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

Peter F Collins RD, Rebecca J Stratton PhD, RD, RNutr, Marinos Elia MD, FRCP.

Institute of Human Nutrition, Faculty of Medicine, University of Southampton, MP 113, Southampton General Hospital, Southampton, SO16 6YD, UK

Key words: nutritional support, COPD, malnutrition, meta-analysis.

Word count
Abstract: 252 (including titles)
Document: 4945 (including titles and within text references)

Abbreviations
COPD – chronic obstructive pulmonary disease
DA – dietary advice
DXA – dual emission X-ray absorptiometry
ETF – enteral tube feeding
FFM – fat-free mass
IBW – ideal body weight
MAMC – mid-arm muscle circumference
ONS – oral nutritional supplements
RCT – randomized controlled trial

Funding
No funding was received.

Corresponding author:
Professor M Elia
Institute of Human Nutrition
University of Southampton,
MP 113
Southampton General Hospital
Southampton
UNITED KINGDOM
SO16 6YD
Tel: +44 (0)23800) 2380 794277
Email: M.Elia@soton.ac.uk
Fax: 02380 796317

ABSTRACT

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

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

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

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

Conclusion: This systematic review and meta-analysis shows nutritional support, mainly in the form of oral nutritional supplements, improves total intake, anthropometry and grip strength in COPD. These results are in contrast to previous analyses that were based only on cross-sectional measures at the end of intervention trials.

BACKGROUND

Malnutrition is a common problem in individuals with chronic obstructive pulmonary disease (COPD) with prevalence rates of between 30-60% of inpatients and 10-45% of outpatients (1). Malnourished COPD patients demonstrate greater gas trapping, lower diffusing capacity and a reduced exercise capacity when compared to heavier, non-malnourished 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 (body mass index (BMI)) would go undetected despite being fat-free mass (FFM) deplete (3, 4). A cross-sectional survey by Cano et al (3) in 300 outpatients with COPD requiring long-term oxygen therapy found 17% of patients to have a low BMI, whereas the prevalence of FFM depletion was more than two-fold higher (38%). This accelerated loss of lean tissue, which may lead to sarcopenia and cachexia, is facilitated by robust inflammatory responses, which may also limit or prevent accretion of lean tissue following nutritional support (5). Wasting of muscles not only detrimentally affects respiratory function, including reduced ability to expectorate to clear a chest infection, but it also promotes fatigability and reduces exercise tolerance and ability to work. However, it has not been possible to establish the exact causality between malnutrition and COPD as malnutrition may be the consequence of a greater 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 not only concluded that nutritional support has no significant effect on improving anthropometric measures such as weight and muscle mass, but also that it produces no demonstrable improvements in lung function and muscle strength. Several nutritional intervention studies have challenged this idea (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 (NICE), referred to the failure of a previous meta-analysis to demonstrate significant changes in weight and other outcomes with nutritional support (7), whilst referring to a previous study which demonstrated such improvements 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 (<20 kg/m^2) stating this was based on grade D evidence (lower quality) rather than the evidence from published systematic reviews and meta-analyses, and evidence from at least one RCT, which according to the NICE criteria qualify for grade A evidence (15).

On examining previous systematic reviews of nutritional support, differences in the methods of analysis were found (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 impact of baseline imbalance on the final point estimates. Treatment effect within groups as well as information on the presence of any variability between the two groups at baseline, beyond the fact that they were not significantly different, was not reported. Therefore, 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 in order 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 (accessed January 7, 2010), Web of Science (accessed January 7, 2010) and OVID (accessed January 7, 2010). In order 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: chronic obstructive pulmonary disease, COPD, emphysema, weight, depletion, diet*, nutrition*, supplement*, protein, carbohydrate, calori*, feed*, malnutrit*, nourish*, sip feed (ready made liquid oral nutritional supplement), nutrition intervention, nutrition support. A combination of these search terms was also used to identify trials. In addition to electronic database searching, manual searching of previous reviews on nutritional support in COPD 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 (PFC and ME), with two disagreements resolved through discussion with a third assessor (RJS) prior to inclusion.

Inclusion and exclusion criteria

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

The intervention could provide either a proportion or all of the daily nutritional requirements for energy, protein and micronutrients and where feeds were

used (e.g. ONS), these could be nutritionally complete or incomplete. Studies using parenteral nutrition were excluded.

Data extraction

Outcome data sought included total nutrient intake (energy and protein), body weight, upper arm anthropometry, body composition, and handgrip strength. Data were collected at baseline and at the end of the intervention phase where possible. Data were collected within data extraction tables allowing data synthesis and analysis from studies with varying populations (nourished/undernourished), intervention types (food strategies, DA, ONS, ETF) and intervention duration. Where data were not reported in the text but illustrated within a figure, the figure was expanded and the data extracted. This was done for energy intake (20, 21) and weight (20, 22). In some papers where mean values were reported without standard deviations (SD) or standard errors (SE), it was possible to calculate SD and SE using reported p values. In one study assessing handgrip strength (10), data reported in kg was considered to be unrealistic and therefore assumed to be in pounds.

Quality assessment

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

Synthesis of data and statistical analysis

Following the extraction of data from included trials, where appropriate and feasible, the results of comparable outcome measures were combined and meta-analysis performed. Statistical analysis was performed using SPSS (version 16.0, Chicago, IL) and meta-analysis (random effects model) using Comprehensive Meta-analysis (Biostat Inc, NJ USA version 2). Analysis was carried out in order to explore differences between groups as well as changes within groups. The effect size was reported as difference in means and standard error. 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 greater than 1.000 due to rounding of reported or calculated SDs, were assumed to have a value of 1.00.

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

RESULTS

A total of 44 studies were identified as potentially eligible from the literature search (5, 8, 9, 11, 13, 20-22, 24, 25, 27-59) and of these 31 were excluded (**Figure 1**). Exclusion reasons included 4 unsuitable study design (38, 41, 56, 58), 5 non-randomized trials (5, 28, 47, 55, 59), 3 target population not suitable (27, 54, 57), 6 no control or placebo group (29, 31, 32, 34, 35, 53), 11 unsuitable intervention (30, 33, 36, 39, 40, 43, 45, 49-52), 2 inadequate intervention duration (44, 60). A large randomized trial comparing an intensive management program versus usual care was not included as nutritional

support was provided to only a subgroup of patients where indicated in both arms (48). A summary of the search process is shown in Figure 1. The review included 13 RCTs of 439 individuals with COPD randomized into either a treatment group (n = 224) or a control group (n=215), (Table 2). Eight studies were performed completely within the outpatient setting (8, 14, 20, 22, 24, 25, 37, 46) three in inpatients (11, 13, 21) and two studies involved both outpatient and inpatient settings (9, 10). Separate analysis of the trial by Schols et al., (11, 13) was performed according to whether the subjects were non-depleted or depleted (Table 2). Patients recruited to the trials had a diagnosis of COPD (<70% predicted FEV_1) and were in a stable condition free from exacerbation. Patients recruited to the trials were classified as having severe COPD, range 30-40% predicted FEV_1 (FEV_1 <50% predicted (stage III)) (61). No study provided results on acute phase proteins or cytokines, and of four studies reporting circulating albumin, three had normal values (20-22) and one close to the lower limit of normal (14).

The majority of trials (11, n 189 intervention *vs*. 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 (Percentage energy: 60% carbohydrate, 20% fat, 20% protein (Respifor ®, Nutricia Ltd) (24, 46), 28.2% carbohydrate, 55.1% fat, 16.7% protein (Pulmocare ®, Abbott)) (37). One trial used nocturnal ETF (n 6 *vs*. 4) (21) and one trial used tailored dietary advice delivered by a dietitian and the provision of a milk powder supplement (n 30 *vs*. 25) (25). There were no trials 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 355 kcal/day (37) to 1080 kcal/day (9).

The majority of studies (n 8) (8-10, 14, 21, 22, 25, 37) were principally of malnourished ('depleted') individuals (BMI < 20 kg/m^2 or % ideal body weight < 90%). The trials by Schols et al., (11, 13) and Steiner et al., (24) included both nourished and undernourished patients as part of a rehabilitation exercise program and performed, or allowed for, subset analysis according to nutritional status (11, 13, 24). Two other studies included both undernourished

and nourished subjects, with a predominance of underweight, since in one the mean BMI was <20 kg/m^2 (<90% IBW) (46) and in the other, %IBW ranged from 61 -108% (20) (Table 2).

All trials (13 RCT) included in the review reported weight and weight change (or it could be calculated). The next most frequently reported anthropometric measures were triceps skinfold thickness and mid arm muscle circumference. Other outcomes included energy (n 11) and protein (n 5) intakes and the functional measure, handgrip strength (n 5) (Table 1).

Dietary intake

Data on total energy intake was available in 11 studies (8, 9, 11, 13, 20-22, 24, 25, 37, 46). When limiting analysis to those studies where nutrition was ingested orally meta-analysis was possible on 5 studies (20, 22, 24, 25, 37). There were no significant differences in daily energy intake between supplemented and control groups at baseline (mean difference 11 SE 87 kcal, p= 0.903) (20, 22, 24, 25, 37) but at the end of nutritional treatment a significant difference was found in favor of the supplemented group (diet + ONS or DA); 236 SE 71 kcal, p<0.001. Information on the mean changes in energy intake was available from 6 studies (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 control group by 318 SD 157 kcal/day (p=0.004, weighted for sample size). Similar significant results were also obtained from the five studies that involved ONS (413 SD 175 kcal/day, p=0.006) (8, 20, 22, 24, 37). Two studies were amenable to meta-analysis (24, 25) with the change in intake favoring the supplemented group (234 SE 63 kcal, p<0.001). Each study, one involving ONS and the other tailored dietary advice and milk powder supplementation, independently yielded significant results 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 two of them) (24, 25). All 5 studies reported mean daily protein intakes that were greater in

the supplemented than control group by 16.5 SD 10.3 g/day (p=0.023, weighted for sample size). Similar results were also obtained in the 4 studies involving ONS (18.2 SD 7.0 g/day, p=0.014). Considering only the two studies that were suitable for meta-analysis (24, 25) protein intake favored the supplemented group by a similar amount 14.8 SE 3.6 g/day, p <0.001. As with energy, both studies were significant in their own right (p<0.001).

Body weight

The trials of nutritional support showed a consistent increase in weight, which was significant in 7 out of 8 individual studies. However, a detailed analysis is undertaken below for comparison of conclusions from previous meta-analyses. Using information on body weight obtained from 8 studies, three sets of meta-analyses were carried out to compare control and intervention groups. These involved baseline weight, end weight, and change in weight (9-11, 13, 14, 21, 24, 25). **Figure 2 (upper)** shows that baseline weight in the intervention and control groups was not statistically different (p=0.240) but on average the control group was 1.217 SE 1.10 kg heavier than the treatment group. **Figure 2 (middle)** illustrates that after nutritional intervention the difference between control and intervention groups remained non-significant (p=0.506; with individual study results on both sides of the reference line) but this time the control group was lighter than the supplemented group by 0.746 SE 1.12 kg. **Figure 2 (lower)** shows that the mean improvement (increase) in weight in the intervention group was greater than in the control group in all eight primary studies, and this was significant in seven of the individual studies. Not surprisingly the overall effect size of the meta-analysis was highly significant, with a mean increase in weight in favor of the intervention group of 1.83 SE 0.262 kg, p<0.001. This corresponds to 3% of initial body weight.

Inspection of the Forest plots (Figure 2) also shows that the variability (indicated by the 95% confidence intervals) between the intervention and control groups, both for the primary studies and the summary effect of all the studies combined, is much smaller for the change in weight (lower plot) than for the baseline weight (upper plot) and end weight (middle plot). Table 3 summarizes these results, and shows that not only is the overall change in

weight significantly greater in the intervention than the control group (by almost 2 kg), the observed variation (SE) at both baseline and end is approximately four times greater than the variation in the change in weight. This is due to a high correlation between pre- and post-weight in both the intervention group and the control group. For the primary studies, r values obtained through meta-analysis were 0.995 (95% CI 0.979, 0.999) for the control group and 0.997 (95% CI 0.974, 1.000) for the intervention group. Simple correlation analysis of mean results (without measures of variation) obtained from the same studies also indicated a very high relationship between baseline and end weight (r = 0.993 and 0.991 for the control and intervention groups respectively and r = 0.985 for the two groups in combination).

A sensitivity analysis (**Figure 3**) was carried out by combining the above eight studies with another five studies that lacked information on variation of weight change, in either the control or intervention groups (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, (SD of the change corresponding to 10% of baseline weight). All 13 primary studies reported a mean weight change in favor of the intervention group (Figure 3). The summary effect size and its significance remained similar (1.69 SE 0.30 kg, 95% CI 1.1, 2.3 kg. p<0.001) to those obtained with the 8 primary studies with complete information (Figure 2). A similar, significant result was also noted when only studies involving ONS were analyzed, 1.63 SE 0.23 kg, p<0.001. The meta-analysis of 13 studies for weight change revealed no evidence of publication bias using funnel plots and tests such as the Begg and Mazumdar (p=0.502) and Egger tests (p=0.686).

When the 13 primary studies were analyzed according to nutritional status (studies with malnourished ('depleted') subjects versus studies that included normally nourished ('non-depleted') subjects) both groups showed a significant increase in weight in favor of the intervention group (non-depleted 1.319 SE 0.368 kg, p<0.001 *versus* depleted 1.940 SE 0.257 kg, p<0.001), but the difference between nourished versus malnourished groups was not

388 significant. Undernourished subjects had a more pronounced response to
389 nutritional support but it should be noted that the two trials including nourished
390 individuals were performed within an exercise rehabilitation program that may
391 have augmented the effects of nutritional support. Meta-regression did not
392 reveal a significant relationship between the magnitude of the weight
393 increase, which favored the intervention group, and the following individual
394 covariates: %IBW at baseline (13 RCTs, slope -0.021 %IBW/kg; p=0.228),
395 target intake from the nutritional intervention (11 RCTs, slope <0.001 kcal/kg;
396 p=0.847), excluding two trials which did not report the target intervention
397 amount (10, 20) and duration of intervention (13 RCTs, slope <0.004 kg/week;
398 p =0.937).
399
400 **Body composition**

401 Assessment of FFM was carried out in 4 studies (11, 13, 24, 37) and although
402 3 out of the 4 trials showed slight improvements in fat-free mass with
403 supplementation (0.17 - 1.0 kg; 0.7 - 2.0 % of baseline), these were not
404 significant. All four studies used different methods to assess FFM
405 (bioelectrical impedance (11, 13), dual energy X-ray absorptiometry (DXA)
406 (24) and skinfold thickness (37)). Seven trials reported data on measured mid-
407 arm muscle circumference (MAMC) (8, 11, 14, 20, 22, 25, 37), an indirect
408 measure of FFM. In six of the seven trials, the mean change favored the
409 intervention group compared to the control group by a mean of 2.4% (range -
410 1.0 - 5.5%, p=0.045, one sample t-test when weighted for sample size). Only
411 3 trials were amenable to meta-analysis (14, 22, 25) and these showed an
412 improvement in favor of the intervention group (effect size 0.296 SE 0.158 cm,
413 p=0.061).

414 Nine studies (8-10, 14, 20-22, 25, 37) used one or more skinfold thicknesses
415 to describe body fat, 7 used triceps skinfolds and 2 studies used the sum of 4
416 skinfold sites (S4SF) (14, 25). It was possible to calculate changes from eight
417 studies (8-10, 14, 20, 21, 25, 37). The mean changes in eight studies favored
418 nutritional support (p=0.008 (sign test)). Two primary studies using S4SF

were appropriate for meta-analysis (14, 25) both of which were significant in their own right. The test of overall effect was +4.2 (SE 1.2) mm, p<0.001.

Maximum voluntary grip strength

Five studies (four with ONS) reported mean changes in handgrip strength, (8, 10, 24, 25, 62) with all studies favoring the intervention group (range 0.3-5.2kg 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% SE 2.7%, p<0.05).

Quality of studies

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

DISCUSSION

This systematic review with meta-analyses aimed to investigate controversies regarding the evidence base for the efficacy of nutritional support in patients with COPD. It found that nutritional support leads to improvements in nutritional intake, body weight, muscle mass (mid-arm muscle circumference) and fat mass (skinfold thickness), as well as an improvement in peripheral muscle strength (handgrip strength). These findings are completely in contrast to 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 intake (dietary intake + nutrition support). The magnitude of these changes are similar to those reported in other reviews involving various clinical conditions including COPD, in which clinical outcomes were improved through nutritional support in (1). It therefore

appears that the discrepancies between the current review and previous ones are mainly due to methodological differences, two of which are clarified below. 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 shows 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 e.g. for body weight a non-significant difference existed between groups at baseline favoring the control group, in order for any improvements to be significant after intervention they would first have to overcome this deficit (masking the magnitude of the effect) and 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-analysis on COPD, the current review included another simpler approach to analyzing randomized controlled trials (t-test and sign test) so that trials without measures of variation could be included. Whilst this approach is not as sophisticated as the standard type of meta-analysis, 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, both with respect to statistical and substantive (clinical) significance of the effect size (energy and protein intake, weight, arm muscle circumference, and grip strength).

A different type of methodological problem concerns the four studies that measured body composition to establish fat- and fat-free mass, all using different techniques (skinfold, bioelectrical impedance, DXA). Currently, there are no reference values for body composition in COPD and the different

methods employed in primary studies have not been adequately validated in this patient group. Although in three out of the four studies the changes favored the intervention group, the effect was generally small (overall ~1% fat-free mass or less than 1% body weight) and statistically not significant. In contrast, a more consistent methodological approach using anthropometric measurements (MAMC) to estimate muscle mass, the largest component of fat-free mass, yielded significant results in 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 or more 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 non-depleted patients who gained weight (>2 kg). However, it was not clear from these studies whether the improved survival rates were adjusted for disease severity, and 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 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 present 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 inter-related. For example, a causal pathway can be proposed, whereby nutritional interventions increase total dietary intake of protein and energy, with resulting increases in weight and muscle mass, which can lead to improvements in muscle strength. The findings of this systematic review are consistent with such a pathway. They are also consistent with a variety of other functional and clinical outcomes previously mentioned (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 three 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 one trial involving only 10 subjects received a score of 4 (21). Second, due to lack of data in the primary papers it was not possible to examine the effect of inflammation on nutritional status and response to nutritional support, nor 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, one involved nocturnal enteral tube feeding and the other involved dietary advice given by a dietitian and provision of milk powder. Therefore, the current evidence is largely based on ONS and it is weak or lacking for other forms of nutritional support, such as snacks, or dietary modification/fortification. This has clinical implications for the first line treatment of malnutrition as The British Dietetic Association currently recommends the first step to improving nutritional intake is done via ordinary foods and fortification with the use of ONS as a secondary step once the initial intervention has failed (67). Finally, of the 13 RCTs, 10 targeted malnourished patients and three targeted malnourished and non-malnourished 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 in those undergoing a rehabilitation program there is an anabolic potential

through increased physical exercise that may augment the effects of additional nutrition.

The fact that 10 of the 13 trials included in the current review were carried out before 2000 may reflect that 2000 coincided with the publication of the first Cochrane Collaboration review, including the majority of the current evidence, concluding that nutritional support has no effect in COPD. This may have dampened interest in the field, however it is hoped the positive findings of this review will highlight the 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 those with infective exacerbations of COPD.

Acknowledgements

Author's contributions

PFC, RJS and ME designed research; PFC performed the systematic review; PFC and ME analyzed the data and reviewed by RJS; ME had primary responsibility for final content. All authors wrote, reviewed and approved the final manuscript.

Competing interests

Peter Collins RD (none declared).

Marinos Elia MD, FRCP (none declared).

Rebecca Stratton PhD RD RNutr is also an employee of Nutricia Ltd.

REFERENCES

1. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence based approach to treatment. Oxford: CABI Publishing (CABI International), 2003.
2. Ezzell L, Jensen GL. Malnutrition in chronic obstructive pulmonary disease. Am J Clin Nutr 2000;72(6):1415-6.
3. Cano NJ, Roth H, Court-Ortune I, et al. Nutritional depletion in patients on long-term oxygen therapy and/or home mechanical ventilation. Eur Respir J 2002;20(1):30-7.
4. Vermeeren MA, Creutzberg EC, Schols AM, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med 2006;100(8):1349-55.
5. Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161(3 Pt 1):745-52.
6. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. Chest 2000;117(3):672-8.
7. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS, White J. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005(2):CD000998.pub2.
8. Efthimiou J, Fleming J, Gomes C, Spiro SG. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988;137(5):1075-82.
9. Fuenzalida CE, Petty TL, Jones ML, et al. The immune response to short-term nutritional intervention in advanced chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;142(1):49-56.
10. Rogers RM, Donahoe M, Costantino J. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. A randomized control study. Am Rev Respir Dis 1992;146(6):1511-7.
11. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med 1995;152(4 Pt 1):1268-74.
12. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(6 Pt 1):1791-7.
13. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonar disease. A placebo-controlled randomzied trial. American Journal of Respiratory and Critical Care Medicine 1995a;152(4):1268-74.
14. Otte KE, Ahlburg P, D'Amore F, Stellfeld M. Nutritional repletion in malnourished patients with emphysema. JPEN J Parenter Enteral Nutr 1989;13(2):152-6.

15. National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre, 2010.
16. Stratton R.J, Elia M. A critical, systematic analysis of the use of oral nutritional supplements in the community. Clinical Nutrition 1999;18(2):29-84.
17. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354.
18. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 The Cochrane Collaboration, 2009.
19. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. CRD: University of York, 2009.
20. Knowles JB, Fairbarn MS, Wiggs BJ, Chan-Yan C, Pardy RL. Dietary supplementation and respiratory muscle performance in patients with COPD. Chest 1988;93(5):977-83.
21. Whittaker JS, Ryan CF, Buckley PA, Road JD. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1990;142(2):283-8.
22. Lewis MI, Belman MJ, Dorr-Uyemura L. Nutritional supplementation in ambulatory patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1987;135(5):1062-8.
23. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12. doi: 0197-2456(95)00134-4 [pii].
24. Steiner MC, Barton RL, Singh SJ, Morgan MD. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. Thorax 2003;58(9):745-51.
25. Weekes CE, Emery PW, Elia M. Dietary counselling and food fortification in stable COPD: a randomised trial. Thorax 2009;64(4):326-31.
26. Borenstein M, Hedges LV, Rothstein HR. Introduction to meta-analysis.: John Wiley & Sons Ltd., 2009.
27. Adams G. Effect of nasogastric feedings on arterial oxygen tension in patients with symptomatic chronic obstructive pulmonary disease. Heart Lung 1988;17(5):594.
28. Aguilaniu B, Goldstein-Shapses S, Pajon A, et al. Muscle protein degradation in severely malnourished patients with chronic obstructive pulmonary disease subject to short-term total parenteral nutrition. JPEN J Parenter Enteral Nutr 1992;16(3):248-54.
29. Akrabawi SS, Mobarhan S, Stoltz RR, Ferguson PW. Gastric emptying, pulmonary function, gas exchange, and respiratory quotient after feeding a moderate versus high fat enteral formula meal in chronic obstructive pulmonary disease patients. Nutrition 1996;12(4):260-5.

30. Baldi S, Aquilani R, Pinna GD, Poggi P, De Martini A, Bruschi C. Fat-free mass change after nutritional rehabilitation in weight losing COPD: role of insulin, C-reactive protein and tissue hypoxia. Int J Chron Obstruct Pulmon Dis 2010;5:29-39.
31. Borum ML, Lynn J, Zhong Z, et al. The effect of nutritional supplementation on survival in seriously ill hospitalized adults: an evaluation of the SUPPORT data. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. J Am Geriatr Soc 2000;48(5 Suppl):S33-8.
32. Broekhuizen R, Creutzberg EC, Weling-Scheepers CA, Wouters EF, Schols AM. Optimizing oral nutritional drink supplementation in patients with chronic obstructive pulmonary disease. Br J Nutr 2005;93(6):965-71.
33. Broekhuizen R, Wouters EF, Creutzberg EC, Weling-Scheepers CA, Schols AM. Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. Thorax 2005;60(5):376-82.
34. Cai B, Zhu Y, Ma Y, et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. Nutrition 2003;19(3):229-32.
35. Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. Nutrition 2003;19(2):120-7.
36. Deacon SJ, Vincent EE, Greenhaff PL, et al. Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;178(3):233-9.
37. DeLetter M. A nutritional intervention for persons with chronic airflow limitation.: Kentucky., 1991.
38. Dore MF, Laaban JP, Orvoen-Frija E, Kouchakji B, Joubert M, Rochemaure J. Role of the thermic effect of food in malnutrition of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155(5):1535-40.
39. Efthimiou J, Mounsey PJ, Benson DN, Madgwick R, Coles SJ, Benson MK. Effect of carbohydrate rich versus fat rich loads on gas exchange and walking performance in patients with chronic obstructive lung disease. Thorax 1992;47(6):451-6.
40. Faager G, Soderlund K, Skold CM, Rundgren S, Tollback A, Jakobsson P. Creatine supplementation and physical training in patients with COPD: a double blind, placebo-controlled study. Int J Chron Obstruct Pulmon Dis 2006;1(4):445-53.
41. Felbinger TW, Suchner U. Nutrition for the malnourished patient with chronic obstructive pulmonary disease: more is better! Nutrition 2003;19(5):471-2.
42. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional supplementation in stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2000(3):CD000998.
43. Ferreira IM, Verreschi IT, Nery LE, et al. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 1998;114(1):19-28.

44. Forli L, Pedersen JI, Bjortuft O, Vatn M, Boe J. Dietary support to underweight patients with end-stage pulmonary disease assessed for lung transplantation. Respiration 2001;68(1):51-7.
45. Fuld JP, Kilduff LP, Neder JA, et al. Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax 2005;60(7):531-7.
46. Goris AH, Vermeeren MA, Wouters EF, Schols AM, Westerterp KR. Energy balance in depleted ambulatory patients with chronic obstructive pulmonary disease: the effect of physical activity and oral nutritional supplementation. Br J Nutr 2003;89(5):725-31.
47. Grigorakos L, Sotiriou E, Markou N, et al. Combined nutritional support in patients with chronic obstructive pulmonary disease (COPD), under mechanical ventilation (MV). Hepatogastroenterology 2009;56(96):1612-4.
48. Hoogendoorn M, van Wetering CR, Schols AM, Rutten-van Molken MP. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? Eur Respir J 2010;35(1):79-87.
49. Iovinelli G, Marinangeli F, Ciccone A, et al. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs medium chain triglycerides. Minerva Anestesiol 2007;73(1-2):65-76.
50. Kubo H, Honda N, Tsuji F, Iwanaga T, Muraki M, Tohda Y. Effects of dietary supplements on the Fischer ratio before and after pulmonary rehabilitation. Asia Pac J Clin Nutr 2006;15(4):551-5.
51. Laviolette L, Lands LC, Dauletbaev N, et al. Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study. J Med Food 2010;13(3):589-98.
52. Marchesani F, Valerio G, Dardes N, Viglianti B, Sanguinetti CM. Effect of intravenous fructose 1,6-diphosphate administration in malnourished chronic obstructive pulmonary disease patients with chronic respiratory failure. Respiration 2000;67(2):177-82.
53. Planas M, Alvarez J, Garcia-Peris PA, et al. Nutritional support and quality of life in stable chronic obstructive pulmonary disease (COPD) patients. Clin Nutr 2005;24(3):433-41.
54. Saudny-Unterberger H, Martin JG, Gray-Donald K. Impact of nutritional support on functional status during an acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;156(3 Pt 1):794-9.
55. Slinde F, Gronberg AM, Engstrom CR, Rossander-Hulthen L, Larsson S. Individual dietary intervention in patients with COPD during multidisciplinary rehabilitation. Respir Med 2002;96(5):330-6.
56. Vargas M, Puig A, de la Maza M, et al. [Patients with chronic airflow limitation: effects of the inspiratory muscle training with threshold load valve, built with appropriate technology, associated to nutritional support]. Rev Med Chil 1995;123(10):1225-34.
57. Vermeeren MA, Wouters EF, Geraerts-Keeris AJ, Schols AM. Nutritional support in patients with chronic obstructive pulmonary disease during hospitalization for an acute exacerbation; a randomized controlled feasibility trial. Clin Nutr 2004;23(5):1184-92.

58. Vermeeren MA, Wouters EF, Nelissen LH, van Lier A, Hofman Z, Schols AM. Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 2001;73(2):295-301.
59. Wilson DO, Rogers RM, Sanders MH, Pennock BE, Reilly JJ. Nutritional intervention in malnourished patients with emphysema. Am Rev Respir Dis 1986;134(4):672-7.
60. Angelillo VA, Bedi S, Durfee D, Dahl J, Patterson AJ, O'Donohue WJ, Jr. Effects of low and high carbohydrate feedings in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. Ann Intern Med 1985;103(6 (Pt 1)):883-5.
61. Global Initiative for Chronic Obstructive Lung Disease (GOLD). A pocket guide to COPD diagnosis, management and prevention. Internet: http://www.goldcopd.com (accessed March 2011).
62. Lewis MI, Belman MJ. Nutrition and the respiratory muscles. Clin Chest Med 1988;9(2):337-48.
63. Ferreira I. Up date nutritional support for patients with COPD. Respiratory Medicine 2008(update 4):127-31.
64. Ferreira I. Chronic obstructive pulmonary disease and malnutrition: why are we not winning this battle? Journal of Pneumologia 2003;29(2):107-15.
65. Collins PF, Stratton RJ, and Elia. M (abstr). Nutritional support and functional outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Clinical Nutrition 2011; 6 (Suppl. 1): 53-54.
66. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. Clinical Nutrition 2008;27(6):793-9.
67. Thomas B. Manual of Dietetic Practice. Third ed. London: Blackwell, 2001.
68. Elia M (ed). The 'MUST' Report: Nutritional Screening for Adults - a multidisciplinary responsibility. Malnutrition Advisory Group (MAG), British Association of Parenteral and Enteral Nutrition (BAPEN): Redditch, 2003.

Figure legend

Figure 1 Study selection process.

Figure 2 Forest plots (Meta-analysis. Random effects model) for 8 studies demonstrating the difference in weight (kg) between control and intervention before (upper) and after intervention (middle) and the change in weight (bottom) induced by the intervention. (* = p<0.0005).

Figure 3 Meta-analysis of the influence of nutritional support on weight (kg) change for 13 studies grouped according to nutritional status (nourished = non-depleted; malnourished = depleted). 4 studies provided nutritional support as part of an exercise rehabilitation program (11, 13, 24, 46). (* = p<0.0005). Overall summary effect (depleted + non-depleted) = 1.69 SE 0.30 kg, p<0.001.

868 **Table 1** Outcome measures of randomized controlled trials included in the
869 systematic review and meta-analyses.
870

Outcome measure	Systematic review		Meta-analysis†	
	No. studies	No. participants treatment/control	No. studies	No. participants treatment/control
Energy intake	11	195/184	5	94/97
Protein intake	5	88/92	2	53/57
Weight	13	225/214	13*	225/214
Body composition	4	115/115	0	-
Mid arm muscle circumference	7	124/125	3	53/51
Skinfold thickness	9	117/107	2	43/40
Handgrip strength	5	87/90	4	77/79

871 * 8 studies if no assumptions were made in order to obtain data on variation
872 (SDs).
873 † Meta-analysis with measures of variation.

Table 2 Summary of the randomized controlled trials included in the systematic review according to intervention.

Study	Sample size Treatment/ control	Characteristics/setting (intervention *vs*. control)	Nutritional intervention (type/prescribed amount/duration)	Control group	Outcome measures	Study quality (Jadad score)†
Oral nutritional supplements						
DeLetter 1991(37) (thesis)	18/17	Malnourished 82.8% IBW Outpatients	ONS (Pulmocare, 1.5kcal/ml) ONS target: 355 kcal/day and 15g protein/day,8 weeks	Usual diet	Energy, Protein, Wt, FFM, MUAC, MAMC, TSF	11000 (2)
Efthimiou et al.,1988(8)	7/7	Malnourished 79.5 *vs*. 81.3% IBW Outpatients 60 *vs*. 64 years	ONS (Build Up, 1.13kcal/ml) ONS target: 640-1280 kcal/day and 36-72g protein/day Encouragement to eat provided to both groups, 12 weeks	Usual diet (with encouragement)	Energy, Protein, Wt, %IBW, MAMC, TSF, HGS	10000 (1)
Goris et al., 2003*(46)	11/9	Nourished and malnourished* 19.8 kg/m^2 (~87% IBW) (19.6 *vs*. 20* kg/m^2) Outpatients 61 *vs*. 62 years	ONS (Respifor, 1.5kcal/ml) ONS target : 563 kcal/day and 28g protein/day. Encouragement to eat provided to both groups, 12 weeks	Usual diet (with encouragement)	Energy, BMI	11000 (2)
Knowles et al., 1988(20)	13/12	Nourished and malnourished 61-108% IBW Outpatients 68 *vs*. 70 years	ONS (Sustacal, 1kcal/ml, 0.043 g protein/kcal) ONS target: To increase total EI by 50%. Weekly encouragement 8 weeks	Usual diet	Energy, Wt, MAMC, TSF	11000 (2)
Lewis et al., 1987(22)	10/11	Malnourished 86.3 *vs*. 84.6 % IBW Outpatients 65 *vs*. 59 years	ONS (Isocal HCN, 2kcal/ml) ONS target: 500-1000 kcal/day and 19-38g protein/day Encouragement 8 weeks	Usual diet	Energy, Protein, Wt, MAMC, TSF, HGS	10000 (1)

Otte et al., 1989(14)	13/15	Malnourished 77 *vs*. 73% IBW outpatients 57 years	ONS (Novo, 1kcal/ml) ONS target: 400 kcal/day and 20g protein/day.Encouragement 13 weeks	Placebo (blinded) (encouragement)	Wt, %IBW, MAMC, skinfold thickness (s4SF)	10111 (4)
Fuenzalida et al., 1990(9)	5/4	Malnourished inpatients and outpatients 78.5% IBW 62 years	ONS (Sustacal HC, 1kcal/ml) ONS target: Up to 1080 kcal/day and up to 46g protein/day 3 wks inpatient + 3 wks outpatient (6 wks total)	Usual diet	Energy, Wt, MAMA, TSF	10000 (1)
Rogers et al., 1992(10)	15/12	Malnourished 78 *vs*. 79% IBW 64 years outpatients (intervention group admitted for first 4 weeks)	ONS (various, self-selected) Tailored to individual dietary habits and dietary advice ONS target: Intakes >1.7 x REE and minimum 1.5g/kg/day protein, 15 weeks	Usual diet	Wt, %IBW, MUAC, TSF, HGS	10000 (1)
Schols et al., 1995(11)	33/38	Nourished 102.4% IBW inpatient PR program (not hospital) mean age unclear	ONS (Mixture of Nutridrink, Protifar, Fantomalt,Oil; seven mixtures of different flavors; 2.1kcal/ml).ONS target: +420 kcal/day and 15g protein/day Encouragement to eat regular meals, 8 weeks	Usual diet (and encouragement with oral diet)	Energy, Wt, MAMC, FM, FFM	10001 (2)
Schols et al., 1995(13)	39/25	Malnourished 84.1% IBW inpatient PR program (not hospital) mean age unclear	ONS (Mixture of Nutridrink, Protifar, Fantomalt,Oil; seven mixtures of different flavors; 2.1kcal/ml). ONS target: +420 kcal/day and 15g protein/day. Encouragement to eat regular meals, 8 weeks	Usual diet (and encouragement with meals)	Energy, Wt, FM, FFM	10001 (2)

Steiner et al., 2003(24)	25/35	nourished/ malnourished ~105% IBW (23.9 *vs*. 23.5 kg/m^2) outpatients PR programme 66 *vs*. 68 years	ONS (Respifor, 1.5kcal/ml) ONS target: +570 kcal/day and 28g protein/day 7 weeks	Placebo (blinded)	Energy, Protein, Wt, FM, FFM, HGS	10111 (4)
Enteral tube feeding						
Whittaker et al., 1990(21)	6/4	malnourished 76 *vs*. 82% IBW Inpatients 71 *vs*. 64 years	Nocturnal ETF (Isocal) ETF target; Feed delivered: at least 1000 kcal/day or 1.7 x REE whichever greater and 34 g protein (Nasoduodenal / jejunal tube feeding),16 days	Placebo ETF (equivalent volume providing <100kcal/night)	Energy, Wt, TSF	11110 (4)
Dietary advice, dietary leaflet plus milk powder						
Weekes et al., 2009(25)	30/25	malnourished ~88%IBW (~19.8 kg/m^2) outpatients 69 years	Tailored dietary advice (DA) + leaflet of information + milk powder DA target: 600 kcal/day (no specific protein target) 6 months	Leaflet of information	Energy, Protein, Wt, MAMC, s4SF, HGS	10001 (2)

** Goris et al., (2003)(46): control group referred to as depleted however, according to UK guidelines the subjects would not be considered to be so (68); Schols et al., (1995) [11, 13]: a third arm investigating anabolic steroids (n 32) was not included in analysis; ONS = oral nutritional supplements; DA = dietary advice (education); ETF = enteral tube feeding; Wt = weight; BMI = body mass index; % IBW = percentage ideal body weight; FM = fat mass; FFM = fat free mass; FFMI = fat-free mass index; MUAC = mid-upper arm circumference; MAMC = mid-arm muscle circumference; MAMA = mid-arm muscle area; TSF = triceps skinfold; s4SF = sum of 4 skinfolds; HGS = handgrip strength; PR program = pulmonary rehabilitation program; REE Resting energy expenditure..*
†The number in parenthesis represents the overall score. The five individual scores represent scores for description and appropriateness of randomization/blinding as well as any description of withdrawals.

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

	Effect size: difference between groups (kg)†	Standard error of the difference (kg)	p value for effect size
Baseline weight (kg)	-1.217	1.036	0.240
End weight (kg)	+0.746	1.122	0.506
Change in weight (kg)	+1.830	0.262	<0.001

† Intervention group minus control group (meta-analysis, random effects model).

Small discrepancies in the sum of the effect size (change in weight) are due to extraction from different data sets provided within manuscripts (Table 3 and Figure 2).