Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis\textsuperscript{1–3}

Peter F Collins, Rebecca J Stratton, and Marinos Elia

ABSTRACT

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

Objective: The objective was to conduct a meta-analysis of randomized controlled trials (RCTs) to clarify the efficacy of nutritional support in improving intake, anthropometric measures, and grip strength in stable COPD.

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

Results: Thirteen RCTs (\(n = 439\)) of nutritional support [dietary advice (1 RCT), oral nutritional supplements (ONS; 11 RCTs), and enteral tube feeding (1 RCT)] with a control comparison were identified. An analysis of the changes induced by nutritional support and those obtained only at the end of the intervention showed significantly greater increases in mean total protein and energy intakes with nutritional support of 14.8 g and 236 kcal daily. Meta-analyses also showed greater mean (\(\pm SE\)) improvements in favor of nutritional support for body weight (1.94 ± 0.26 kg, \(P < 0.001\); 11 studies, \(n = 308\)) and grip strength (5.3%, \(P < 0.050\); 4 studies, \(n = 156\)), which was not shown by ANOVA at the end of the intervention, largely because of bias associated with baseline imbalance between groups.

Conclusion: This systematic review and meta-analysis showed that nutritional support, mainly in the form of ONS, improves total intake, anthropometric measures, and grip strength in COPD. These results contrast with the results of previous analyses that were based on only cross-sectional measures at the end of intervention trials. Am J Clin Nutr 2012;95:1385–95.

INTRODUCTION

Malnutrition is a common problem in individuals with chronic obstructive pulmonary disease (COPD)\textsuperscript{4} with prevalence rates in inpatients of between 30% and 60% and in outpatients of between 10% and 45% (1). Malnourished COPD patients have greater gas trapping, lower diffusing capacity, and a lower exercise capacity when compared with heavier, nonmalnourished patients with a similar severity of disease (2). Observational studies have shown that if nutritional assessment includes only body weight and unintentional weight loss, some patients with normal body weight for height (BMI) would go undetected despite being deplete of fat-free mass (FFM) (3, 4). A cross-sectional survey by Cano et al (3) in 300 outpatients with COPD requiring long-term oxygen therapy found that 17% of patients had a low BMI, whereas the prevalence of FFM depletion was >2-fold higher (38%). This accelerated loss of lean tissue, which may lead to sarcopenia and cachexia, is facilitated by robust inflammatory responses, which may also limit or prevent accretion of lean tissue after nutritional support (5). Wasting of muscles not only detrimentally affects respiratory function, including a reduced ability to expelorate to clear a chest infection, but also promotes fatigability and reduces exercise tolerance and the ability to work. However, it has not been possible to establish the exact causality between malnutrition and COPD because malnutrition may be the consequence of greater disease severity, leading to a compromised nutritional intake (loss of body weight) and reduced physical activity (muscle atrophy). Conversely, severe respiratory disease may be preceded by wasting of the muscles involved in breathing. The effect of nutritional support in malnourished patients has also been controversial. Traditional thinking has tended to regard weight loss as an irreversible consequence of COPD, a view that has been reinforced by recent meta-analyses (6, 7). Such analyses have concluded that nutritional support not only has no significant effect on improving anthropometric measures, such as weight and muscle mass, but also produces no demonstrable improvements in lung function and muscle strength. Several nutritional intervention studies have challenged this idea (8–13), with the result that there remains confusion about whether there is a need to identify and treat malnutrition in COPD. For example, in its 2010 updated report on COPD, the National Clinical Guideline Centre, which develops clinical guidelines for the National Institute for Health and Clinical Excellence, referred to the failure of a previous meta-analysis to demonstrate significant changes in weight and other outcomes with nutritional support (7), but also referred to a previous study that showed such im-

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\textsuperscript{4} Abbreviations used: COPD, chronic obstructive pulmonary disease; DA, dietary advice; ETF, enteral tube feeding; FFM, fat-free mass; IBW, ideal body weight; MAMC, midarm muscle circumference; ONS, oral nutritional supplements; RCT, randomized controlled trial.

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provenements with the use of oral nutritional supplements (ONS) (14). Despite these apparent inconsistencies, the guideline recommended that ONS should be given to patients with a low BMI (in kg/m²; <20) based on grade D evidence (lower quality) rather than on evidence from published systematic reviews and meta-analyses and evidence from at least one RCT, which, according to the National Institute for Health and Clinical Excellence criteria, qualify for grade A evidence (15).

An examination of previous systematic reviews of nutritional support showed differences in the methods of analysis (1, 6, 7, 16). Unlike previous reviews (1, 6), the latest Cochrane review (7) examined the differences between control and intervention groups at the end of the intervention period but not the changes induced by either intervention or control or the effect of baseline imbalance on the final point estimates. The treatment effect within groups and information on the presence of any variability between the 2 groups at baseline, beyond the fact that they were not significantly different, were not reported. Therefore, we undertook a systematic review of randomized controlled trials (RCTs) of nutritional support in patients with COPD to examine such issues more closely and to establish greater clarity of the evidence base for nutritional support to inform policy.

SUBJECTS AND METHODS

Search strategy and identification of trials

The review was planned, conducted, and reported according to published guidelines (17–19). A systematic search of the literature was conducted in July 2010 to identify RCTs investigating nutritional support in COPD. Potentially relevant studies were identified by searching electronic databases. The databases searched included PubMed (http://www.ncbi.nlm.nih.gov/pubmed; accessed 7 January 2010), Web of Science (http://apps.webofknowledge.com; accessed 7 January 2010), and OVID (http://gateway.ovid.com/autologin.html; accessed 7 January 2010). To identify the largest number of trials, a broad search strategy was implemented; however, trials were restricted to English-language citations only. The search terms and mesh headings used included the following: chronic obstructive pulmonary disease, COPD, emphysema, weight, depletion, diet*, nutrition*, supplement*, protein, carbohydrate, calori*, feed*, malnutrit*, nourish*, sip feed (ready-made liquid ONS), nutrition intervention, and nutrition support. A combination of these search terms was also used to identify trials. In addition to an electronic database search, a manual search of previous reviews on nutritional support in COPD as well as references of identified trials was undertaken.

Studies were initially screened by reading the abstract, and the full article was reviewed when a study could not be excluded. The assessment of trial eligibility was done by 2 independent assessors (PFC and ME), with 2 disagreements resolved through discussion with a third assessor (RJS) before inclusion.

Inclusion and exclusion criteria

Studies were deemed eligible for inclusion in the review if they conformed to the predetermined inclusion and exclusion criteria. To investigate the overall efficacy of nutritional support [food strategies (food fortification, food snacks), dietary advice (DA), ONS, and enteral tube feeding (ETF)], the following inclusion criteria for trials were devised: 1) randomized trials; 2) intervention with food strategies, DA, ONS, or ETF; 3) duration of intervention >2 wk; 4) control group receiving placebo or no dietary intervention (eg, usual care, which could include advice and encouragement to eat); 5) stable patients with a diagnosis of COPD (not exacerbating); 6) human studies only; and 7) English language only. The intervention could provide either a proportion or all of the daily nutritional requirements for energy, protein, and micronutrients, which could be nutritionally complete or incomplete when feeds were used (eg, ONS). Studies using parenteral nutrition were excluded.

Data extraction

Outcome data sought included total nutrient intake (energy and protein), body weight, upper arm anthropometric measures, body composition, and handgrip strength. Data were collected at baseline and at the end of the intervention phase when possible. Data were collected within data extraction tables, which allowed data synthesis and analysis from studies with varying populations (nourished or undernourished), intervention types (food strategies, DA, ONS, or ETF), and intervention duration. When data were not reported in the text but were illustrated within a figure, the figure was expanded and the data extracted. This was done for energy intake (20, 21) and weight (20, 22). In some articles in which the mean values were reported without SDs or SEs, it was possible to calculate the SDs or SEs by using reported \( P \) values. In one study that assessed handgrip strength (10), data reported in kilograms were considered to be unrealistic and therefore assumed to be in pounds.

Quality assessment

The quality of included studies was assessed by using the most commonly used scoring system (Jadad scoring system), which comprises 3 components addressing whether a study is described as randomized, whether the study is described as double-blind, and whether dropouts were accounted for. It then scores according to the appropriateness of randomization and blinding (23). A quality assessment of the trials was performed by one researcher (PFC) and was independently verified by another assessor (RJS). Disagreements were resolved by discussion with a third assessor (ME).

Synthesis of data and statistical analysis

After the extraction of data from the included trials, where appropriate and feasible, the results of comparable outcome measures were combined and a meta-analysis was performed. Statistical analysis was performed by using SPSS (version 16.0), and the meta-analysis (random-effects model) used Comprehensive Meta-analysis (Biostat Inc, version 2). The analysis was carried out to explore differences between groups and changes within groups. The effect size was reported as the difference in mean ± SE. Only a minority of the values reported in the various studies adjusted for baseline values (11, 13, 24, 25). The correlation coefficient between baseline and end measurements was calculated (26). Any computed values that were slightly >1.000, because of rounding of reported or calculated SDs, were assumed to have a value of 1.00.
Prespecified subgroup analysis was performed according to type of nutritional support (ONS, ETF, or DA) and baseline nutritional status [nourished (“nondepleted”) compared with malnourished (“depleted”)]. Malnutrition was considered to be present if the mean BMI was <20 or the mean percentage ideal body weight (%IBW) was ≤90%. Meta-regression analysis was used to investigate whether the duration or amount of the intervention influenced the effect size for each outcome. The overall treatment difference was considered statistically significant if the P value was <0.05, and Forest plots were used to present effect size.

RESULTS

A total of 44 studies were identified as potentially eligible from the literature search (5, 8, 9, 11, 13, 20–22, 24, 25, 27–60), 31 of which were excluded (Figure 1). Reasons for exclusion included an unsuitable study design in 4 studies (38, 41, 56, 58), non-randomized trials in 5 studies (5, 28, 47, 55, 59), target population not suitable in 3 studies (27, 54, 57), no control or placebo group in 6 studies (29, 31, 32, 34, 35, 53), an unsuitable intervention in 11 studies (30, 33, 36, 39, 40, 43, 45, 49–52), and an inadequate intervention duration in 2 studies (44, 60). A large randomized trial comparing an intensive management program compared with usual care was not included because nutritional support was provided to only a subgroup of patients where indicated in both arms (48). A summary of the search process is shown in Figure 1. The review included 13 RCTs of 439 individuals with COPD randomly assigned into either a treatment group (n = 224) or a control group (n = 215) (Table 1). Eight studies were performed completely within the outpatient setting (8, 14, 20, 22, 24, 25, 37, 46), 3 in inpatients (11, 13, 21), and 2 in both outpatient and inpatient settings (9, 10). A separate analysis of the trial by Schols et al (11, 13) was performed according to whether the subjects were nourished or malnourished (Table 1). Patients recruited to the trials had a diagnosis of COPD (<70% predicted forced expiratory volume in 1 s) and were in a stable condition—free from exacerbation. Patients recruited to the trials were classified as having severe COPD—range 30–40% predicted forced expiratory volume in 1 s (<50% predicted, stage III) (61). No study provided results on acute phase proteins or cytokines. Of 4 studies reporting circulating albumin, 3 had normal values (20–22) and 1 had values close to the lower limit of normal (14).

Most of the trials (11; n = 189 intervention compared with 185 control) provided nutritional support by ONS (8–11, 13, 14, 20, 22, 24, 37, 46), mostly liquid supplements, some of which were specifically formulated for use in patients with COPD [60% of energy as carbohydrate, 20% as fat, 20% as protein (Respiforicia Ltd) (24, 46); 28.2% as carbohydrate, 55.1% as fat, and 16.7% as protein (Pulmocare; Abbott)] (37). One trial used nocturnal ETF (n = 6 compared with 4) (21), and 1 trial used tailored DA

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**TABLE 1**
Outcome measures of randomized controlled trials included in the systematic review and meta-analyses

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Systematic review</th>
<th>Meta-analysis注</th>
<th>Systematic review</th>
<th>Meta-analysis注</th>
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<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td>No. of participants (treatment/control)</td>
<td>No. of studies</td>
<td>No. of participants (treatment/control)</td>
</tr>
<tr>
<td>Energy intake</td>
<td>11</td>
<td>195/184</td>
<td>5</td>
<td>94/97</td>
</tr>
<tr>
<td>Protein intake</td>
<td>5</td>
<td>88/92</td>
<td>2</td>
<td>53/57</td>
</tr>
<tr>
<td>Weight</td>
<td>13</td>
<td>225/214</td>
<td>13注</td>
<td>225/214</td>
</tr>
<tr>
<td>Body composition</td>
<td>4</td>
<td>115/115</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Midarm muscle circumference</td>
<td>7</td>
<td>124/125</td>
<td>3</td>
<td>53/51</td>
</tr>
<tr>
<td>Skinfold thickness</td>
<td>9</td>
<td>117/107</td>
<td>2</td>
<td>43/40</td>
</tr>
<tr>
<td>Handgrip strength</td>
<td>5</td>
<td>87/90</td>
<td>4</td>
<td>77/79</td>
</tr>
</tbody>
</table>

注1 Meta-analysis with measures of variation.
注2 Eight studies if no assumptions were made to obtain data on variation (SDs).
delivered by a dietitian and the provision of a milk powder supplement \((n = 30\) compared with 25) \((25)\). There were no trials of food snacks or food fortification alone. The intervention period ranged from 16 d \((21)\) to 6 mo \((25)\), with the amount of nutritional support prescribed ranging from 355 kcal/d \((37)\) to 1080 kcal/d \((9)\).

Most of the studies \((n = 8)\) \((8–10, 14, 21, 22, 25, 37)\) were principally of malnourished (“depleted”) individuals \((\text{BMI} < 20 \text{ or } \% \text{IBW} < 90\%\)). The trials by Schols et al \((11, 13)\) and Steiner et al \((24)\) included both nourished and undernourished patients, and the functional measure handgrip strength is frequently reported anthropometric measures were triceps skinfold thickness and midarm muscle circumference \((\text{MAMC})\). Other outcomes included energy \((n = 11)\) and protein \((n = 5)\) intakes and the functional measure handgrip strength \((n = 5)\) (Table 2).

### Dietary Intake

Data on total energy intake were available in 11 studies \((8, 9, 11, 13, 20–22, 24, 25, 37, 46)\). When the analysis was limited to those studies in which nutrition was ingested orally, a meta-analysis was possible for 5 studies \((20, 22, 24, 25, 37)\). No significant differences in daily energy intake were found between the supplemented and control groups at baseline \((\text{mean } \pm \text{SE} \text{ difference: } 11 \pm 87 \text{ kcal; } P = 0.903)\) \((20, 22, 24, 25, 37)\), but a significant difference was found in favor of the supplemented group at the end of nutritional treatment \((\text{diet + ONS or DA; } 236 \pm 71 \text{ kcal; } P < 0.001)\). Information on the mean changes in energy intake was available from 6 studies \((8, 14, 22, 25, 37, 46)\) after excluding the ETF trial \((21)\), although measures of variation were available in only 2 trials. In all 6 studies, the mean changes in energy intake were greater in the intervention group than in the control group by \(318 \pm 157 \text{ kcal/d (} P = 0.004\), weighted for sample size). Similar significant results were also obtained from the 5 studies that involved ONS \((413 \pm 175 \text{ kcal/d; } P = 0.006)\) \((8, 20, 22, 24, 37)\). Two studies were amenable to meta-analysis \((24, 25)\), with the mean \((\pm \text{SE})\) change in intake favoring the supplemented group \((234 \pm 63 \text{ kcal; } P < 0.001)\). Each study, one involving ONS and the other tailored DA and milk powder supplementation, independently yielded significant results favoring intervention.

Information on mean changes in protein intake was available in 5 studies \((8, 22, 24, 25, 37)\), but measures of variation were available in only 2 of them \((24, 25)\). All 5 studies reported mean \((\pm \text{SD})\) daily protein intakes that were greater in the supplemented group than in the control group by \(16.5 \pm 10.3 \text{ g/d; (} P = 0.023\), weighted for sample size). Similar results were also obtained in the 4 studies involving ONS \((18.2 \pm 7.0 \text{ g/d; } P = 0.014)\). Considering only the 2 studies that were suitable for meta-analysis \((24, 25)\), protein intake favored the supplemented group by a similar amount \((\text{mean } \pm \text{SE}: 14.8 \pm 3.6 \text{ g/d; } P < 0.001)\). As with energy, both studies were significant in their own right \((P < 0.001)\).

### Body Weight

The trials of nutritional support showed a consistent increase in weight, which was significant in 7 of 8 individual studies. However, a detailed analysis is undertaken below for comparison of conclusions from previous meta-analyses. With the use of information on body weight obtained from 8 studies, 3 sets of meta-analyses were carried out to compare the control and intervention groups. These meta-analyses involved baseline weight, end weight, and change in weight \((9–11, 13, 14, 21, 24, 25)\). Baseline weight in the intervention and control groups was not statistically different \((P = 0.240; \text{Figure 2}, \text{top})\); however, on average, the control group was \(1.217 \pm 1.036 \text{ (SE) kg heavier than the treatment group}\). After the nutritional intervention, the difference between the control and intervention groups remained nonsignificant \((\text{Figure 2}, \text{middle}; \ P = 0.506, \text{with individual study results on both sides of the reference line})\); however, this time the control group was lighter than the supplemented group by a mean \((\pm \text{SE})\) of \(0.746 \pm 1.122 \text{ kg}\). The mean improvement \((\text{increase})\) in weight in the intervention group was greater than that in the control group in all 8 primary studies, significantly so in 7 of the individual studies \((\text{Figure 2}, \text{bottom})\). Not surprisingly, the overall effect size of the meta-analysis was highly significant, with a mean \((\pm \text{SE})\) increase in weight in favor of the intervention group of \(1.830 \pm 0.262 \text{ kg (} P < 0.001\). This corresponds to 3% of initial body weight.

Inspection of the Forest plots \((\text{Figure 2})\) also showed that the variability \((\text{indicated by the 95\% CIs})\) between the intervention and control groups, for both the primary studies and the summary effect of all the studies combined, is much smaller for the change in weight \((\text{lower plot})\) than for the baseline weight \((\text{upper plot})\) and end weight \((\text{middle plot})\). These results are summarized in Table 3. Not only was the overall change in weight significantly greater in the intervention group than in the control group \((\text{by almost 2 kg})\), the observed variation \((\text{SE})\) at both baseline and the end of the study was \(\sim 4\) times the variation in the change in weight. This was due to a high correlation between pre- and postweight in both the intervention group and the control group. For the primary studies, \(r\) values obtained through meta-analysis were \(0.995 \text{ (95\% CI: 0.979, 0.999)}\) for the control group and \(0.997 \text{ (95\% CI: 0.974, 1.000)}\) for the intervention group. Simple correlation analysis of the mean results \((\text{without measures of variation})\) obtained from the same studies also indicated a very high correlation between baseline and end weight \((r = 0.993 \text{ and 0.991})\) for the control and intervention groups, respectively, and \(r = 0.985 \text{ for the 2 groups combined})\).

A sensitivity analysis \((\text{Figure 3})\) was carried out by combining the above 8 studies with another 5 studies that lacked information on variation in weight change in either the control or the intervention group \((8, 20, 22, 37, 46)\). The SD of the final weight for one trial \((37)\) was obtained from a previous review \((7)\). For these studies a very large estimate of the SD of the change was assumed \((\text{SD of the change corresponding to 10\% of baseline weight})\). All 13 primary studies reported a mean \((\pm \text{SE})\) weight change in favor of the intervention group \((\text{Figure 3})\). The summary effect size and its significance remained similar \((1.69 \pm 0.30 \text{ kg; 95\% CI: 1.1, 2.3 kg; } P < 0.001\) to those obtained with the 8 primary studies with complete information \((\text{Figure 2})\). A similar significant result was also noted when only studies involving ONS were analyzed: \(1.63 \pm 0.23 \text{ (SE) kg (} P <
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (treatment/control)</th>
<th>Characteristics, setting (intervention compared with control)</th>
<th>Nutritional intervention (type, prescribed amount, duration)</th>
<th>Control group</th>
<th>Outcome measures</th>
<th>Study quality [Jadad score]</th>
</tr>
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<tbody>
<tr>
<td>Oral nutritional supplements</td>
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<tr>
<td>DeLetter, 1991 (37) (thesis)</td>
<td>18/17</td>
<td>Malnourished, 82.8 %IBW, outpatients</td>
<td>ONS (Pulmocare, 1.5 kcal/mL), ONS target: 355 kcal/d and 15 g protein/d, 8 wk</td>
<td>Usual diet</td>
<td>Energy, protein, weight, FFM, MUAC, MAMC, TSF</td>
<td>11000 [2]</td>
</tr>
<tr>
<td>Efthimiou et al, 1988 (8)</td>
<td>7/7</td>
<td>Malnourished, 79.5 compared with 81.3 %IBW, outpatients, 60 compared with 64 y</td>
<td>ONS (Build Up, 1.13 kcal/mL), ONS target: 640–1280 kcal/d and 36–72 g protein/d, encouragement to eat provided to both groups, 12 wk</td>
<td>Usual diet (with encouragement)</td>
<td>Energy, protein, weight, %IBW, MAMC, TSF, HGS</td>
<td>10000 [1]</td>
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<tr>
<td>Goris et al, 2003 (46)</td>
<td>11/9</td>
<td>Nourished and malnourished, BMI (in kg/m²) 19.8 (~87 %IBW) (BMI: 19.6 compared with 20), outpatients, 61 compared with 62 y</td>
<td>ONS (Respifor, 1.5 kcal/mL), ONS target: 563 kcal/d and 28 g protein/d, encouragement to eat provided to both groups, 12 wk</td>
<td>Usual diet (with encouragement)</td>
<td>Energy, BMI</td>
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<td>Knowles et al, 1988 (20)</td>
<td>13/12</td>
<td>Nourished and malnourished, 61–108 %IBW, outpatients, 68 compared with 70 y</td>
<td>ONS (Sustacal, 1 kcal/mL, 0.043 g protein/kcal), ONS target: to increase total EI by 50% weekly, encouragement, 8 wk</td>
<td>Usual diet</td>
<td>Energy, weight, MAMC, TSF</td>
<td>11000 [2]</td>
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<tr>
<td>Lewis and Belman, 1987 (22)</td>
<td>10/11</td>
<td>Malnourished, 86.3 compared with 84.6 %IBW, outpatients, 65 compared with 59 y</td>
<td>ONS (Isocal HCN, 2 kcal/mL), ONS target: 500–1000 kcal/d and 19–38 g protein/d, encouragement, 8 wk</td>
<td>Usual diet</td>
<td>Energy, protein, weight, MAMC, TSF, HGS</td>
<td>10000 [1]</td>
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<tr>
<td>Otte et al, 1989 (14)</td>
<td>13/15</td>
<td>Malnourished, 77 compared with 73 %IBW, outpatients, 57 y Malnourished inpatients and outpatients, 78.5 %IBW, 62 y</td>
<td>ONS (Novo, 1 kcal/mL), ONS target: 400 kcal/d and 20 g protein/d, encouragement, 13 wk</td>
<td>Placebo (blinded) (encouragement)</td>
<td>Weight, %IBW, MAMC, skinfold thickness (s4SF)</td>
<td>10111 [4]</td>
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<td>Fuenzalida et al, 1990 (9)</td>
<td>5/4</td>
<td>Malnourished, 78 compared with 79 %IBW, 64 y, outpatients (intervention group admitted for first 4 wk)</td>
<td>ONS (various, self-selected) tailored to individual dietary habits and DA ONS target: intakes &gt;1.7 × REE and minimum 1.5 g protein/kg per day, 15 wk</td>
<td>Usual diet</td>
<td>Weight, %IBW, MUAC, TSF</td>
<td>10000 [1]</td>
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<tr>
<td>Rogers et al, 1992 (10)</td>
<td>15/12</td>
<td>Malnourished, 102.4 %IBW, inpatient PR program (not hospital) mean age unclear</td>
<td>ONS (Mixture of Nutridrink, Protifar, Fantomalt, Oil; 7 mixtures of different flavors; 2.1 kcal/mL), ONS target: +420 kcal/d and 15 g protein/d, encouragement to eat regular meals, 8 wk</td>
<td>Usual diet (and encouragement with oral diet)</td>
<td>Energy, weight, MAMC, FFM</td>
<td>10001 [2]</td>
</tr>
<tr>
<td>Schols et al, 1995 (11)</td>
<td>33/38</td>
<td>Malnourished, 84.1 %IBW, inpatients, PR program (not hospital) mean age unclear</td>
<td>ONS (Mixture of Nutridrink, Protifar, Fantomalt, Oil; 7 mixtures of different flavors; 2.1 kcal/mL), ONS target: +420 kcal/d and 15 g protein/d, encouragement to eat regular meals, 8 wk</td>
<td>Usual diet (and encouragement with meals)</td>
<td>Energy, weight, FM, FFM</td>
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<td>Schols et al, 1995 (13)</td>
<td>39/25</td>
<td>Malnourished, 105 %IBW, inpatient PR program (not hospital) mean age unclear</td>
<td>ONS (Mixture of Nutridrink, Protifar, Fantomalt, Oil; 7 mixtures of different flavors; 2.1 kcal/mL), ONS target: +420 kcal/d and 15 g protein/d, encouragement to eat regular meals, 8 wk</td>
<td>Usual diet (and encouragement with oral diet)</td>
<td>Energy, weight, FM, FFM</td>
<td>10001 [2]</td>
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<tr>
<td>Steiner et al, 2003 (24)</td>
<td>25/35</td>
<td>Nourished/malnourished ~105 %IBW (BMI: 23.9 compared with 23.5), outpatients, PR program, 66 compared with 68 y</td>
<td>ONS (Respifor, 1.5 kcal/mL), ONS target: +570 kcal/d and 28 g protein/d, 7 wk</td>
<td>Placebo (blinded)</td>
<td>Energy, protein, weight, FM, FFM, HGS</td>
<td>10111 [4]</td>
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### TABLE 2  
(Continued)

<table>
<thead>
<tr>
<th>Characteristics, setting</th>
<th>Nutritional intervention</th>
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<tr>
<td>Sample size (treatment/control)</td>
<td></td>
</tr>
<tr>
<td>6/4</td>
<td>Placebo ETF (equivalent volume providing &lt; 100 kcal/night)</td>
</tr>
<tr>
<td>Mahnourished, 76 compared with 64 y</td>
<td>Nocturnal ETF, ETF target; feed delivered: ≥ 1000 kcal/d or 1.7 × REE, whichever greater and 34 g protein (nasojejunal/bowel feeding), 16 d</td>
</tr>
<tr>
<td>Mahnourished, 88 %IBW (BMI 62.9 kg/m²)</td>
<td>Tailored DA + leaflet of information + milk powder, DA target: 600 kcal/d or 1.7 × REE</td>
</tr>
<tr>
<td>DA, dietary leaflet</td>
<td></td>
</tr>
<tr>
<td>Whirledge et al, 1990 (22)</td>
<td></td>
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<tr>
<td>Weekes et al, 2009 (25)</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics, setting compared with control</th>
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<tbody>
<tr>
<td>Eger et al, 1990 (21)</td>
<td>Mahnourished, 67 compared with 71 compared with 64 y</td>
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<tr>
<td></td>
<td>DA, dietary advice (education); EI, energy intake; ETF, enteral tube feeding; FFM, fat-free mass; HGS, handgrip strength; MAMA, midarm muscle area; MAMC, midarm muscle circumference; ONS, oral nutritional supplements; PR, pulmonary rehabilitation; REE, resting energy expenditure; SDS, sum of 4 skinfold thicknesses; TSF, triceps skinfold thicknesses; TSB, total skinfold thicknesses.</td>
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</tbody>
</table>

#### Study quality measures
- Jadad score: [4]
- [Energy, weight, TSF](#)11110
- [Energy, protein, weight, s4SF, HGS](#)20091
- [Energy, weight, TSF](#)[10002](#)
- [Energy, weight, TSF](#)[10002](#)

#### Control group
- Leaflit of information

#### Nutritional intervention amount, duration
- Feeding
  - Placebo ETF
  - Enteral tube feeding: FFM, fat-free mass; HGS, handgrip strength; MAMA, midarm muscle area; MAMC, midarm muscle circumference; ONS, oral nutritional supplements; PR, pulmonary rehabilitation; REE, resting energy expenditure; SDS, sum of 4 skinfold thicknesses; TSF, triceps skinfold thicknesses; TSB, total skinfold thicknesses.

#### Study quality
- [Jadad score](#)2

#### Measure of effect
- Energy, weight, TSF
- Energy, weight, TSF
- Energy, weight, TSF
- Energy, weight, TSF

#### Measurement of FFM
- Bioelectrical impedance (11, 13), dual-energy X-ray absorptiometry (24), and skinfold thickness (37).

#### Body composition
- Assessment of FFM was carried out in 4 studies (11, 13, 24, 37), and, although 3 of the 4 trials showed slight improvements in FFM with supplementation (0.17–1.0 kg; 0.7–2.0% of baseline), the improvements were not significant. All 4 studies used different methods to assess FFM [bioelectrical impedance (11, 13), dual-energy X-ray absorptiometry (24), and skinfold thickness (37)]. Seven trials reported data on measured MAMC (8, 11, 14, 20, 22, 25, 37), an indirect measure of FFM. In 6 of the 7 trials, the mean change favored the intervention group compared with the control group by a mean of 2.4% (range: −1.0 to 5.5%, P = 0.045; a one-sample t-test when weighted for sample size). Only 3 trials were amenable to meta-analysis (14, 22, 25), which showed a mean (±SE) improvement in favor of the intervention group (effect size: 0.296 ± 0.158 cm; P = 0.061).

#### Maximum voluntary grip strength
- Five studies (4 with ONS) reported mean changes in handgrip strength (8, 10, 24, 25, 62), with all studies favoring the intervention group (range: 0.3–5.2 kg, or 1.3–18.5%). Four studies were amenable to meta-analysis (8, 10, 24, 25), with results also favoring the intervention group [+5.3 ± 2.7% (SE); P < 0.05].

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The meta-analysis of 13 studies for weight change showed no evidence of publication bias with the use of funnel plots and tests such as the Begg and Mazumdar (P = 0.502) and Egger (P = 0.686) tests.

When the 13 primary studies were analyzed according to nutritional status [studies with malnourished (“depleted”) subjects compared with studies that included normally nourished (“nondepleted”) subjects], both groups showed a significant increase (mean ± SE) in weight in favor of the intervention group: nondepleted (1.319 ± 0.368 kg; P < 0.001) compared with depleted (1.940 ± 0.257 kg; P < 0.001). However, the difference between the nourished and malnourished groups was not significant. Undernourished subjects had a more pronounced response to nutritional support, but it should be noted that the 2 trials including nourished individuals were performed within an exercise rehabilitation program, which may have augmented the effects of nutritional support. Meta-regression did not show a significant relation between the magnitude of the weight increase, which favored the intervention group, and the following individual covariates: %IBW at baseline (13 RCTs, slope −0.021%IBW/kg; P = 0.228); target intake from the nutritional intervention (11 RCTs, slope < 0.001 kcal/kg; P = 0.847), excluding 2 trials that did not report the target intervention amount (10, 20); and duration of intervention (13 RCTs, slope < 0.004 kg/wk; P = 0.937).
Quality of studies

The review identified 3 studies assessed to be of high quality (≥4) (14, 21, 24) and 10 of lesser quality (≤2) with the Jadad scoring system (23) (Table 1).

DISCUSSION

This systematic review with meta-analyses aimed to investigate controversies regarding the evidence base for the efficacy of nutritional support in patients with COPD. It found that nutritional support leads to improvements in nutritional intake, body weight, muscle mass (MAMC), fat mass (skinfold thickness), and an improvement in peripheral muscle strength (handgrip strength). These findings are completely in contrast with those of previous reviews and meta-analyses (6, 7, 42, 63, 64), which reported no significant differences between intervention and control groups. The previous meta-analyses (6, 7, 42) did not examine changes in dietary intake. If total dietary intake in the intervention group did not increase significantly above that of the control group it could explain why these reviews and meta-analyses reported a lack of demonstrable effect of nutritional support on a range of outcomes. However, the current review did examine nutritional intake and found that nutritional support resulted in a significantly greater increase in both protein and energy intakes (dietary intake + nutrition support). The magnitude of these changes is similar to that reported in other reviews involving various clinical conditions, including COPD, in which clinical outcomes were improved through nutritional support in reference 1. It therefore appears that the discrepancies between the current review and previous ones are mainly due to methodologic differences, two of which are clarified below. First, the current study explored the possibility that pre- and post-intervention variability can mask significant within- and between-group changes, even when no significant differences between groups exist at either time point. This analysis showed that the end values, which are mostly unadjusted for baseline, have been used
as the basis of calculations in previous meta-analyses. These end values may primarily reflect those at baseline, rather than the changes induced by the intervention (eg, for body weight a nonsignificant difference existed between groups at baseline, favoring the control group); in order for any improvements to be significant after the intervention, they would first have to overcome this deficit (masking the magnitude of the effect) and the variability associated with it. In contrast, when the weight changes induced by the intervention were used as the basis of the calculations, there was a substantial increase in precision, resulting in a significant improvement in favor of nutritional support, which was also observed in several of the primary studies. Second, unlike the previous systematic reviews and meta-analyses on COPD, the current review included another simpler approach to analyzing RCTs (t test and sign test) so that trials without measures of variation could be included. Although this approach is not as sophisticated as the standard type of meta-analysis, which involves measures of variation, it adds a broader quantitative perspective of the evidence base and supports the overall conclusions of the meta-analyses by considering trials that would not otherwise have been included. It is also more informative and complementary to a narrative description of individual studies. The combined approach adds confidence to the conclusions of the review by supporting all the major findings of the more sophisticated meta-analyses, with respect to both the statistical and substantive (clinical) significance of the effect size (energy and protein intake, weight, arm muscle circumference, and grip strength).

A different type of methodologic problem concerns the 4 studies that measured body composition to establish fat mass and FFM, all of which used different techniques (skinfold thickness, bioelectrical impedance, or dual-energy X-ray absorptiometry). Currently, there are no reference values for body composition in COPD, and the different methods used in primary studies have not been adequately validated in this patient group. Although the changes favored the intervention group in 3 of the 4 studies, the effect was generally small (overall ~1% FFM or <1% body weight) and statistically not significant. In contrast, a more consistent methodologic approach using anthropometric measurements (MAMC) to estimate muscle mass, the largest component of FFM, yielded significant results in favor of the intervention group. Similarly, use of the raw skinfold measurements also indicated improvements in favor of the intervention group.

The statistical findings of this systematic review also need to be considered from a clinical perspective. We have previously reported that a weight gain of approximately ≥2 kg in COPD (similar to the magnitude of the mean weight change in favor of the intervention group observed in this review) is likely to be associated with functional and clinical benefits (1). In addition, post hoc observational analysis of a prospective nutritional intervention trial (11, 13) found that weight loss was reversible through nutritional support and that a significant improvement in survival occurred in depleted and nondepleted patients who gained weight (>2 kg). However, it was not clear from these studies whether the improved survival rates were adjusted for disease severity. In addition, the analysis is confounded by the inclusion of a number of individuals from the placebo group who gained >2 kg (12). Although the improvements in arm muscle circumference and muscle strength observed in this study are only mild to moderate (~3% on average but as high as 7% in one study), in patients who have already become depleted and who have already lost a substantial amount of weight and

### TABLE 3
Summary statistics of effect size and its variation based on 8 primary studies with data on baseline weight, end weight, and change in weight

<table>
<thead>
<tr>
<th>Effect size: difference between groups</th>
<th>SE of the difference</th>
<th>P for effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline weight</td>
<td>1.217</td>
<td>1.036</td>
</tr>
<tr>
<td>End weight</td>
<td>+0.746</td>
<td>1.122</td>
</tr>
<tr>
<td>Change in weight</td>
<td>+1.830</td>
<td>0.262</td>
</tr>
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</table>

1 Intervention group minus control group (meta-analysis, random-effects model). Small discrepancies in the sum of the effect size (change in weight) are due to extraction from different data sets provided within manuscripts (Table 3 and Figure 2).

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**FIGURE 3.** Meta-analysis of the influence of nutritional support on weight (kg) change in 13 studies grouped according to nutritional status (nourished = nondepleted; malnourished = depleted). Four studies provided nutritional support as part of an exercise rehabilitation program (11, 13, 24, 46). *P < 0.0005. Overall summary effect (depleted + nondepleted) = 1.69 ± 0.30 (SE) kg (P < 0.001).
function (which seems likely for most of the malnourished patient groups included in this meta-analysis), small changes in muscle mass might be expected to produce substantial functional or clinical benefit in those who are close to the threshold of disability. In addition, studies included in the current analysis also reported improvements in other clinically relevant outcomes, such as respiratory muscle strength, quality of life, and walking distance (65).

Policies and guidelines on nutritional support also need to consider the plausibility of the results and how they may be interrelated. For example, a causal pathway can be proposed whereby nutritional interventions increase total dietary intake of protein and energy, with resulting increases in weight and muscle mass, which can lead to improvements in muscle strength. The findings of this systematic review are consistent with such a pathway and are also consistent with a variety of other functional and clinical outcomes previously mentioned (65).

This review has also identified the limitations of the current literature on nutritional support in COPD. First, the conclusions are based on a limited number of studies (n = 13), most that were judged to be of poor quality (n = 10), with only 3 studies considered to be of high quality (score of 4) on the Jadad scale [0 (poorest quality), 5 (highest quality)]. A limitation of the Jadad grading system is that it does not account for statistical power, which meant that 1 trial involving only 10 subjects received a score of 4 (21). Second, because of a lack of data in the primary articles, it was not possible to examine the effect of inflammation on nutritional status and response to nutritional support nor to characterize the subjects as cachectic, according to an endorsed definition (66). Third, of the 13 primary studies included in this systematic review, 11 involved ONS, 1 involved nocturnal ETF, and the other involved DA given by a dietician and the provision of milk powder. Therefore, the current evidence is largely based on ONS, and it is weak or lacking for other forms of nutritional support (eg, snacks) or dietary modification/fortification. This has clinical implications for the first-line treatment of malnutrition because The British Dietetic Association currently recommends the first step to improving nutritional intake is done via ordinary foods and fortification with the use of ONS as a secondary step once the initial intervention has failed (67). Finally, of the 13 RCTs, 10 targeted malnourished patients and 3 targeted malnourished and nonmalnourished patients (11, 20, 24), with some trials allowing for subset analysis according to nutritional status (11, 13, 24). Therefore, the evidence base for nutritional support primarily involves malnourished rather than well-nourished patients, although there is an anabolic potential through increased physical exercise that may augment the effects of additional nutrition in those undergoing a rehabilitation program.

The fact that 10 of the 13 trials included in the current review were carried out before 2000 may reflect that 2000 coincided with the publication of the first Cochrane Collaboration review, including most of the current evidence, concluding that nutritional support has no effect in COPD. This may have dampened interest in the field; however, it is hoped that the positive findings of this review will highlight the need to undertake further work, including an examination of the interactions that might exist between nutritional supplementation and factors such as malnutrition, inflammatory status, and graded physical activity in both stable disease and infective exacerbations of COPD.

The authors’ responsibilities were as follows—PFC, RJS, and ME: designed the research; PFC: performed the systematic review; PFC and ME: analyzed the data; RJS: reviewed the data; and ME: had primary responsibility for the final content. All authors wrote, reviewed, and approved the final manuscript. RJS is an employee of Nutricia Ltd. None of the other authors declared a conflict of interest.

REFERENCES


