Nutritional support and functional capacity in chronic obstructive pulmonary disease: A systematic review and meta-analysis

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ABSTRACT

Currently, there is confusion about the value of using nutritional support to treat malnutrition and improve functional outcomes in chronic obstructive pulmonary disease (COPD). This systematic review and meta-analysis of randomized, controlled trials (RCT) aimed to clarify the effectiveness of nutritional support in improving functional outcomes in COPD. A systematic review identified 12 RCT (n = 448) in stable COPD patients investigating the effects of nutritional support (dietary advice (1 RCT), oral nutritional supplements (10 RCT), enteral tube feeding (1 RCT)) versus control on functional outcomes. Meta-analysis of the changes induced by intervention found that while respiratory function (forced expiratory volume in 1 s, lung capacity, blood gases) was unresponsive to nutritional support, both inspiratory and expiratory muscle strength (maximal inspiratory mouth pressure +3.86 standard error (SE) 1.89 cm H2O, P = 0.041; maximal expiratory mouth pressure +11.85 SE 5.54 cm H2O, P = 0.032) and handgrip strength (+1.35 SE 0.69 kg, P = 0.05) were significantly improved and associated with weight gains of ≥2 kg. Nutritional support produced significant improvements in quality of life in some trials, although meta-analysis was not possible. It also led to improved exercise performance and enhancement of exercise rehabilitation programmes. This systematic review and meta-analysis demonstrates that nutritional support in COPD results in significant improvements in a number of clinically relevant functional outcomes, complementing a previous review showing improvements in nutritional intake and weight.

Key words: chronic obstructive pulmonary disease, functional capacity, meta-analysis, nutritional support.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ETF, enteral tube feeding; FEV1, forced expiratory volume in 1 s; HGS, handgrip strength; IBW, ideal body weight; ONS, oral nutritional supplements; PE max, maximal expiratory mouth pressure; PI max, maximal inspiratory mouth pressure; QoL, quality of life; RCT, randomized, controlled trial; SD, standard deviation; SE, standard error.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive multi-organ systemic disease and a major cause of morbidity and disability in aging. While COPD has its primary effects in the lungs, adverse structural and functional changes also occur in the tissues of the heart and skeletal muscle, leading to individuals with COPD experiencing a range of disabilities that impact on their well-being and ability to perform daily activities. Reduced respiratory function and a decline in fat-free mass result in reduced exercise tolerance and peripheral muscle weakness, both disabling features of COPD, which are associated with a poorer quality of life (QoL). Fat-free mass depletion (even if body mass index (BMI) is within the ideal range) has recently been found to be a significant independent predictor of disability even after adjustment for disease severity.

Disease-related malnutrition is a common problem in individuals with COPD, with between 30% and 60% of inpatients and 10% and 45% of outpatients said to be at risk. Malnourished COPD patients demonstrate greater gas trapping, lower diffusing capacity and a reduced exercise performance when compared with heavier non-malnourished patients with a similar severity of disease. However, the exact causal links between malnutrition and COPD are difficult to establish. Malnutrition may be the consequence of greater disease severity. Alternatively, malnutrition may be responsible for the wasting of the muscles involved in breathing, exacerbating the progressive nature of COPD. Similarly, in chronic anorexia nervosa, the loss of body weight includes substantial loss of lung tissue, which develops emphysematous-like changes. In addition to the uncertainty about the causal links between malnutrition and COPD, there...
are controversies about how effective nutritional support is in this patient group. Previous reviews and meta-analyses suggested that malnutrition fails to respond to nutritional treatment in COPD finding no significant improvements in anthropometric or functional measures. These conclusions have been challenged by several randomized, controlled trials (RCT), and a recently published meta-analysis concluded that nutritional support was able to significantly increase nutritional intake (energy and protein), which was associated with a significant improvement in a variety of anthropometric measures. The contrast in conclusions between the reviews has been largely attributed to methodological differences in data analysis discussed at length in the paper. In essence, the previous Cochrane Collaboration review carried out cross-sectional analysis between intervention and control groups but failed to account for baseline variability. The other review accounted for pre- and post-intervention variability finding a number of significant within-group improvements to be masked by cross-sectional analysis. Nevertheless, confusion remains over whether the recent positive findings translate beyond nutritional intake and body weight, and into functional improvements. The aim of this current systematic review is to establish whether nutritional support results in significant improvements in functional capacity and QoL in patients with COPD.

**METHODS**

**Search strategy and identification of trials**

The review was planned, conducted and reported according to published guidelines. The same methodological approach to that of the previous review was used; however, an updated systematic search of the literature was carried out in July 2012 (databases accessed up to 4 July 2012) in order to identify any additional RCT investigating nutritional support in COPD reporting functional outcomes. Potentially relevant studies were identified by searching electronic databases. The databases searched included PubMed (accessed 4 July 2012), Web of Science (accessed 4 July 2012) and OVID (accessed 4 July 2012). In order to identify the largest number of trials, a broad search strategy was implemented, although trials were restricted to English language citations only. The search terms and mesh headings used included: chronic obstructive pulmonary disease, COPD, emphysema, weight, depletion, diet, nutrition, supplement, protein, carbohydrate, calori, feed, malnutrition, nourish, sip, nutrition intervention, nutrition support. These search terms were also systematically combined in order to identify trials. In addition to electronic database searching, manual searching 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 where a study could not be excluded, the full article was reviewed. The assessment of trial eligibility was done by two independent assessors (P.F.C. and M.E.), with any disagreement discussed prior to inclusion.

**Inclusion and exclusion criteria**

Studies were deemed eligible for inclusion in the review if they conformed to the pre-determined inclusion criteria. To investigate the overall efficacy of nutritional support (food strategies (food fortification, food snacks, dietary advice), oral nutritional supplements (ONS) and enteral tube feeding (ETF), the following inclusion criteria for trials were devised: (i) randomized trials; (ii) intervention with food strategies, ONS or ETF; (iii) duration of intervention >2 weeks; (iv) control group receiving placebo or no dietary intervention (e.g. usual care, which could include advice and encouragement to eat), but otherwise the same treatment as the intervention group; (v) stable patients with a diagnosis of COPD (not exacerbating); (vi) human studies only; and (vii) English language only.

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

Functional outcome data sought included respiratory function (forced expiratory volume in 1 s (FEV₁)), respiratory muscle strength (maximal inspiratory mouth pressure (PI max) and maximal expiratory mouth pressure (PE max)), peripheral muscle strength (maximum voluntary handgrip strength (HGS)), exercise performance (walking distance), QoL and additional outcomes including immunological measures. In trials where mean values were reported without standard deviations (SD) or standard errors (SE), they were calculated from reported P-values. In one trial that assessed HGS,[15] data reported in kilograms were considered to be unrealistic and therefore assumed to be in pounds. Whenever possible, data from individual subjects were used to calculate the summary values from specific studies.[15,21] Graphical data were also used to establish summary values either when there were no other data reported or when reported results were imprecise due to rounding.[22]

Quality assessment

The quality of included studies was assessed by one researcher (P.F.C.) and independently verified by another assessor (R.J.S.) using the most commonly used scoring system (Jadad scoring system).[23] The Jadad scoring system comprises of three components addressing whether a study is described as randomized, whether it is double-blind and whether drop-outs were accounted for. It then scores on the appropriateness of the randomization and blinding. The Jadad scoring system does not assess the sample size of trials.

Synthesis of data and statistical analysis

Following the extraction of data from included trials, where appropriate and feasible, the results of comparable outcome measures were combined in order to carry out random effects meta-analyses using Comprehensive Meta-analysis (Biostat, Inc., Englewood, NJ, USA, version 2) (Table 1). The overall treatment difference was considered statistically significant if the P-value was <0.05. Analysis explored differences between groups as well as within group changes. The effect size was reported as the difference in mean ± SE. Four studies reported values adjusted for baseline data.[16,22,24,25] Meta-analysis was subjected to sensitivity analysis whenever imputation of missing data was carried out (this involved imputation of SD for the change for the control arm of one study).[13] Meta-regression was undertaken to examine whether the differences in functional outcomes between the two arms of the studies were related to each of the following moderators: duration of intervention, % ideal body weight (IBW) and age.

RESULTS

A total of 49 studies were identified as potentially eligible from the literature search;[13,16,21,22,24-66] of these, 37 failed to achieve the inclusion criteria (Fig. 1). Reasons for exclusion included an unsuitable study design or review in 10 studies,[28,37-38,40,46,56,58,61-63] limited or no nutrition provided in 9 studies,[32,36,39,41,43,49,51,64,65] 5 non-randomized trials,[27,35,45,55,59] 5 studies involving an unsuitable population,[26,30,47,54,57] 5 studies with no control or placebo,[31,33,35,53,60] and inadequate intervention duration in 2 studies.[29,42] Goris et al.[44] which was included in the previous review, could not be included as it reported no functional outcomes. The review included 12 RCT involving 448 individuals with COPD who were randomized into either a treatment group (n = 232) or a control group (n = 216) (Table 2). Seven studies were performed completely within the outpatient setting,[13,24,25,48,50,52,66] three in the inpatient setting,[16,21,22] and two involving periods in both of these settings.[14,15] The study by Schols et al.[16,22] is referred to as two separate trials in order to distinguish between patients who were considered to be adequately nourished[16] and undernourished[22] (Table 2). All the patients recruited to the earlier trials had a diagnosis

Table 1 Functional outcome measures from 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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. studies</td>
<td>No. participants treatment/control</td>
</tr>
<tr>
<td>FEV₁</td>
<td>10</td>
<td>102/105[1]</td>
</tr>
<tr>
<td>PI max</td>
<td>8</td>
<td>153/124</td>
</tr>
<tr>
<td>PE max</td>
<td>6</td>
<td>81/59</td>
</tr>
<tr>
<td>HGS</td>
<td>5</td>
<td>87/90</td>
</tr>
<tr>
<td>Walk and shuttle tests</td>
<td>7</td>
<td>150/149</td>
</tr>
<tr>
<td>QoL and breathlessness</td>
<td>6</td>
<td>85/90</td>
</tr>
<tr>
<td>Immunological</td>
<td>3</td>
<td>24/20</td>
</tr>
<tr>
<td>ADL</td>
<td>1</td>
<td>23/18</td>
</tr>
</tbody>
</table>

[1]Numbers refer to only eight studies. An additional two studies involving 217 patients reported changes in FEV₁ without specifying the number that completed the tests in each group.[16,17] Numbers reported are for those subjects that completed the intervention phase. ADL, activities of daily living; FEV₁, forced expiratory volume in 1 s; HGS, handgrip strength; PE max, maximum expiratory pressure; PI max, maximum inspiratory pressure; QoL, quality of life.
Table 2  Summary of the randomized, controlled trials included in the systematic review according to intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (treatment/control)</th>
<th>Characteristics/setting (intervention vs 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>
</thead>
<tbody>
<tr>
<td>ONS</td>
<td>18/17</td>
<td>Malnourished 82.8% IBW Outpatients</td>
<td>ONS (Pulmocare, 1.5 kcal/mL) 1 can/day ONS target: +355 kcal/day and 15 g protein/day 9 weeks</td>
<td>Usual diet</td>
<td>FEV₁, 6MWT</td>
<td>11000 (2)</td>
</tr>
<tr>
<td>DeLetter et al</td>
<td>7/7</td>
<td>Malnourished 79.5% versus 81.3% IBW Outpatients</td>
<td>ONS (Build Up, 1.13 kcal/mL) ONS target: +640–1280 kcal/day and 36–72 g protein/day, encouragement to eat provided to both groups 12 weeks</td>
<td>Usual diet (with encouragement)</td>
<td>FEV₁, PI max, PE max, sternomastoid strength, HGS, 6MWT, breathlessness scale, general well-being</td>
<td>10000 (1)</td>
</tr>
<tr>
<td>Knowles et al</td>
<td>13/12</td>
<td>Nourished and malnourished 61–108% IBW Outpatients</td>
<td>ONS (Sustacal, 1 kcal/mL, 0.043 g protein/kcal) ONS target: To increase total EI by 50% Weekly encouragement: 8 weeks</td>
<td>Usual diet</td>
<td>FEV₁, PI max, PE max, lymphocyte count, serum transferring</td>
<td>11000 (2)</td>
</tr>
<tr>
<td>Lewis et al</td>
<td>10/11</td>
<td>Malnourished 86.3% versus 84.6% IBW Outpatients</td>
<td>ONS (Isocal HCN, 2 kcal/mL) ONS target: 500–1000 kcal/day and 19–38 g protein/day, encouragement 8 weeks</td>
<td>Usual diet</td>
<td>FEV₁, PI max, PE max, HGS</td>
<td>10000 (1)</td>
</tr>
<tr>
<td>Otte et al</td>
<td>13/15</td>
<td>Malnourished 77% versus 73% IBW Outpatients</td>
<td>ONS (Novo, 1 kcal/mL) ONS target: +400 kcal/day and 20 g protein/day, encouragement 13 weeks</td>
<td>Placebo (blinded) (encouragement)</td>
<td>FEV₁, 12MWT, well-being</td>
<td>10111 (4)</td>
</tr>
<tr>
<td>Fuenzalida et al</td>
<td>5/4</td>
<td>Malnourished inpatients and outpatients 78.5% IBW</td>
<td>ONS (Sustacal HC, 1 kcal/mL) ONS target: Up to 1080 kcal/day and up to 46 g protein/day 3 weeks inpatient + 3 weeks outpatient (6 weeks total)</td>
<td>Usual diet</td>
<td>FEV₁, Lymphocyte count, T-helper/suppressor cells</td>
<td>10000 (1)</td>
</tr>
<tr>
<td>Rogers et al</td>
<td>15/12</td>
<td>Malnourished 78% versus 79% IBW 64 years</td>
<td>ONS (various, self-selected) tailored to individual dietary habits and dietary advice ONS target: Intakes &gt;1.7× REE and minimum 1.5 g protein/kg per day 15 weeks</td>
<td>Usual diet</td>
<td>PI max, PE max, HGS, 12MWT, breathlessness rating, QoL</td>
<td>10000 (1)</td>
</tr>
<tr>
<td>Schols et al</td>
<td>33/38</td>
<td>Nourished 102.4% IBW inpatient PR programme (not hospital) mean age unclear</td>
<td>ONS (Mixture of Nutridrink, Protifar, Fantomalt,Oil; seven mixtures of different flavours; 2.1 kcal/mL) ONS target: +420 kcal/day and 15 g protein/day, encouragement to eat regular meals 8 weeks</td>
<td>Usual diet (and encouragement with oral diet)</td>
<td>FEV₁, PI max, 12MWT</td>
<td>10001 (2)</td>
</tr>
<tr>
<td>Study</td>
<td>Sample size (treatment/control)¹</td>
<td>Characteristics/setting (intervention vs control)</td>
<td>Nutritional intervention (type/prescribed amount/duration)</td>
<td>Control group</td>
<td>Outcome measures</td>
<td>Study quality (Jadad score)²</td>
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<tr>
<td>Schols et al.²²</td>
<td>39/25</td>
<td>Malnourished 84.1% IBW Inpatient PR programme (not hospital) Mean age unclear</td>
<td>ONS (Mixture of Nutridrink, Protifar, Fantomalt, Oil; seven mixtures of different flavours; 2.1 kcal/mL) ONS target: +420 kcal/day and 15 g protein/day, encouragement to eat regular meals</td>
<td>Usual diet and encouragement with meals</td>
<td>FEV₁, PI max, 12MWT</td>
<td>10001 (2)</td>
</tr>
<tr>
<td>Steiner et al.²⁴</td>
<td>42/43</td>
<td>Nourished/malnourished (~105% IBW (23.9 vs 23.5 kg/m²) Outpatients PR programme 66 versus 68 years</td>
<td>ONS (Respifor, 1.5 kcal/mL) ONS target: +570 kcal/day and 28 g protein/day</td>
<td>Placebo (blinded)</td>
<td>HGS, ISWT, ESWT, QoL</td>
<td>10111 (4)</td>
</tr>
<tr>
<td>Whittaker et al.²¹</td>
<td>6/4</td>
<td>Malnourished 76% versus 82% IBW Inpatients 71 versus 64 years</td>
<td>ETF Nocturnal ETF (Isocal) ETF target; feed delivered: at least 1000 kcal/day or 1.7× REE whichever greater and 34 g protein (nasoduodenal/jejunal tube feeding) 16 days</td>
<td>Placebo ETF (equivalent volume providing &lt;100 kcal/night)</td>
<td>FEV₁, PI max, PE max, adductor pollicis muscle function, lymphocyte count, transferrin</td>
<td>11110 (4)</td>
</tr>
<tr>
<td>Weekes et al.²⁵</td>
<td>31/28</td>
<td>Malnourished (~88%)IBW (~19.8 kg/m²) outpatients 69 years</td>
<td>Tailored DA + leaflet of information + milk powder DA target: 600 kcal/day (no specific protein target)</td>
<td>Leaflet of information</td>
<td>FEV₁, PI max, PE max, HGS, QoL, activities of daily living</td>
<td>10001 (2)</td>
</tr>
</tbody>
</table>

¹ Sample size at baseline (this occasionally differed from the sample size associated with results over time).
² The number in parenthesis represents the overall score. The five individual scores represent scores for description and appropriateness of randomization/blinding as well as any description of withdrawals.

6MWT, 6-min walk test; 12MWT, 12-min walk test; DA, dietary advice (education); EI, energy intake; ESWT, endurance shuttle walk test; ETF, enteral tube feeding; FEV₁, forced expiratory volume in 1 s; HGS, handgrip strength; IBW, ideal body weight; ISWT, incremental shuttle walk test; ONS, oral nutritional supplements; PE max, maximum expiratory pressure; PI max, maximum inspiratory pressure; PR programme, pulmonary rehabilitation programme; QoL, quality of life; REE, resting energy intake.
of COPD (FEV1/forced vital capacity <0.70), which was severe\(^6\) (mean FEV1 <50% predicted (stage III) in all trials). The patients were in a stable condition free from exacerbation. Studies involving patients with acute exacerbations were excluded.

Out of the 12 trials included in the analyses, 10 \((n = 379);\) intervention 195 vs control 184\) provided nutritional support by ONS, \(^{13,14,16,21,22,25,48,50,52,66}\) mostly ready-made, liquid supplements, some of which were specifically formulated for use in patients with COPD. One trial used nocturnal ETF \((n 6 vs 4)\), \(^{21}\) and another used tailored dietary advice delivered by a dietitian and the provision of whole milk powder \((n 31 vs 28)\). \(^{25}\)

No trials were found involving interventions of food snacks or food fortification alone. The intervention period ranged from 16 days\(^21\) to 6 months, \(^{25}\) with the amount of nutritional support prescribed ranging from 35566 to 1080 kcal/day. \(^{13}\)

Eight studies \((n 8)\) \(^{13,15,21,22,25,50,52,66}\) principally involved malnourished (‘depleted’) individuals \((\text{BMI} <20 \text{ kg/m}^2 \text{ or } \% \text{IBW} <90\%)\). Three trials included both adequately nourished and undernourished patients who participated in a rehabilitation exercise programme, \(^{13,22,24}\) but subgroup analysis according to nutritional status was undertaken to examine some of the outcomes. The remaining study included both undernourished and nourished subjects \((\text{Table } 2)\) but with a predominance of underweight individuals \((\text{over half with <85\% IBW})\). \(^{48}\)

The most commonly reported outcome was pulmonary function \((\text{FEV}_1)\) reported in 10 trials, \(^{13,14,16,21,22,25,48,50,52,66}\) 9 of which \(^{13,14,16,21,22,25,48,50,52,66}\) provided separate information in intervention and control groups. However, the results were presented in different ways: two reported no significant differences in the change in \(\text{FEV}_1\) over time, \(^{25,52}\) seven reported no significant change in either group over time, \(^{13,16,21,22,25,48,52}\) and two reported the mean values of \(\text{FEV}_1\) at the start and end of the study period, but because they were virtually identical\(^5\) or very close to each other\(^6\) within the control and the intervention groups, it can be deduced that there were no significant changes over time in either group and no significant differences between groups. Indeed, there was no evidence from any of the studies that the changes in \(\text{FEV}_1\) or changes in other measures of respiratory function, such as forced vital capacity, \(^{13,21,25,48,50,52}\) \(\text{FEV}_1/\text{forced vital capacity}\), \(^{13,21,25,48,50,52}\) total lung capacity \(^{13,21,48}\) and blood gases \(^{48,50,52}\) differed between intervention and control groups. Two studies reporting measured \(\text{FEV}_1\) \(^{25}\) and percentage predicted \(\text{FEV}_1\) \(^{52}\) were meta-analysed using standardized differences. Nutritional support was not associated with any improvement in \(\text{FEV}_1\) \((-0.213 \text{ SE } 0.22 \text{ L, } P = 0.335\).\

\(\text{PI max}\) was reported in eight studies \(^{13,15,16,21,22,25,48,50}\) of ONS \((n 6);\) ETF \((n 1)\) and dietary advice \((n 1)\). Five of these studies \(^{13,15,16,21,25}\) were amenable to meta-analysis, four of which favoured nutritional support \((\text{Fig. } 2)\). The overall summary measure obtained using random effects meta-analysis was significant in

<table>
<thead>
<tr>
<th>Study name</th>
<th>Difference in means</th>
<th>Standard error</th>
<th>(P)-value</th>
<th>Difference in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effthiomiou et al.(^{13})</td>
<td>5.800</td>
<td>4.803</td>
<td>0.227</td>
<td></td>
</tr>
<tr>
<td>Rogers et al.(^{15})</td>
<td>6.567</td>
<td>3.899</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td>Weekes et al.(^{25})</td>
<td>-0.100</td>
<td>3.639</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>Whittaker et al.(^{21})</td>
<td>11.667</td>
<td>8.987</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>Schois et al.(^{16})</td>
<td>3.770</td>
<td>3.320</td>
<td>0.256</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Random effects meta-analysis of five studies measuring changes in maximal inspiratory mouth pressure \((\text{PI max})\) \((\text{cm H}_2\text{O})\) in nutritional intervention \((n 91)\) and control groups \((n 88)\). The forest plot shows the difference in the mean changes between groups. CI, confidence interval.
favour of nutritional support (+4.04 SE 1.86 cm H2O, \( P = 0.030 \)). The meta-analysis was undertaken assuming that the SD of the change in the control group of one of the studies\textsuperscript{13} was the same as that of the ONS group. The latter was established from the combination of the reported mean change in PI max and a \( P \)-value of 0.05 (but because the reported \( P \)-value was <0.05, the calculated value is larger than the true value). When a sensitivity analysis was carried out assuming the SD of the change ranged from 75\% to 125\% of that in the ONS group, there was little change in the overall point estimate (+4.11 SE 1.83 cm H2O, \( P = 0.024 \) and +3.98, SE 1.90 cm H2O, \( P = 0.049 \), respectively). The associated weight change in the same five studies also favoured nutritional support (+2.17 SE 0.44 kg; \( P < 0.001 \)). Meta-regression found no significant relationship between PI max (cm H\(_2\)O) and each of the following variables: duration of intervention (weeks) (slope = -0.294, SE 0.250, \( P = 0.239 \)), \% IBW (slope = -0.124, SE 0.187, \( P = 0.058 \)) and age (years) (slope = -0.867, SE 0.779, \( P = 0.266 \)); excluding the study of Schols et al.,\textsuperscript{16,22} which did not report the mean age of the patients who had the PI max tests.

Of the three studies that could not be included in the meta-analysis, one found a significant increase in PI max over time in the ONS group and not in the control group,\textsuperscript{48} one reported PI max to be unchanged,\textsuperscript{50} and the final study did not report the relevant data needed for inclusion in the meta-analysis.\textsuperscript{22}

PE max was reported in six studies, four involving ONS,\textsuperscript{13,15,21,24,48,50} one ETF\textsuperscript{21} and one using dietary advice,\textsuperscript{25} but meta-analysis was only possible in four of them\textsuperscript{13,15,21,25} (Fig. 3). This meta-analysis found that nutritional support significantly improved PE max in favour of the intervention group (+13.06 SE 5.81 cm H\(_2\)O, \( P = 0.025 \)), with all four studies favouring the intervention group and two significant in their own right (one involving ETF\textsuperscript{21} and the other involving ONS\textsuperscript{15}) (Fig. 3). The meta-analysis of PE max was undertaken assuming that the SD of the change in the control group of one of the studies\textsuperscript{13} was the same as that in the ONS group. When a sensitivity analysis was carried out assuming that the SD of the change ranged from 75\% to 125\% of that of the ONS group, there was virtually no change in the point estimate obtained by the random effects meta-analysis (+13.02, SE 5.83 cm H\(_2\)O, \( P = 0.026 \); and +13.12 SE 5.78 cm H\(_2\)O, \( P = 0.024 \), respectively). The associated weight change in the same four studies also significantly favoured the nutritional support group (+3.10 SE 0.67 kg; \( P < 0.001 \)). Meta-regression found no significant relationship between PE max (cm H\(_2\)O) and each of the following variables: duration of intervention (weeks) (slope = -0.071, SE 0.430, \( P = 0.669 \)), \% IBW (slope = -0.321, SE 0.809, \( P = 0.691 \)) and age (years) (slope = 1.494, SE 1.224, \( P = 0.266 \)).

Of the two studies that could not be included in the meta-analysis, one reported no significant difference in measurements between groups\textsuperscript{48} and the other no significant change within groups.\textsuperscript{59}

To assess respiratory accessory muscle strength, a further study measured sternomastoid strength and fatigability, and found that ONS resulted in significantly increased strength (\( P < 0.05 \)) and reduced fatigability after 3 months of supplementation, while non-significant changes in the opposite direction occurred in the control group. The differences between groups returned towards baseline after cessation of treatment.\textsuperscript{13}

Other functional measures

**Maximum voluntary peripheral (non-respiratory) muscle strength**

Five studies assessed peripheral muscle strength using HGS,\textsuperscript{13,15,24,25,50} with four of the five providing nutritional support using ONS. Four studies\textsuperscript{13,15,24,25} were amenable to meta-analysis and all favoured intervention, two significant in their own right\textsuperscript{13,15} (Fig. 4). The mean changes were +1.41 SE 0.66 kg, \( P = 0.032 \) (range 0.3–5.2 kg (1.3–18.5\%) above baseline in favour of the intervention group). In undertaking

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### Change in PE max (cm H\(_2\)O)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Difference in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in means</td>
<td>Standard error</td>
</tr>
<tr>
<td>Effimiuo et al.\textsuperscript{13}</td>
<td>3.000</td>
<td>3.115</td>
</tr>
<tr>
<td>Rogers et al.\textsuperscript{15}</td>
<td>23.367</td>
<td>9.511</td>
</tr>
<tr>
<td>Weeckes et al.\textsuperscript{25}</td>
<td>9.200</td>
<td>6.057</td>
</tr>
<tr>
<td>Whitaker et al.\textsuperscript{21}</td>
<td>30.417</td>
<td>11.432</td>
</tr>
<tr>
<td></td>
<td>13.055</td>
<td>5.813</td>
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</tbody>
</table>

Figure 3 Random effects meta-analysis of four studies measuring changes in maximal expiratory mouth pressure (PE max) (cm H\(_2\)O) in nutritional intervention (\( n = 58 \)) and control groups (\( n = 48 \)). The forest plot shows the difference in the mean changes between groups. CI, confidence interval.
this meta-analysis, two assumptions were made: the SD of the change for the control group in the study of Efthimiou et al., was the same as that for the ONS group, and the unrealistically high grip strength values reported for both intervention and control groups in the study of Rogers et al. were in pounds rather than in kilograms. To address the latter uncertainty about the units of measurement, the meta-analysis was repeated using standardized differences (overall point estimate 0.56, SE 0.22; P = 0.009, Figure 4). To address the former uncertainty, a sensitivity analysis was undertaken by altering the SD of the change by ±25% (75–125%), which produced little change in the overall point estimate and the associated statistical significance of the differences between groups (using a value of 75% for the SD of the change, the overall effect size in the meta-analysis was 0.59, SE 0.23 (P = 0.010); and with 125% for the SD of the change, the effect size was 0.52, SE 0.20 (P = 0.008)). Even when the sensitivity analysis involved an alteration of the SD of the change by as much as ±50% (50–150%), there was little overall impact on the effect sizes and P-values (effect sizes ranging from 0.48 to 0.58 and P-values from 0.021 to 0.018, respectively). The associated change in body weight in the same four studies significantly favoured the intervention group (+2.06 SE 0.65 kg; P = 0.001). Meta-regression found no significant relationship between HGS (kg) and each of the following variables: duration of intervention (weeks) (slope = −0.033, SE 0.041, P = 0.428) and % IBW (slope = −0.322, SE 0.035, P = 0.364).

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

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

Walking distance and endurance during walking
Seven studies examined the influence of nutritional support on improving exercise tolerance. Four studies favoured the intervention group, and the remaining two studies did not provide the necessary information to assess which group was favoured. Meta-analysis was not performed due to the use of different methodologies, types of tests, and ways of reporting results (e.g. some reporting median values and others mean values) and lack of measures of variation and/or P-values for some of the within-group changes.

Using the 6-min walk test, Efthimiou et al. reported significant improvements in the ONS group (53 m (+12.8%); P < 0.05) but not in the control group (1 m (+1.4% non-significant), and DeLetter did the same (+35.4 m (+11.6%) vs −1.2 m (−0.4%)). Using the 12-min walk test, Rogers et al. found that the distance walked increased significantly more in the ONS group (34 m (−7%) at 4 weeks and 143 m (−28%) at 4 months) compared with the control group (a deterioration of 42 m (−8%) at 4 weeks and 0.3 m (−0.1%) at 4 months) (P = 0.03 for the difference in the mean change between the two groups). Otte et al. reported no significant changes in the 12-min walking distance in either the ONS or control groups (−81 m (−9.0%) vs +50 m (−6.3%), respectively). Schols et al. reported an improvement in the 12-min walking distance in subgroups of depleted (173 m, 29%) and non-depleted (147 m, 24%) patients undergoing pulmonary rehabilitation, with no significant differences between the intervention and control groups. Using the shuttle walk tests in subjects undergoing pulmonary rehabilitation, Steiner et al. found that performance improved to a greater extent in the intervention (ONS) than control group with respect to

Figure 4 Random effects meta-analysis of four studies measuring changes in peripheral muscle strength (standardized differences) in nutritional intervention (n = 77) and control groups (n = 79). The forest plot shows the difference in the standardized mean changes between groups. CI, confidence interval.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efthimiou et al.</td>
<td>1.071</td>
<td>0.572</td>
<td>0.061</td>
</tr>
<tr>
<td>Rogers et al.</td>
<td>1.080</td>
<td>0.414</td>
<td>0.009</td>
</tr>
<tr>
<td>Weekes et al.</td>
<td>0.148</td>
<td>0.271</td>
<td>0.586</td>
</tr>
<tr>
<td>Steiner et al.</td>
<td>0.501</td>
<td>0.266</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>0.565</td>
<td>0.217</td>
<td>0.009</td>
</tr>
</tbody>
</table>
endurance walk tests (mean increase in distance walked, 60.0 m vs 42.6 m; −29% vs 19%; *P* = 0.102) and the incremental walk tests (median increase in duration, 328 s (−x2 baseline value vs 191 s, −x0.9 baseline value; *P* = 0.172), but the differences were not significant.

**QoL and subjective measures of breathlessness**

Five studies examined the effect of nutritional support on QoL, but because the results were obtained using different tools and reported in different ways, they were not subjected to meta-analysis.13,15,24,25,52 One study reported a significant improvement in total score in favour of the intervention group: the St George’s Respiratory questionnaire (with the components also favouring the intervention group: Activity (*P* = 0.06), Impacts (*P* = 0.004), symptoms (*P* = 0.73) using the intention-to-treat analysis), as well as the short-form 36, which measured health change. The overall scores represented an improvement of 18% and 55% improvement, respectively, according to the intention-to-treat analysis.25 These changes were mirrored by significant differences in breathlessness. Another study reported a significant improvement in general well-being of the nutrition intervention (ONS) group (−27%) and not in the control group (−6%),13 which was paralleled by a significant improvement in breathlessness in the intervention and not in the control group. A third study of ONS reported that a greater proportion of subjects felt that their well-being had improved as a result of the nutrition intervention compared with control (23% vs 13%) and a smaller proportion felt that it had deteriorated (15% vs 33%), but given the small sample size (13 vs 15), the differences were not statistically significant.52 This same study reported a tendency for breathlessness to improve in favour of the intervention group (*P* = 0.20). One of the two remaining studies briefly reported no significant differences in health-related QoL assessed at enrolment or at 4 months using the Sickness Impact Scores53 and no significant differences in breathlessness scores, which contributed to the overall QoL. The final study involving subjects undergoing exercise rehabilitation found significant improvements in health-related QoL and in breathlessness (both assessed using the self-reported Chronic Respiratory Questionnaire) in both the control and intervention groups,25 with no significant differences between them.

**Other outcomes**

The only study that examined activities of daily living in malnourished patients with COPD reported that the nutrition intervention group found it significantly easier to perform everyday activities compared with the control group (*P* = 0.009 in the per-protocol analysis and *P* = 0.06 in the intention-to-treat analysis, the difference in the changes being about 18% and 11% of the baseline values, respectively.25).

Four studies reported changes in immunological tests.14,21,48,52 One of these14 found significant improvements in delayed cutaneous hypersensitivity and total circulating lymphocyte count, without associ-ated changes in circulating immunoglobulin concentrations, during nutritional repletion of malnourished patients with COPD. Two trials, one involving ETF21 and one ONS50 briefly reported that lymphocyte counts remained unchanged over the study period. Finally, a study48 involving ONS reported no significant changes in T-helper/T-suppressor ratio and mitogen reaction of T lymphocytes to phytohemagglutinin. None of these three studies reported separately the changes that occurred in each group. Furthermore, none of these three studies or any of the other studies included in this systematic review measured cytokines or acute phase proteins.

**DISCUSSION**

This review found that nutritional support in COPD produces significant improvements in several functional outcomes including respiratory and limb muscle strength. These findings demonstrate the positive effects of nutritional support on respiratory muscle tests and other functional outcomes, building on the conclusions of a recent review that nutritional support significantly improves energy and protein intakes with resulting increase in body weight.17 This earlier review did not consider functional outcomes other than change in HGS, which was reported as a percentage change rather than in kilogram as in this review. However, it did consider methodological issues, including those involved in an earlier Cochrane review. The findings of the present review also strengthen the argument that a causal pathway exists linking increased nutritional intake provided primarily by standard ONS to increased body weight and function. The current findings are in contrast with the previous Cochrane review including the same trials that reported no effect of nutritional support in COPD.22 probably because it considered only cross-sectional differences between groups at the end of the intervention period and not within-group changes induced by the interventions (see Collins et al.17 for a discussion on methodological issues). However, an updated Cochrane review, which appeared very recently following submission of the present review for peer review, changed its conclusions. A comparison of this review with the updated Cochrane review is provided after the main findings of the present review are discussed.

The current review with a series of meta-analyses found that for each of the tests used to document improved respiratory muscle function (PI max and PEmax) and non-respiratory (handgrip/quadriceps) muscle strength, there was a highly significant increase in body weight of more than 2 kg (2.1–3.1 kg) in favour of the nutrition intervention group. Schols et al.48 found that both an improved inspiratory mouth pressure (PI max) and a weight gain of >2 kg were associated with significantly improved survival in keeping with a previous review reporting that significant functional improvements were seen in malnourished patients receiving ONS when weight gain was >2 kg.7 It appears that this level of weight gain should be a therapeutic target in malnourished COPD.
patients, especially as recently reviewed evidence highlights that this level of weight gain is achievable in malnourished COPD patients.\textsuperscript{77} The current review confirms that weight gain of this magnitude is associated with functional improvements in this patient group.

In the clinical setting, increasing importance is being placed on the assessment of functional outcomes. HGS is not only a reliable marker of peripheral muscle strength but it also predicts clinical outcomes\textsuperscript{27} such as mortality, morbidity, postoperative complications and increased length of hospital stay. In the elderly, a loss of grip strength often means a loss of independence. Although muscle strength is closely related to mid-arm muscle area,\textsuperscript{79} whole body protein content,\textsuperscript{71} and even body weight and BMI,\textsuperscript{72} a variety of studies suggest that changes in muscle function can occur independently of muscle mass.\textsuperscript{7} It has recently been suggested that muscle strength responds faster to nutritional depletion and repletion than anthropometric measures such as BMI and fat-free mass\textsuperscript{68} probably as a result of increased availability of energy, electrolytes and micronutrients in muscle. Therefore, the improvement in muscle strength induced by nutritional intervention in malnourished COPD patients is likely to be due to a combination of increased force generated by the available muscle and increased muscle mass, which is consistent with the increase in mid-arm muscle circumference (or area) reported in RCT of COPD\textsuperscript{27} and other conditions.\textsuperscript{73} Mid-arm muscle area has been found to be a better predictor of mortality than BMI in patients with COPD.\textsuperscript{74} Therefore, nutritional support leading to weight gain (>2 kg) and increased mid-arm muscle circumference could confer survival benefits as suggested by previous studies.\textsuperscript{68,75}

Exercise tests in COPD have also been found to predict outcomes,\textsuperscript{76} such as mortality and postoperative complications.\textsuperscript{77,78} This review examined the effect of nutritional support in COPD patients undertaking different types of walking and shuttle tests performed on a flat surface, but the reviewed studies were not amenable to meta-analysis. However, four of the five studies favoured the nutritional support group, and the only studies reporting significant improvements in performance also favoured those receiving nutritional support. While these tests have limitations (e.g. some patients still have difficulties walking faster on flat surfaces as their condition improves, but they can walk up a steeper slope), they at least assess important aspects of the patient’s ability to function in ways that are relevant to everyday life.\textsuperscript{79}

The evidence based on the effect of nutritional support on immunological function is very limited not least because none of the three studies\textsuperscript{4,21,48} that assessed restricted aspects of immune function reported the results separately for the intervention and control groups. In addition, the total absence from these studies of cytokine measurements and acute phase proteins as markers of the inflammatory response highlights the need to examine immune/inflammatory-nutrition interactions. This is because the immune system not only helps prevent and aid recovery from respiratory infections but also because it is linked to the processes involved in nutritional depletion and repletion of body tissues and their responsiveness to nutritional support.\textsuperscript{34} Whether exercise has a pro- or anti-inflammatory role in COPD is unclear;\textsuperscript{60,81} however, a recent trial\textsuperscript{82} involving a combination of low-intensity exercise education sessions and an ONS with immunomodulatory properties (immunonutrition) in a cohort of malnourished (mean BMI 18.0 kg/m\textsuperscript{2}) patients with moderate COPD produced some very promising results that included improvements in weight, peripheral and respiratory muscle strength, exercise capacity, QoL, and a reduction in muscle inflammation (measured by interleukin-6, interleukin-8, tumour necrosis factor-\alpha, high sensitive C-reactive protein levels). Further work is required to examine whether these improvements are due to the exercise intervention, the immunonutrition (or other components of the ONS) or a combination of these. Further work is also needed to examine the extent to which the changes in outcome could be reproduced by using a standard ONS.

An outcome that was found to be unresponsive to nutritional support in the current review was lung function (assessed by tests such as FEV\textsubscript{1}, forced vital capacity and blood gases), but this is likely to reflect the irreversible nature of lung pathology in COPD. It may seem surprising that the lack of an effect of nutritional support on objective tests of lung function were sometimes associated with significant improvements in subjective measures of breathlessness. However, because malnutrition has effects on the central nervous system, including modulation of the sensitivity of the respiratory centre to hypoxic stimulation,\textsuperscript{81} it is plausible that nutritional support influences the sensation of breathlessness through centrally mediated mechanisms. Interestingly, cross-sectional studies of men with COPD have reported that breathlessness is inversely related to BMI independently of respiratory function tests (diffusing capacity to carbon monoxide, partial arterial oxygen concentration, P\textsubscript{a}O\textsubscript{2}/P\textsubscript{a}I\textsubscript{max}).\textsuperscript{83} Breathlessness influences QoL, which probably explains the striking concordance between them, both within and between groups of the reviewed RCT.

The extent to which changes in functional outcome measures reflect clinically relevant improvements in patient well-being can be difficult to establish. For example, a small change in muscle strength (which may be as little as a few percent, as in some of the reviewed studies) may go totally unnoticed in strong well-nourished subjects, but in malnourished patients who are close to the threshold of disability,\textsuperscript{84} they may be easily noticed and make the difference between being able to get up and not get up from a bed or a chair, and between being independent and dependent on others. Nevertheless, attempts have been made to establish the minimum clinically relevant changes associated with some of these tests. For example, it has been conservatively estimated that the minimum clinically important difference in 6-min walking distance is 54–80 m\textsuperscript{65}, which exceeds that found in the only two nutrition intervention studies that employed the 6-min walk test (an improvement
in favour of ONS by a mean of 47.1 and 37 m. However, much larger changes have been found with the 12-min walk test, for example, an improvement of 143 m has been attributed to ONS in the study of Rogers et al. The minimum clinically important improvement in incremental shuttle walk test has been estimated to be 47.5 m. The minimum benefit distinguishable by patients relates to 78.7 m. Of the studies considered in the present systematic review, the only one that used the incremental shuttle walk test to examine the effects of ONS during pulmonary rehabilitation found improvements in walking distance in favour of the nutrition intervention group that were less than the suggested thresholds. However, the patients were studied during pulmonary rehabilitation and the effect of ONS in combination with the other treatments showed a statistically significant overall improvement of 60 m. Because both non-malnourished (87%) and malnourished patients (13%) received ONS if they were randomized to the nutritional support arm of the study, it is possible that those with malnutrition responded differently from those without malnutrition, but such information was not reported. The benefits of exercise rehabilitation are well established, however, as alluded to by Steiner and colleagues, it can produce a negative energy balance that might require reversal by supplementation before an improvement in training outcomes can be demonstrated. A recent RCT of patients with chronic respiratory failure, the majority of whom had COPD, participating in an exercise rehabilitation programme and classified as malnourished (BMI 21.5, SD 3.8 kg/m² and fat-free mass depleted) found that nutritional support (ONS 3 × per day), education and oral testosterone undecanoate led to significant improvements in body weight, fat-free mass, strength and function above control. At present, it is unclear whether all malnourished COPD patients undertaking exercise training should receive additional nutritional support or indeed whether training should commence in those who are malnourished without nutritional support. It would appear pertinent to recommend that all COPD patients at risk of malnutrition should receive some form of nutritional support during rehabilitation and recommendations are required.

The present analysis also examined the effect of potential explanatory variables, such as duration of intervention with nutritional support, % IBW and age of the participants, on functional outcomes (PI max, PE max and HGS), but generally, they were not found to be significantly related to the outcomes. This is not too surprising given that the meta-regressions involved a small numbers of studies that differed in design and prescribed amounts of nutritional support (see Table 2), and also involved examination of each variable individually. In addition, there was only small variation between the mean age of the populations involved with different studies (62–69 years) and in some cases involved significant effects on outcomes followed short periods of supplementation (e.g. significant improvement in PE max reported in one study after 16 days of supplementation). Further insights might emerge if individual patient data (instead of mean study data) were analysed together, but unfortunately, such data are not available.

To understand the significance, strengths and limitations of this review and the way it differs from the updated Cochrane review, it is necessary to consider certain methodological issues. Although the conclusions of both reviews appear to be similar (and both at variance with those of the earlier Cochrane review, the two should not be confused because apart from not addressing the same issues, they have used different methodology to meta-analyse different studies, which were selected according to different criteria.

The present review excluded three studies, which were also absent from the previous Cochrane review. However, in the updated Cochrane review, these three studies contributed to the assessment of almost all of the functional outcomes, dominating some of the analyses such as the overall health-related QoL (accounting for three out of the four studies) and their domains (two out of three studies in each domain and the 6-min walk test (three out of five studies). The studies totally dominated the meta-analyses of quadriceps strength (only two studies), yet in the present review, data on quadriceps strength from another paper were able to be used. Two of the three papers were excluded from the present review because they both incorporated an exercise programme in the nutritional support arm of the study and not in the control arm and one of them also included additional interventions in the nutritional support arm and not the control arm. The depleted patients who received nutritional support in this study accounted for minority of the population, which was predominantly overweight with mild COPD.) These study designs make it difficult to isolate the effects of nutritional support. The multiple reported functional outcomes in favour of nutritional support arm may have been due to the non-nutritional interventions or a combination of nutritional and non-nutritional interventions. The third study was not included in the present review because it became available after the literature search was carried out. It involved a nutritional supplement with immunomodulatory properties, which can be attributed to an anti-inflammatory whey peptide, pharmacological doses of the anti-oxidant vitamins C, E and A, and fish oils. Arguably, this study should be treated separately from other studies, none of which involved an immunonutrition feed.

In the present review, the meta-analyses examined whether the changes induced by the interventions differed between the two arms of studies, whereas in both the previous and updated Cochrane reviews, most of the meta-analyses, including those involving PI max and PE max, involved only the values at the end of the intervention period. It is considered preferable to generally use the ‘change’ method than the ‘end value’ method to assess the impact of interventions, especially when there is a relatively large baseline imbalance (which could fortuitously affect the two arms of individual studies in opposite directions (e.g. for variables such as PI max and PE max)). Another difference between the two reviews concerns

Respirology (2013) 18, 616–629

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the uncertainty associated with imputation of missing data (missing SE or SD). In the present review, imputation involved only 1 of the 12 studies, affected only the control group (for PI max, PE max and HGS), and was always accompanied by sensitivity (uncertainty) analysis, which assessed the potential errors associated with imputation. The uncertainty associated with the some of the analyses in the updated Cochrane review appears is less clear because imputation involved 5 out of 14 studies (and more than half of the studies in some meta-analyses, such as those involving changes in anthropometry including weight, and 6-min walk test), often both arms of some studies or the difference between them and in the absence of sensitivity analyses.

Although the type of functional outcomes examined by the two reviews was similar, the present review systematically considered HGS and immunological function, which was not the case with either of the Cochrane reviews. In addition, the present review provided new data using meta-regression (involving duration of intervention, % IBW, age and as moderators) and considered the minimally important clinical differences and related the findings associated with one type of outcome variable to that of another another (e.g. the extent of weight gain associated with improvements in functional outcomes). In contrast, the Cochrane review, following the formal format of Cochrane Collaboration to produce a document of almost 100 pages long, included more detailed information about individual studies, listed the excluded studies and undertook some subgroup meta-analyses, such as those involving the components of QoL (made possible by inclusion of the three new studies that did not feature in this review). However, the present review included a semiquantitative and narrative description of QoL data and well-being that were not synopsized by the Cochrane review.

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

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