

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

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18 **Abbreviations**

19 COPD – chronic obstructive pulmonary disease

20 DA – dietary advice

21 DXA – dual emission X-ray absorptiometry

22 ETF – enteral tube feeding

23 FFM – fat-free mass

24 IBW – ideal body weight

25 MAMC – mid-arm muscle circumference

26 ONS – oral nutritional supplements

27 RCT – randomized controlled trial

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48 **ABSTRACT**

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

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

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

59 **Results:** Thirteen RCTs (n 439) of nutritional support (dietary advice (1 RCT),
60 oral nutritional supplements (11 RCTs), and enteral tube feeding (1 RCT))
61 versus control were identified. Analysis of the changes induced by nutrition
62 support, as well as those obtained only at the end of the intervention, revealed
63 significantly greater increases in mean total protein and energy intake with
64 nutritional support by 14.8 g and 236 kcal daily. Meta-analyses also
65 demonstrated greater improvements in favor of nutrition support for body
66 weight (1.94 SE 0.26 kg, $p < 0.001$; 11 studies, n 308) and grip strength (5.3%,
67 $p < 0.050$, 4 studies (n 156)), which could not be demonstrated by analysis of
68 values at the end of the intervention, largely due to bias associated with
69 baseline imbalance between groups.

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

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87 **BACKGROUND**

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89 Malnutrition is a common problem in individuals with chronic obstructive
90 pulmonary disease (COPD) with prevalence rates of between 30-60% of
91 inpatients and 10-45% of outpatients (1). Malnourished COPD patients
92 demonstrate greater gas trapping, lower diffusing capacity and a reduced
93 exercise capacity when compared to heavier, non-malnourished patients with
94 a similar severity of disease (2). Observational studies have shown that if
95 nutritional assessment includes only body weight and unintentional weight
96 loss, some patients with normal body weight for height (body mass index
97 (BMI)) would go undetected despite being fat-free mass (FFM) deplete (3, 4).
98 A cross-sectional survey by Cano et al (3) in 300 outpatients with COPD
99 requiring long-term oxygen therapy found 17% of patients to have a low BMI,
100 whereas the prevalence of FFM depletion was more than two-fold higher
101 (38%). This accelerated loss of lean tissue, which may lead to sarcopenia and
102 cachexia, is facilitated by robust inflammatory responses, which may also limit
103 or prevent accretion of lean tissue following nutritional support (5). Wasting of
104 muscles not only detrimentally affects respiratory function, including reduced
105 ability to expectorate to clear a chest infection, but it also promotes fatigability
106 and reduces exercise tolerance and ability to work. However, it has not been
107 possible to establish the exact causality between malnutrition and COPD as
108 malnutrition may be the consequence of a greater disease severity leading to
109 a compromised nutritional intake (loss of body weight) and reduced physical
110 activity (muscle atrophy). Conversely, severe respiratory disease may be
111 preceded by wasting of the muscles involved in breathing. The effect of
112 nutritional support in malnourished patients has also been controversial.
113 Traditional thinking has tended to regard weight loss as an irreversible
114 consequence of COPD, a view that has been reinforced by recent meta-
115 analyses (6, 7). Such analyses have not only concluded that nutritional
116 support has no significant effect on improving anthropometric measures such
117 as weight and muscle mass, but also that it produces no demonstrable
118 improvements in lung function and muscle strength. Several nutritional
119 intervention studies have challenged this idea (8-13) with the result that there
120 remains confusion about whether there is a need to identify and treat

121 malnutrition in COPD. For example, in its 2010 updated report on COPD, the
122 National Clinical Guideline Centre, which develops clinical guidelines for the
123 National Institute for Health and Clinical Excellence (NICE), referred to the
124 failure of a previous meta-analysis to demonstrate significant changes in
125 weight and other outcomes with nutritional support (7), whilst referring to a
126 previous study which demonstrated such improvements with the use of oral
127 nutritional supplements (ONS) (14). Despite these apparent inconsistencies
128 the guideline recommended that ONS should be given to patients with a low
129 BMI (<20 kg/m²) stating this was based on grade D evidence (lower quality)
130 rather than the evidence from published systematic reviews and meta-
131 analyses, and evidence from at least one RCT, which according to the NICE
132 criteria qualify for grade A evidence (15).

133 On examining previous systematic reviews of nutritional support, differences
134 in the methods of analysis were found (1, 6, 7, 16). Unlike previous reviews
135 (1, 6), the latest Cochrane review (7) examined the differences between
136 control and intervention groups at the end of the intervention period, but not
137 the changes induced by either intervention or control, or the impact of
138 baseline imbalance on the final point estimates. Treatment effect within
139 groups as well as information on the presence of any variability between the
140 two groups at baseline, beyond the fact that they were not significantly
141 different, was not reported. Therefore, we undertook a systematic review of
142 randomized controlled trials (RCTs) of nutritional support in patients with
143 COPD to examine such issues more closely and to establish greater clarity of
144 the evidence base for nutritional support in order to inform policy.

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146 **SUBJECTS AND METHODS**

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148 **Search strategy and identification of trials**

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150 The review was planned, conducted and reported according to published
151 guidelines (17-19). A systematic search of the literature was conducted in July
152 2010 to identify RCTs investigating nutritional support in COPD. Potentially
153 relevant studies were identified by searching electronic databases. The

154 databases searched included PubMed (accessed January 7, 2010), Web of
155 Science (accessed January 7, 2010) and OVID (accessed January 7, 2010).
156 In order to identify the largest number of trials a broad search strategy was
157 implemented however trials were restricted to English language citations only.
158 The search terms and mesh headings used included: chronic obstructive
159 pulmonary disease, COPD, emphysema, weight, depletion, diet*, nutrition*,
160 supplement*, protein, carbohydrate, kalori*, feed*, malnutrit*, nourish*, sip
161 feed (ready made liquid oral nutritional supplement), nutrition intervention,
162 nutrition support. A combination of these search terms was also used to
163 identify trials. In addition to electronic database searching, manual searching
164 of previous reviews on nutritional support in COPD as well as references of
165 identified trials was undertaken.
166 Studies were initially screened by reading the abstract and where a study
167 could not be excluded the full article was reviewed. The assessment of trial
168 eligibility was done by two independent assessors (PFC and ME), with two
169 disagreements resolved through discussion with a third assessor (RJS) prior
170 to inclusion.

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172 **Inclusion and exclusion criteria**

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

184

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

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

189

190 **Data extraction**

191

192 Outcome data sought included total nutrient intake (energy and protein), body
193 weight, upper arm anthropometry, body composition, and handgrip strength.

194 Data were collected at baseline and at the end of the intervention phase

195 where possible. Data were collected within data extraction tables allowing

196 data synthesis and analysis from studies with varying populations

197 (nourished/undernourished), intervention types (food strategies, DA, ONS,

198 ETF) and intervention duration. Where data were not reported in the text but

199 illustrated within a figure, the figure was expanded and the data extracted.

200 This was done for energy intake (20, 21) and weight (20, 22). In some papers

201 where mean values were reported without standard deviations (SD) or

202 standard errors (SE), it was possible to calculate SD and SE using reported p

203 values. **In one study assessing handgrip strength (10), data reported in kg**

204 **was considered to be unrealistic and therefore assumed to be in pounds.**

205

206 **Quality assessment**

207

208 The quality of included studies was assessed using the most commonly used

209 scoring system (Jadad scoring system) which comprises three components

210 addressing whether a study is described as randomized, whether the study is

211 described as double blind and whether drop-outs were accounted for. It then

212 scores according to the appropriateness of randomization and blinding (23).

213 Quality assessment of trials was performed by one researcher (PFC) and

214 independently verified by another assessor (RJS). Disagreements were

215 resolved by discussion with a third assessor (ME).

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220 **Synthesis of data and statistical analysis**

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222 Following the extraction of data from included trials, where appropriate and
223 feasible, the results of comparable outcome measures were combined and
224 meta-analysis performed. Statistical analysis was performed using SPSS
225 (version 16.0, Chicago, IL) and meta-analysis (random effects model) using
226 Comprehensive Meta-analysis (Biostat Inc, NJ USA version 2). Analysis was
227 carried out in order to explore differences between groups as well as changes
228 within groups. The effect size was reported as difference in means and
229 standard error. Only a minority of the values reported in the various studies
230 adjusted for baseline values (11, 13, 24, 25). The correlation coefficient
231 between baseline and end measurements was calculated (26). Any computed
232 values that were slightly greater than 1.000 due to rounding of reported or
233 calculated SDs, were assumed to have a value of 1.00.

234 Pre-specified sub-group analysis was performed according to type of
235 nutritional support (oral nutritional supplements (ONS), enteral tube feeding
236 (ETF), dietary advice (DA)) and baseline nutritional status (nourished ('non-
237 depleted') *versus* malnourished ('depleted')). Malnutrition was considered to
238 be present if the mean BMI was less than 20 kg/m² or mean ideal body weight
239 was less than 90%. Meta-regression analysis was used to investigate whether
240 duration or amount of intervention influenced the effect size for each outcome.
241 The overall treatment difference was considered statistically significant if the p
242 value was <0.05 and forest plots were used to present effect size.

243

244 **RESULTS**

245

246 A total of 44 studies were identified as potentially eligible from the literature
247 search (5, 8, 9, 11, 13, 20-22, 24, 25, 27-59) and of these 31 were excluded
248 (**Figure 1**). Exclusion reasons included 4 unsuitable study design (38, 41, 56,
249 58), 5 non-randomized trials (5, 28, 47, 55, 59), 3 target population not
250 suitable (27, 54, 57), 6 no control or placebo group (29, 31, 32, 34, 35, 53), 11
251 unsuitable intervention (30, 33, 36, 39, 40, 43, 45, 49-52), 2 inadequate
252 intervention duration (44, 60). A large randomized trial comparing an intensive
253 management program versus usual care was not included as nutritional

254 support was provided to only a subgroup of patients where indicated in both
255 arms (48). A summary of the search process is shown in Figure 1. The review
256 included 13 RCTs of 439 individuals with COPD randomized into either a
257 treatment group (n = 224) or a control group (n=215), (Table 2). Eight studies
258 were performed completely within the outpatient setting (8, 14, 20, 22, 24, 25,
259 37, 46) three in inpatients (11, 13, 21) and two studies involved both
260 outpatient and inpatient settings (9, 10). Separate analysis of the trial by
261 Schols et al., (11, 13) was performed according to whether the subjects were
262 non-depleted or depleted (Table 2). Patients recruited to the trials had a
263 diagnosis of COPD (<70% predicted FEV₁) and were in a stable condition free
264 from exacerbation. Patients recruited to the trials were classified as having
265 severe COPD, range 30-40% predicted FEV₁ (FEV₁ <50% predicted (stage
266 III)) (61). No study provided results on acute phase proteins or cytokines, and
267 of four studies reporting circulating albumin, three had normal values (20-22)
268 and one close to the lower limit of normal (14).

269

270 The majority of trials (11, n 189 intervention vs. 185 control) provided
271 nutritional support by ONS (8-11, 13, 14, 20, 22, 24, 37, 46), mostly liquid
272 supplements, some of which were specifically formulated for use in patients
273 with COPD (Percentage energy: 60% carbohydrate, 20% fat, 20% protein
274 (Respifor®, Nutricia Ltd) (24, 46), 28.2% carbohydrate, 55.1% fat, 16.7%
275 protein (Pulmocare®, Abbott)) (37). One trial used nocturnal ETF (n 6 vs. 4)
276 (21) and one trial used tailored dietary advice delivered by a dietitian and the
277 provision of a milk powder supplement (n 30 vs. 25) (25). There were no trials
278 of food snacks or food fortification alone. The intervention period ranged from
279 16 days (21) to 6 months (25), with the amount of nutritional support
280 prescribed ranging from 355 kcal/day (37) to 1080 kcal/day (9).

281

282 The majority of studies (n 8) (8-10, 14, 21, 22, 25, 37) were principally of
283 malnourished ('depleted') individuals (BMI < 20 kg/m² or % ideal body weight
284 < 90%). The trials by Schols et al., (11, 13) and Steiner et al., (24) included
285 both nourished and undernourished patients as part of a rehabilitation
286 exercise program and performed, or allowed for, subset analysis according to
287 nutritional status (11, 13, 24). Two other studies included both undernourished

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

291

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

297

298 **Dietary intake**

299

300 Data on total energy intake was available in 11 studies (8, 9, 11, 13, 20-22,
301 24, 25, 37, 46). When limiting analysis to those studies where nutrition was
302 ingested orally meta-analysis was possible on 5 studies (20, 22, 24, 25, 37).
303 There were no significant differences in daily energy intake between
304 supplemented and control groups at baseline (mean difference 11 SE 87 kcal,
305 $p= 0.903$) (20, 22, 24, 25, 37) but at the end of nutritional treatment a
306 significant difference was found in favor of the supplemented group (diet +
307 ONS or DA); 236 SE 71 kcal, $p<0.001$. Information on the mean changes in
308 energy intake was available from 6 studies (after excluding the ETF trial) (21)
309 although measures of variation were available in only 2 trials. In all 6 studies
310 the mean changes in energy intake were greater in the intervention group
311 than control group by 318 SD 157 kcal/day ($p=0.004$, weighted for sample
312 size). Similar significant results were also obtained from the five studies that
313 involved ONS (413 SD 175 kcal/day, $p=0.006$) (8, 20, 22, 24, 37). Two studies
314 were amenable to meta-analysis (24, 25) with the change in intake favoring
315 the supplemented group (234 SE 63 kcal, $p<0.001$). Each study, one involving
316 ONS and the other tailored dietary advice and milk powder supplementation,
317 independently yielded significant results favoring intervention.

318

319 Information on mean changes in protein intake was available in 5 studies (8,
320 22, 24, 25, 37) (but measures of variation were available in only two of them)
321 (24, 25). All 5 studies reported mean daily protein intakes that were greater in

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

328 **Body weight**

329 The trials of nutritional support showed a consistent increase in weight, which
330 was significant in 7 out of 8 individual studies. However, a detailed analysis is
331 undertaken below for comparison of conclusions from previous meta-
332 analyses. Using information on body weight obtained from 8 studies, three
333 sets of meta-analyses were carried out to compare control and intervention
334 groups. These involved baseline weight, end weight, and change in weight (9-
335 11, 13, 14, 21, 24, 25). **Figure 2 (upper)** shows that baseline weight in the
336 intervention and control groups was not statistically different ($p=0.240$) but on
337 average the control group was 1.217 SE 1.10 kg heavier than the treatment
338 group. **Figure 2 (middle)** illustrates that after nutritional intervention the
339 difference between control and intervention groups remained non-significant
340 ($p=0.506$; with individual study results on both sides of the reference line) but
341 this time the control group was lighter than the supplemented group by 0.746
342 SE 1.12 kg. **Figure 2 (lower)** shows that the mean improvement (increase) in
343 weight in the intervention group was greater than in the control group in all
344 eight primary studies, and this was significant in seven of the individual
345 studies. Not surprisingly the overall effect size of the meta-analysis was highly
346 significant, with a mean increase in weight in favor of the intervention group of
347 1.83 SE 0.262 kg, $p < 0.001$. This corresponds to 3% of initial body weight.

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

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

366
367 A sensitivity analysis (**Figure 3**) was carried out by combining the above eight
368 studies with another five studies that lacked information on variation of weight
369 change, in either the control or intervention groups (8, 20, 22, 37, 46). The SD
370 of the final weight for one trial (37) was obtained from a previous review (7).
371 For these studies a very large estimate of the SD of the change was
372 assumed, (SD of the change corresponding to 10% of baseline weight). All 13
373 primary studies reported a mean weight change in favor of the intervention
374 group (Figure 3). The summary effect size and its significance remained
375 similar (1.69 SE 0.30 kg, 95% CI 1.1, 2.3 kg. $p < 0.001$) to those obtained with
376 the 8 primary studies with complete information (Figure 2). A similar,
377 significant result was also noted when only studies involving ONS were
378 analyzed, 1.63 SE 0.23 kg, $p < 0.001$. The meta-analysis of 13 studies for
379 weight change revealed no evidence of publication bias using funnel plots and
380 tests such as the Begg and Mazumdar ($p = 0.502$) and Egger tests ($p = 0.686$).

381
382 When the 13 primary studies were analyzed according to nutritional status
383 (studies with malnourished ('depleted') subjects versus studies that included
384 normally nourished ('non-depleted') subjects) both groups showed a
385 significant increase in weight in favor of the intervention group (**non-depleted**
386 **1.319 SE 0.368 kg, $p < 0.001$ versus depleted 1.940 SE 0.257 kg, $p < 0.001$),**
387 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

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

421

422 **Maximum voluntary grip strength**

423

424 Five studies (four with ONS) reported mean changes in **handgrip** strength, (8,
425 10, 24, 25, 62) with **all studies favoring the intervention group** (range 0.3-
426 5.2kg or 1.3-18.5%). Four studies were amenable to meta-analysis (8, 10, 24,
427 25) with results also favoring the intervention group (+5.3% SE 2.7%, $p < 0.05$).

428

429 **Quality of studies**

430

431

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

434

435 **DISCUSSION**

436

437 This systematic review with meta-analyses aimed to investigate controversies
438 regarding the evidence base for the efficacy of nutritional support in patients
439 with COPD. It found that nutritional support leads to improvements in
440 nutritional intake, body weight, muscle mass (mid-arm muscle circumference)
441 and fat mass (skinfold thickness), as well as an improvement in peripheral
442 muscle strength (handgrip strength). These findings are completely in contrast
443 to those of previous reviews and meta-analyses (6, 7, 42, 63, 64), which
444 reported no significant differences between intervention and control groups.
445 The previous meta-analyses (6, 7, 42) did not examine changes in dietary
446 intake. If total dietary intake in the intervention group did not increase
447 significantly above that of the control group it could explain why these reviews
448 and meta-analyses reported a lack of demonstrable effect of nutritional
449 support on a range of outcomes. However, the current review did examine
450 nutritional intake and found that nutritional support resulted in a significantly
451 greater increase in both protein and energy intake (dietary intake + nutrition
452 support). The magnitude of these changes are similar to those reported in
453 other reviews involving various clinical conditions including COPD, in which
454 clinical outcomes were improved through nutritional support in (1). It therefore

455 appears that the discrepancies between the current review and previous ones
456 are **mainly** due to methodological differences, two of which are clarified below.
457 First, the current study explored the possibility that pre- and post-intervention
458 variability can mask significant within- and between-group changes, even
459 when no significant differences between groups exist at either time point. This
460 analysis shows that the end values, which are mostly unadjusted for baseline,
461 have been used as the basis of calculations in previous meta-analyses.
462 These end values may primarily reflect those at baseline, rather than the
463 changes induced by the intervention e.g. for body weight a non-significant
464 difference existed between groups at baseline favoring the control group, in
465 order for any improvements to be significant after intervention they would first
466 have to overcome this deficit (masking the magnitude of the effect) and
467 variability associated with it. In contrast, when the weight changes induced by
468 the intervention were used as the basis of the calculations there was a
469 substantial increase in precision, resulting in a significant improvement in
470 favor of nutritional support, which was also observed in several of the primary
471 studies. Second, unlike the previous systematic reviews and meta-analysis on
472 COPD, the current review included another simpler approach to analyzing
473 randomized controlled trials (t-test and sign test) so that trials without
474 measures of variation could be included. Whilst this approach is not as
475 sophisticated as the standard type of meta-analysis, which involves measures
476 of variation, it adds a broader quantitative perspective of the evidence base,
477 and supports the overall conclusions of the meta-analyses by considering
478 trials that would not otherwise have been included. It is also more informative
479 and complementary to a narrative description of individual studies. The
480 combined approach adds confidence to the conclusions of the review by
481 supporting all the major findings of the more sophisticated meta-analyses,
482 both with respect to statistical and substantive (clinical) significance of the
483 effect size (energy and protein intake, weight, arm muscle circumference, and
484 grip strength).

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

489 methods employed in primary studies have not been adequately validated in
490 this patient group. Although in three out of the four studies the changes
491 favored the intervention group, the effect was generally small (overall ~1% fat-
492 free mass or less than 1% body weight) and statistically not significant. In
493 contrast, a more consistent methodological approach using anthropometric
494 measurements (MAMC) to estimate muscle mass, the largest component of
495 fat-free mass, yielded significant results in favor of the intervention group.
496 Similarly, use of the raw skinfold measurements also indicated improvements
497 in favor of the intervention group.

498

499 The statistical findings of this systematic review also need to be considered
500 from a clinical perspective. We have previously reported that a weight gain of
501 approximately 2 or more kg in COPD (similar to the magnitude of the mean
502 weight change in favor of the intervention group observed in this review) is
503 likely to be associated with functional and clinical benefits (1). In addition,
504 post-hoc observational analysis of a prospective nutritional intervention trial
505 (11, 13) found that weight loss was reversible through nutritional support, and
506 that a significant improvement in survival occurred in depleted and non-
507 depleted patients who gained weight (>2 kg). However, it was not clear from
508 these studies whether the improved survival rates were adjusted for disease
509 severity, and in addition the analysis is confounded by the inclusion of a
510 number of individuals from the placebo group who gained >2 kg (12).

511 Although the improvements in arm muscle circumference and muscle strength
512 observed in this study are only mild to moderate (~ 3% on average but as
513 high as 7% in one study), in patients who have already become depleted and
514 who have already lost a substantial amount of weight and function (which
515 seems likely for most of the malnourished patient groups included in this
516 meta-analysis), small changes in muscle mass might be expected to produce
517 substantial functional or clinical benefit in those who are close to the threshold
518 of disability. In addition, studies included in the present analysis also reported
519 improvements in other clinically relevant outcomes such as respiratory muscle
520 strength, quality of life and walking distance (65).

521

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

530

531 This review has also identified the limitations of the current literature on
532 nutritional support in COPD. First, the conclusions are based on a limited
533 number of studies (n 13), most that were judged to be of poor quality (n 10),
534 with only three studies considered to be of high quality (score of 4) on the
535 Jadad scale (0 (poorest quality), 5 (highest quality)). A limitation of the Jadad
536 grading system is that it does not account for statistical power, which meant
537 one trial involving only 10 subjects received a score of 4 (21). Second, due to
538 lack of data in the primary papers it was not possible to examine the effect of
539 inflammation on nutritional status and response to nutritional support, nor
540 characterize the subjects as cachectic, according to an endorsed definition
541 (66). Third, of the 13 primary studies included in this systematic review 11
542 involved ONS, one involved nocturnal enteral tube feeding and the other
543 involved dietary advice given by a dietitian and provision of milk powder.
544 Therefore, the current evidence is largely based on ONS and it is weak or
545 lacking for other forms of nutritional support, such as snacks, or dietary
546 modification/fortification. This has clinical implications for the first line
547 treatment of malnutrition as The British Dietetic Association currently
548 recommends the first step to improving nutritional intake is done via ordinary
549 foods and fortification with the use of ONS as a secondary step once the initial
550 intervention has failed (67). Finally, of the 13 RCTs, 10 targeted malnourished
551 patients and three targeted malnourished and non-malnourished patients (11,
552 20, 24) with some trials allowing for subset analysis according to nutritional
553 status (11, 13, 24). Therefore, the evidence base for nutritional support
554 primarily involves malnourished rather than well-nourished patients, although
555 in those undergoing a rehabilitation program there is an anabolic potential

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

558

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

569

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571

572 **Author's contributions**

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

577

578 **Competing interests**

579 Peter Collins RD (none declared).

580 Marinos Elia MD, FRCP (none declared).

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

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835 **Figure legend**

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837 **Figure 1** Study selection process.

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

843

844 **Figure 3** Meta-analysis of the influence of nutritional support on weight (kg)
845 change for 13 studies grouped according to nutritional status (nourished =
846 non-depleted; malnourished = depleted). 4 studies provided nutritional
847 support as part of an exercise rehabilitation program (11, 13, 24, 46). (* =
848 $p < 0.0005$). Overall summary effect (depleted + non-depleted) = 1.69 SE 0.30
849 kg, $p < 0.001$.

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

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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)
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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)
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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)
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* 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).