on the date of screening was obtained for 401 of the outpatients. Severity of COPD was assessed using the GOLD criteria, and social deprivation determined using the Index of Multiple Deprivation (Nobel et al., 2008).
Results: The overall prevalence of malnutrition (medium + high risk) was 22%, with 32% of current smokers at risk (who accounted for 19% of the total COPD population). In comparison 19% of non-smokers and ex-smokers were likely to be malnourished (odds ratio 1.965 (95% CI, 1.133 - 3.394; p = 0.015)). Smoking status remained an independent risk factor for malnutrition even after adjustment for age, social deprivation and disease-severity (odds ratio 2.048 (95% CI, 1.085-3.866; p = 0.027)) using binary logistic regression. After adjusting for age, disease severity, social deprivation, smoking status, malnutrition remained a significant predictor of 1-year mortality (odds ratio (medium + high risk *vs*. low risk), 2.161 (1.021-4.573; p=0.044) whereas smoking status did not (odds ratio for smokers *vs*. ex-smokers + non-smokers was 1.968, (95% CI 0.788 -4.913; p=0.147)).
Discussion: This study highlights the potential importance of combined nutritional support and smoking cessation in order to treat malnutrition. The close association between smoking status and malnutrition risk in COPD suggests smoking is an important consideration in the nutritional management of malnourished COPD outpatients.
Conclusion: Smoking status in COPD outpatients is a significant independent risk factor for malnutrition and a weaker (non-significant) predictor of 1-year mortality. Malnutrition significantly predicted 1 year mortality.

References: Cochrane WJ & Afolabi OA (2004) Investigation into the nutritional status, dietary intake and smoking habits of patients with chronic obstructive pulmonary disease. *J Hum Nutr Diet* 17 (1), 3-11.
Collins PF, Stratton RJ, Kurukulaaratchy R, Warwick H, Cawood AL & Elia M (2010) 'MUST' predicts 1-year survival in outpatients with chronic obstructive pulmonary disease. Clin Nutr 5 (2): 17.
Elia M (Ed) (2003) The 'MUST' report. BAPEN (www.bapen.org.uk).
Nobel M, McLennan D, Wilkinson K, Whitworth A & Barnes H (2008) The English indices of deprivation 2007 (www.communities.gov.uk)

Abstract 9 Journal of Human Nutrition & Dietetics (2011) 24 (4): 382.
British Dietetic Association Annual Conference: London UK 9th-11th May 2011.

The influence of deprivation domains on malnutrition risk in outpatients with chronic obstructive pulmonary disease. PF Collins, M Elia, RJ Stratton. Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, SO16 6YD.

Introduction: Deprivation assessed using the Index of Multiple Deprivation (IMD) has been shown to be an independent risk factor for both malnutrition and mortality in outpatients with chronic obstructive pulmonary disease (COPD) (Collins et al., 2010a and Collins et al., 2010). IMD consists of a range of different deprivation domains but it is unclear which ones are most closely linked to malnutrition. The aim of the current study was to investigate whether the relationship between malnutrition and deprivation was a general one, affecting all domains in a consistent manner, or specific, affecting only certain domains.

Methods: 424 outpatients with COPD were routinely screened for malnutrition using the 'Malnutrition Universal Screening Tool', 'MUST' (Elia, 2003); 222 males, 202 females; mean age 73 (SD 9.9) years; mean body mass index 25.9 (SD 6.4) kg/m^2. IMD was established according to the geographical location of each patient's home address and related to malnutrition risk according to 'MUST'. IMD ranks the 32, 482 postcodes in England, from 1 which is the most deprived to 32,482 which is the least deprived (Nobel et al., 2008).

Results: Those at risk of malnutrition (medium + high risk) were more likely to reside in areas that were deprived for all the individual deprivation domains (Table).

Table 1 the influence of deprivation domains on malnutrition risk

Rank deprivation domains	'MUST' risk (Low risk) (n = 331)	(Medium + High risk) (n = 93)	p
Overall rank IMD	20147 (8233)	17545 (8214)	0.007
Income	18185 (8081)	16579 (8169)	0.092
Employment	19513 (7524)	17783 (7516)	0.051
Health deprivation & disability	21521 (8012)	18675 (8141)	0.003
Education skills & training	16677 (8594)	14936 (9222)	0.090
Barriers to housing	17792 (8103)	15684 (7364)	0.024
Crime	18702 (9076)	15882 (8875)	0.008
Living environment	20949 (7961)	18101 (8245)	0.003

Analysis using t-test, values mean (SD), lower values (rank) = greater deprivation.

Discussion: This study highlighted that the prevalence of malnutrition in COPD is influenced by several social deprivation domains. Social deprivation could help identify groups of patients who are particularly at risk of malnutrition and allow for a more focused allocation of resources.

Conclusion: Compared to non-malnourished individuals those with malnutrition are more likely to suffer from a range of interrelated deprivation domains rather than a single domain. Deprivation is a risk factor that should be considered in the prevention and nutritional management of malnourished COPD outpatients.

References: Collins PF, Elia M, Kurukulaaratchy R, Smith TR, Cawood AL & Stratton RJ (2010a) The influence of deprivation on malnutrition risk in outpatients with COPD. Clinical Nutrition, **5** (2): 165. Collins PF, Stratton RJ, Kurukulaaratchy R & Elia M (2010) Deprivation is an independent risk factor for 1-year mortality in outpatients with chronic obstructive pulmonary disease. Thorax, **65**: A74-75. Elia M (Ed) (2003) The 'MUST' report. BAPEN (www.bapen.org.uk). Nobel M, McLennan D, Wilkinson K, Whitworth A & Barnes H (2008) The English indices of deprivation 2007 (www.communities.gov.uk) Accessed 31/3/2011.

Abstract 10 Clinical Nutrition (2011), Volume 6 (Suppl. 1): 153.
33rd ESPEN Congress, Gothenburg, Sweden, 3-6 September 2011.

Nutritional support in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. By P.F. COLLINS, R.J. STRATTON, and M. ELIA. *Institute of Human Nutrition, University of Southampton, Southampton, UK.*

Rationale: A Cochrane review concluded nutritional support in COPD had no effect on anthropometry and functional outcomes (Ferreira et al., 2005) but other reviews suggest this may not be so (Stratton et al., 2003). This review aimed to clarify the current evidence base. **Methods:** A systematic review identified 13 randomised controlled trials (n 419) of nutritional support (dietary advice, oral nutritional supplements (ONS), tube feeding) vs. control. Meta-analysis was performed of nutritional intake, weight, mid-arm muscle circumference (MAMC) and handgrip strength (HGS) (Comprehensive Meta-analysis v2). In contrast to previous Cochrane reviews, which examined only data at the end of intervention, this review examined the changes induced by the intervention. **Results:** Eleven of the 13 studies used ONS. Meta-analysis found nutritional support significantly increased energy intake (227 SE 53 kcal/d, $p<0.001$, fixed effect model), body weight (1.95 SE 0.24 kg, $p<0.001$ (undernourished) and 1.3 SE 0.34 kg, $p<0.001$ (nourished)) and HGS (5.3 SE 2.7%, $p<0.05$ random effects model). Where data on dispersion was not available, significant improvements were also found using mean values (one-sample t-test) for MAMC (3%, range 0.7-7%, $p = 0.034$) and protein intakes (17 SD 6.7 g/d, $p=0.005$). **Conclusion:** In contrast to the findings of a Cochrane review, this review concludes that nutritional support, mostly involving ONS, significantly improves nutritional intake, body weight, muscle mass and HGS in COPD. **References:** Ferreira I et al., (2005) Cochrane Database of Systematic Reviews 2005 Issue 2; Stratton RJ et al., (2003) Disease-related malnutrition: an evidence-based approach to treatment, CABI: Oxford.

Abstract 11 Clinical Nutrition (2011), Volume 6 (Suppl. 1): 153-154.
33rd ESPEN Congress, Gothenburg, Sweden, 3-6 September 2011.

Nutritional support and functional capacity in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. By P.F. COLLINS, R.J. STRATTON, and M. ELIA. *Institute of Human Nutrition, University of Southampton, Southampton, UK.*

Rationale: Controversies exist about the value of using nutritional support to improve functional outcomes in COPD with a Cochrane review reporting no evidence of benefit (Ferreira et al., 2005). This updated review aimed to re-examine the evidence base. **Methods:** A systematic review identified 13 randomised controlled trials (n 419) of nutritional support (dietary advice (n 1), oral nutritional supplements (n 11) or enteral tube feeding (n 1)) versus control in COPD. Respiratory muscle strength (PI max and PE max), handgrip strength (HGS), walking distance and quality of life (QoL) were investigated (Comprehensive Meta-analysis v2). In contrast to the Cochrane review which examined only between group differences, this review examined the changes induced by the intervention. **Results:** Compared to the control group, those receiving nutritional support showed a significantly greater increase in PE max (15.2 SE 4.88 cm H_2O, p=0.002), a non-significant increase in PI max (0.36 SE 0.34 cm H_2O, p=0.143) and a significant increase in HGS (0.9 SE 0.366 kg, p=0.014 fixed effect model; 1.3 SE 0.69 kg, p=0.05 random effects model). Walking distance was reported in five trials, four of which favoured the intervention group. Two of these were meta-analysable (p=0.59) with only one favouring the intervention group. Two studies examined QoL (non-meta-analysable) each reporting clinically and statistically significant improvements favouring nutritional support (p=0.001 to p<0.05). **Conclusion:** Unlike the Cochrane review, this systematic review found that nutritional support in COPD results in improved respiratory and peripheral muscle strength and quality of life. **Reference:** Ferreira I et al. (2005) Cochrane Database of Systematic Reviews 2005 Issue 2.

Abstract 12 Thorax (2011) Volume 66 (Suppl. 4): A173-A174.
British Thoracic Society Winter Meeting 2011, London.

Oral nutritional supplements in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. By P.F. COLLINS[1], R.J. STRATTON[1] and M. ELIA[1], *[1]Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, SO16 6YD*

Malnutrition is common in patients with COPD affecting up to 45% of outpatients and 60% of inpatients [1]. Oral nutritional supplements (ONS) are often used to treat malnutrition but the latest Cochrane review on nutritional support in COPD concluded that nutrition support, mainly involving ONS, did not lead to improvements in anthropometry and other functional outcomes [2]. The latest NICE guidelines for the management of COPD recommend the use of ONS but state it is based on grade D evidence (a low level of evidence) [3] despite previous reviews suggesting otherwise [1]. The aim of this review was to clarify the evidence base for the use of ONS in COPD.

A systematic review identified 11 randomised controlled trials using ONS vs. control (189 *vs*. 185). ONS provided between 355 to 1280 kcal for 6-12 weeks. Control subjects tended to consume their usual diet with encouragement. Meta-analysis was performed of nutritional intake, weight, mid-arm muscle circumference (MAMC) and handgrip strength (HGS) (Comprehensive Meta-analysis v2). Quality of life, exercise capacity and respiratory outcomes were also examined. In contrast to previous Cochrane reviews, which examined only data at the end of intervention [2], this review examined the changes induced by ONS.

Significantly improved energy intake was reported in 6 out of 7 studies of which 4 were meta-analysable (+262 SE 104 kcal/d, p=0.012, random effect model, 4 RCT). Meta-analysis found ONS significantly improved body weight (+1.85 kg SE 0.25 kg, p<0.001 (malnourished) and +1.31 SE 0.34 kg, p<0.001 (nourished), 11 studies) and had a tendency to improve MAMC (+0.21 SE 0.19 kg, p=0.277, fixed effect model; I^2 =0; 2 studies). Improved HGS was found in 3 of 4 studies, 2 significant in their own right with meta-analysis favouring ONS (+2.14 SE 1.1 kg, p=0.054, random effect model (+8.3% improvement)). No improvements were reported in FEV_1 (8 studies) however, respiratory muscle strength appeared more responsive to ONS with PI max improved in 3 out of 5 studies (NS), PE max significantly improved in 2 out of 4 studies and sternomastoid strength significantly improved in 1 study. Exercise tolerance (6 out of 7 studies), dyspnoea and general well-being (3 out of 5 studies) and quality of life were (2 out of 2 studies) significantly improved with ONS, although meta-analysis was not possible.

Supplementation using ONS results in significant improvements in nutritional intake and body weight and a tendency for improvements in several functional outcomes. In light of this review, a case can be made for increasing the level of evidence from grade D, as recommended by NICE, to grade A.

[1] Stratton RJ et al., (2003) Disease-related malnutrition: an evidence-based approach to treatment, CABI: Oxford.
[2] Ferreira I et al., (2005) Cochrane Database of Systematic Reviews 2005 Issue 2.
[3] National Clinical Guideline Centre (2010) Clinical Guideline 101 (CG101).
Acknowledgement: funded by an unrestricted educational grant by Nutricia Ltd.

Abstract 13 Nutrition & Dietetics (2012) volume 69 (Suppl. 1): 163.
International Congress of Dietetics, 2012, Sydney, Australia.

The effect of deprivation and disease-severity on malnutrition risk in chronic obstructive pulmonary disease (COPD).

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Deprivation has previously been shown to be an independent risk factor for the high prevalence of malnutrition observed in COPD (Collins et al., Clin. Nutr. 2010; 5 (2): 165). It has been suggested the socioeconomic gradient observed in COPD is greater than any other chronic disease (Prescott & Vestbo, Thorax. 1999; 54: 737-41). The current study aimed to examine the influence of disease severity and social deprivation on malnutrition risk in outpatients with COPD. 424 COPD outpatients were screened using the 'Malnutrition Universal Screening Tool' ('MUST'). COPD disease severity was recorded in accordance with the GOLD criteria and deprivation was established according to the patient's geographical location (postcode) at the time of nutritional screening using the UK Government's Index of Multiple Deprivation (IMD). IMD ranks postcodes from 1 (most deprived) to 32,482 (least deprived). Disease severity was positively associated with an increased prevalence of malnutrition risk ($p<0.001$) both within and between groups, whilst rank IMD was negatively associated with malnutrition ($p=0.020$), i.e. those residing in less deprived areas were less likely to be malnourished. Within each category of disease severity the prevalence of malnutrition was two-fold greater in those residing in the most deprived areas compared to those residing in the least deprived areas. This study suggests that deprivation and disease severity are independent risk factors for malnutrition in COPD both contributing to the widely variable prevalence of malnutrition. Consideration of these issues could assist with the targeted nutritional management of these patients.

Funded by an unrestricted educational grant from Nutricia Ltd, UK.

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Appendix 2 'Build yourself up' dietary advice leaflet. Produced by the Department of Nutrition and Dietetics, Southampton Universities Hospital NHS Trust.

BUILD YOURSELF UP

A GUIDE TO HELP INCREASE THE CALORIES AND PROTEIN IN YOUR DIET

This is not a "special diet", but just some practical tips on how to build yourself up.

This advice will help you to get your energy back and keep your strength up. If you have lost weight these tips may help you to put some pounds back on.

COPD Oral Nutrition Support Trial. Ethics ref: 07/Q1702/70

WHEN SHOULD I EAT?

Try to eat something between your meals. This is particularly important if you have a reduced appetite and can only manage small meals.

Aim to eat something, or have a milky drink, six times per day, i.e.:

- ✓ Breakfast
- ✓ Mid-morning snack
- ✓ Lunch
- ✓ Mid-afternoon snack
- ✓ Evening meal
- ✓ Bedtime snack

Everyone's appetite varies between good and bad days and from hour to hour. Make the most of the good times by eating and treating yourself to your favourite foods.

ARE THERE ANY FOODS I SHOULD AVOID?

There are no particular foods you should avoid or foods that you must eat, unless you are allergic to something. Everyone is different: if you find that certain foods upset you, avoid them! Try to have as wide a variety of foods as possible.

Often people, when they are well, are told to avoid fat and sugar. This is not relevant to you. In fact, it is these foods that will help you put some pounds back on if you have lost weight.

Smoking tends to reduce your appetite. If you are off your food, cutting back on smoking will help.

HOW CAN I INCREASE THE CALORIES AND PROTEIN IN THE FOODS THAT I EAT?

MILK: Milk can be fortified by adding milk powder. Mix 2oz (4 tbsp) of milk powder with a little warm milk to form a paste. Then stir in a pint of cold full cream milk. Keep the fortified milk in the fridge and use it as you would normal milk or water to make drinks soups, custards, jellies, blancmanges and puddings.

BREAKFAST CEREALS: Use fortified milk, and add sugar, honey or syrup freely. Many people enjoy breakfast cereals as between meal snacks and at bedtime.

CASSEROLES AND SOUPS: Add minced meat, lentils, beans or noodles to soups. Cream is an easy way to add calories to soups and casseroles, and tastes really good! Make up packet and condensed soups with fortified milk.

MEAT POULTRY AND FISH: These foods are very good for you as they are an excellent source of protein. Serve with sauces made with fortified milk such as cheese, white or parsley, for added protein and calories. Try adding half a teaspoon of Marmite or Bovril for extra vitamins. Sauces are particularly helpful if you have a dry or a sore mouth.

POTATO: Potatoes can be fortified by adding butter or margarine and fortified milk, pr by sprinkling cheese on top.

VEGETABLES: Melt butter or margarine on top of hot vegetables or garnish with grated cheese or a hardboiled egg. Sauces such as cheese or white sauce are tasty on cauliflower, leeks and marrow and represent another good way to fortify vegetables. Mayonnaise and salad cream can also add extra calories to salads.




DESSERTS: Try to have a dessert after meals. If necessary wait a while between the main course and dessert. Add ice-cream, cream or evaporated milk to puddings. Use sugar, honey or syrup liberally. Make instant desserts, custards and milk puddings with fortified milk. Try jelly made with evaporated milk. Thick and creamy yoghurts or fromage frais are also good. Cream cakes are excellent desserts for extra calories.

DRINKS: Milky drinks are better than just tea between meals. Use fortified milk when making coffee and milky drinks. Milk shakes are a useful source of calories and protein and are very good as between meal snacks. Fresh fruit juice is a good source of vitamins particularly if you are not eating much fruit.

NIBBLES: Keep snacks like nuts, fruit, crisps, biscuits, sweets and chocolate handy to nibble between meals.

WHAT CAN I DO IF I HAVE LOST MY APPETITE OR WHEN I FEEL TOO TIRED TO COOK?

This is a time to make use of take-away meals and quick convenience foods. Many meals can be bought readymade and just need to be reheated. The following list may give you some ideas for snacks and easy meals.

ON TOAST: Cheese, baked beans, scrambled eggs, sardines, pilchards, mackerel, pate, spaghetti, ravioli, tinned mushrooms, toast toppers.

If you have a toasted sandwich maker, use it to make a hot snack, both savoury (e.g. ham & tomato, cheese and pickle or tuna and mayonnaise) and sweet (e.g. banana and honey, apple and sultana).

FILLED OMELETTES: Ham, cheese, mushroom

SANDWICHES AND FILLED ROLLS: Try fillings such as cheese, cheese spreads, tuna or other fish, egg mayonnaise, pate, cold meats (e.g. corned beef, ham, beef), bacon, peanut butter, jam, marmalade, banana.

BAKED POTATOES: Butter, cheese, baked beans, tuna coleslaw

INSTANT, FROZEN AND MICROWAVE MEALS: Avoid the slimming varieties. A great variety of meals are now available in single portions, e.g. roast dinners, pasta dishes, curries, pies, paella etc.

SOUPS: These can make quick nutritious meals whether they are tinned, packet or home made.

BUFFET FOODS: Keep a supply of foods you like to eat at a buffet. e.g. chicken legs, cold sausages, sausage rolls, pasties, pies, quiches, flans, scotch eggs etc. Bread sticks and dips also make good snacks.

ALCOHOL: If you have lost your appetite, a glass of sherry or brandy before a meal may stimulate your appetite.

WHAT FOODS SHOULD I KEEP IN STOCK?

The list of foods you keep in your kitchen will depend on your own likes and dislikes, but here are some ideas of extra foods to put on your shopping list.

IN THE STORE CUPBOARD

Longlife milk (UHT) and milk powder
Baked beans, macaroni cheese, spaghetti
Tinned meats, fish and stews (e.g. corned beef, tuna)
Packet and tinned soups and sauces
Tinned puddings e.g. rice pudding, sponge puddings
Tinned vegetables, potatoes and fruit in syrup
Tinned cream, evaporated and condensed milk
Cartons of milk puddings, custard, mousse and jelly
Nibble snacks e.g. nuts, crisps, sweets and chocolates
Dried fruits, e.g. dates, currants and apricots
Sweet and savoury biscuits, variety of breakfast cereals
Horlicks, Ovaltine or drinking chocolate
Jam, marmalade, peanut butter, lemon curd

IN THE FRIDGE

Fruit juice, milk, eggs, yoghurts, fromage frais, crème caramel or other desserts
Cheese – cream and hard varieties
Flans, quiches, pastries, pies
Cooked meats e.g. ham, chicken

IN THE FREEZER
Instant meals e.g. cottage pie, roast dinner
Pies, pizza, fish fingers, sausages and burgers
Boil in the bag meals e.g. cod in sauce.
Ice cream and frozen vegetables

SAMPLE MEAL PLAN:

Breakfast
Fortified porridge or cereal and milk
Cooked breakfast e.g. bacon, sausage, tomato
Bread/toast with butter and marmalade

Mid-morning
Snack and/or drink e.g. milky coffee
with a slice of cake
Glass of milk and a sandwich
Crisps or biscuits

Lunch
Fortified soup
Large portion of meat, fish egg or cheese
Vegetables
Fortified potato
Dessert
Cheese and biscuits

Mid-afternoon
Snack with drink e.g. scone and tea
Fruit juice with toast or a sandwich

Dinner
As lunch, or sandwich with fillings such as meat, fish cheese or egg
Dessert or yoghurt

Bedtime
Hot chocolate or Horlicks made with fortified milk with biscuit, cake, toast or cereal

Appendix 3 Nutritional composition of the oral nutritional supplements (ONS) used in the trial

ONS		Composition per ONS
Fortisip Extra (Milkshake style)		200ml 320 kcal 20g Protein (25% total energy) 36.2g Carbohydrate (45% total energy) 10.6g Fat (30% total energy) 0g Fibre 50% RNI for vitamins and minerals excluding Sodium, Potassium, chloride and magnesium.
Forticreme Complete (Dessert style)		125g 200 kcal 11.9g Protein (24% total energy) 24g Carbohydrate (48% total energy) 6.25g Fat (28% total energy) Negligible fibre Nutritionally complete
Fortisip Yoghurt style (milkshake style)		200ml 300 kcal 12g Protein (16% total energy) 36.8g Carbohydrate (49% total energy) 11.6g Fat (35% total energy) 0g Fibre Nutritionally complete
Fortijuce (Juice style)		200ml 300 kcal 8g Protein (11% total energy) 67g Carbohydrate (89% total energy) 0g Fat* (0% total energy) 0g Fibre *not nutritionally complete

Fortisip fruit dessert (Apple dessert)		150g 200 kcal 10.5g Protein (21% total energy) 25g Carbohydrate (52% total energy) 6g Fat (27% total energy) 4g Fibre
Specialised ONS		
Calogen (Fat emulsion)		90ml/day typical dose 405 kcal 0 g Protein 4 g Carbohydrate* 45g Fat (long chain triglyceride) 0g Fibre *neutral Calogen contains 0g Carbohydrate
Respifor (milkshake style) Specialist ONS for COPD patients		Typical value per serving: 188 kcal 9g Protein (20% total energy) 28g Carbohydrate (60% total energy) 4g Fat (20% total energy) 0g Fibre
Scandishake mix (Milkshake style; 85g sachet made with 240ml whole milk)		Typical value per serving: 598 kcal 11.7g Protein (8% total energy) 69.5g Carbohydrate (46% total energy) 30.4g Fat (46% total energy) 0g Fibre
Fortisip savoury multi-fibre (soup style)		200ml 300 kcal 15g Protein (20% total energy)

ONS = oral nutritional supplement. All ONS were provided by Nutricia Ltd Trowbridge, UK.

Appendix 4 'Malnutrition Universal Screening Tool' ('MUST') www.bapen.org.uk

BAPEN
Advancing Clinical Nutrition

'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.

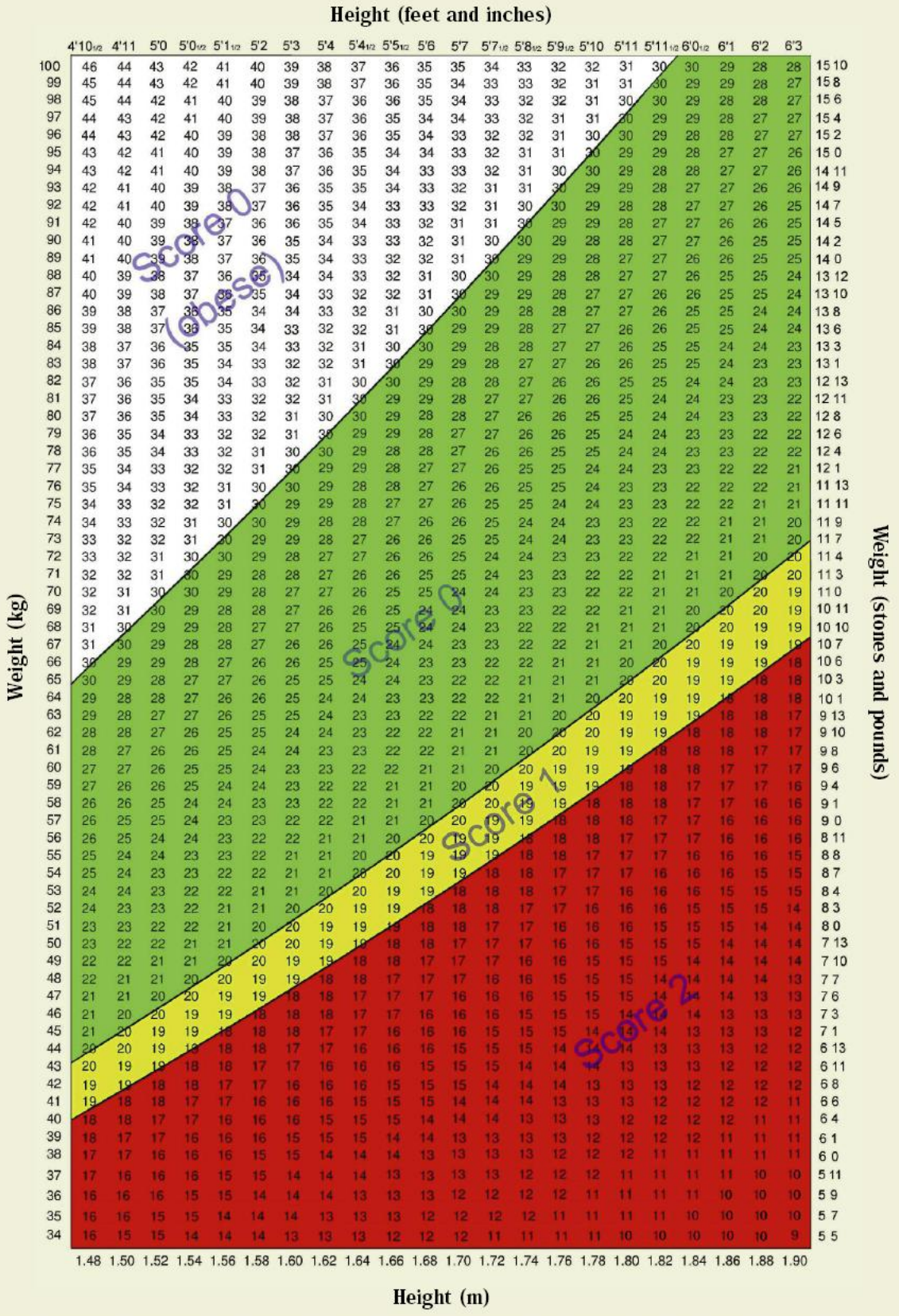
Step 3
Establish acute disease effect and score.

Step 4
Add scores from steps 1, 2 and 3 together to obtain overall risk of malnutrition.

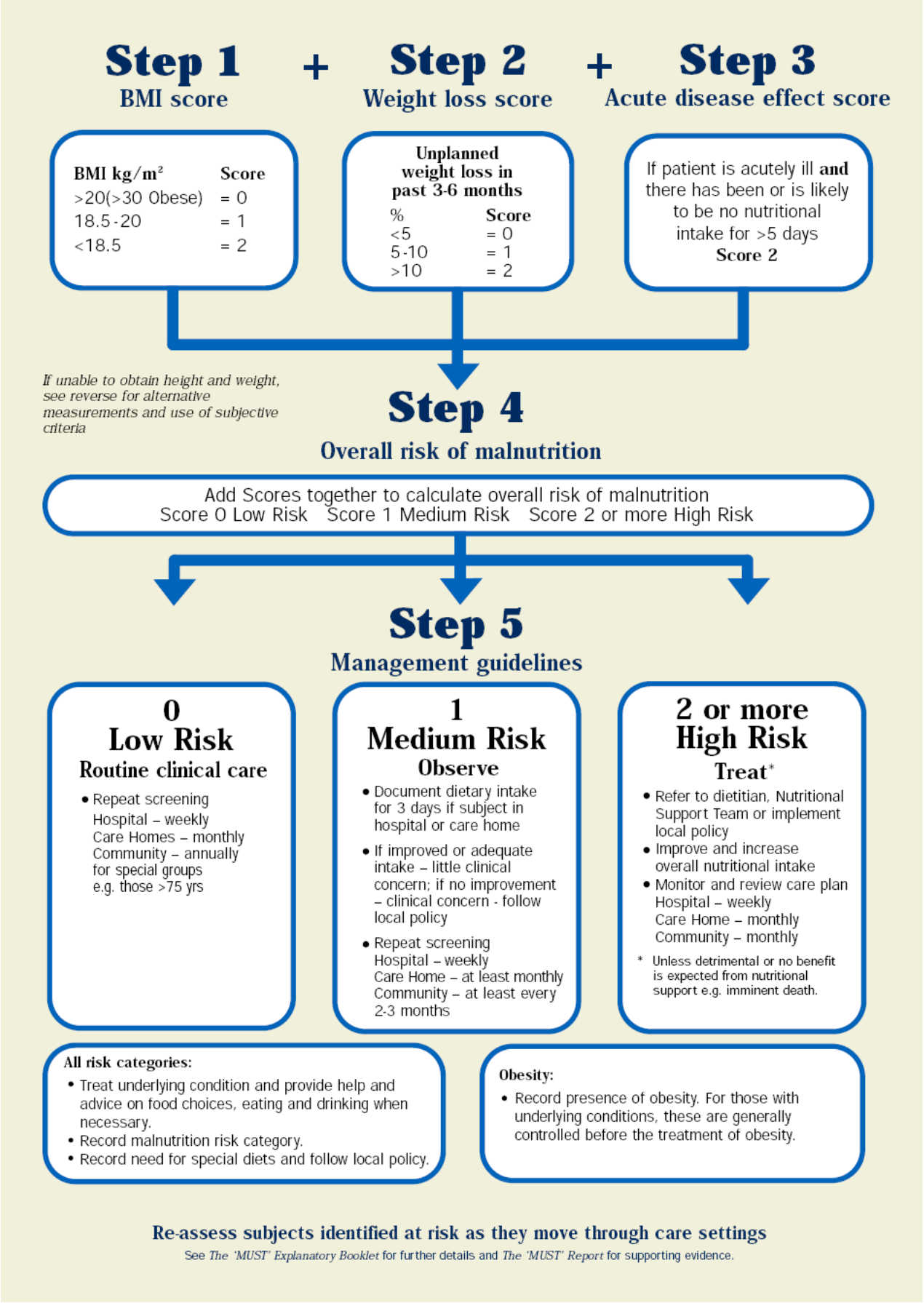
Step 5
Use management guidelines and/or local policy to develop care plan.

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.**

Step 1 – BMI score (& BMI)



Note : The black lines denote the exact cut off points (30,20 and 18.5 kg/m²), figures on the chart have been rounded to the nearest whole number.


Step 1
BMI score
+
Step 2
Weight loss score
+
Step 3
Acute disease effect score
BMI kg/m²
Score
>20(>30 Obese) = 0
18.5-20 = 1
<18.5 = 2
Unplanned weight loss in past 3-6 months
%
Score
<5 = 0
5-10 = 1
>10 = 2
If patient is acutely ill and there has been or is likely to be no nutritional intake for >5 days
Score 2
If unable to obtain height and weight, see reverse for alternative measurements and use of subjective criteria
Step 4
Overall risk of malnutrition
Add Scores together to calculate overall risk of malnutrition
Score 0 Low Risk Score 1 Medium Risk Score 2 or more High Risk
Step 5
Management guidelines
0
Low Risk
Routine clinical care
• Repeat screening
Hospital – weekly
Care Homes – monthly
Community – annually
for special groups
e.g. those >75 yrs
1
Medium Risk
Observe
• Document dietary intake for 3 days if subject in hospital or care home
• If improved or adequate intake – little clinical concern; if no improvement – clinical concern - follow local policy
• Repeat screening
Hospital – weekly
Care Home – at least monthly
Community – at least every 2-3 months
2 or more
High Risk
Treat*
• Refer to dietitian, Nutritional Support Team or implement local policy
• Improve and increase overall nutritional intake
• Monitor and review care plan
Hospital – weekly
Care Home – monthly
Community – monthly
* Unless detrimental or no benefit is expected from nutritional support e.g. imminent death.
All risk categories:
• Treat underlying condition and provide help and advice on food choices, eating and drinking when necessary.
• Record malnutrition risk category.
• Record need for special diets and follow local policy.
Obesity:
• Record presence of obesity. For those with underlying conditions, these are generally controlled before the treatment of obesity.
Re-assess subjects identified at risk as they move through care settings
See The 'MUST' Explanatory Booklet for further details and The 'MUST' Report for supporting evidence.

Step 2 – Weight loss score

Weight before weight loss (kg)

	SCORE 0 Wt Loss < 5%	SCORE 1 Wt Loss 5-10%	SCORE 2 Wt Loss > 10%
34 kg	<1.70	1.70 – 3.40	>3.40
36 kg	<1.80	1.80 – 3.60	>3.60
38 kg	<1.90	1.90 – 3.80	>3.80
40 kg	<2.00	2.00 – 4.00	>4.00
42 kg	<2.10	2.10 – 4.20	>4.20
44 kg	<2.20	2.20 – 4.40	>4.40
46 kg	<2.30	2.30 – 4.60	>4.60
48 kg	<2.40	2.40 – 4.80	>4.80
50 kg	<2.50	2.50 – 5.00	>5.00
52 kg	<2.60	2.60 – 5.20	>5.20
54 kg	<2.70	2.70 – 5.40	>5.40
56 kg	<2.80	2.80 – 5.60	>5.60
58 kg	<2.90	2.90 – 5.80	>5.80
60 kg	<3.00	3.00 – 6.00	>6.00
62 kg	<3.10	3.10 – 6.20	>6.20
64 kg	<3.20	3.20 – 6.40	>6.40
66 kg	<3.30	3.30 – 6.60	>6.60
68 kg	<3.40	3.40 – 6.80	>6.80
70 kg	<3.50	3.50 – 7.00	>7.00
72 kg	<3.60	3.60 – 7.20	>7.20
74 kg	<3.70	3.70 – 7.40	>7.40
76 kg	<3.80	3.80 – 7.60	>7.60
78 kg	<3.90	3.90 – 7.80	>7.80
80 kg	<4.00	4.00 – 8.00	>8.00
82 kg	<4.10	4.10 – 8.20	>8.20
84 kg	<4.20	4.20 – 8.40	>8.40
86 kg	<4.30	4.30 – 8.60	>8.60
88 kg	<4.40	4.40 – 8.80	>8.80
90 kg	<4.50	4.50 – 9.00	>9.00
92 kg	<4.60	4.60 – 9.20	>9.20
94 kg	<4.70	4.70 – 9.40	>9.40
96 kg	<4.80	4.80 – 9.60	>9.60
98 kg	<4.90	4.90 – 9.80	>9.80
100 kg	<5.00	5.00 – 10.00	>10.00
102 kg	<5.10	5.10 – 10.20	>10.20
104 kg	<5.20	5.20 – 10.40	>10.40
106 kg	<5.30	5.30 – 10.60	>10.60
108 kg	<5.40	5.40 – 10.80	>10.80
110 kg	<5.50	5.50 – 11.00	>11.00
112 kg	<5.60	5.60 – 11.20	>11.20
114 kg	<5.70	5.70 – 11.40	>11.40
116 kg	<5.80	5.80 – 11.60	>11.60
118 kg	<5.90	5.90 – 11.80	>11.80
120 kg	<6.00	6.00 – 12.00	>12.00
122 kg	<6.10	6.10 – 12.20	>12.20
124 kg	<6.20	6.20 – 12.40	>12.40
126 kg	<6.30	6.30 – 12.60	>12.60

Weight before weight loss (st lb)

	SCORE 0 Wt Loss < 5%	SCORE 1 Wt Loss 5-10%	SCORE 2 Wt Loss > 10%
5st 4lb	<4lb	4lb – 7lb	>7lb
5st 7lb	<4lb	4lb – 8lb	>8lb
5st 11lb	<4lb	4lb – 8lb	>8lb
6st	<4lb	4lb – 8lb	>8lb
6st 4lb	<4lb	4lb – 9lb	>9lb
6st 7lb	<5lb	5lb – 9lb	>9lb
6st 11lb	<5lb	5lb – 10lb	>10lb
7st	<5lb	5lb – 10lb	>10lb
7st 4lb	<5lb	5lb – 10lb	>10lb
7st 7lb	<5lb	5lb – 11lb	>11lb
7st 11lb	<5lb	5lb – 11lb	>11lb
8st	<6lb	6lb – 11lb	>11lb
8st 4lb	<6lb	6lb – 12lb	>12lb
8st 7lb	<6lb	6lb – 12lb	>12lb
8st 11lb	<6lb	6lb – 12lb	>12lb
9st	<6lb	6lb – 13lb	>13lb
9st 4lb	<7lb	7lb – 13lb	>13lb
9st 7lb	<7lb	7lb – 13lb	>13lb
9st 11lb	<7lb	7lb – 1st 0lb	>1st 0lb
10st	<7lb	7lb – 1st 0lb	>1st 0lb
10st 4lb	<7lb	7lb – 1st 0lb	>1st 0lb
10st 7lb	<7lb	7lb – 1st 1lb	>1st 1lb
10st 11lb	<8lb	8lb – 1st 1lb	>1st 1lb
11st	<8lb	8lb – 1st 1lb	>1st 1lb
11st 4lb	<8lb	8lb – 1st 2lb	>1st 2lb
11st 7lb	<8lb	8lb – 1st 2lb	>1st 2lb
11st 11lb	<8lb	8lb – 1st 3lb	>1st 3lb
12st	<8lb	8lb – 1st 3lb	>1st 3lb
12st 4lb	<9lb	9lb – 1st 3lb	>1st 3lb
12st 7lb	<9lb	9lb – 1st 4lb	>1st 4lb
12st 11lb	<9lb	9lb – 1st 4lb	>1st 4lb
13st	<9lb	9lb – 1st 4lb	>1st 4lb
13st 4lb	<9lb	9lb – 1st 5lb	>1st 5lb
13st 7lb	<9lb	9lb – 1st 5lb	>1st 5lb
13st 11lb	<10lb	10lb – 1st 5lb	>1st 5lb
14st	<10lb	10lb – 1st 6lb	>1st 6lb
14st 4lb	<10lb	10lb – 1st 6lb	>1st 6lb
14st 7lb	<10lb	10lb – 1st 6lb	>1st 6lb
14st 11lb	<10lb	10lb – 1st 7lb	>1st 7lb
15st	<11lb	11lb – 1st 7lb	>1st 7lb
15st 4lb	<11lb	11lb – 1st 7lb	>1st 7lb
15st 7lb	<11lb	11lb – 1st 8lb	>1st 8lb
15st 11lb	<11lb	11lb – 1st 8lb	>1st 8lb
16st	<11lb	11lb – 1st 8lb	>1st 8lb
16st 4lb	<11lb	11lb – 1st 9lb	>1st 9lb
16st 7lb	<12lb	12lb – 1st 9lb	>1st 9lb

Alternative measurements and considerations

Step 1: BMI (body mass index)

If height cannot be measured

- Use recently documented or self-reported height (if reliable and realistic).
- If the subject does not know or is unable to report their height, use one of the alternative measurements to estimate height (ulna, knee height or demispan).

If height & weight cannot be obtained

- Use mid upper arm circumference (MUAC) measurement to estimate BMI category.

Step 2: Recent unplanned weight loss

If recent weight loss cannot be calculated, use self-reported weight loss (if reliable and realistic).

Subjective criteria

If height, weight or BMI cannot be obtained, the following criteria which relate to them can assist your professional judgement of the subject's nutritional risk category. Please note, use of these criteria is not designed to assign a score.

1. BMI

- Clinical impression – thin, acceptable weight, overweight. Obvious wasting (very thin) and obesity (very overweight) can also be noted.

2. Unplanned weight loss

- Clothes and/or jewellery have become loose fitting (weight loss).
- History of decreased food intake, reduced appetite or swallowing problems over 3-6 months and underlying disease or psycho-social/physical disabilities likely to cause weight loss.

3. Acute disease effect

- No nutritional intake or likelihood of no intake for more than 5 days.

Further details on taking alternative measurements, special circumstances and subjective criteria can be found in *The 'MUST' Explanatory Booklet*. A copy can be downloaded at www.bapen.org.uk or purchased from the BAPEN office. The full evidence-base for 'MUST' is contained in *The 'MUST' Report* and is also available for purchase from the BAPEN office.

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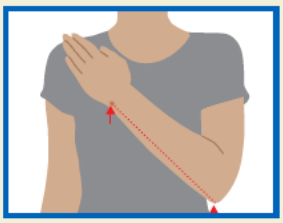
Alternative measurements: instructions and tables

If height cannot be obtained, use length of forearm (ulna) to calculate height using tables below. *(See The 'MUST' Explanatory Booklet for details of other alternative measurements (knee height and demispan) that can also be used to estimate height).*

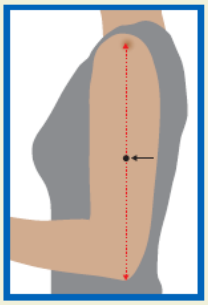
Estimating height from ulna length



Measure between the point of the elbow (olecranon process) and the midpoint of the prominent bone of the wrist (styloid process) (left side if possible).

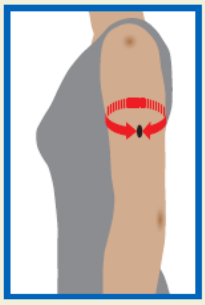
HEIGHT (m)	Men (<65 years)	1.94	1.93	1.91	1.89	1.87	1.85	1.84	1.82	1.80	1.78	1.76	1.75	1.73	1.71
	Men (>65 years)	1.87	1.86	1.84	1.82	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.67
	Ulna length (cm)	32.0	31.5	31.0	30.5	30.0	29.5	29.0	28.5	28.0	27.5	27.0	26.5	26.0	25.5
HEIGHT (m)	Women (<65 years)	1.84	1.83	1.81	1.80	1.79	1.77	1.76	1.75	1.73	1.72	1.70	1.69	1.68	1.66
	Women (>65 years)	1.84	1.83	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.66	1.65	1.63
HEIGHT (m)	Men (<65 years)	1.69	1.67	1.66	1.64	1.62	1.60	1.58	1.57	1.55	1.53	1.51	1.49	1.48	1.46
	Men (>65 years)	1.65	1.63	1.62	1.60	1.59	1.57	1.56	1.54	1.52	1.51	1.49	1.48	1.46	1.45
	Ulna length (cm)	25.0	24.5	24.0	23.5	23.0	22.5	22.0	21.5	21.0	20.5	20.0	19.5	19.0	18.5
HEIGHT (m)	Women (<65 years)	1.65	1.63	1.62	1.61	1.59	1.58	1.56	1.55	1.54	1.52	1.51	1.50	1.48	1.47
	Women (>65 years)	1.61	1.60	1.58	1.56	1.55	1.53	1.52	1.50	1.48	1.47	1.45	1.44	1.42	1.40

Estimating BMI category from mid upper arm circumference (MUAC)



The subject's left arm should be bent at the elbow at a 90 degree angle, with the upper arm held parallel to the side of the body. Measure the distance between the bony protrusion on the shoulder (acromion) and the point of the elbow (olecranon process). Mark the mid-point.

Ask the subject to let arm hang loose and measure around the upper arm at the mid-point, making sure that the tape measure is snug but not tight.



If MUAC is < 23.5 cm, BMI is likely to be <20 kg/m².
If MUAC is > 32.0 cm, BMI is likely to be >30 kg/m².

The use of MUAC provides a general indication of BMI and is not designed to generate an actual score for use with 'MUST'. For further information on use of MUAC please refer to *The 'MUST' Explanatory Booklet.*

Appendix 5 Medical Research Council (MRC) dyspnoea scale

In the past month, have you become breathless when you
do any physical activity? Yes __ No __

Please read the statements in the left column and circle the relevant number in the right column.

My breathing does not limit my physical activity	0
I only get breathless with strenuous exercise	1
I get short of breath when hurrying on the level or up a slight hill	2
I walk slower than people of the same age on the level because of breathlessness OR have to stop for breath when walking at my own pace on the level	3
I stop for breath after walking 100 yards or after a few minutes on the level	4
I am too breathless to leave the house	5

Appendix 6 St George's Respiratory Questionnaire (SGRQ)

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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St. George's Respiratory Questionnaire
Part 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

more than 3 attacks ☐
3 attacks ☐
2 attacks ☐
1 attack ☐
no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

a week or more ☐
3 or more days ☐
1 or 2 days ☐
less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

No good days ☐
1 or 2 good days ☐
3 or 4 good days ☐
nearly every day is good ☐
every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

No ☐
Yes ☐

St. George's Respiratory Questionnaire
Part 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problem	☐

If you have ever had paid employment.

Please tick (✓) *one*:

My chest trouble made me stop work altogether	☐
My chest trouble interferes with my work or made me change my work	☐
My chest trouble does not affect my work	☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire
Part 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
My cough hurts	□	□
My cough makes me tired	□	□
I am breathless when I talk	□	□
I am breathless when I bend over	□	□
My cough or breathing disturbs my sleep	□	□
I get exhausted easily	□	□

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	□	□
My chest trouble is a nuisance to my family, friends or neighbours	□	□
I get afraid or panic when I cannot get my breath	□	□
I feel that I am not in control of my chest problem	□	□
I do not expect my chest to get any better	□	□
I have become frail or an invalid because of my chest	□	□
Exercise is not safe for me	□	□
Everything seems too much of an effort	□	□

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
My medication does not help me very much	□	□
I get embarrassed using my medication in public	□	□
I have unpleasant side effects from my medication	□	□
My medication interferes with my life a lot	□	□

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in ***each box*** that applies to you ***because of your breathing***:	True	False
I take a long time to get washed or dressed	□	□
I cannot take a bath or shower, or I take a long time	□	□
I walk slower than other people, or I stop for rests	□	□
Jobs such as housework take a long time, or I have to stop for rests	□	□
If I walk up one flight of stairs, I have to go slowly or stop	□	□
If I hurry or walk fast, I have to stop or slow down	□	□
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	□	□
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	□	□
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	□	□

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***:	True	False
I cannot play sports or games	□	□
I cannot go out for entertainment or recreation	□	□
I cannot go out of the house to do the shopping	□	□
I cannot do housework	□	□
I cannot move far from my bed or chair	□	□

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do □

It stops me doing one or two things I would like to do □

It stops me doing most of the things I would like to do □

It stops me doing everything I would like to do □

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

SGRQ scores in healthy subjects

Means (95% confidence intervals) for SGRQ scores in normal subjects with no history of respiratory disease (*Jones et al., 2003*).

N	Age - years	FEV1 as % predicted	Symptoms Score	Activity Score	Impacts Score	Total Score
74	46 range 17-80	95 (91-99)	12 (9-15)	9 (7-12)	2 (1-3)	6 (5-7)

Appendix 7 EQ-5D Euroqol.

Mobility		
I have no problems in walking about	❑	1
I have some problems in walking about	❑	2
I am confined to bed	❑	3
Self-Care		
I have no problems with self-care	❑	1
I have some problems washing or dressing myself	❑	2
I am unable to wash or dress myself	❑	3
Usual Activities (e.g. work, study, housework, family or leisure activities)		
I have no problems with performing by usual activities	❑	1
I have some problems with performing my usual activities	❑	2
I am unable to perform my usual activities	❑	3
Pain/Discomfort		
I have no pain or discomfort	❑	1
I have moderate pain or discomfort	❑	2
I have extreme pain or discomfort	❑	3
Anxiety/Depression		
I am not anxious or depressed	❑	1
I am moderately anxious or depressed	❑	2
I am extremely anxious or depressed	❑	3
Compared with my general level of health over the past 12 months, my health state today is:		
Better	❑	1
Much the same	❑	2
Worse	❑	3

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today