Nutritional assessment and therapy in COPD: a European Respiratory Society statement

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ABSTRACT Nutrition and metabolism have been the topic of extensive scientific research in chronic obstructive pulmonary disease (COPD) but clinical awareness of the impact dietary habits, nutritional status and nutritional interventions may have on COPD incidence, progression and outcome is limited. A multidisciplinary Task Force was created by the European Respiratory Society to deliver a summary of the evidence and description of current practice in nutritional assessment and therapy in COPD, and to provide directions for future research. Task Force members conducted focused reviews of the literature on relevant topics, advised by a methodologist. It is well established that nutritional status, and in particular abnormal body composition, is an important independent determinant of COPD outcome. The Task Force identified different metabolic phenotypes of COPD as a basis for nutritional risk profile assessment that is useful in clinical trial design and patient counselling. Nutritional intervention is probably effective in undernourished patients and probably most when combined with an exercise programme. Providing evidence of cost-effectiveness of nutritional intervention is required to support reimbursement and thus increase access to nutritional intervention. Overall, the evidence indicates that a well-balanced diet is beneficial to all COPD patients, not only for its potential pulmonary benefits, but also for its proven benefits in metabolic and cardiovascular risk.

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This article has supplementary material available from erj.ersjournals.com

Received: April 15 2014 | Accepted after revision: June 29 2014 | First published online: Sept 18 2014

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Introduction

Nutrition has been the topic of extensive scientific research in chronic obstructive pulmonary disease (COPD). This article will examine the impact that dietary habits, nutritional status and nutritional interventions may have on the incidence, progression and outcome of COPD. The article aims to raise awareness about diet and nutrition in COPD, and to deliver a resource that will assist clinicians and academics in providing high-quality nutritional assessment and care to individuals with COPD.

The topics discussed range from understanding altered metabolism and related therapeutic targets in COPD, to improving dietary habits, outcome and cost-effectiveness of nutritional interventions including recommendations for future translational, epidemiological and clinical research. Topic selection was based on scientific importance and clinical relevance to ensure the article would be of interest to members of the European Respiratory Society (ERS).

Methods

A multidisciplinary Task Force was created by the ERS, consisting of 12 members representing a broad range of respiratory clinicians involved in delivery of care to individuals with COPD, basic scientists, nutritional caregivers specialised in practical challenges of dietary intervention, epidemiologists, and a health economist. Several representatives were also members of the European Society for Clinical Nutrition and Metabolism (ESPEN) in order to guarantee optimal alignment between this ERS statement and updated ESPEN guidelines on nutrition in COPD. Conflicts of interest were dealt with according to ERS standard procedures. This document was created by combining a firm evidence-based approach and the clinical expertise of the Task Force members. However, a formal grading of the evidence was not performed and, therefore, this document does not contain recommendations for clinical practice. The process adopted for this statement was agreed by all Task Force members. A statement is not a systematic review of the literature but the method by which literature was identified and incorporated for this statement was agreed before work commenced on the document. A hierarchy of evidence was agreed upon, and data from systematic reviews and well-designed randomised controlled trials were, accordingly, given priority in the evaluation process. Members of the Task Force reviewed the scientific evidence relevant to the delegated subject area. Publications that were in print between 2006 and 2013 were selected for further examination. Systematic reviews and randomised controlled trials from Medline/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL and the Cochrane Collaboration were collected. In addition, the references of the selected papers were scrutinised for further relevant evidence. Each topic was presented by the assigned author at the initial meeting in Lausanne, Switzerland (June 2012), and drafts were presented and discussed during meetings in Maastricht, the Netherlands (December 2012), and Barcelona, Spain (September 2013). The final document was drawn together by the chairs of the Task Force. The draft manuscripts were reviewed by all Task Force members to ensure appropriateness and relevance, and the final document was accepted by all Task Force members.

Scope

COPD is an important global health problem. The disease is characterised by persistent airflow obstruction resulting from inflammation and remodelling of the airways, and may include development of emphysema. Furthermore, systemic disease manifestations and acute exacerbations influence disease burden and mortality risk [1]. Extending the classical descriptions of the ''pink puffer'' and ''blue bloater'', recent unbiased statistical approaches [2, 3] support the concept that body weight and body composition discriminate pulmonary phenotypes, and are predictors of outcome independent of lung function impairment. Incorporation of body composition into nutritional assessment has been a major step forward in understanding systemic COPD pathophysiology and nutritional potential. While initially being considered an indicator of inevitable and terminal progression of the disease process, there is now convincing evidence that unintended weight loss is not an adaptive mechanism to decrease metabolic rate in advanced COPD [4] but an independent determinant of survival, arguing for weight maintenance in patient care. An important role of muscle loss and decreased muscle oxidative metabolism in impaired physical performance has been demonstrated, providing new evidence for nutritional supplementation as an adjunct to exercise training, not only confined to advanced disease but also in earlier disease stages. In addition, a pivotal role of osteoporosis, visceral adiposity and poor dietary quality in COPD risk and progression has emerged, which positions dietary awareness and intervention as integral part of disease management, from prevention to chronic respiratory failure.

Nutritional assessment

In order to develop and evaluate effective prevention and intervention strategies, stratification of the patient population into specific metabolic phenotypes is required. While it is accepted that body weight and body

composition variables represent a continuous spectrum, clear definitions and reference values for phenotypes that predict outcome and response to treatment have been developed over the past decade, as shown in table 1. These different conditions reflect a complex interaction between the effects of (epi)genetics, lifestyle and disease triggers on muscle, bone and adipose tissue. Numerous statement documents focus on individual metabolic phenotypes as intervention target [6, 7]. In view of the coexistence of different metabolic phenotypes during the course of COPD, members of this Task Force have established a nutritional risk profile, based on prospective assessment of body weight (change) and body composition (fig. 1). This nutritional risk stratification diaphragm will be useful in clinical trial design and in individually tailoring nutritional management. In this risk profile, an adapted World Health Organization classification of body mass index (BMI) is used based on the lowest standardised rate of death from recent population studies [8, 9]. As a rule of thumb, involuntary weight loss >5% during the last 6 months is considered clinically significant, taking natural variations into account. Recent weight loss can be assessed by patient recollection, although standardised weight measurements at regular intervals by caregivers or self-monitoring are often incorporated and more informative. Weight changes and BMI classification do not take body compositional shifts, including fat mass and distribution, lean mass and distribution, and bone mineral density (BMD) into account. To distinguish between low and normal fat-free mass (FFM) (FFM = lean mass + BMD), body composition needs to be assessed. Appropriate measurements of body composition and surrogate markers in research and clinical practice are presented in table 2. In normal to underweight COPD patients, age- and sex-adjusted fat-free mass index (FFMI) (FFMI = FFM/height^2) <10th percentile is defined as abnormally low based on well-established adverse effects of low FFMI on physical performance and survival. In the age range of most Caucasian COPD patients at risk, this corresponds to a FFMI <17 kg·m^{-2} for males and <15 kg·m^{-2} for females as clinically useful proxies in normal to underweight patients with COPD [10]. Sarcopenia is characterised by low skeletal muscle index (SMI) (SMI = lean appendicular mass (assessed by dual-energy X-ray absorptiometry (DEXA))/height^2), *i.e.* equal to or below the mean minus two standard deviations of that of healthy persons between 20 and 30 years of age of the same ethnic group [11]. Sarcopenia imposes additional risk of skeletal muscle weakness in an increasing proportion of older and overweight patients. An important difference between the risk stratification diagram and conventional nutritional risk scores, such as the Malnutrition Universal Screening Tool [12] or Mini Nutritional Assessment [13], is that the latter are primarily focused on malnutrition and do not take abnormal body composition into account.

Metabolic phenotypes and nutritional risk profile in COPD

Recent, large population studies have revealed that the age-standardised rate of death from any cause was lowest among participants with a BMI of 22.5–24.9 kg·m^{-2} and of 20–25 kg·m^{-2} in analyses restricted to those who never smoked [8, 9]. In patients with moderate to severe airflow obstruction, a BMI <25 kg·m^{-2} was consistently associated with increased mortality risk relative to overweight and even obese patients [14–16]. This prognostic advantage of increased BMI in COPD, also referred to as the ''obesity paradox'', could be related to the direct effect of adipose tissue on lung mechanics (*e.g.* relative reduction in static volumes in obese COPD patients [17]). However, it might also be an epiphenomenon of other, yet unknown disease characteristics that confer both a reduced mortality risk and preserved fat mass and/or FFM. Furthermore, it is not yet clear whether it is excessive fat or preserved FFM that contributes to the survival advantage in COPD, as low FFMI (<10th percentile), independent of BMI and fat mass, is a strong predictor of mortality [18]. The prevalence of underweight in COPD increases with disease severity [18] and is clearly associated with the presence of emphysema [19]. In normal to overweight patients, a low FFMI implies a proportionally high fat mass index. Furthermore, fat mass may be redistributed from subcutaneous to visceral adipose tissue, which has been associated with increased cardiovascular risk in mild to moderate COPD [20]. COPD patients with underweight or low FFM are more prone to loss of BMD than overweight patients [21]. DEXA is most appropriate for combined screening of osteoporosis, FFM and fat mass. Although distinction between abdominal visceral and subcutaneous fat mass requires more advanced imaging technologies (*e.g.* computed tomography and magnetic resonance imaging), a clinically useful estimate can be derived by DEXA.

Pathophysiology of abnormal body composition and targets for nutritional intervention

Understanding the pathophysiology and cross-talk of muscle loss and adiposity in COPD is essential for the development of targeted nutritional interventions to address specific metabolic phenotypes. A comprehensive overview of this pathophysiology is beyond the scope of this article. Hence, we present a brief summary relevant to alterations in nutritional status and nutritional intervention. For a more detailed account of skeletal muscle wasting in COPD, the reader is directed to the recently updated American Thoracic Society/ERS statement on lower limb muscle dysfunction in COPD [22].

DOI: 10.1183/09031936.00070914

TABLE 1 Metabolic phenotypes

Metabolic phenotype	Definition	Clinical risk
Obesity	BMI 30–35 kg·m^{-2}	Increased cardiovascular risk
Morbid obesity	BMI >35 kg·m^{-2}	Increased cardiovascular risk Impaired physical performance
Sarcopenic obesity	BMI 30–35 kg·m^{-2} and SMI <2 SD below mean of young M and F reference groups [5]	Increased cardiovascular risk Impaired physical performance
Sarcopenia	SMI <2 SD below mean of young M and F reference groups	Increased mortality risk Impaired physical performance
Cachexia	Unintentional weight loss >5% in 6 months and FFMI <17 kg·m^{-2} (M) or <15 kg·m^{-2} (F)	Increased mortality risk Impaired physical performance
Precachexia	Unintentional weight loss >5% in 6 months	Increased mortality risk

BMI: body mass index (weight/height^2); SMI: appendicular skeletal muscle index (appendicular lean mass/height^2); M: male; F: female; FFMI: fat-free mass index (fat-free mass/height^2).

Fat loss

Loss of body weight and fat mass occurs when energy expenditure exceeds energy availability. Eating *per se* is an activity that can adversely affect haemoglobin saturation and increase dyspnoea in patients with severe COPD [23]. Ageing is also a contributing factor to reduced dietary intake in COPD due to symptoms (*e.g.* loss of taste, poor dentition, dysphagia, poor chewing and swallowing ability, poor appetite, or food aversion), social problems (*e.g.* living or eating alone, or poverty) and inability to self-feed [24]. Anorexia is, however, not the primary trigger of a disturbed energy balance in clinically stable disease, as generally, a normal appetite to increased dietary intake is reported in underweight patients [25, 26]. Moreover, while the normal response to semi-starvation is a reduced metabolic rate and depressed whole-body protein turnover, weight-losing COPD patients may display elevated resting energy expenditure and increased whole-body protein turnover [27]. Furthermore, in addition to an increased cost of ventilation due to abnormal pulmonary mechanics, a higher ATP cost of muscular contraction [28] may contribute to decreased mechanical efficiency of lower limb exercise [29] and elevated daily energy requirements in some COPD patients [30]. In support of this, weight gain after lung volume reduction surgery was associated with improved lung function and reduced work of breathing [31]. Collectively, this indicates a hypermetabolic

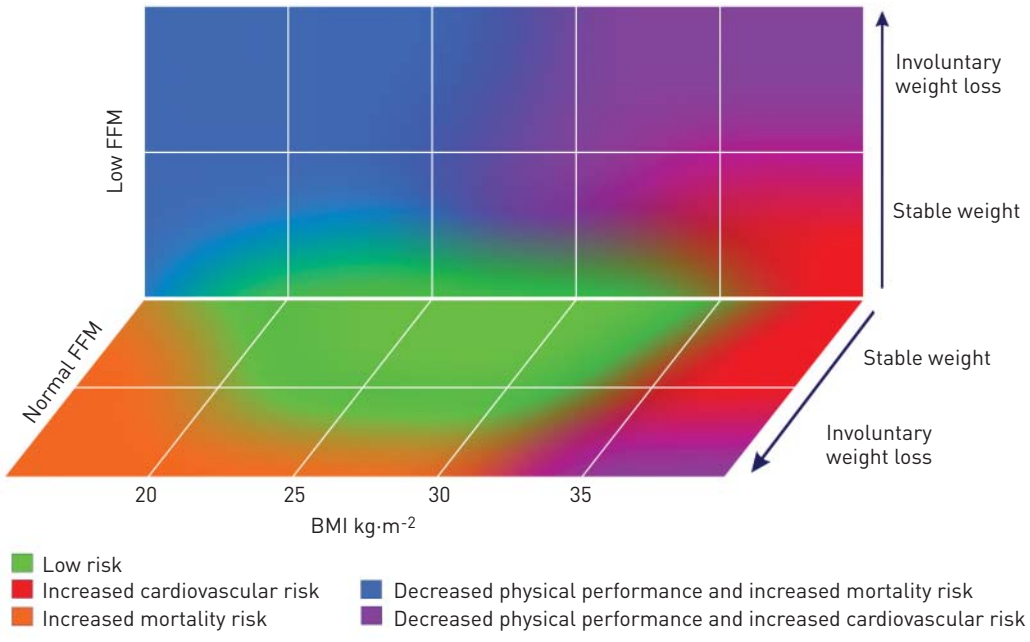

FIGURE 1 Nutritional risk stratification diagram. FFM: fat-free mass; BMI: body mass index.

TABLE 2 Appropriate measurements of body composition and surrogate markers in research and clinical practice

Variable	Research	Clinical practice
Fat-free mass/fat mass	Deuterium dilution	DEXA, single-frequency BIA Anthropometry (sum of four skin folds)
Intracellular mass	Deuterium dilution combined with bromide dilution	Multifrequency BIA
Muscle mass	CT MRI Biomarkers (*i.e.* D_3-creatine dilution)	DEXA Ultrasonography Biomarkers (*i.e.* creatine height index) Anthropometry (mid-arm muscle circumference)
Abdominal fat	CT	DEXA
Abdominal visceral fat	MRI Biomarkers (*i.e.* PAI-1)	Anthropometry (*i.e.* sagittal diameter and/or waist/hip circumference) Ultrasonography
Bone mass and density	DEXA	DEXA HRCT
Muscle strength and related physical performance	Isokinetic quadriceps strength (Repetitive) magnetic stimulation Timed up-and-go test Stair-climb power test Cycle ergometry	One-repetition maximum Handgrip strength Timed up-and-go test Stair-climb power test

DEXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance; CT: computed tomography; MRI: magnetic resonance imaging; PAI: plasminogen-activator inhibitor; HRCT: high-resolution computed tomography.

state that may contribute to weight loss if energy requirements are not fully met and provides a convincing rationale for caloric supplementation to maintain or increase fat mass. Early concerns about adverse effects of carbohydrate supplementation in COPD due to increased carbon dioxide production, resulting from carbohydrate oxidation loading ventilation, have not been substantiated in more recent studies but were only observed after hyperalimentation [32]; this is, in practice, unlikely to happen with oral nutrition, especially in patients with poor appetite, and can easily be avoided by smaller meal portions well spread over the day.

Muscle loss

Muscle mass is determined by the net balance of muscle protein synthesis and protein breakdown. There is evidence for increased muscle protein degradation rate in cachectic COPD patients characterised by low BMI and low FFMI [33]. Analyses of the effector pathways of protein degradation showed consistent elevation of components of the ubiquitin 26S proteasome system [34] and enhanced autophagy [35]. Conversely, distal protein synthesis signalling cues (insulin-like growth factor I and phospho-Akt expression levels) are mainly unaltered [34]. More research is required to exclude any impairment in protein synthesis signalling (*i.e.* its responsiveness to catabolic triggers), but assuming this is not the case [36], stimulating protein synthesis more proximally using nutritional intervention to counterbalance elevated proteolysis may contribute to muscle mass maintenance in the presence of increased protein turnover in cachectic patients. Nutritional intervention targeted at provision of sufficient amino acids to support protein synthesis signalling could evoke a compensatory response to increases in proteolysis cues, obviously presuming a positive energy balance [36]. Stimulation of protein synthesis depends on the availability of amino acids in the blood stream. COPD patients with low FFM have low plasma levels of branched-chain amino acids (BCAAs) compared with age-matched controls [37]. It is well-known that BCAAs, particularly leucine, are able to stimulate muscle protein synthesis. The extraction of dietary nutrients, especially amino acids, by the intestine has a critical influence on their availability to peripheral tissues and, therefore, on whole-body amino acid requirements. Lower splanchnic extraction associated with an enhanced anabolic response to a protein meal [38] was found in sarcopenic patients with COPD, which might be related to compromised intestinal function [39]. Supplementation of soy protein with BCAAs altered inter-organ metabolism even further in favour of the muscle compartment in COPD [40]. Further research is required to investigate if the anabolic potential of high-quality protein is less in chronic respiratory failure or in the cachexia-susceptible emphysematous phenotype, as the latter also exhibited a blunted whole-body protein turnover after acute exercise [41]. Increased levels of oxidative stress have been consistently reported in the skeletal muscle of COPD patients. Of signalling pathways sensitive to oxidative stress and involved in muscle mass regulation, muscle biopsy analyses have suggested activation of FOXO (fork head box O), MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor, κ-light chain activator of B-cells).

DOI: 10.1183/09031936.00070914

MAPK and NF-κB signalling is also initiated by inflammation and increased inflammatory cell infiltration, and pro-inflammatory cytokine expression has indeed been reported in some studies. These catabolic pathways (or upstream triggers such as oxidative stress and inflammation) may therefore be suitable targets for nutritional modulation [34].

Bone mineral density loss

Osteoporosis is a skeletal disease characterised by low bone mass and microarchitectural deterioration with a net increase in bone fragility and, hence, susceptibility to fracture [42]. Hip fractures are directly related to falls, causing hospitalisation and excess mortality. Vertebral fractures more often occur silently and are thought to result from routine activities such as bending or lifting. In patients with COPD, vertebral and rib cage fractures may lead to increased kyphosis, reduced rib cage mobility and further reduction of pulmonary function. COPD and osteoporosis often coincide. Prevalence data vary from 5% to 60% depending on the diagnostic methods used, the population setting and the severity of the disease [43]. One reason for this association is the presence of common risk factors such as ageing, smoking, underweight, sarcopenia and physical or functional limitation. Additionally, systemic inflammation, the use of systemic corticosteroids and the high prevalence of vitamin D deficiency, which are frequently observed in more severe stages of COPD, unequivocally contribute to a further loss of bone and muscle mass [43, 45]. Observational studies also suggest that emphysema represents a particular phenotype that is associated with musculoskeletal impairment but the underlying mechanisms remain unclear [46–48]. Bone tissue is continuously renewed throughout life. After reaching a peak bone mass at the age of 25 to 30 years, bone formation balances back to resorption with an annual loss of 0.5–1%. On the cellular level, remodelling and bone renewal consist of an interaction between osteoblasts, cells producing osteoid protein matrix that subsequently mineralises, and osteoclasts, which absorb bone and release calcium back from its stores. This interaction is tightly regulated by NF-κB and its ligand (receptor activator of NF-κB (RANK)/RANK ligand (RANKL) system) expressed on the surfaces of both cell types. Vitamin D plays a key role in the regulation of calcium and bone homeostasis but other factors, including several proinflammatory cytokines, also act on this pathway. Low 25-hydroxyvitamin D (25-OHD) levels stimulate the production of parathyroid hormone, which, through the activation of the RANK/RANKL system, activates osteoclasts into bone resorption, calcium release and subsequent stabilisation of blood calcium levels [49]. Significant associations between low 25-OHD levels and BMD have been shown in different populations, including COPD patients [45, 50]. Low 25-OHD levels are also associated with muscle weakness and increased risk of falls, so that sufficient intake of vitamin D and calcium, in addition to lifestyle modifications (increased physical activity, spending more time outside, smoking cessation and limited alcohol use), still composes the basis of all prevention and treatment strategies of osteoporosis [51].

Adiposity

In patients with advanced disease, respiratory failure is the most common cause of death, with sarcopenia and cachexia as important risk factors. In contrast, in patients with mild-to-moderate disease, the primary cause of death is ischaemic cardiovascular disease, for which adiposity is an important lifestyle-induced risk factor [52]. There is increasing evidence that adipose tissue in COPD patients with relative or absolute fat abundance is a significant contributor to the systemic inflammatory load [53]. Abdominal visceral fat is more strongly associated with cardiovascular risk than subcutaneous fat, which could be related to a higher inflammatory capacity. In mild to moderate, nonobese COPD patients, a fat redistribution was shown towards more abdominal visceral fat compared with controls, despite comparable total fat mass [20]. It is yet unclear to what extent this redistribution reflects unhealthy lifestyle or is disease-induced and whether the two act synergistically [54]. Obese COPD patients have increased dyspnoea at rest and poorer health status compared with normal-weight patients, while static lung hyperinflation is reduced, irrespective of the severity of disease [17]. The combined effects of obesity and COPD on exercise tolerance seem to depend on the type of exercise (weight-bearing *versus* non-weight-bearing) that is performed. While peak cycling capacity is preserved in obese COPD patients compared with nonobese patients, and dyspnoea ratings are consistently lower during cycling in obese patients, the 6-min walk distance (6MWD) is reduced and the degree of fatigue is increased in obese patients [55]. No studies have systematically investigated the effects of weight loss interventions on adiposity, functionality and systemic inflammatory profile in patients with COPD. Although weight maintenance after a short period of weight loss is reported as a major challenge in other risk populations, even modest reductions in weight can reduce the cardiovascular disease risk through improvements in body fat distribution [56]. A combination of dietary intervention and aerobic exercise may achieve this goal best as aerobic exercise training improves insulin sensitivity, induces mitochondrial biogenesis in skeletal muscle and also induces loss of visceral fat mass [54]. Feasibility and efficacy of this approach, however, may be limited in advanced COPD by ventilatory restraints on exercise intensity. Alternatively or as an adjunct, intervention with bioactive nutrients (*e.g.* polyphenols, polyunsaturated fatty

acids (PUFAs) and vitamin B_3) has been proposed to boost muscle mitochondrial metabolism and limit ectopic fat accumulation [57], but this requires adequate clinical trials in COPD in the future.

Acute exacerbations

Weight loss and wasting of muscle and bone tissue may be induced or accelerated during severe acute exacerbations requiring hospitalisation, due to convergence of different catabolic stimuli including malnutrition [58], physical inactivity [59], hypoxia, inflammation [60] and systemic glucocorticoids [61]. Moreover, this may be a time when energy intake may be compromised by practical difficulties in providing adequate nutrition due to breathlessness or other treatments such as noninvasive ventilation. Furthermore, impaired responsiveness to signalling cues of muscle regeneration and protein synthesis may delay recovery and increase the risk for readmission [62]. In the acute phase of respiratory exacerbations, loss of appetite and reduced dietary intake are often experienced in concert with elevated systemic levels of the appetite-regulating hormone leptin and pro-inflammatory cytokines [58, 60]. Next to nutritional risk screening and early intervention in primary care, hospitalisations could be considered an additional opportunity for detailed nutritional assessment and implementation of longer term nutritional management, as they represent a period of heightened ''nutritional risk'' that may, in itself, require intensive nutritional therapy [63]. The impact of such intensive regimes on clinical outcomes and underlying mechanisms is yet to be clearly established.

Dietary management and nutritional supplementation

Due to the ubiquitous nature of nutrition and the multiple metabolic effects induced by each food, nutrient or micronutrient, randomised clinical trials in this area face specific obstacles. By their nature, some obstacles are difficult to resolve, such as having a placebo or proper blinding of food. Due to the multiple metabolic impacts of nutrients, choosing a primary outcome and the determination of sample size are particularly difficult. Nutritional research on single foods is also complex because it exploits a multitude of bioactive compounds acting on an extensive network of interacting processes.

Treatment of weight loss in COPD

A patient who is in a negative energy balance and losing weight will need to increase their energy intake, as additional reduction of energy expenditure is highly undesirable in COPD. A suitable energy- and protein-enriched diet can be achieved by several small portions spread throughout the whole day [64]. The energy- and protein-enriched diet often has a higher fat content (45% of total energy) than in recommendations for healthy individuals. Due to the high proportion of fat, consideration needs to be given to the quality of the fat, especially in choice of fat used for cooking, to minimise the proportion of saturated fat. It is generally recommended in current guidelines that protein should provide 20% of the total energy intake. Fortification products can be used to increase energy and protein content in different meals [65]. A dietician is able to tailor the energy- and protein-enriched diet taking into account each subject's eating habits, lifestyle, symptoms, likes and dislikes. At low energy intakes, it can be hard to fulfil the needs for vitamins, minerals and trace elements. Oral nutritional supplements (as powders, puddings or liquids) can be used to supplement the diet when nutrient requirements cannot be satisfied through normal food and drink.

While the rationale for nutritional support to maintain or increase energy availability and muscle protein synthesis in weight-losing and underweight COPD patients is compelling, randomised clinical trials investigating the clinical efficacy are generally small and initial meta-analyses revealed small estimates of effect only. The Cochrane review by Ferreira *et al.* [66] was recently updated and now includes 17 trials (632 participants) of $\geqslant$2 weeks of nutritional support (figs 2 and 3). The post-treatment values were pooled for all outcomes and the changes from baseline scores (change scores) were pooled for primary outcomes. The updated review also incorporated the Grading of Recommendations Assessment, Development and Evaluation [89] approach to determine the quality of the evidence (*i.e.* risk of bias of included studies, inconsistency of results, indirectness of the evidence, imprecision of the data and possible publication bias). This increased body of evidence gives a clearer picture of the overall effects of nutritional supplementation and the impact in specific COPD subgroups. Moderate-quality evidence (due to mixed risks of bias) suggests that nutritional supplementation promotes weight gain among patients with COPD, especially if undernourished. This was demonstrated using both pooled estimates: post-intervention and change scores. Only the change scores were significant for the weight gain of the overall population (both nourished and undernourished), but undernourished patients showed significant weight gain, regardless of the method used. There was significant improvement in anthropometric measures (FFM, mid-arm muscle circumference and triceps skin folds) (fig. 3), 6MWD, respiratory muscle strength (maximal inspiratory and expiratory pressures) and overall health-related quality of life as measured by the St George's Respiratory Questionnaire in undernourished patients with COPD. The increase in 6MWD reached the minimal

DOI: 10.1183/09031936.00070914

clinically important difference in severe COPD [90, 91].The quality of evidence supporting other outcomes was low, mainly because of multiple risks of biases and imprecision of the data (due to small numbers). This means that future research is very likely to impact on our confidence in the estimates of the effect and is likely to change the estimates. Furthermore, a multicentre, phase III trial seems justified.

COLLINS and co-workers [92, 93] also published recent meta-analyses using different methods. They did not include all of the same papers, but their findings were broadly in line with the Cochrane review. They also included significant positive findings for total energy intake, and handgrip and quadriceps strength.

The results of recent systematic reviews and meta-analyses now suggest that nutritional supplementation should be considered in the management of undernourished patients with COPD. Five out of 17 trials included in the updated meta-analysis [66], specifically the trials that had FFM as an outcome, had nutritional supplementation combined with exercise. It is likely that the benefits of supplementation will be maximised if combined with exercise, although based on the current literature, the effects of nutrition and exercise cannot clearly be distinguished, which is a subject for future research.

First author [ref.]	Difference mean±SE	Experimental total	Control total	Weight %	Mean difference IV, random (95% CI)
Undernourished					
DELETTER [67]#	1.2±0.4123	18	17	18.0	1.20 (0.39–2.01)
EFTHIMIOU [68]#	4.1±1.5071	7	7	1.3	4.10 (1.15–7.05)
FUENZALIDA [69]#	1.22±1.4284	5	4	1.5	1.22 (-1.58–4.02)
LEWIS [70]#	1.2±0.442	10	11	15.7	1.20 (0.33–2.07)
OTTE [71]	1.36±0.4579	13	15	14.6	1.36 (0.46–2.26)
ROGERS [72]	2.8±1.8243	15	12	0.9	2.80 (-0.78–6.38)
SCHOLS [73]¶	2.4±0.5967	39	25	8.6	2.40 (1.23–3.57)
SUGAWARA [74]	1.91±0.7184	17	14	5.9	1.91 (0.50–3.32)
HOOGENDOORN [75], VAN WETERING [76–79]	2.8±0.9745	16	14	3.2	2.80 (0.89–4.71)
WEEKES [65, 80]	2.1±1.607	30	25	1.2	2.10 (-1.05–5.25)
RYAN [81], WHITTAKER [82]	3±0.8944	6	4	3.8	3.00 (1.25–4.75)
Subtotal (95% CI)		176	148	74.8	1.73 (1.29–2.17)
Heterogeneity: Tau-squared 0.06; Chi-squared 11.21, df 10 (p=0.34); I^2=11%					
Test for overall effect: Z=7.70 (p<0.00001)					
Nourished					
SCHOLS [73]	1.5±0.8061	33	38	4.7	1.50 (-0.08–3.08)
Subtotal (95% CI)		33	38	4.7	1.50 (-0.08–3.08)
Heterogeneity: not applicable					
Test for overall effect: Z=1.86 (p=0.06)					
Combined population of undernourished and nourished					
KNOWLES [83]#	2.05±3.1791	13	12	0.3	2.05 (-4.18–8.28)
STEINER [84–86]	1.21±0.779	25	35	5.0	1.21 (-0.32–2.74)
SUGAWARA [87–88]	1.5±0.4486	17	14	15.2	1.50 (0.62–2.38)
Subtotal (95% CI)		55	61	20.5	1.44 (0.68–2.19)
Heterogeneity: Tau-squared 0.00; Chi-squared 0.14, df 2 (p=0.93); I^2=0%					
Test for overall effect: Z=3.72 (p=0.00002)					
Total (95% CI)	1.5±0.8061	264	247	100.0	1.62 (1.27–1.96)
Heterogeneity: Tau-squared 0.00; Chi-squared 11.66, df 14 (p=0.63); I^2=0%					
Test for overall effect: Z=9.24 (p<0.00001)					
Test for subgroup differences: Chi-squared 0.45, df 2 (p=0.80), I^2=0%					

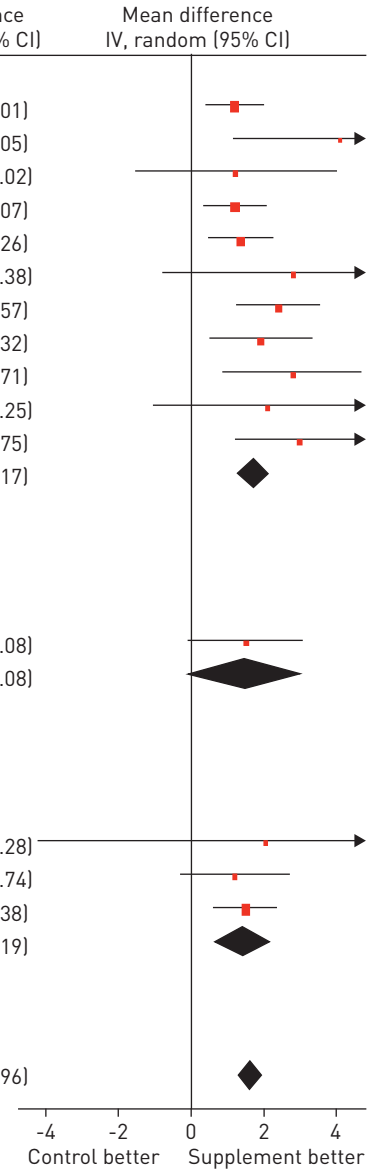

FIGURE 2 Forest plot of comparison between nutritional supplementation and placebo or usual diet with change in weight (kg) as the outcome. df: degrees of freedom. #: imputed standard error; ¶: depleted. Reproduced and modified from [67] with permission from the publisher.

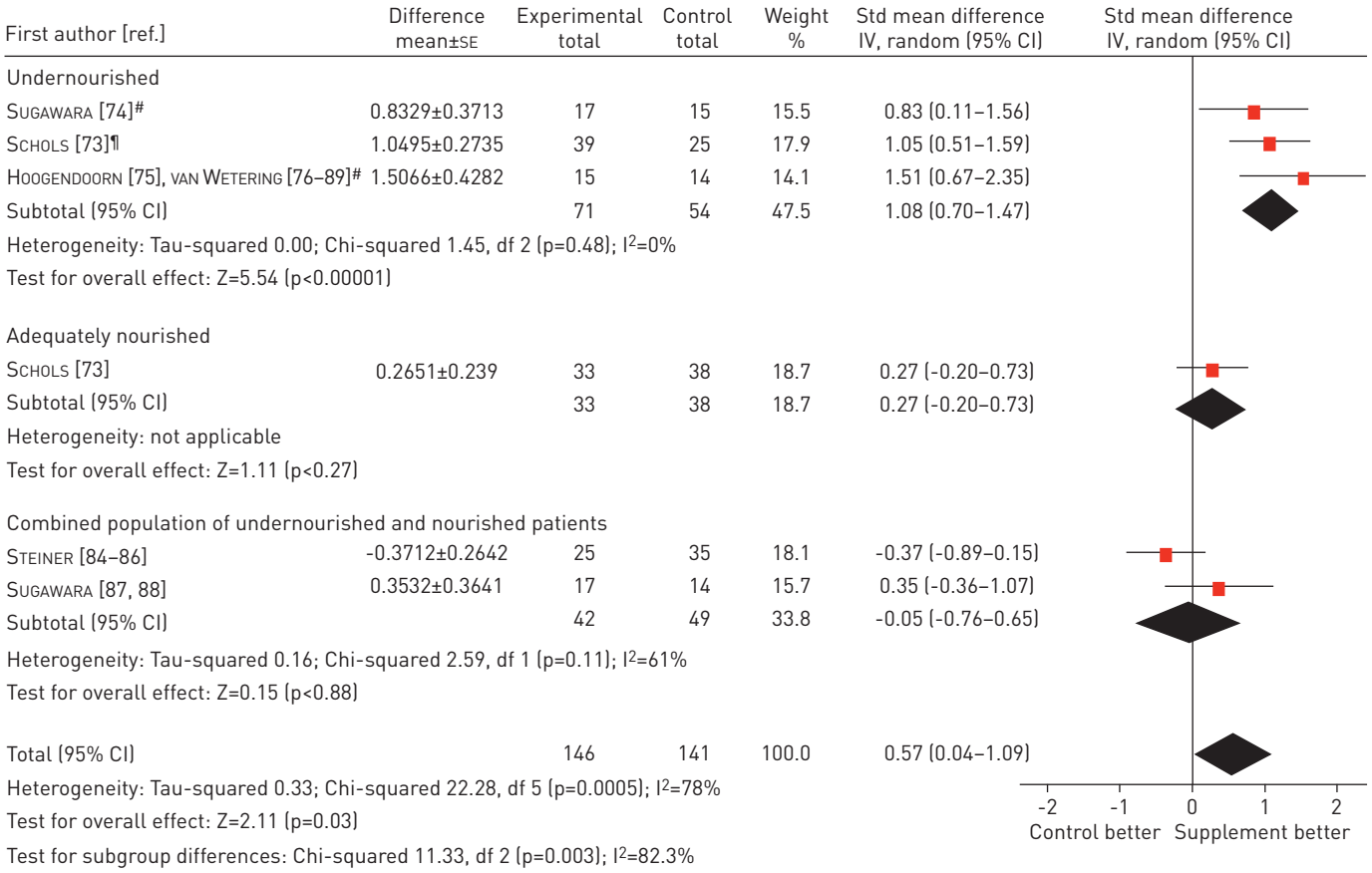

FIGURE 3 Forest plot of comparison between nutritional supplementation and placebo or usual diet with change in fat-free mass (FFM) (kg) as the outcome. df: degrees of freedom; Std: standardised mean difference. #: FFM index ($kg \cdot m^{-2}$); ¶: FFM measured as bioelectrical resistance. Reproduced and modified from [66] with permission from the publisher.

Nutrition as ergogenic aid

The importance of nutrition to enhance performance and training has long been recognised in the fields of sports and athletics. There is evidence for the benefits of ensuring adequate carbohydrate and protein intake (depending on the athletic discipline) in optimising performance [94] and evidence that some specific nutrients (*e.g.* creatine, PUFAs and nitrate) may enhance physical performance [95–98]. Enhancing physical performance is a key therapeutic goal in COPD and, therefore, there are theoretical reasons for hypothesising that nutritional intervention might improve performance in this population or enhance the outcome of exercise training, an intervention that is of proven clinical and physiological benefit in COPD. Aerobic exercise training is of established efficacy in COPD but it remains uncertain whether the magnitude of benefit is comparable to similar aged healthy subjects. Moreover, lower limb muscles in COPD are characterised by a decreased proportion of type I muscle fibres associated with decreased levels of muscle oxidative metabolic markers and nutrient sensing regulators of cellular energy state (*e.g.* peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1, PPARs, AMP-activated kinase and sirtuins) [99]. These observations support the rationale for augmenting exercise training with nutritional therapies and there is a limited number of trials investigating the impact of nutritional therapies on exercise performance or training in COPD, as recently reviewed by Task Force members [96]. These involved a variety of interventions including carbohydrate and fat-rich supplements [85], essential amino acids [100], whey protein (rich in BCAAs) [88], creatine [101–103] and PUFAs (natural ligands of PPARs) [104]. The literature is characterised by considerable heterogeneity in the nature of the intervention, the populations enrolled and the exercise outcomes that were studied. Many studies were underpowered and most were single-centre investigations. Early macronutrient studies involving fat-rich supplements did not suggest a performance advantage in the intervention groups, but subsequent studies using a carbohydrate-rich supplement and PUFAs suggested the outcome or exercise training might be enhanced in selected patients [85, 104].

DOI: 10.1183/09031936.00070914

Small pilot investigations have suggested potential benefits of whey protein and carnitine, but had insufficient statistical power for wider conclusions to be drawn. Three trials have tested the effect of creatine supplementation during exercise training in COPD with no consistent positive effect, as confirmed by a subsequent systematic review and meta-analysis [105]. In a group of overall non-wasted COPD patients, protein and carbohydrate supplementation after resistance exercise did not augment functional or molecular exercise responses [106]. The question whether nutritional support can augment the performance outcomes of exercise training and pulmonary rehabilitation remains largely unanswered.

Cost-effectiveness issues

Nutritional counselling and oral nutritional supplements compete with other treatments for a part of the publicly funded healthcare budget; it is therefore important to assess their cost-effectiveness. There are virtually no data on the economic implications of these interventions in COPD. Numerous studies, however, reported on the association between nutritional status and healthcare utilisation, focusing on patients hospitalised for a COPD exacerbation or predictors thereof. The studies showed that being undernourished in COPD is likely to be associated with longer in-patient hospital stays [107, 108], a higher probability of being readmitted [62, 109] and an increase in healthcare utilisation [110] in comparison with normally nourished patients. Three randomised controlled trials in COPD investigated the effects of nutritional supplementation on healthcare utilisation and/or costs [65, 76, 111]. Two studies did not find a difference in hospital admissions. It is, however, likely that in these studies, the duration of follow-up of $\leqslant$6 months was too short to detect an effect on healthcare utilisation. The only full economic evaluation, which was the pre-specified subgroup analysis of the 24-month Interdisciplinary Community-Based COPD Management Program trial, comparing nutritional rehabilitation with usual care in COPD patients with low muscle mass, did find a significant reduction in hospital costs [76]. The mean total COPD and non-COPD related costs per patient after 2 years were €12 830 for the intervention group and €14 025 for the usual care group, resulting in net savings of €1195 (95% CI -7905–5759). Compared with the usual care group, the intervention group had a significant decrease in hospitalisation costs €-4724 (95% CI -7704– -1734). Because of these net cost savings, no cost-effectiveness ratio was calculated. There is a clear need for more cost-effectiveness studies of nutritional counselling and supplementation to support decision making about reimbursement of these interventions in COPD. There are several possibilities. One is the conventional approach of designing randomised clinical trials in which the additional costs and benefits of adding a nutritional intervention to usual care is investigated. Because usual care is most likely a multimodal pulmonary rehabilitation programme or disease management programme that already includes nutritional counselling, the newly designed trials should focus on assessing the added value of the oral supplements or of long-term nutritional counselling. Given the current lack of any cost-effectiveness data, these trials could recruit patients from different target groups including end-stage COPD patients with both muscle loss and weight loss (cachexia) as well as weight-stable COPD patients with muscle wasting (sarcopenia). In addition, we need better data on the longitudinal association between changes in the risk factors weight change, BMI and FFMI, and the risk of COPD exacerbations and hospitalisations. Such data could come from observational studies. They could be used in cost-effectiveness modelling studies to simulate potential long-term effects of changes in weight, BMI and FFM on health status, healthcare utilisation and costs. The latter is necessary because the costs of nutritional intervention in sarcopenic COPD patients are likely to precede the benefits by far.

Dietary quality and nutrient deficiencies

Vitamin D deficiency and insufficient intake of vitamins with antioxidant capacity (vitamins A, C and E) have been reported in COPD. Vitamin D has an important role in bone and calcium homeostasis but effects may occur beyond bone health, as anti-inflammatory, anti-infectious and anti-tumoural actions, as well as neuromuscular improvements, have been attributed to vitamin D [112]. Vitamin D status is assessed by the measurement of serum levels of 25-OHD, a precursor of the active hormone. In a general population, vitamin D status is an independent predictor of all-cause mortality, upper airway respiratory infections and pulmonary function. For COPD, conflicting evidence exists on whether 25-OHD levels correlate with lung function decline, infectious exacerbations and muscular function [113–116]. Vitamin D status is determined by the synthesis capacity of the skin, hours of sun (ultraviolet) exposure, genetic variation in key enzymes of the involved pathway and supplemental intake in food. In COPD, vitamin D deficiency frequently occurs because of smoke-induced skin ageing, reduced outdoor activity and low-quality dietary intake. Based on internationally accepted cut-offs, vitamin D deficiency (25-OHD levels $<$20 ng·mL^{-1}) is highly prevalent in COPD and increases with disease severity. The hypothesis that such deficiency may also causally contribute to pathogenesis of COPD is much debated but recent prospective epidemiological evidence associates vitamin D deficiency with an increased incidence of COPD and a more rapid decline of pulmonary function in subjects with COPD [117]. The higher prevalence in more advanced COPD and in

nutritionally depleted states suggests that screening for vitamin D deficiency may be of value in these populations. It may restrict lifelong supplementation to vitamin D deficient patients, in whom the beneficial effects on the bones and fall prevention, especially if combined with calcium intake, are proven. Daily intakes in addition to a minimal amount of ultraviolet radiation exposure vary with age but a dose of 800 IU with 1 g calcium is considered to be largely sufficient. The potential of high-dose supplementation to obtain other than calcaemic effects, including lung function decline and COPD exacerbations, needs further exploration [118].

Insufficient intake of fresh fruits and vegetables may result in deficiency of vitamins with antioxidant capacity. Conversely, long-term supplementation with vitamin E has been shown to reduce the risk of COPD [119] but no evidence exists on the positive effects of additional vitamin intake on clinical outcome in a COPD population. As smoking and lung inflammation in COPD are known to cause significant oxidative stress, a reduction of the antioxidative capacity may have negative effects on the course of COPD. Large, population-based epidemiological studies have shown that a prudent diet is associated with better pulmonary function, less lung function decline and reduced risk of COPD [120–122]. More specifically, greater intake of dietary fibre has been consistently associated with reduced COPD risk, better lung function and reduced respiratory symptoms [123]. Three studies have reported associations between frequent or high

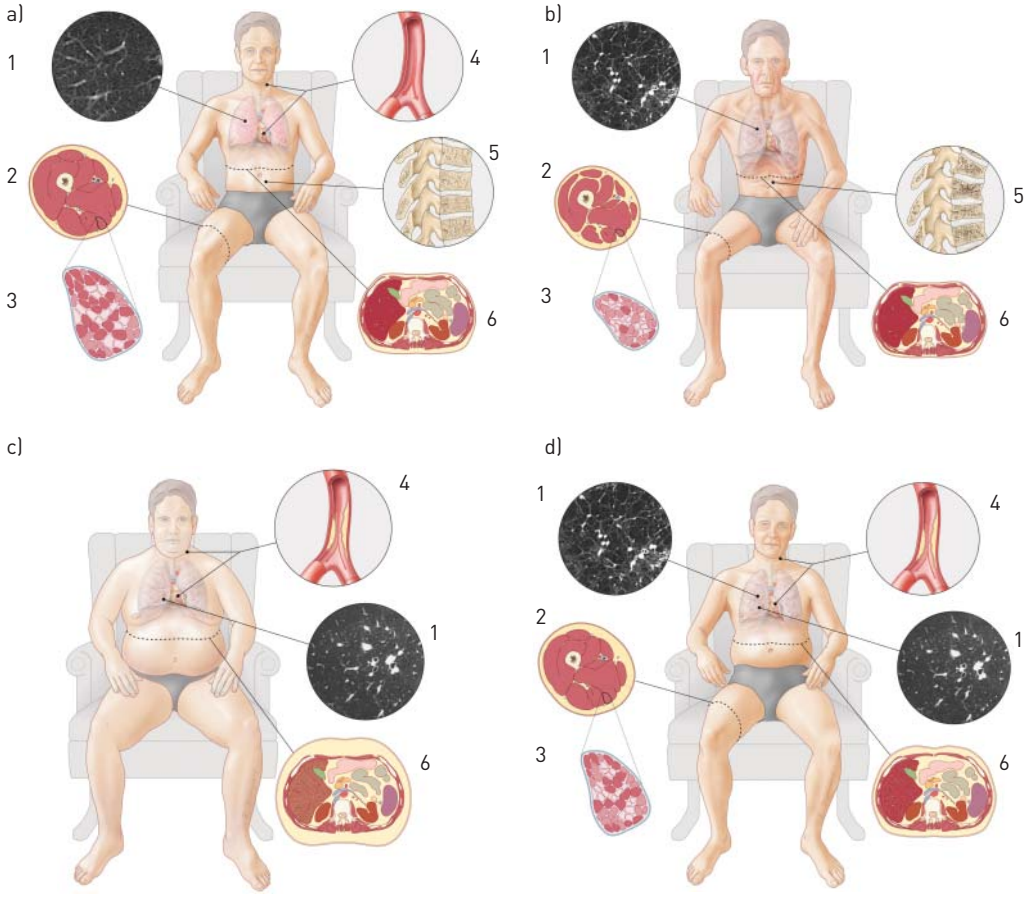

FIGURE 4 Abnormal metabolic phenotypes and related nutritional risk in chronic obstructive pulmonary disease. a) Healthy (reference) with: 1) normal high-resolution computed tomograph of lung tissue; 2) graphic representation of magnetic resonance imaging (MRI) with quadriceps muscle (red) and adipose tissue (yellow); 3) normal quadriceps muscle cross sectional area and fibre type distribution (red: type I; pink: type IIA; white: type IIX); 4) healthy arterial blood vessel; 5) normal bone tissue; and 6) graphic representation of MRI image of abdomen showing visceral and subcutaneous adipose tissue (yellow). b) Cachexia is often linked to 1) emphysema and hyperinflation, with 2) loss of skeletal muscle mass combined with 3) muscle fibre atrophy, and a type I to II shift leading to decreased skeletal muscle function, 5) osteoporosis and 6) wasting of fat mass. c) Obesity is often linked to 1) chronic bronchitis with 6) increased subcutaneous and visceral adipose tissue, and 4) arterial stiffness and increased cardiovascular risk. d) Sarcopenia and hidden obesity is not clearly linked to a specific pulmonary phenotype, but is characterised by 2) loss of skeletal muscle mass combined with 3) muscle fibre atrophy and a type I to II shift leading to decreased muscle function, preservation of fat mass but redistribution of adipose tissue towards increased 6) visceral adipose tissue, 4) arterial stiffness and increased cardiovascular risk.

DOI: 10.1183/09031936.00070914

consumption of cured meats and increased risk of developing COPD [120, 124, 125]. A recent study has extended this association to include the evolution of the disease, revealing that high cured meat consumption is linked to a higher risk of readmission to hospital with COPD [126]. Finally, albeit rarely assessed in clinical practice, iron deficiency often occurs in COPD, which may be caused by several factors including systemic inflammation, malabsorption of iron from the gut, renal failure (as a consequence of concomitant chronic kidney disease or diabetes mellitus), and medications such as angiotensin-converting enzyme inhibitors and corticosteroids [127]. Overall, the evidence indicates that a well-balanced diet with sufficient intake of fresh fruits and vegetables is beneficial to COPD patients, not only for its potential benefits on the lung, but also for its proven benefits on metabolic and cardiovascular risk.

Nutrition as part of integrated disease management

Nutritional intervention has so far been studied either as single treatment or as adjunct to exercise training in depleted COPD patients, often in the context of pulmonary rehabilitation. The efficacy of nutritional supplementation could be enhanced by additional interventions including smoking cessation, correction of hypoxaemia and/or hypercapnia with long-term oxygen therapy and/or noninvasive ventilation, reduction of static and dynamic hyperinflation by long-acting bronchodilators or lung volume reduction, or androgens either to correct hypogonadism or to boost muscle anabolism. Two studies have shown the potential of a multimodal rehabilitation programme consisting of nutritional supplementation, androgens and exercise training in improving clinical outcome and even survival in malnourished patients with advanced COPD [73, 128]. Long-term multimodal intervention studies are lacking that demonstrate if these modalities are indeed able to significantly change the natural history of weight loss and muscle wasting, and reduce morbidity and mortality. Attempts to prevent or correct weight loss during acute exacerbations are scarce and, in fact, only one placebo-controlled randomised clinical trial so far has proved the feasibility and efficacy of nutritional supplementation in hospitalised COPD patients in maintaining energy balance and

TABLE 3 Future research priorities

Nutritional assessment
Validate the criteria for risk stratification phenotypes as set out in figure 1
Investigate whether these phenotypes are characterised by specific mechanisms/pathophysiology
Standardise protocols for lifestyle determinants (diet, smoking and physical activity level) and for metabolic phenotyping to facilitate between-centre comparisons and multicentre studies
Pathophysiology of abnormal body composition
Explore the role of systemic inflammation and of inflammatory genotypes on body composition changes
Explore the role of adipose tissue macrophages in the systemic inflammatory response and related extra pulmonary pathology, consider sex differences in adipose tissue metabolism and inflammation, and investigate effects of COPD exacerbations on adipose tissue inflammation and metabolism
Investigate the aetiology of muscle wasting on a cellular basis by analysing the regulatory and effector pathways of muscle protein and myonuclear turnover in muscle biopsies of in well-deep phenotyped COPD patients and by longitudinal data collection
Investigate the added value of pharmacological modulation of regulatory pathways of proteolysis, including NF-κB, FOXO, MAPK, or their triggers oxidative stress and inflammation on the outcome of anabolic nutritional and multimodal interventions
Analyse the impaired response to anabolic stimuli after acute nutritional, pharmacological or exercise challenges in analogy to the glucose tolerance test
Investigate the putative influence of abnormal microbiota shifts in the lung or intestine on abnormal metabolic phenotypes
Nutritional intervention
Confirmatory clinical trials of nutritional support in specific metabolic phenotypes
Determine whether targeting exacerbations with intensive nutritional therapy (perhaps combined with exercise and anabolic drugs) would improve outcome
Determine the effectiveness and safety of weight reduction programmes in obese patients with COPD
Outcome analysis
More focus on PROs and the broader societal benefits
Cost-effectiveness
Assess the added value of oral nutritional supplements and long-term nutritional counselling in terms of costs and effects in different phenotypes in RCTs
Use of real-life data from continuous patient registries in weight-losing patients for cost-effectiveness analysis of dietary counselling and nutritional supplements
Use longitudinal real-life data from patient registries to study the association between change in body composition and disease progression risk, functional impairment, hospitalisations and mortality; this information can be used to perform a model-based analysis of long-term cost-effectiveness of nutritional interventions

NF-κB: nuclear factor, κ-light chain activator of B-cells; FOXO: fork head box O; MAPK: mitogen-activated protein kinase; PRO: patient-reported outcome; RCT: randomised controlled trial.

increasing protein intake [58]. The added value of enteral nutritional support for COPD patients who do not respond to oral nutritional supplementation has not been systematically investigated.

The pink puffer and blue bloater revisited

In 1968, FILLEY *et al.* [4] already included body habitus in the clinical presentation of two contrasting types of end-stage COPD patients, *i.e.* the emphysematous type (pink puffer) and the bronchial type (blue bloater). As an extension of this classification, considering not only pulmonary impairment but also comorbidity, three metabolic phenotypes are presented in figure 4 that illustrate the influence of (epi)genetics, lifestyle and pulmonary-derived triggers on muscle, bone and adipose tissue, and related functional and cardiovascular risk, as discussed in this article. Figure 4 also indicates the need for an integrated, often multimodal intervention approach. The metabolic phenotypes are based on current scientific evidence but will probably be refined in the near future. In the online supplementary material, three cases of these metabolic phenotypes are presented to aid clinical diagnosis and practice.

Conclusions and directions for future research

1) Nutritional status is an important determinant of outcome of COPD.

2) Nutritional risk can be assessed by longitudinal measurement of body weight and body composition.

3) The prevalence of vitamin D nutrient deficiency is high in COPD and could be incorporated into nutritional risk screening.

4) The nutritional risk profiles associated with different metabolic phenotypes of COPD patients could be useful in patient counselling.

5) Nutritional intervention is likely to be effective in undernourished patients (based on the Cochrane review [66]) and is probably most effective if combined with an exercise programme.

6) Providing evidence of the cost-effectiveness of nutritional intervention is required to support reimbursement of, and thus increase access to, nutritional intervention.

7) Overall, the evidence indicates that a well-balanced diet with sufficient intake of fresh fruits and vegetables is beneficial to COPD patients, not only for its potential benefits on the lung but also for its proven benefits on metabolic and cardiovascular risk.

Directions for future research identified by the Task Force are presented in table 3.

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DOI: 10.1183/09031936.00070914