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Undernutrition state in patients with chronic obstructive pulmonary disease. A critical appraisal on diagnostics and treatment

Gunnar Akner [a, *, 1], Kjell Larsson [b]

[a] Geriatric Medicine at Linnæus University, Geriatric Medicine at Karolinska Institutet, Dept. of Medicine and Optometry, Linnæus University, Nygatan 18B, 392 34 Kalmar, Sweden
[b] Pulmonary Medicine at Karolinska Institutet, Lung and Airway Research, Institute of Environmental Medicine, Karolinska Institutet, 171 77 Stockholm, Sweden

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ABSTRACT

'*Undernutrition state*' (UNS) is an ominous condition, in particular when associated with chronic obstructive pulmonary disease (COPD). In this review we discuss pathophysiological mechanisms and how UNS is defined and diagnosed. It seems unlikely that COPD-patients with established UNS have similar potential of reversibility (treatability) upon nutrition interventions as patients at a risk of developing such a condition, i.e. patients with low energy/nutrient intake, since pathophysiological, biochemical and metabolic conditions may differ substantially.

We summarize the results of 7 of 17 published randomized controlled trials of nutritional supplementation in COPD-patients with defined UNS in the latest Cochrane review (2012). We thus excluded 10 of 17 trials included in review (2012), mostly because those studies also included patients with 'risk of' UNS.

The seven included trials exhibit extensive heterogeneity for all studied variables. Most studies did not show beneficial effects of nutritional supplementation, although some reported minor increase in body weight and physical function of unclear clinical relevance.

In contrast to the Cochrane review we conclude that it is difficult to draw firm conclusions regarding the effect of nutritional supplements in patients with COPD and UNS. Improved knowledge in this area is of utmost importance and some factors which should be considered in future studies are suggested.

1. Introduction

Chronic obstructive pulmonary disease (COPD) constitutes an increasing health problem globally and is today the third most common cause of death [1]. In addition to a high prevalence of comorbidities, COPD is associated with a number of negative prognostic local and systemic disease manifestations such as acute exacerbations, severe dyspnea and fatigue, and weight loss. It is well known that unintentional weight loss in COPD is an independent risk factor of poor prognosis and increased mortality [2–4]. The increased knowledge about body composition and assessment of nutritional status in COPD has been of importance in the understanding of systemic aspects of the disease. In addition it constitutes a basis for the assumption that weight maintenance is beneficial for patients suffering from COPD.

The aim of this review is to critically explore the effects of nutritional supplementation in patients with established COPD and undernutrition state (UNS) based on a critical evaluation of a Cochrane review published in 2012 [5]. By additional literature search for randomized controlled trials of COPD-patients with UNS, we have also considered supplementary literature published after 2012.

1.1. Undernutrition state versus undernutrition

In this review, the medical diagnosis undernutrition state (UNS) is used rather than *undernutrition*, to emphasise the fact that this is an identifiable condition in the morbid individual (the body). The term undernutrition should be reserved to describe an intake of energy and/or nutrients that falls below a given individual's biological needs (i.e. a risk situation), which over time can lead to an

* Corresponding author.
E-mail addresses: gunnar.akner@lnu.se (G. Akner), kjell.larsson@ki.se (K. Larsson).
[1] Homepage: www.gunnar-akner.se.

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UNS.

An UNS implies an excessive loss of protein, fat, vitamins and/or minerals, which has resulted in altered body structure (e.g. reduction of fat-free mass) and function (e.g. physical function). This condition can worsen the primary disease(s), as well as in itself create a risk of increased morbidity, functional impairments, increased consumption of healthcare (e.g. hospitalisation or extended hospital stays) and increased risk of mortality. Examples of functional consequences, beyond impaired physical function, include:

- weakened immune system, including increased susceptibility to infection and/or impaired wound healing [6,7].
- reduced erythropoiesis (nutritional anaemia) [8].
- cognitive dysfunction [9].
- mental health symptoms [10].

The most commonly used term for UNS in the literature is 'malnutrition', even though semantically, the term malnutrition refers to both undernutrition and overnutrition states. Malnutrition is often further specified as protein-energy malnutrition (PEM), implying a deficiency in both protein and energy. In addition to this, there are often various combinations of vitamin and/or mineral (micronutrient) deficiencies, but this has rarely been assessed in published trials. Other expressions used in the literature for UNS include wasting, depletion, cachexia and sarcopenia [11]. One particular form of malnutrition is kwashiorkor, which is a lack of protein despite an adequate energy intake and is found in many developing countries. Kwashiorkor leads to a risk for oedema and ascites. Given present proposed definitions for these conditions, there is a partial overlap between them [12].

A proposed common, international definition of the related concepts of sarcopenia and cachexia was published in 2010 based on low body mass index (BMI < 18.5 kg/m^2) or a combination of unintentional weight loss and low fat-free mass index (FFMI) or low BMI [13].

However, there are no generally accepted operational criteria defining UNS and thus, no gold standard for diagnostic methods. This in turn means that the definition of UNS varies from trial to trial. Some trials have used a combination of criteria including impaired body structure (e.g. current body weight, ongoing weight loss, BMI, FFMI), function (e.g. physical function), energy metabolism, metabolic or biochemical blood markers etc. In some trials the diagnosis of UNS have also included assessed intake of food and drink (i.e. intake of energy, nutrients and water), although a low intake rather implies a risk for development of UNS than a criterion for the condition.

The lack of diagnostic stringency has led to wide variations in the estimated prevalence of UNS. Table 1 shows the reported prevalence of UNS in some common chronic health problems [14].

Moreover, in clinical practice, the diagnosis UNS is seldom assessed and coded according to the WHO disease classification, ICD10 [15]. In Sweden, the official statistics from the National Board of Health and Welfare shows that the diagnosis of UNT ('malnutrition') was only made in 150–300 patients per year in all hospitalized patients during a period of 15 years 1998–2012 [16]. This is not in agreement with the alleged prevalence of UNS in 11–45% of all patients in acute hospital settings [17] and thus implies more than 99% underdiagnosis of UNS.

Table 1
Prevalence of malnutrition associated with certain chronic conditions.

- Chronic obstructive pulmonary disease 10–60%
- Chronic heart failure 10–25%
- Post-stroke conditions 15–25%
- Dementia 12–50%
- Chronic renal failure 40–75%
- Rehabilitation after hip fracture ≈ 50%
- Rheumatoid arthritis 25–70%
- Multiple illnesses in the elderly 20–50%

1.2. Undernutrition state in COPD

The literature on UNS in patients with COPD differs from other medical fields because UNS associated with COPD has often been defined by comparing the patients' current body weight to an "ideal body weight" (IBW), i.e. the weight that on average results in the longest remaining life expectancy for the individual's age according to tables provided by life insurance companies [18]. UNS in conjunction with COPD has usually been defined as having a body weight of ≤80% or ≤90% of IBW. In many other fields of medicine, the diagnosis of UNS is usually made by the type of criteria mentioned above. This makes it difficult to compare COPD treatment trials as regards prevalence, incidence, treatment results etc.

1.2.1. Prevalence

Patients with COPD often have concurrent UNS; the prevalence has been reported to vary between 10 and 60% for the entire COPD group, divided into 10–45% of outpatients and 30–60% of COPD inpatients [19]. There are several possible reasons for this wide variation:

- Varying definitions of UNS, often mixing up the concepts 'risk of undernutrition' and 'established UNS' (clearly defined, functionally significant); see above.
- Lack of stringency regarding the COPD diagnosis and inclusion of patients with varying degrees of COPD; for example trials of patients in inpatient and outpatient care.

1.2.2. Pathophysiology

The nutrition state represents a balance between intake and metabolism of energy and nutrients (Fig. 1).

As a general rule, there are two principal causes of UNS, which are frequently combined in clinical practice.

1. *Insufficient intake/uptake* of energy and/or nutrients, with a normal metabolism: Intake of energy and nutrients below the individual's biological needs may be due to e.g. reduced appetite, difficulties in eating, dysphagia or lack of food, e.g. starvation in developing countries or iatrogenic starvation in hospitals or institutional care. This may also include poor nutrient gastrointestinal uptake (malabsorption).
2. *Increased metabolism* of energy and/or nutrients: This may be related to hypermetabolism or catabolism, while the individual's intake of energy and/or nutrients may be normal or even above the person's biological needs. In this situation the body can not assimilate the energy and/or nutrients because of the pathological energy-metabolic condition.

Examples of mechanisms that can contribute to hypermetabolism and/or catabolism in COPD-patients are:

- Increased energy expenditure at rest (increased resting metabolic rate, RMR) due to an increased energy cost of breathing [20–22].
- Increased nutrient-induced thermogenesis (NIT); i.e. the increase in energy metabolism that follows intake of nutrients, particularly proteins [20,23,24].

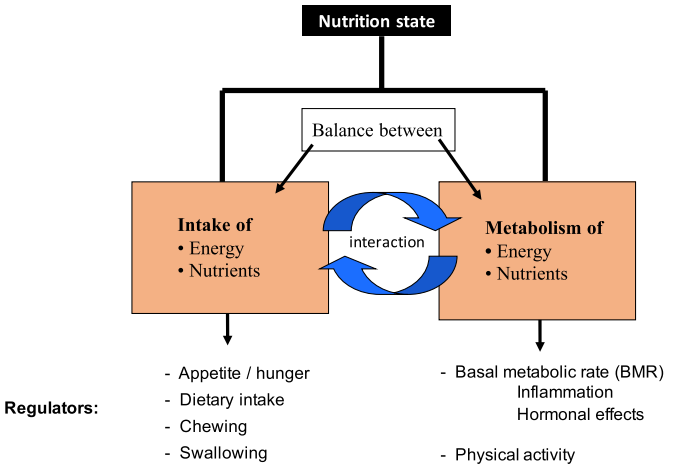

Fig. 1. The nutrition state represents a balance between intake and metabolism of energy and nutrients. An undernutrition state may develop when the intake is reduced and/or metabolism increased.

- Increased energy expenditure in connection with physical activity level, PAL [22]. Due to mechanical characteristics and gas exchange inefficiencies in COPD-patients, the work of breathing at rest is 3–7 times higher than in healthy subjects leading to enhanced energy consumption [25,26].
- Chronic, inflammatory catabolic activity as in COPD is associated with low-grade systemic inflammation [27,28].
- Systemic treatment with glucocorticoids

UNS in conjunction with COPD is primarily related to the degree of emphysema and diffusion impairment and less related to the degree of airflow obstruction [29]. COPD patients may demonstrate a significant reduction in fat-free mass, while BMI remains normal; i.e. a relatively higher breakdown of non-adipose tissues compared with adipose tissues [30].

In a study using the doubly labelled water method to determine total metabolic rate (total energy expenditure), it was found that energy expenditure was about 20% higher in COPD patients than in matched controls [22]. The basal metabolic rate was not elevated, but the COPD patients had a higher energy expenditure during physical exercise and increased nutrient-induced thermogenesis [23].

It has been discussed that body weight loss primarily develops in connection with acute exacerbations of COPD, when all of the above pathophysiological factors may be active. Reduced intake of energy and nutrients may be a far more important negative factor in such a situation than during more stable phases of the disease [31]. Moreover, there is evidence that the metabolic adaptation in COPD patients is incomplete [32].

The impaired physical ability in connection with COPD is in part due to reduced pulmonary function and in part to hypotrophy and dysfunction of the skeletal musculature, including the respiratory muscles [29,33,34], the expiratory muscles being relatively more weakened than the inspiratory muscles [35]. The impaired muscle function is reminiscent of the myopathy that can be observed with primary starvation syndromes, in which the impairment of respiratory muscle function is often greater than the degree of respiratory muscle hypotrophy [35,36].

There is a reason to believe that the cardiac muscle also suffer hypotrophy in COPD, which may contribute to the development of heart failure and possible incidence of cor pulmonale. However, this has not been studied and remains a hypothesis.

1.2.3. Prognosis

In COPD patients with similar pulmonary function impairment according to spirometry, patients with lower body weight have increased 5 five-year mortality [37,38]. Once continuous involuntary body weight loss commences the average survival time of COPD patients has been found to be 2.9 years [2–4]. There is evidence that successful turning of involuntary weight loss into weight gain in COPD patients can reduce the risk of mortality [38].

1.3. Randomized controlled trials in patients with both COPD and UNS

A systematic review summarised the literature regarding the effects of nutritional support on UNS in conjunction with various chronic diseases, including COPD [14]. A review from the Cochrane collaboration in 2008 [39] covering 14 randomized controlled trials, RCTs (of which 9 were considered high-quality, 2 double-blind) and a total of 487 COPD patients with and without UNS summarised that nutritional support of patients with stable COPD had no significant effect on body structure (anthropometric measures), pulmonary function or physical function. An updated Cochrane review from 2012 [5] based on 17 RCTs (632 participants) revised these results and found moderate quality evidence for significant improvement regarding changes from baseline for body weight (1.65 kg), and low quality evidence for improvement from baseline of the fat-free mass/fat-free mass index (standard mean difference 0.57), mid-arm circumference, MAC (mean difference 0.29) and six-minute walk distance (mean difference 40 m). They concluded that patients with UNS had a higher average response to nutritional supplements than nourished patients. These results were confirmed by a systematic review and meta-analysis based on 13 RCTs (of which 3 were of high-quality) and a total of 439 COPD patients [19]. The study also took differences in baseline values of various endpoints into consideration and summarised that nutritional support significantly increases body weight by on average 1.9 kg (3%), fat-free mass by 2.4% and maximum hand grip strength by 5.3%.

Many publications in the above quoted systematic reviews included COPD patients with established UNS mixed with patients considered to be at risk of UNS. In order to study the effect of nutrition supplementation in only COPD patients with established UNS, all studies including patients with ‘at risk’ of UNS should be excluded.

Table 2 shows a summary of the 7 published RCTs regarding nutritional support in COPD patients with established UNS.

Compared with the latest Cochrane review including 17 studies [5], the following 10 publications were excluded:

- Knowles 1988 [46]: The study included patients with both UNS and risk of UNS.
- DeLetter 1991 [47]: The study is a non-published PhD thesis.
- Schols 1995 [48]: The study included patients with both UNS and risk of UNS and was designed to compare the effects of nutritional supplement with the effect of androgens.
- Steiner 2003 [49]: Most patients included did not have UNS.
- Teramoto 2004 [50]: Only published as a poster.
- Ali 2007 [51]: Only published as a meeting abstract.
- Weekes 2009 [52]: Only patients with risk of UNS.
- Sugawara 2010 [53]: The intervention group received both nutrition 400 kcal/day and an exercise program. The control group did not receive the exercise program.
- Van Wetering 2010 [54]: The study was a subgroup analysis and the authors considered it exploratory and hypothesis generating. Moreover, the intervention group received both nutrition and intensive supervised exercise training. The control group did not receive an exercise program.

Table 2
Summary of the 7 published RCTs regarding nutritional support in COPD patients with established UNS in ambulatory care [41–44], hospital care [31,35] or combined out- and inpatient care [45].

Reference	Type of care	Patients						Nutritional treatment		
		Number (% females)		Age (years, mean)		Criteria for COPD	Criteria for undernutrition state	Type	Energy suppl	Energy intake/ RMR
		I	C	I	C					
Goris 2003 [41]	Amb	11 (45%)	9 (45%)	61	62	Not mentioned	BMI ≤ 22 Or BMI ≤ 25 + recent BW↓ > 5%	ONS Volume: 375 ml/d	565 kcal/d	Not reported
Otte 1989 [42]	Amb	13 (77%)	15 (80%)	56	54	FEV_1 < 70% of pred	BW < 80% of IBW	ONS Volume: 400 ml/d	400 kcal/d	2.0 × RMR
Efthimiou 1988 [43]	Amb	7 (43%)	7 (43%)	60	64	FEV_1 0.71 L FEV_1/FVC: 0.37 −0.38	BW < 90% of IBW Stable BW 3 months before study	ONS Sachetes	640–1280 kcal/d	Not reported
Lewis 1987 [44]	Amb	10 (20%)	11 (36%)	65	59	FEV_1 < 1,2 L FEV_1/FVC: 0.31 −0.32	Two of: • BW < 90% of IBW • MAMC < 10th percentile • TSF < 10th percentile	ONS Volume 240 −500 ml/d	500–1000 kcal/d	1.74 × BMR
Rogers 1992 [31]	Hosp	15	12	64	64	FEV_1/FVC < 60% of pred	BW < 90% of IBW	Individual ONS and food advice (meal plan)	Not reported	1.7 × RMR
Whittaker 1990 [35]	Hosp	6 (33%)	4 (75%)	71	64	FEV_1 40% of pred FEV_1/ FVC = 0.35 −0.70	BW < 85% of IBW	Enteral tube	≥1000 kcal/d	2.2 × RMR
Fuenzalida 1990 [45]	Amb + Hosp	5	4	62	62	FEV_1 30–50% of pred	>5% BW ↓ during last year	ONS Volume 720 ml	1080 kcal/d	Not reported

All stated treatment endpoints (↑ = increase, ↓ = decrease) are significant in comparison with the control group.
FEV_1 = Forced exspiratory volume 1 s, BW = Body weight, MAC = Mid-arm circumference, TSF = Triceps skin fold, SFS = sum of four skinfolds, IBW = Ideal body weight, FFM = Fat-free mass.
ONS = Oral nutritional supplements, RMR = resting metabolic rate, BMI = body mass index, kcal/d = kilocalories/day, g/d = grams/day, MEP = maximal expiratory pressure, MIP = Maximal inspiratory pressure.
N = nutrition, P = plasma, PaO2 = arterial oxygen partial pressure, i.m. = intramuscular, MVC = maximal voluntary contraction force.
Amb = ambulatory care, Hosp = hospital care, I = intervention and C = control.

- Sugawara 2012 [55]: The COPD-patients did not have UNS (IBW < 110%).

Table 3 shows an overview of the heterogeneity of the 7 included studies.

Table 4 shows an overview of the study quality.

The seven included RCTs were published between 1987 and 2003. They were performed in five different western countries: USA [3], Canada [1] and three European countries in three different settings: ambulatory care [4], hospital care [2] and combined hospital and ambulatory care [1]. All studies were based on small patient samples (9–28 patients), which implies problems with statistical power.

There was an extensive heterogeneity for all studied variables:

1.3.1. Patients

- Age: The mean age was 54–71 years. For comparison, the mean age at COPD diagnosis in Sweden was 73 years in 1999 and 66 years in 2009 [56].
- Gender: The ratio of female patients in the studies varied from 0 to 80%. No study reported treatment effect divided by gender.
- Smoking: The number of patients who were active smokers varied much between the studies, and was not described in detail.
- Criteria COPD: Each study used different criteria of COPD and included patients with both mild and severe disease, where the potential reversibility from nutrition supplementation may be different.
- Medical drugs: No study presented a detailed specification of ongoing medical drug treatment for COPD. As an example, oral glucocorticosteroid treatment has been shown to significantly impair the response to nutritional supplementation [57].
- Criteria UNS: Each study used different criteria to define UNS. The degree of UNS was not defined in any of the studies, but may have varied substantially.
- Comorbidity: No study reported any detailed analysis of co-occurring diseases/injuries. Different multimorbidity clusters may exhibit different response to nutritional treatment.

1.3.2. Treatment

- Volume: The oral nutritional supplement (ONS) volume varied between 240 and 720 ml/day (3 times).

Nutritional treatment				Significan positive effects			
Protein suppl	Time	Compliance		Anthropo-metry	Function	Biochemistry	Mortality
		Method	Results				
28 g/d	12 weeks	7-day dietary records	Energy and protein intake similar in the groups	0	Not reported	Not reported	Not reported
20 g/d	13 weeks	7-day dietary records	Not reported	BW ↑ (1.5 kg)SFS ↑ (2.7 mm)	0	S-Albumin ↑	Not reported
36–72 g/d	12 weeks	7-day dietary records	Energy intake ↑ 690 kcal/d (48%) Protein ↑ 37 g/d (70%)	BW ↑ (4.2 kg; range 0.7–8.2 kg) MAC ↑ TSF ↑	General well being score ↑ Breathlessness ↓ 6 min walking distance ↑ Maximal insp pressure ↑ Maximum exp pressure ↑ Handgrip strength ↑ Sternomastoid muscle MVC ↑	0	Not reported
18–36 g/d	8 weeks	Food records	Mean energy intake ↑ 300 kcal/d (16%) Mean protein intake ↑ 15 g/d (23%)	0	0	0	Not reported
1.5 g/kg/d	16 weeks	3-day food records	Mean energy intake ↑ (0.3 × RMR)	BW ↑ (2.4 kg)	Handgrip strength ↑ Maximal exspiratory pressure ↑ 12 min walking distance ↑	0	Not reported
0	2 weeks	Food records	Energy intake ↑ 1200 kcal/d (85%)	BW ↑ (2.4 kg)	Maximal exspiratory pressure ↑	0	Not reported
43 g/d	3 weeks	3-day food records	No difference in energy intake between groups	0	No differences between groups	No differences between groups	Not reported

- Administration: The nutrient supplement was provided by fluid ONS (4 studies), sachets [1], food [1] and enteral nutrition [1]. There are no published RCTs in which the effects of parenteral nutrition in COPD patients with malnutrition have been studied, only controlled clinical studies have been conducted [58].
- Content: The content of nutrition supplementation varied widely: Energy 400–1280 kcal/day (3 times) and protein 18–72 g/day (4 times). The intake of micronutrients (vitamins and/or minerals) was only mentioned in two studies when the oral supplement was described [41,42], but was otherwise not specified. In four of the seven studies the energy intake was specified as 1.7–2.0 × the resting metabolic rate [31,35,42,44]. One study used individualized nutrition treatment [31].
- Duration: The treatment duration varied from 2 to 16 weeks (8 times). The potential response to nutritional treatment may vary widely dependent on duration.
- Compliance: Four of the seven studies reported compliance to intervention with increased energy intake, with an average variation between 16 and 85% increase compared with baseline [31,35,43,44]. In two studies there were no difference in energy intake between the intervention and control group [41,42] and in one study no information about energy intake was provided [31]. In three studies, the energy intake from food was reduced during the nutritional supplement period [35,43,44].

1.3.3. *Treatment effect (outcome)*

- Anthropometry: Body weight was reported in six of the seven studies. In three studies no increase in body weight was found, whereas significant mean body weight increases of 1.5–4.2 kg was demonstrated in four studies. In two of the studies showing body weight gain, there was also significant improvement in skinfold thickness, indicating increase in fat mass.
- Physical function: Physical function was reported in six of the seven studies. Two studies did not find any positive effects on physical function outcome. Three studies showed a significant improvement of mean maximal expiratory pressure and two studies showed improved handgrip strength. Two studies showed improved physical capacity as assessed by the 6- and 12 min walking tests.
- Health related quality of life (HRQoL): Only one of the seven studies investigated the effect on HRQoL using sickness impact profile (SIP), but did not find any positive effects [31]. One study

Table 3
Overview of the heterogeneity of the 7 included studies structured according to population, diagnostics, treatment, treatment effects (outcome).

			Ambulaory care				Hospital care		Hospital + ambulatory care
Author			Goris	Otte	Eftimiou	Lewis	Rogers	Whittaker	Fuenzalida
Year			2003	1989	1988	1987	1992	1990	1990
Country			The Netherlands	Denmark	UK	USA	USA	Canada	USA
Place			Horn	Nevle	London	Duarte/CA	Pittsburgh/PA	Vancouver/BC	Denver
Population	Number of patients		20	28	14	21	27	10	9
	Mean age I/C (years)		61/62	56/54	60/64	65/59	64/64	71/64	62
	Female gender I/C (%)		45/45	77/80	43/43	20/36	?	50/50	0
Diagnostics	Criteria for COPD	FEV_1 < 1.2 L				*			
		FEV_1/FVC mean 0.38			*				
		FEV_1/FVC 0.3–0.5							*
		FEV_1/FVC 0.35–0.70						*	
		FEV_1/FVC <0.70		*					
		FEV_1/FVC <0.60					*		
		Not reported	*						
	Criteria for UNS	BW for hight and frame size < 90% of IBW			*	*	*		
		BW for hight and frame size < 85% of IBW						*	
		Mid arm circumference < 10th percentile				*			
		Triceps skin fold < 10th percentile				*			
		BMI ≤ 22	*						
		BMI ≤ 25 and recent BW ↓ >5%	*						
		>5% BW ↓ during last year							*
Treatment	Volume (ml/d)		375	400	Sachetes	240–500	Individual meal plan	Not reported (enteral tube)	720
	Energy (kcal/d)		565	400	640–1280	500–1000	?	1000	1080
	Energy intake/BMR		?	2.0	?	1.74	1.73	1.7	?
	Protein (gram/d)		28	20	36–72	18–36		?	43
	Protein (gram/kg BW/d)						1.5		
	Treatment time (weeks)		12	13	12	8	16	2	3
	Compliance	Enegy increase kcal/d (%)	No difference	No information	690 (48%)	300 (16%)	0.3 × RMR	1200 (85%)	No difference
		Protein increase g/d (%)	No difference	No information	37 (70%)	15 (23%)			No difference
Treatment effects (Outcome)	Anthropometry	BW	*	*	*	*	*		*
		Mid Arm Circumference (MAC)		*	*	*	*		
		Mid Arm Muscle Area (MAMA)							*
		Triceps skin fold (TSF)			*	*	*		*
		Sum of four skinfolds (SFS)		*					
		Whole body potassium							*
	Physical function	Handgrip strength			*	*	*		
		M. adductor policicis strength						*	
		12 min walking test		*			*		
	Respiratory function	Maximal inspiratory pressure			*	*	*	*	
		Maximal exspiratory pressure			*	*	*	*	
		Maximal sustained ventilatory capacity				*			
		Sternomastoid muscle maximal voluntary contraction force (MVC)			*				
		Forced exspiratory volume 1 s (FEV_1)		*	*		*	*	*
		Functional vital capacity (FVC)		*	*		*	*	*
		FEV_1/FVC					*	*	
		Residual volume (RV)						*	
		Total lung capacity (TLC)			*		*	*	*
		Maximal ventilatory volume (MVV)		*					

Table 3 (*continued*)

		Ambulaory care			Hospital care		Hospital + ambulatory care
	Maximum mid-exspiratory flow (MMEF)						*
	RV/TLC					*	
	Transfer factor (Kco)		*				
	Diffusing capacity/ alveolar volume (DLCO/ VA)					*	
	Not investigated	*					
Biochemistry	Sedimentation rate						*
	Hemoglobin		*		*		
	Plasma Creatinine				*	*	
	Plasma Urea					*	
	Blood Urea nitrogen				*		
	Blood sugar				*		
	Plasma Total protein				*		
	Serum Prealbumin (=Serum Thyretin)						*
	Serum Albumin		*	*	*		*
	Serun Transferrin		*				
	Plasa Retinol binding protein				*		
	Serum Sodium			*		*	*
	Serum Potassium			*		*	*
	Serum Calcium			*		*	
	Serum Magnesium			*		*	
	Serum Phosphate			*		*	
	Liver function tests						*
	Plasma Cortisol						*
	Thyroid function tests						*
	Serum Ascorbic acid (vitamin C)						*
	Arterial partial pressure oxygen (aPO2)		*	*			*
	Arterial partial pressure carbon dioxide (aPCO2)		*	*			*
	Immunological blood markers and skin reactivity						*
	Not investigated	*					
Health related quality of life	Sickness impact profile (SIP)					*	
	General well being scale			*			
	Not investigated	*	*		*	*	*

The asterisks (*) represent that the indicated variable was used in the respective study.
COPD = Chronic obstructive pulmonary disease, FEV_1 = Forced exspiratory volume in 1 s, FVC = Forced vital capacity.
UNS = Undernutrition state, BW = Body weight, IBW = Ideal body weight, BMI = Body mass index.
BMR = Basal metabolic rate, RMR = Resting metabolic rate.

found a positive effect on a “general wellbeing score” [43], whereas the other five studies did not assess HRQoL.

- Biochemistry: Serum-Albumin increased significantly in one study, but there were no changes in any of several other blood biomarkers.
- Mortality – was not reported in any of the trials.

1.3.4. Study quality

In one study the authors mentioned a power calculation based on the effect of physical activity on energy balance, but power for the effect of nutritional supplementation was not calculated [41]. The other six studies did not report any power calculations.

The authors of the Cochrane review from 2012 evaluated seven defined types of biases and reported ‘unclear risk’ regarding four of these biases in all seven of the studies included in our review and ‘low risk’ regarding three of these biases in three studies [5]. See summary in Table 4.

1.4. Studies after 2012

The aim was to base this overview on the latest systematic review by the Cochrane Library. In order to also cover publications after 2012 we conducted an additional literature search in PubMed. Using the MeSH terms undernutrition, nutritional supplementation and chronic obstructive pulmonary disease we found five studies of the effect of nutritional supplementation in patients with COPD written in English 2012–2016. Of those three were meta-analyses [4,19,40], which are discussed in the manuscript. A small prospective 8 weeks study did not demonstrate any beneficial patient-related outcomes when pulmonary rehabilitation in combination with nutritional supplementation was compared with pulmonary rehabilitation without nutritional supplementation, and did thus not add information to the Cochrane report [59]. The fifth study focused on health economy and did not report patient-related outcomes [60].

Table 4
Overview of the study quality based on power calculations and evaluation of bias according to the latest Cochrane review [5].

			Ambulaory care				Hospital care		Hospital + ambulatory care
Author			Goris	Otte	Eftimiou	Lewis	Rogers	Whittaker	Fuenzalida
Year			2003	1989	1988	1987	1992	1990	1990
Country			The Netherlands	Denmark	UK	USA	USA	Canada	USA
Place			Horn	Nevle	London	Duarte/CA	Pittsburgh/PA	Vancouver/BC	Denver
Study quality									
Power	Calculation of power	Yes	*						
		No		*	*	*	*	*	*
		Comment	Only based on the effect of physical activity on energy balance	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Bias	Selection bias 1 (random generation)	Low risk	*	*			*		
		High risk							
		Unclear			*	*		*	*
	Selection bias 2 (allocation concealment)	Low risk							
		High risk							
		Unclear	*	*	*	*	*	*	*
	Performance bias (blinding patients/ staff)	Low risk		*	*			*	
		High risk				*			
		Unclear	*				*		*
	Detection bias (blinded outcome assessment)	Low risk		*	*			*	
		High risk							
		Unclear	*			*	*		*
	Attrition bias (incomplete outcome data)	Low risk	*	*	*	*	*	*	*
		High risk							
		Unclear							
	Reporting bias (selective reporting)	Low risk	*	*	*	*	*	*	*
		High risk							
		Unclear							
	Other bias	Low risk	*	*	*	*	*	*	*
		High risk							
		Unclear							

The asterisks (*) represent that the indicated variable was used/evaluated in the respective study.
The six types of bias were defined in Ref. [5], see also text.

2. Discussion

The seven included randomized controlled trials of COPD-patients with UNS exhibited extensive heterogeneity in all studied variables. In the latest Cochrane review the authors included another ten studies with even larger heterogeneity, e.g. combining nutritional supplements with physical exercise, accepting unpublished material, inclusion of both patients with a somehow defined UNS and patients with estimated risk to develop such a condition [5]. It is unlikely that COPD-patients with established UNS have a similar potential reversibility (treatability) upon nutrition interventions as patients with a risk to develop such a condition, since the pathophysiological, biochemical and metabolic conditions may differ substantially.

There are several possible explanations as to why nutrition supplementation to COPD-patients with UNS does not provide clear positive results.

- *Inhibition of dietary intake*: For several reasons, it can be difficult to supplement sufficiently large amounts of energy and proteins orally to COPD patients with UNS: Some trials have found that dietary supplements tend to reduce the intake of regular food [35,43,44]. High doses of dietary supplements can lead to side effects such as bloating or gas and diarrhoea [44]. Patients with COPD may run a risk of desaturation and arterial hypoxia in connection with meals, which can hamper nutritional treatment [61,62].
- *Low compliance*: Compliance with nutritional supplement prescriptions is poor in outpatient care [31,43].
- *Anabolic block*: Some patients with non-voluntary loss of body weight may exhibit an 'anabolic block', i.e. a resistance to intervention with proteins possibly related to insulin resistance, that may be difficult or impossible to overcome by increased energy and protein intake [63,64].
- *Refeeding syndrome*: Supplementing large quantities of carbohydrates to sick individuals (e.g. COPD patients) who have adapted to their state of UNS can trigger a refeeding syndrome, which is characterised by electrolyte imbalances (primarily hypophosphatemia) and multiple organ failure (including effects on the central nervous system, heart and lungs) [65–67]. The risk is particularly enhanced with enteral/parenteral nutrition, but does also exist with oral nutrition [67].
  Several interacting mechanisms can contribute to refeeding syndrome:
  - Nutrient-induced thermogenesis [20,22–24].
  - High carbohydrate intake may increase the production of carbon dioxide and thus put added strain on the respiration for two reasons, both leading to increase of the respiratory quotient (RQ), i.e. the ratio of carbon dioxide produced to oxygen consumed: a) An increase in the relative proportion of carbohydrate oxidation in relation to the total substrate oxidation, b) If carbohydrate intake exceeds the total energy requirements for energy homeostasis, lipogenesis occurs with increased carbon dioxide production, which also raises the respiratory quotient.
- *Research design*: The RCT is considered the method-of-choice to study treatment effects. However, comparing group mean values between intervention- and control groups may not be

appropriate to demonstrate treatment effects in groups with great heterogeneity, such as COPD-patients with UNS. Even a strict randomization by the book aimed to provide similarity between the groups at baseline may give rise to differences, since it is only possible to stratify the randomization for a limited number of variables. Thus, there may be a number of 'responders' to nutrition supplementation that are hidden by the group-mean design [68].

In a recent RCT, 30 COPD patients with a body weight below 90% of IBW were given three weeks of dietary supplements with a high fat content (55% of the total energy) and low carbohydrate content (28% of the total energy). As expected, RQ decreased in the treatment group compared with the control group. In addition FEV_1 increased and resting minute ventilation decreased significantly in the treatment group compared with controls, indicating an improvement of pulmonary function as a consequence of nutritional supplementation [69]. Caution should be taken about drawing broad conclusions from this small short-term trial, but it shows that nutritional support may affect pulmonary function in COPD patients with no link to effects on body composition.

Based on the published RCTs in COPD-patients with UNS we conclude that the extensive heterogeneity between studies makes it difficult to pool data from the different studies for a systematic review and/or metaanalysis. In the present state of scientific knowledge, it does not seem warranted to draw firm conclusions regarding the effect of nutritional supplements in patients with COPD and UNS.

In clinical practice it is still necessary to manage nutrition-related aspects in COPD-patients with UNS, even though the scientific evidence is very weak. Such management must rely on systematized experience and individual evaluation based on published guidelines. In the GOLD strategy document, nutritional support is briefly mentioned and nutritional supplementation is recommended, alone or as an adjunct to physical training [70]. In a recent statement the beneficial effect of a well-balanced diet in COPD-patients is emphasized, not only because of potential pulmonary effects, but also because of beneficial effects on metabolic and cardiovascular parameters [71].

2.1. Focus for future trials

2.1.1. Inclusion

- Stringent definition of inclusion criteria for both 'stable COPD' and 'UNS'
- Careful characterization of the COPD patients according to age, gender, lung function, inflammatory profile, response to pharmacological treatment (eg. steroids) etc.
- Careful characterization of UNS according to age, gender, body composition, energy metabolism, metabolic/biochemical profile, dietary intake etc.

2.1.2. Treatment/intervention

- The nutritional intervention should be individualized based upon measurement or estimation of both resting metabolic rate and physical activity level (PAL). Different doses (amounts) of energy and protein should be used to investigate possible dose-response relations.
- The compliance to intervention should be carefully monitored, both regarding intake of supplements as well as total intake of energy and nutrients.

2.1.3. Treatment effects/outcome

- Outcome variables should include:
  - patient related outcomes such as symptoms and health-related quality of life
  - structure and function, i.e. combined effects on body composition (e.g. fat-free mass) and body function (e.g. muscle strength, hand grip strength, gait speed as well as measure of respiratory muscle function and lung function)
  - effects on exacerbations
  - health care utilization
  - mortality
- Body weight should be avoided as primary outcome variable, as much of the weight gain that may occur with nutritional support (energy + nutrients) consists of fat mass, also in patients who participate in structured physical training [49]. Moreover, as the fat-free mass consists largely of protein and water, an increase in fat-free mass cannot automatically be translated into an increase in muscle mass; it may also correspond to an increase in overall body fluids, even if there is no visible oedema.
- Treatment duration must be analysed in detail. There is evidence that water retention can occur early on when treating UNS with increased energy and nutrient intake. The sequence of events has been referred to as 'staggered increments in body composition', in which the treatment outcome may appear in the following sequence: Increase in total body fluids → increase in body fat → increase in muscle mass [45,46].

2.1.4. Data presentation

- Data from RCTs in patients with COPD and UNS should preferably be presented in a table format like Table 2. This would alleviate the labour-intense work to re-write reports with very different layout into a similar overview to allow comparison between studies.

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