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Increased energy and/or protein intake improves anthropometry and muscle strength in chronic obstructive pulmonary disease patients: a systematic review with meta-analysis on randomised controlled clinical trials

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Abstract

Compromised nutritional status is associated with a poor prognosis in chronic obstructive pulmonary disease (COPD) patients. However, the impact of nutritional support in this group of patients is controversial. The present study systematically reviewed the effect of energy and or protein supplements or food fortification on anthropometry and muscle strength of COPD patients. We searched MEDLINE (PubMed), EMBASE, Cochrane Library and Scopus for all published randomised clinical trials without language restriction up to May 2021. Three reviewers performed study selection and data extraction independently. We judged the risk of bias by RoB 2 and the certainty of evidence by the GRADE approach. We included thirty-two randomised controlled trials and compiled thirty-one of them (1414 participants) in the random-effects model meta-analyses. Interventions were energy and/or protein oral nutritional supplements or food fortification added to the diet for at least one week. Pooled analysis revealed that nutritional interventions increased body weight (muscle circumference (MD) = 1·44 kg, 95 % CI 0·81, 2·08, I2 = 73 %), lean body mass (standardised mean difference (SMD) = 0·37; 95 % CI 0·15, 0·59, I2 = 46 %), midarm muscle circumference (MD = 0·29 mm^2, 95 % CI 0·02, 0·57, I2 = 0 %), triceps skinfold (MD = 1·09 mm, 95 % CI 0·01, 2·16, I2 = 0 %) and handgrip strength (SMD = 0·39, 95 % CI 0·07, 0·71, I2 = 62 %) compared with control diets. Certainty of evidence ranged from very low to low, and most studies were judged with some concerns or at high risk of bias. This meta-analysis revealed, with limited evidence, that increased protein and/or energy intake positively impacts anthropometric measures and handgrip strength of COPD patients.

Key words: **COPD: Nutrition: Oral Nutrition Therapy: Nutritional Status: Oral Nutrition Supplements: Food Fortification**

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable clinical condition, characterised by persistent respiratory symptoms and progressive airflow limitation due to airway and/or alveolar abnormalities usually resulting from significant exposure to harmful particles or gases[(1)]. At a global level, COPD prevalence is about 12·2 %[(2)], and according to WHO[(3)], the disease was the third leading mortality cause in 2020, responsible for approximately 6 % of all deaths. Recent epidemiological findings indicate an increase in COPD prevalence, associated with the world population ageing[(2)].

In addition to pulmonary involvement, the disease has an extra-pulmonary component evidenced by its systemic effects,

Abbreviations BW, body weight; COPD, chronic obstructive pulmonary disease; FF, fortified food; FM, fat mass; LBM, lean body mass; MD, muscle circumference; ONS, oral nutritional supplements; SMD, standardised mean difference.

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which affect the nutritional status of patients[1]. The nutritional abnormalities manifested mainly as reduced muscle mass, strength and/or function and involuntary weight loss – regardless of BMI values[4], low body weight (BW) and nutrient deficiencies[5] tend to coexist and predict worse outcomes, including poor pulmonary function[6], impaired exercise capacity[7], health-related quality of life[8], higher hospital readmissions[9], length of hospital stay[10,11], health costs[11,12] and mortality rates[11,13,14].

Compromised nutritional status prevalence among COPD patients has been reported to be as high as 45 %[15], depending on assessment method, diagnostic criteria and cutoffs applied, as well the studied population. The pathogenesis of nutritional abnormalities in COPD is complex and involves multiple factors interaction, including increased systemic inflammation and oxidative stress, hypoxia, acute exacerbations, corticosteroids use[16,17], COPD symptoms and patient-related factors such as age, genetics, lifestyle and psychological aspects[17].

The impact of nutritional status on the general condition of COPD patients manifests itself mainly through weight loss and muscle wasting. Unintentional weight loss occurs in almost 50 % of the patients with severe COPD and about 15 % of patients with mild-to-moderate COPD[18]. The decline in pulmonary function[19,20], acceleration in disease progression[16] and impaired resistance to infections can be expected in malnourished COPD patients[17]. In addition, COPD patients present peripheral muscle dysfunction and atrophy, expressed as muscle strength and endurance reduction[21]. Dynamometric parameters are negatively associated with the disease stage[22] and with peak inspiratory flow rate generation[23].

In clinical practice, oral nutritional supplements (ONS) or fortified food (FF) prescription is the therapeutic first choice for patients with or at risk of malnutrition[1,24,25]. However, the first meta-analysis[26] investigating the ONS (energetic supplementation for at least 2 weeks) influence in stable COPD patients outcomes, involving nine trials (n 277 subjects), failed to show consistent benefits on anthropometric measurements, lung function and exercise capacity in patients with COPD. There is a growing literature on the effect of energy and protein-based supplementation or FF on nutritional and clinical outcomes in the COPD population. The latest published meta-analyses of randomised controlled trials (RCT) evaluating the effect of nutritional support in COPD patients concluded that ONS[27–29], mainly in depleted patients, resulted in statistically significant increases in BW, midarm muscle circumference, skinfold thickness and in respiratory muscle strength. However, these reviews have emphasised the need for more high-quality RCT to confirm the role of nutritional support in COPD.

Two of the meta-analyses cited above had several analytical limitations[27,28]. The authors did not report whether a dose–response gradient was performed and did not make the subgroups analysis considering features, including patients' clinical status and energy and/or protein quantities prescribed[27,28]. In addition, since 2012, more than forty references about this topic were published. Furthermore, a more recent systematic review[30] of twenty-two studies (observational and intervention design) investigated the current evidence supporting the use of any nutritional supplementation (vitamins, PUFA, protein, carbohydrates, etc.) to improve outcomes during PR in stable COPD patients, concluded that the results are controversial and pointed to the need for further studies in this area. However, the authors performed only a narrative synthesis of the evidence. The current systematic review aimed to overcome the limitations of previously published systematic reviews addressing the effects of energy and/or protein ONS or FF on anthropometry, body composition and muscle strength of COPD patients and to provide an up-to-date evidence synthesis.

Methods

Study design

This systematic review of RCT was conducted according to the recommendations of Cochrane Handbook for Systematic Reviews of Interventions Version 6·11[31] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[32]. We registered its protocol in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42020207577.

Research question

The objective of this study was to evaluate the available evidence from RCT for the following clinical question: 'What is the effect of dietary interventions with energy and/ or protein ONS and/or FF on nutritional status parameters in COPD patients?'.

We defined the intervention as any nutritional therapy based on energy and/or protein (e.g. creatine or whey protein or amino acid metabolites) and/or amino acids (e.g. isolated or in combination form) ONS or FF added to the diet for one or more week. And we defined the control group as a usual diet or placebo or dietary advice, as reported by authors in the primary studies.

Eligibility criteria

We developed inclusion and exclusion criteria using the Patient, Intervention, Comparators, Outcome, and Study Design (PICOS) method (Table 1). We included all RCT (parallel or crossover design) that assessed the effects of different ONS or FF reporting at least one of the outcomes of interest: (a) BW; (b) lean body mass (LBM); (c) fat mass (FM) and (d) peripheral muscle strength. The studies should be performed in adults over 40 years of age with a COPD diagnosis.

We excluded studies that used the following interventions: 1. Enteral or parenteral nutrition. 2. ONS with different macronutrient distribution between the groups. 3. Comparison between two active ONS, but with distinct energy proposes. 4. Comparison between two protein sources ONS. 5. ONS of antioxidants or nitrate. Moreover, we excluded studies with COPD patients under mechanical ventilation, observational studies, literature reviews, opinion papers, non-randomised trials and abstracts with irretrievable full-text after two attempts to contact the authors.

Search methods for identification of studies

We identified studies through a comprehensive search strategy developed and conducted by S.B. and F.M.S. in the following

Table 1. PICO strategy for inclusion and exclusion criteria

	Criteria	
Parameter	Inclusion	Exclusion
Participants	COPD patients	• Asthma-COPD overlap syndrome • Mechanical ventilation
Intervention (s)	Any nutritional therapy based on energy and/or protein (e.g. creatine or whey protein or amino acid metabolites) and/or amino acids (e.g. isolated or in combination form) ONS or FF added to the diet	• Parenteral nutrition • Enteral feeding • Anabolic steroids or drugs • Different macronutrient distribution and similar energy supply
Comparison (s)	Placebo or habitual/usual diet or no intervention or usual medical standard or nutrition advice/counseling	• Comparison of two levels of energy intake with the same supplement • Comparison of same energetic supply and proportion of macronutrients, differing only in a specific dietary compound source
Outcome (s)	• Body weight • Lean body mass • Fat mass • Peripheral muscle strength	
Study design	Randomised controlled trial	
Time of intervention	One week or more	

electronic databases on 2 September 2020: MEDLINE (PubMed), EMBASE, Cochrane Library and Scopus. There were no restrictions to language or date of publication. We identified appropriate controlled vocabulary (e.g. MeSH terms and Emtree terms) and free-text terms (considering, for example, spelling variants, synonyms, acronyms) in all databases: COPD (population); nutrition therapy, dietary supplements, food supplements and FF (interventions). Supplementary Table S1 presents the full search strategy performed in PubMed. We updated the search on 18 May 2021.

Selection of studies

We screened records by title and abstract in a reference manager software (EndNote X9.3.1, Clarivate Analytics) based on the eligibility criteria by two independent investigators (S.B. and F.M.S.) after the automatic exclusion of duplicates. Bibliographic references of all studies included in this systematic review were hand-searched to identify additional RCT not identified through electronic searching. Also, we used the 'cited by' link function in PubMed for each article included in this review to identify potential eligible RCT. To explore the grey literature, we searched the USA National Library of Medicine (ClinicalTrials.gov). After exclusion of irrelevant records, we assessed full-text articles for eligibility through a standardised electronic form in Google Forms® by each investigator in an independent manner (S.B. and V.K./S.B. and C.F.B.). A third researcher (F.M.S.) resolved any disagreement between reviewers through discussion before inclusion.

Data collection

Data were also independently extracted by three reviewers grouped in pairs (S.B., V.K. and C.F.B.) through a standardised electronic form in Google Forms®, and subsequently cross-checked in conjunction with F.M.S. before computing entries in structured tables in Microsoft Office Excel®. We extracted the following data from each study: first author; year of publication; study design; country of study; intervention time; measured endpoints; inclusion and exclusion criteria; sample size; male percentage of sample; sample mean age; sample mean baseline values of BMI or ideal BW percentage and sample mean baseline forced expiratory volume in the first second in liters and/or predicted%. We also collected information about the setting of nutritional intervention, considering a Pulmonary Rehabilitation setting when the study referred to it as such or if the trial applied an exercise resistance training systematic, regardless of its period and frequency. Detailed descriptions of each intervention were also extracted, as well as baseline and at the end of the intervention measurements of the outcomes values – as mean and standard deviation (SD) in each intervention. When studies report only median values, standard error, CI, interquartile intervals and minimum and maximum, we transformed these values, obtained by the calculations presented in the Cochrane Handbook[31].

Assessment of risk of bias in included studies

The risk of bias within individual trials was assessed by two independent investigators (S.B. and F.M.S.) using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[33], and final judgements were established by consensus. Each study was evaluated with regard to the five following domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome and (5) bias in the selection of the reported result. The overall risk of bias judgement was (a) low risk of bias, if the trial judgement was at low risk of bias for all domains; (b) some concerns, if the trial judgement raised some concerns in at least one domain for this result, but not was at high risk of bias for any domain and

(c) high risk of bias, if the trial judgement was at high risk of bias in at least one domain or some concerns for multiple domains in a way that substantially lowered confidence in the results.

Grading of Recommendations, Assessment, Development and Evaluations assessment of the certainty of the evidence

We assessed the overall certainty of the evidence for each outcome across studies following the Grading of Recommendations, Assessment, Development and Evaluations approach[34]. Certainty of evidence was considered 'high' by default and thereafter downgraded to 'moderate', 'low' or 'very low' depending on the seriousness of the limitations in five criteria: within-study risk of bias, the directness of evidence, inconsistency, the precision of effect estimates and risk of publication bias.

Data synthesis and analysis

We collected the mean change of the data values between post- and pre-treatment of the study (delta) and the SD of this value (delta SD) in each arm of the study for the outcome of interest. If the primary studies did not report mean change in each group, we obtained it by subtracting the post-intervention mean from the baseline. While in delta SD absence, we estimated it assuming a correlation of 0·5 between the baseline and final measures within each group, according to the formula of Follmann *et al.*[35], as proposed in the Cochrane guidelines[31]. Equal variance was assumed among trials and between intervention and controls.

We performed our meta-analyses using DerSimonian and Laird random-effects model regardless of statistical heterogeneity, assuming that there is not one single true effect size across studies due to clinical and methodological diversity between studies. Statistical tests of the significance of τ^2 to choose between fixed and random-effects models are not recommended by the Cochrane Handbook[31] because these tests have undesirable statistical properties and fundamentally should not determine the most appropriate meta-analytic model. Instead, we used our desired inference to guide which model to use. The choice of random effects allows for *unconditional* inferences that are not restricted to the observed studies[36]. In addition, the meta-analytic model was adjusted using the Hartung–Knapp–Sidik–Jonkman method[37] to produce more robust estimates with more conservative results.

We calculated continuous outcomes and presented them as weighted mean differences (WMD) of changes from baseline with means and SD for BW, midarm muscle circumference and triceps skinfold when studies measured outcomes in the same way and as standardised mean difference (SMD) and 95 % CI for LBM and FM, and handgrip and quadriceps strength presented as Hedges' g[31] to combine trials that measure the same outcome but used different units of measurement (e.g. for fat-free mass in kg, percent and kg/m^2). As a rough guide, effect sizes in SMD are interpreted as suggested by Cohen[38]. Small effects 'that cannot be discerned by the naked eye' are around 0·2; medium effects are around 0·5 and large effects 'that can be seen by the naked eye' are around 0·8. For outcomes reported in SMD, we also performed stratified analyses based on the original measurement scale presented as WMD to enhance the interpretability of our results. All results are presented with point estimates along with 95 % CI.

Assessment of heterogeneity, exploratory analyses and publication bias

We assessed the magnitude of statistical heterogeneity using the I^2, accordingly the following interpretation[31]: values from 0 % to 40 % might not be important; 30 % to 60 % may represent moderate heterogeneity; 50 % to 90 % may represent substantial heterogeneity and 75 % to 100 % considerable heterogeneity. Aiming to identify potential sources of heterogeneity and effect mediators, we planned to perform several exploratory subgroup analyses based on: (a) within-study risk of bias, (b) whether the intervention consisted of an energy supplement, protein supplement or energy-protein supplement, (c) clinical status (stable *v.* unstable patients) and (d) baseline overall sample BMI (with 22 kg/m^2 as the cutoff point). Furthermore, we performed univariate meta-regression analyses to further investigate the statistical heterogeneity and to identify potential associations between our primary outcomes and the following study-level covariates as continuous variables: (a) baseline overall sample BMI; (b) intervention duration (in weeks); (c) total amount of prescribed supplement energy content in the intervention arm and (d) total amount of prescribed supplement protein content in the control group. In the presence of crossover RCT design, we temporarily excluded these studies to determine whether its removal altered the results of the meta-analysis. Where there were at least ten studies (BW, LBM, HGS and QS), we used funnel plots to visually assess the risk for publication bias and small-study effects, along with Egger's regression test. The trim-and-fill method was used to adjust for publication bias.

Changes in the review protocol

During the review process, we opted to perform two modifications in the study protocol, due to the high amount of data extracted. First, we restricted the intervention to oral nutritional supplements or food fortification adding energy and/or protein. Second, we opted by presenting the results in two independent publications: the first one is the current and will answer the research question 'effect of nutrition therapy in anthropometric parameters, body composition and peripheral muscle strength in COPD patients', while the second one will answer the research question 'effect of nutrition therapy in clinical and functional outcomes in COPD patients'. It was included in the PROSPERO.

Results

Selection and general characteristics of included studies

We initially identified a total of 3807 articles through database searches, of which 490 were duplicates. We assessed the full text of forty-eight studies for eligibility and included thirty-two[39–70] of them in the current systematic review (Fig. 1). The number of studies included in the meta-analysis varied according to the outcomes. Supplementary Table S2 presents the list of excluded

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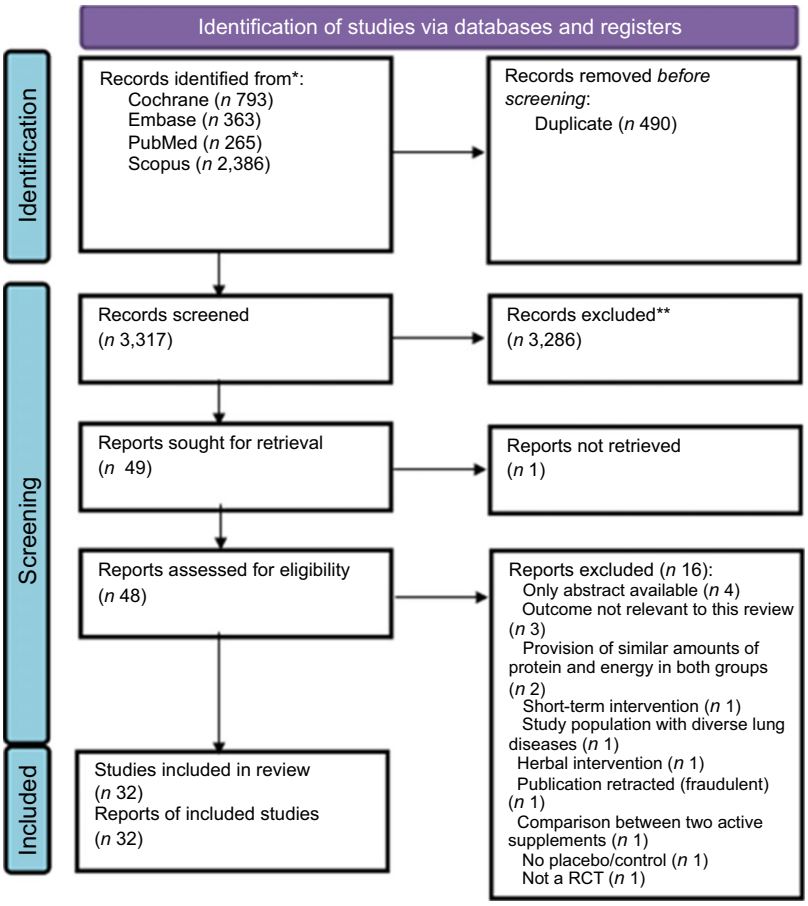

Fig. 1. Flow diagram of study selection.

studies after inspection of the full report and a justification for this exclusion[71–86].

Table 2 presents general features of eligible studies for this systematic review. Trials were conducted in a variety of countries including Canada[51,70], Denmark[57,62], India[58], Iran[64], Italy[48,49,52,56,60], Japan[50,53], Netherlands[41,43,63,69], Spain[66], Sweden[45,59], Switzerland[68], Turkey[55,61], England[40,42,44,46,47,54] and USA[39,65,67]. The studies were published between 1987 [39] and 2020[63,64], most of which (*n* 21; 1252 participants)[41–50,54–61,63,64] from the year 2003. Almost all manuscripts were available in the English language, except for one in German[68] and another in Spanish[66]. Only one study applied a crossover design (twenty-five participants), with eight weeks of the intervention period (no washout period reported)[51]. The remaining thirty-one studies were parallel-group design, with a mean intervention duration of about 12 weeks (ranging from nine days[43] to 12 months[63,68]).

The thirty-two studies included in this review randomised a total of 1680 participants. Of these, we included 1414 in the statistical analysis because most studies reported only an analysis per protocol, excluding participants who dropped out of the study or did not complete the protocol sufficiently. The mean sample size was equal to 52·5 participants (ranging from nine[65] to 233[69]), with a mean age of 67·0 years (ranging from 54·2[58] to 77·7[50]), of which approximately 70 % were male (although in six studies[50,56,66–69] gender information was unavailable). The mean of forced expiratory volume in one second was equal to 42·1 % of predicted values (ranging from 31·4[40] to 56 %[60]) – data not reported in eight studies[39,49,52,57,65,67–69] – and mean of BMI was equal 22·3 kg/m^2 (ranging from 17·2[61] to 30·9 kg/m^2[60]) (data not reported in eleven studies[39,40,53,62,65,66,68–70]).

Twenty-nine studies included COPD patients in stable clinical condition (1554)[39–41,44–47,49–52,54–58,60–64,68], and the majority of them were outpatient based (1256 participants). In twelve studies, the patients participated in a pulmonary rehabilitation program (798 participants)[42,44–46,48,50,53–55,57,59,69]; in three studies, the nutritional intervention started in inpatient base and continued in an outpatient modality after discharge (sixty-five participants),[48,65,67] of which one study (twenty-eight participants) took place in pulmonary rehabilitation in the outpatient part,[48] and in one study (233 participants) the intervention was entirely in an inpatient pulmonary rehabilitation[69]. On the other hand, three studies included only COPD patients admitted to the hospital for an acute exacerbation (126 participants)[43,66,70].

Treatment groups of the included studies received the following interventions, stratified according to ONS composition (online Supplementary Table S3):

(1) Supplement of energy and high protein (≥ 20 % of total energy from protein): it was the intervention in fourteen

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Table 2. General characteristics of included randomised controlled trial (RCT) (*n* 32) investigating the effect of oral nutrition therapy on nutritional parameters of chronic obstructive pulmonary disease (COPD) patients
(Mean values and standard deviations)

Author/year Country	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics							
					Randomised (*n*)	Analysed (*n*)	Age (years)		Male (%)	BMI (kg/m^2)	FEV_1	[% of predict or in liters (l)]	FEV_1/FVC	
							Mean	SD					Mean	SD
Lewis/1987[39] USA	Parallel	Outpatient	8	NR	21	NR	62·1	15·2	71·4	NR	0·8	(0·3) l	31·3	6·3
Efthimiou/1988[40] UK	Parallel	Outpatient	12	NR	14	NR	62	7·9	57·1	NR	31·4 0·7	9·7 % (0·2) l	37·7	9·2
Knowles/1988[51] Canada	Crossover (wash-out NR)	Outpatient	8	NR	25	25	69·0	9·2	84·0	NR	37·0	11·0 %	NR	
Otte/1989[62] Denmark	Parallel	Outpatient	13	Zero	28	28	54·8	7·9	21·4	NR	39·9	17·7 %	NR	
Fuenzalida/ 1990[65] USA	Parallel	Inpatient at CRC (part 1) and outpatient (part 2)	6	Zero	9	9	62·4	5·6	100·0	NR	1·2	(0·9) l	NR	
Entrenas -Costa/ 1991[66] Spain	Parallel	Hospital	2·25	NR	37	NR	NR		NR	NR	33·0	16·4 %	NR	
Rogers/1992[67] USA	Parallel	Inpatient at CRU and outpatient	3	1	28	27	64·0	7·3	NR	NR	1·0	(0·4) l	35·8	7·6
Ganzoni/1994[68] Switzerland	Parallel	Outpatient	48	8 2 (NR)	30	20	66		NR	NR	NR		NR	
Schols/1995[69] Netherlands	Parallel	Inpatient PRP	8	30	233	217	65·0	8·6	NR	NR	NR		NR	
Saudny-Unterberger/ 1997[70] Canada	Parallel	Hospital	2	9	33	24	69·3	8·3	62·5	NR	33·8	13·3 %	NR	
Goris/2003[41] Netherlands	Parallel	Outpatient	12	NR	20	19	62·0	11·0	55·0	19·8	40·0	16·0 %	NR	
Steiner/2003[42] UK	Parallel	Outpatient PRP	7	25	85	60	67·0	8·5	62·4	23·9	34·6 0·9	13·9 % 0·3	NR	
Vermeeren/ 2004[43] Netherlands	Parallel	Hospital	1·29	9	56	47	66·5	8·7	66·1	21·1	34·6	11·5 %	47·5	14·2
Fuld/2005[44] UK	Parallel	Outpatient PRP	12	13	38	25	62·8	8·9	60·5	23·8	45·4 1·1	14·9 % (0·4) l	38·5	10·2
Faager/2006[45] Sweden	Parallel	Outpatient PRP	8	NR	23	23	66·0	6·0	43·5	23·7	43 1·2	17 % (0·6) l	NR	
Deacon/2008[46] UK	Parallel	Outpatient PRP	1·71	20	100	80	68·0	7·8	62·5	26·7	44·1 1·1	20·4 % (0·6) l	NR	
Weekes/2009[47] UK	Parallel	Outpatient	24	29	66	40	68·1	9·8	50·9	19·7	31·8	13·6 %	0·4	0·1
Baldi/2010[48] Italy	Parallel	Inpatient/outpatient PRP	12	2	28	26	71·6	6·0	71·4	20·5	42·5	14·0 %	43·8	14·1
Dal Negro/ 2010[49] Italy	Parallel	Outpatient	12	NR	32	NR	75·0	7·0	78·1	20·2	0·9	(0·2) l	38·5	9·4

Table 2. (*Continued*)

Author/year Country	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics							
					Randomised (*n*)	Analysed (*n*)	Age (years)		Male (%)	BMI (kg/m^2)	FEV_1	[% of predict or in liters (l)]	FEV_1/FVC	
							Mean	SD					Mean	SD
Sugawara/ 2010[50] Japan	Parallel	Outpatient PRP	12	NR	32	32	77·7	6·7	NR	18·3	55·6 1·3	25·7 % (0·6) l	43·8	14·9
Dal Negro/ 2012[52] Italy	Parallel	Outpatient	12	NR	88	NR	74·0	6·7	69·3	20·0	0·8	(0·3) l	38·6	9·74
Sugawara/ 2012[53] Japan	Parallel	Outpatient PRP	12	5	36	31	77·2	5·3	94·4	NR	44·5 1·1	16·9 % (0·4) l	39·0	10·6
Constantin/ 2013[54] UK	Parallel	Outpatient PRP	8	9	59	50	68·0	7·2	55·9	25·9	46·8 1·1	16·9 % (0·0) l	40·2	10·1
Gurgun/2013[55] Turkey	Parallel	Outpatient PRP	8	NR	30	NR	65·4	18·0	93·3	18·9	41·9	28·3	51·2	24·2
Marinari/2013[56] Italy	Parallel	Outpatient	8	NR	55	NR	73·5	8·2	NR	30·1	42·3	12·3 %	NR	
Ahnfeldt-Mollerup/ 2015[57] Denmark	Parallel	Outpatient PRP	9	18	53	35	68·4	8·7	43·4	23·8	NR		NR	
Khan/2016[58] India	Parallel	Outpatient	12	5	60	60	54·2	10·3	90	18·0	51·6	11·8 %	67	8·1
van de Bool/ 2017[59] Netherlands	Parallel	Outpatient PRP	16	8	81	81	62·5	8·2	50·6	22·7	55·1	19·8 %	43·1	12·2
De Benedetto[60] Italy	Parallel	Outpatient	8	NR	90	90	73	7·0	75·5	30·9	56	19·9 %	NR	
Degirmenci/ 2018[61] Turkey	Parallel	Hospital and out-patient	12	23	63	40	74·7	10·3	97·5	17·2	41·4	20·9 %	81	28·5
van Beers/ 2020[63] Netherlands	Parallel	Outpatient	48	20	81	81	62·5	8·2	51	22·7	55·1	19·6 %	43·1	12·2
Ahmadi/2020[64] Iran	Parallel	Outpatient	8	2	46	44	62·8	7·1	100·0	21·1	43·8	15·4 %	NR	

NR, not reported; FEV_1, forced expiratory volume in 1 s; FVC, forced vital Capacity; CRC, Clinical Research Centre; CRU, Clinical Research Unit; PRP, pulmonary rehabilitation program.
* There is one other group in this study not included in our analysis that was not considered for us since the intervention in this study arm was anabolic steroid-based.

RCT (659 participants)[40,43,51,53,54,57,59,61,63,67,68], the mean energy density was 1·3 kcal/ml (ranging from 0·54 to 1·5) and it provided a mean of 528·6 kcal (ranging from 312·5[59,63] to 960[40] kcal) and 27·2 grams of protein (ranging from 10·4[63] – 54[40] g protein);

(2) Protein-based and amino acids supplements: it was the intervention in ten studies (560 participants)[44–46,48,49,52,56,58,60,64], of which five used creatine (306 participants)[44–46,56,60], three prescribed essential amino acids mixture (148 participants)[48,49,52], one used whey protein (forty-six participants)[64], one prescribed a 'protein powder', but did not specify its sources (sixty participants)[58];

(3) Energy supplement (< 20 % of total energy from protein): it was the intervention in eight studies (461 participants)[39,47,50,55,65,66,69,70], the mean of ONS energy density was 1·6 kcal/ml (ranging from 1·0[50] to 2·1[69]) and it provided mean daily energy of 565 kcal (ranging from 400[50] to 720[39,65]) and 18·9 grams of protein (ranging from 9·0[47] to 28·8[65]).

Most comparisons involved ONS *v.* placebo[42–46,49,54,56,59,60,62,63,69], but we found a variety of other comparisons including usual diet[39,40,51,58,67] hospital diet[65,66,70], nutritional advice[41,64], leaflet providing advice (content was never discussed)[47], monthly general education program[50], normal energy diet[68], normal meals alone with dietary instruction[53] and the remaining three trials not informed the comparators[48,57,61] (online Supplementary Table S3).

Eighteen studies assessed the compliance with the study protocol[42,43,45–48,53–55,57–59,62–64,68,69], of which half of them reported results[42,43,46–48,59,61,64,65] (online Supplementary Table S3) with inconsistent definitions and measurement units, which made it impossible to estimate the general rates of patient compliance among the studies that report it. Nineteen papers did not inform regarding funding.

Risk of bias in primary studies

Supplementary Fig. S1 summarises the bias risk assessment results for the studies included in this systematic review accordingly RoB 2 tool. Our judgement of the overall risk of bias did not result in any study ranked as 'low', while we judge fourteen studies as 'some concerns'[39,41–43,48–50,52,56,58–60,64,69] and eighteen studies as 'high' risk of bias[40,44–47,51,53–55,57,61–63,65–68,70].

In the first domain of RoB 2 (bias arising from the randomisation process) all studies were judged as 'some concerns', except one study judged as 'high' risk of bias[66]; while in the second domain (deviations from intended interventions), twelve studies were judged as 'low'[42–47,49,54,56,59,60], fifteen as 'some concerns'[39,41,48,50,53,55,57,61,63,64,67–70] and the five remaining studies as 'high'[40,51,62,65,66]. Regarding to missing outcome data (third domain), nine studies were judged as 'low'[39,41,43,48,50,58,62,64,69], fifteen as 'some concerns'[40,42,49,51–57,65–67] and eight as 'high'[44–47,61,63,68,70]. In addition, all studies were considered as having low risk for the domain measurement of the outcome, while twenty-eight studies were assessed as 'low'[39–50,52,55–67,69,70] and four studies as 'some concerns'[51,53,54,68] in fifth domain (selection of the reported results). Supplementary Table S4 presents the reasons for these judgments.

Effect of intervention on body weight

Twenty-seven RCT (1164 participants)[39–53,55,58,59,62–70] measured BW as an outcome, of which twenty-six[39–53,55,58,59,62–67,69,70] of them reported data that could be pooled. We found a statistically significant benefit of nutritional intervention on BW using the random-effects model (MD = 1·44 kg, 95 % CI 0·81 to 2·08, $P < 0·01$, $I^2 = 73$ %, (1144 participants)) (Fig. 2). We excluded Ganzoni *et al.*'s study[68] from the meta-analysis because it did not report sufficient information to impute the measures of dispersion of the treatment effect. In this study, the intervention group (*n* 15) received advice to follow a high-energy diet (energy supply corresponding to 1·8 times the basal metabolic rate, i.e. ~ 2840 kcal/d) supplemented with the ONS (Fresubin®, OP 200 ml), once or twice a day, while the control group (*n* 15) followed a normal energy diet. Although the intervention group obtained more weight gain (7·0 kg), the difference relative to the control group (weight gain of 2·3 kg) was not statistically significant ($P = 0·08$).

In sensitivity analysis, the exclusion of the only crossover RCT did not materially change the results (MD = 1·18 kg, 95 % CI 0·66 to 1·70, $P < 0·01$, $I^2 = 55·1$ %, (1094 participants)). Table 3 describes the results of the subgroup analysis for the BW outcome. The magnitude of BW gain was significantly higher in BMI < 22 kg/m^2 subgroup compared with BMI ≥ 22 kg/m^2 subgroup, and it was also significantly higher in studies conducted with stable COPD patients compared with unstable COPD patients. On the other hand, we did not observe significant differences for BW between the three intervention subgroups, neither between the studies grouped by the risk of bias of primary studies. In univariate meta-regression analyses (online Supplementary Table S5) for between-group differences in BW, the amount of energy and protein prescribed, as well as the length of intervention, were able to partially explain the observed statistical heterogeneity ($R^2 = 16·66$ to 45·95 %), but were not statistically significantly associated with between-group changes in BW. Univariate meta-regression analysis using baseline BMI as the predictor variable did not explain the heterogeneity and was not significantly associated with between-group differences in BW.

Visual inspection of the funnel plot (online Supplementary Fig. S2) suggests no substantial asymmetry, with non-significant Egger's test (intercept: 0·34, (CI 95 % −0·83, 1·52); $P = 0·57$).

We judged the certainty of evidence regarding this outcome as low, due to within-study risk of bias that was classified as some concerns in twelve studies[39,41–43,48–50,52,59,64,69] and high in fourteen studies[40,44–47,51,53,55,62,63,65–67,70], the persistent inconsistency that could not be explained in subgroup analyses or meta-regression and the low precision of effect estimates (Table 4).

Effect of nutritional interventions in lean body mass

Sixteen RCT (933 participants)[42–44,46,48–50,52,53,55,56,59,60,63,64,69] measured LBM as an outcome; however, only thirteen

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lewis, 1987	1·00	3·00	10	0·22	4·00	11	2·8%	0·78 [–2·23, 3·79]
Efthimiou, 1988	4·20	3·50	7	–0·70	9·57	7	0·6%	4·90 [–2·65, 12·45]
Knowles, 1988	0·97	11·63	25	–1·38	11·46	25	0·8%	2·35 [–4·05, 8·75]
Otte, 1989	1·52	1·41	13	0·16	0·93	15	7·0%	1·36 [0·46, 2·26]
Fuenzalida, 1990	4·44	6·82	5	3·21	6·78	4	0·5%	1·23 [–7·71, 10·17]
Entrenas Costa, 1991	–1·20	10·34	16	–1·80	11·60	21	0·7%	0·60 [–6·49, 7·69]
Rogers, 1992	1·70	5·10	15	0·40	8·26	12	1·2%	1·30 [–4·04, 6·64]
Schols, 1995	2·03	10·28	72	–0·08	11·96	63	2·0%	2·11 [–1·68, 5·90]
Saudny-Unterberger, 1997	0·21	2·54	14	–0·08	0·63	10	5·8%	0·29 [–1·10, 1·67]
Goris, 2003	0·20	1·20	11	0·30	2·35	8	4·9%	-0·10 [–1·88, 1·68]
Steiner, 2003	0·63	1·45	25	–0·58	1·54	35	7·3%	1·21 [0·45, 1·97]
Vermeeren, 2004	1·37	1·30	23	1·12	1·20	24	7·4%	0·25 [–0·47, 0·97]
Fuld, 2005	1·10	2·52	14	0·10	0·88	11	5·7%	1·00 [–0·42, 2·42]
Faager, 2006	1·24	16·28	13	1·04	13·69	10	0·2%	0·20 [–12·06, 12·46]
Deacon, 2008	0·70	1·67	38	0·20	1·92	42	7·2%	0·50 [–0·29, 1·29]
Weekes, 2009	2·01	1·10	22	–0·94	0·60	18	7·7%	2·95 [2·41, 3·49]
Baldi, 2010	3·80	2·60	13	–0·10	1·10	13	5·4%	3·90 [2·37, 5·43]
Dal Negro, 2010	5·53	8·79	16	–1·07	6·44	16	1·2%	6·60 [1·26, 11·94]
Sugawara, 2010	1·40	5·30	17	–1·00	5·85	15	1·9%	2·40 [–1·49, 6·29]
Dal Negro, 2012	5·53	8·99	44	–1·89	6·60	44	2·5%	7·42 [4·12, 10·72]
Sugawara, 2012	1·30	8·30	17	–0·20	4·30	14	1·5%	1·50 [–3·04, 6·04]
Gurgun, 2013	1·10	0·90	15	0·60	0·70	15	7·6%	0·50 [–0·08, 1·08]
Khan, 2016	1·48	3·30	30	–0·17	2·50	30	5·6%	1·65 [0·17, 3·13]
van de Bool, 2017	1·90	11·02	42	0·30	10·62	39	1·4%	1·60 [–3·11, 6·31]
van Beers, 2020	0·64	3·43	42	–0·90	3·37	39	5·6%	1·54 [0·06, 3·02]
Ahmadi, 2020	0·52	2·19	23	0·64	2·68	21	5·6%	–0·12 [–1·57, 1·33]
Total (95% CI)			582			562	100·0%	1·44 [0·81, 2·08]

Heterogeneity: $Tau^2 = 1·23$; $\chi^2 = 94·26$, df = 25 ($P < 0·01$); $I^2 = 73\%$

Test for overall effect: $P < 0·01$

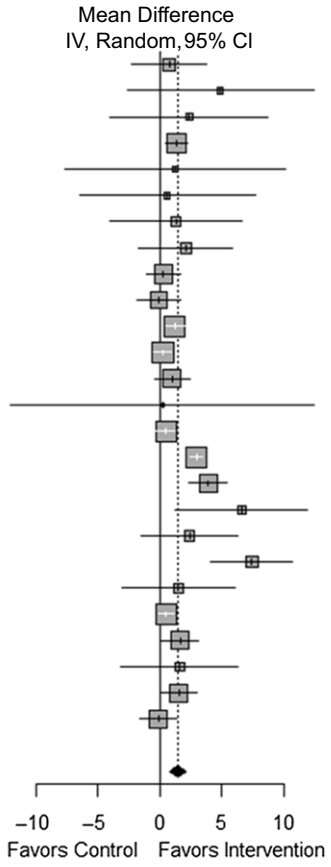

Fig. 2. Forest plot diagrams for body weight.

(*n* 657)[43,44,46,48–50,52,53,55,56,60,63,64] studies included data that could be pooled of a statistically significant increase in LBM with the nutritional intervention (SMD = 0·37; 95 % CI, 0·15, 0·59, $P < 0·01$, I2 = 46 %) (Fig. 3). LBM was measured using bioelectrical impedance (BIA) in eight trials[43,46,49,52,55,56,60,64], while three trials used dual-energy x-ray absorptiometry (DEXA)[44,48,63], and two trials[50,53] did not report body composition assessment methods. Of the three studies that could not be included in the meta-analysis because they used different units to report LBM, two studies[59,69] found no significant improvement in the proportion of LBM (presented as fat-free mass/kg[69] and skeletal muscle mass[59]) for the ONS group, while one study[42] observed clinically relevant LBM gains only in the placebo group.

In subgroup analysis, we investigated whether the method of LBM measurement was associated with the observed results, which were not statistically significantly different between subgroups ($P_{for\ interaction} = 0·48$). We also performed subgroup analysis for LBM according to BMI, intervention and risk of bias. No clinically relevant differences in intervention effects between these three subgroups were found, with non-significant tests for subgroup differences (Table 3).

Visual inspection of the funnel plot and Egger's test (intercept: −3·63, (CI 95 % 1·39, 5·86); $P = 0·0087$) were compatible with publication bias (online Supplementary Fig. S3). There was very-low quality evidence (risk of bias in primary studies, heterogeneity and publication bias) for LBM outcome (Table 4). The results of the trim-and-fill results suggest that four trials might have been missing such that their addition would change the overall effect on LBM to (number of studies combined: k = 17 (with added four studies); SMD = 0·17 (95 % CI, −0·0782, 0·4267, $P = 0·1762$)).

Regarding midarm muscle circumference, the pooled differences in change from baseline values of seven studies (325 participants)[39,40,47,51,62,66,69] resulting in a small, but statistically significant increment circumference (MD 0·29 mm^2; 95 % CI 0·02 to 0·57, $P = 0·03$, $I^2 = 0$ %) in the intervention group as compared with the control group (Fig. 4). There was low-quality evidence (due to risk of bias and unfeasibility to estimate the risk of publication bias) (Table 4) for this outcome.

Effect of intervention in fat mass

Nine RCT (*n* 523)[42–44,46,50,53,59,60,63] reported data on FM. Pooled results showed no statistically significant differences for this outcome (SMD = 0·16; 95 % CI, −0·07, 0·40, $P = 0·18$, $I^2 = 43$ %) (Fig. 5). The certainty of evidence for FM was very low (due to risk of bias, imprecision, heterogeneity and the unfeasibility to investigate risk of publication bias) (Table 4).

We included six trials (158 participants)[39,40,51,65–67] in the analysis of nutritional intervention effects on triceps skinfold. The pooled MD was 1·09 mm (95 % CI, 0·01 to 2·16, $P = 0·05$,

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Table 3. Subgroup analysis for randomised controlled trials on body weight, lean mass, handgrip strength and quadriceps strength (Numbers and percentages; odd ratios and 95 % confidence intervals)

	Body weight						Lean body mass					
Analysis	Studies (*n*)	Patients (*n*)	MD	95 % CI	I^2, %	*P*-value	Studies (*n*)	Patients (*n*)	SMD	95 % CI	I^2, %	*P* value
BMI												
< 22 kg/m^2	9	384	2·22	0·41, 4·03	90	0·09	7	295	0·37	0·07, 0·67	36	0·87
≥ 22 kg/m^2	7	295	0·85	0·37, 1·33	36	5	331	0·42	0·01, 0·82	68		
Clinical status*												
Stable	23	1,036	1·64	0·93, 2·34	73	< 0·01	–			–	–	–
Unstable	3	108	0·26	0·16, 0·36	Zero	–			–	–		
Type of intervention												
Energy	8	328	1·38	0·41, 2·35	83	0·24	2	62	0·56	–0·03, 1·15	24	0·38
Energy and high protein	10	438	0·90	0·44, 1·35	Zero	3	155	0·18	–0·14, 0·50	Zero		
Protein based	8	378	2·22	0·04, 4·40	81	8	440	0·44	0·12, 0·77	62		
Overall risk of bias												
Some concerns	12	645	1·89	0·61, 3·18	74	0·38	8	410	0·36	0·06, 0·66	53	0·85
High	14	499	1·28	0·75, 1·80	74	5	247	0·40	0·04, 0·77	45		
Pulmonary rehabilitation												
Yes	10	523	1·27	0·56, 1·98	53·3	0·65	6	224	0·44	0·09, 0·79	34·8	
No	16	621	1·54	0·61, 2·47	77·6	7	433	0·33	0·03, 0·63	57·3	0·64	
Study design†												
Crossover	1	50	2·35	–4·05, 8·75	Zero	0·78	–			–	–	–
Parallel	25	1,094	1·44	0·81, 2·06	74·5	–			–	–		

	Handgrip strength						Quadriceps strength					
Analysis	Studies (*n*)	Patients (*n*)	SMD	95 % CI	I^2, %	*P*-value	Studies (*n*)	Patients (*n*)	SMD	95 % CI	I^2, %	*P*-value
BMI												
< 22 kg/m^2	5	154	0·41	–0·13, 0·95	77	0·75	8	435	0·13	–0·09, 0·35	24	0·51
≥ 22 kg/m^2	3	107	0·30	–0·08, 0·69	Zero	2	75	0·30	–0·16, 0·76	Zero		
Clinical status												
Stable	10	383	0·50	0·16, 0·84	59	0·04	9	467	0·16	–0·05, 0·38	25	0·88
Unstable	2	65	–0·13	–0·62, 0·36	Zero	1	43	0·11	–0·48, 0·71	NA		
Type of intervention												
Energy	3	86	–0·02	–0·45, 0·40	Zero	0·19	2	32	0·29	–0·21, 0·78	4	0·82
Energy and high protein	5	183	0·42	0·00, 0·84	45	5	315	0·12	–0·11, 0·34	Zero		
Protein based	4	179	0·60	–0·04, 1·24	73	3	128	0·18	–0·64, 1·00	74		
Overall risk of bias												
Some concerns	5	257	0·45	–0·07, 0·98	75	0·68	4	116	0·25	–0·02, 0·52	Zero	0·45
High	7	191	0·32	–0·08, 0·72	44	6	294	0·09	–0·22, 0·40	38		
Pulmonary rehabilitation												
Yes	3	107	0·30	–0·08, 0·69	Zero	0·68	8	386	0·19	–0·06, 0·45	31	0·51
No	9	341	0·42	0·01, 0·84	69·8	2	124	0·05	–0·30, 0·40	Zero		

MD, mean difference; SMD, standard mean difference.
* Analyses for lean body mass did not perform since none study that reported this outcome was conducted with unstable patients.
† Analyses for lean body mass did not perform since none study that reported this outcome was a crossover randomised controlled trial.

Table 4. Summary of findings: nutritional supplementation or food fortification compared with placebo or usual diet or no intervention effect on nutritional parameters of chronic obstructive pulmonary disease (COPD) patients

Population: COPD patients
Settings: One RCT was inpatient; three RCT were at hospital; three RCT combined inpatient and outpatient; twenty-five RCT were outpatient
Intervention: nutritional supplementation or food fortification
Comparison: placebo or usual diet or no intervention

Outcomes	Studies (*n*)	Patients (*n*)	Compiled studies	Heterogeneity (I^2, %)	Effect size		Quality of evidence (GRADE)
					MD[1]/ SMD[2]	95 % CI	
Body weight (kg)	26	1144	(39–53,55,58,59,62–67,69,70)	73	1·44	0·81, 2·08[1]	⊕◯◯◯ LOW§
Midarm muscle circumference (cm)	7	325	(39,40,47,51,62,66,69)	Zero	0·29	0·02, 0·57[1]	⊕◯◯◯ LOW‖
Triceps skinfold (mm)	6	158	(39,40,51,65–67)	Zero	1·09	0·01, 2·16[1]	◯◯◯◯ VERY LOW¶
Lean body mass*	13	657	(43,44,46,48–50,52,53,55,56,60,63,64)	46	0·37	0·15, 0·59[2]	◯◯◯◯ VERY LOW**
Fat mass (kg)	9	523	(42–44,46,50,53,59,60,63)	43	0·16	–0·07, 0·40[2]	◯◯◯◯f VERY LOW††
Handgrip strength†	12	448	(39,40,42–45,47,49,61,64,67,70)	62	0·39	0·07, 0·71[2]	◯◯◯◯ VERY LOW‡‡
Quadriceps strength‡	10	510	(42–46,50,54,57,59,63)	15	0·15	–0·04, 0·35[2]	⊕◯◯◯ LOW§§

MD, mean difference; SMD, standard mean difference; GRADE, Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence(42).

* Parameters and units of measurement applied in the studies for lean body mass: free-fat mass (FFM) in kilogram (kg) (*n* 8 studies)(41,42,44,46,47,50,51,62), FFM index in kilogram per square meter (kg/m^2) (*n* 3 studies)(48,53,54), FFM (%) (*n* 1 study)(58) and appendicular skeletal muscle mass in kg (*n* 1 study)(61).

† Units of measurement applied in the studies for handgrip strength: kilogram-force (kgf) (*n* 5 studies)(10,16,21,23,24) and kilogram (kg) (*n* 7 studies)(11,19,22,26,30,39,41).

‡ Units of measurement applied in the studies for quadriceps strength: kgf (*n* 1 study)(21), kg (*n* 1 study)(29), Newton-meter (*n* 7 studies)(22–25,32,37,40) and Newtons per kg (*n* 1 study)(35).

§ Due to within-study risk of bias that was classified as some concerns in twelve studies(39,41–43,48–50,52,58,59,64,69), high in fourteen studies(40,44–47,51,53,55,62,63,65–67,70) and the inconsistency that could not be explained in the subgroup analysis and meta-regression and the imprecision of effect estimates.

‖ Due to within-study risk of bias that was classified as some concerns in two studies (39,69), high in five studies(40,47,51,62,66) and the unfeasibility of investigate risk of publication bias because of the reduced number of studies.

¶ Due to within-study risk of bias that was classified as some concerns in one study(39), high in five studies(40,51,65–67) and the imprecision of effect estimates and the unfeasibility of investigate risk of publication bias because of the reduced number of studies.

** Due to within-study risk of bias that was classified as some concerns on eight(43,48–50,52,56,60,64), studies and high in five studies(44,46,53,55,63) and the moderate heterogeneity that could not be explained in subgroup analysis and meta-regression, and publication bias.

†† Due to within-study risk of bias that was classified as some concerns in five studies(42,43,50,59,60), high in four studies(44,46,53,63) and the imprecision of effect estimates, the moderate heterogeneity and the unfeasibility of investigate risk of publication bias because of the reduced number of studies.

‡‡ Due to within-study risk of bias that was classified as some concerns in five studies(39,42,43,49,64), high in seven studies(40,44,45,47,61,67,70) and the inconsistency that could not be explained in the subgroup analysis and meta-regression and the imprecision of effect estimates.

§§ Due to within-study risk of bias that was classified as some concerns in four studies(42,43,50,59), high in six studies(44–46,54,57,63) and the imprecision of effect estimates.

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std· Mean Difference IV, Random, 95% CI
Vermeeren, 2004	−0·50	2·60	21	−0·40	2·70	22	7·6%	−0·04 [−0·64, 0·56]
Fuld, 2005	2·00	1·64	14	0·40	0·89	11	4·7%	1·13 [0·27, 1·99]
Deacon, 2008	0·90	2·43	38	0·80	2·64	42	10·4%	0·04 [−0·40, 0·48]
Baldi, 2010	1·50	2·60	13	−0·10	2·30	13	5·4%	0·63 [−0·16, 1·42]
Dal Negro, 2010	3·59	4·29	16	−0·13	4·19	16	6·0%	0·86 [0·13, 1·58]
Sugawara, 2010	0·30	0·92	17	0·00	1·18	15	6·3%	0·28 [−0·42, 0·98]
Dal Negro, 2012	3·66	4·52	44	3·80	4·33	44	10·8%	−0·03 [−0·45, 0·39]
Sugawara, 2012	0·80	5·50	17	−0·10	2·49	14	6·2%	0·20 [−0·51, 0·91]
Gurgun, 2013	0·60	0·50	15	0·10	0·60	15	5·7%	0·88 [0·13, 1·64]
Marinari, 2013	3·70	5·50	30	−0·60	1·70	25	8·1%	1·00 [0·44, 1·57]
De Benedetto, 2018	1·10	4·40	45	1·00	4·40	45	10·9%	0·02 [−0·39, 0·44]
van Beers, 2020	0·17	1·36	42	−0·22	1·31	39	10·4%	0·29 [−0·15, 0·73]
Ahmadi, 2020	2·85	4·65	23	0·78	2·62	21	7·6%	0·53 [−0·07, 1·14]
Total (95% CI)			335			322	100·0%	0·37 [0·15, 0·59]

Heterogeneity: $Tau^2 = 0·07$; $\chi^2 = 22·09$, df = 12 ($P = 0·04$); $I^2 = 46\%$
Test for overall effect: $P < 0·01$

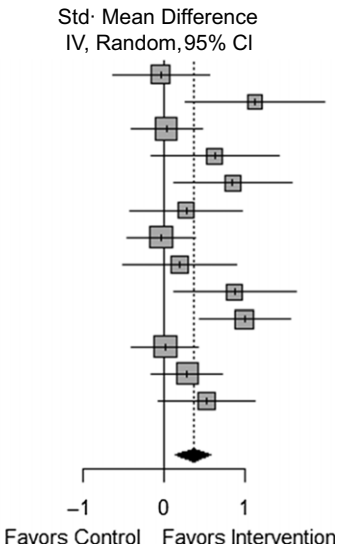

Fig. 3. Forest plot diagrams for lean body mass.

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lewis, 1987	0·10	1·61	10	0·40	3·00	11	1·8%	−0·30 [−2·33, 1·73]
Efthimiou, 1988	0·70	0·80	7	0·10	3·00	7	1·4%	0·60 [−1·70, 2·90]
Knowles, 1988	0·82	3·16	25	1·50	3·06	25	2·5%	−0·68 [−2·40, 1·04]
Otte, 1989	0·10	0·54	13	−0·03	0·58	15	42·9%	0·13 [−0·29, 0·55]
Entrenas Costa, 1991	−0·10	1·83	16	−0·50	2·15	21	4·5%	0·40 [−0·88, 1·68]
Schols, 1995	0·40	1·70	72	−0·10	1·80	63	21·0%	0·50 [−0·09, 1·09]
Weekes, 2009	−0·10	0·90	22	−0·60	0·82	18	25·9%	0·50 [−0·03, 1·03]
Total (95% CI)			165			160	100·0%	0·29 [0·02, 0·57]

Heterogeneity: $Tau^2 = 0$; $\chi^2 = 3·28$, df = 6 ($P = 0·77$); $I^2 = 0\%$
Test for overall effect: $P = 0·03$

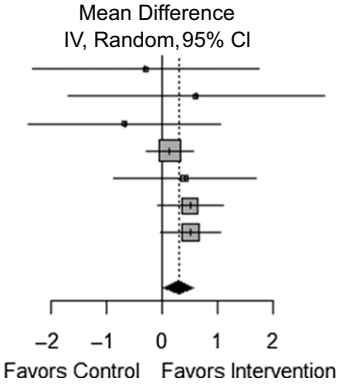

Fig. 4. Forest plot diagrams for midarm muscle circumference.

$I^2 = 0\%$) (Fig. 6), though from low-quality evidence concerning for FM (due to risk of bias, imprecision, heterogeneity and the unfeasibility to investigate risk of publication bias) (Table 4).

Effect of intervention in handgrip and quadriceps strength

Twelve trials (448 participants)[39,40,42–45,47,49,61,64,67,70] assessed peripheral muscle strength by HGS, resulting in a pooled SMD of 0·39 (95 % CI, 0·07, 0·71, $P = 0·02$, $I^2 = 62\%$) (Fig. 7).

Our subgroup analysis showed that the nutritional intervention for COPD patients at stable clinical conditions resulted in a higher effect on handgrip strength than in their unstable counterparts (Table 3). The univariate meta-regression analysis performed, considering the length of intervention and BMI as predictors (online Supplementary Table S6), was unable to satisfactorily explain the substantial heterogeneity for handgrip strength. No evidence of publication bias was found based on the funnel plot visual inspection (online Supplementary Fig. S4), and the Egger's test was not statistically significant (intercept: −1·81 (CI 95 %, −5·72, −2·10); $P = 0·39$). There was very low-quality evidence (due to risk of bias, inconsistency and imprecision (Table 4)).

Ten trials (n 510)[42–46,50,54,57,59,63] reported the effect of intervention on QS (SMD, 0·15, 95 % CI −0·04, 0·35, $P = 0·12$, $I^2 = 15\%$) (Fig. 8). Seven studies measured QS by isometric strength[42,43,46,54,57,59,63], two studies by isokinetic strength[44,45], while one study did not report the methodology applied[50]. In subgroup analysis investigating whether units of measurement was associated with the observed results, we found that only for the studies reporting QS in Newton-meters unit[43–46,54,59,63] (seven reports, 383 participants) there was a significant effect in QS (MD = 2·53; 95 % CI 0·44, 4·63, $P = 0·02$, $I^2 = 0\%$), with a significant test for subgroup differences ($P = 0·04$). Subgroup analyses revealed no statistically significant associations between explanatory variables (clinical status, type of intervention, BMI and overall risk of bias of primary studies) on QS outcomes, and univariate meta-regression analysis with BMI as the predictor variable only partially ($R^2 = 25·93\%$) explained the observed statistical heterogeneity with no significant association with the outcome ($P = 0·23$) (online Supplementary Table S6).

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std· Mean Difference IV, Random, 95% CI
Steiner, 2003	0·67	2·04	25	−0·76	1·66	35	11·4%	0·77 [0·24, 1·31]
Vermeeren, 2004	1·70	2·50	21	1·50	2·50	22	9·9%	0·08 [−0·52, 0·68]
Fuld, 2005	−1·70	2·16	14	−0·60	0·67	11	6·4%	−0·63 [−1·44, 0·18]
Deacon, 2008	−0·70	2·00	38	−0·40	1·92	42	13·9%	−0·15 [−0·59, 0·29]
Sugawara, 2010	−0·04	1·27	17	−0·17	1·22	15	8·1%	0·10 [−0·59, 0·80]
Sugawara, 2012	1·30	1·60	17	0·00	3·02	14	7·7%	0·54 [−0·18, 1·26]
van de Bool, 2017	1·20	2·20	42	0·20	8·45	39	14·0%	0·16 [−0·27, 0·60]
De Benedetto, 2018	−1·10	4·40	45	−1·00	4·40	45	14·8%	−0·02 [−0·44, 0·39]
van Beers, 2020	0·86	3·24	42	−0·22	1·31	39	13·9%	0·43 [−0·01, 0·87]
Total (95% CI)			261			262	100·0%	0·16 [−0·07, 0·40]

Heterogeneity: $Tau^2 = 0·05$; $\chi^2 = 13·98$, df = 8 ($P = 0·08$); $I^2 = 43\%$
Test for overall effect: $P = 0·18$

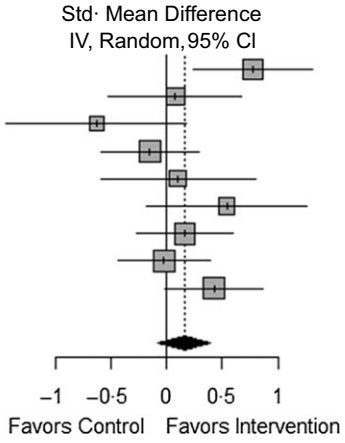

Fig. 5. Forest plot diagrams for fat mass.

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lewis, 1987	0·10	2·65	10	−0·70	3·56	11	16·3%	0·80 [−1·87, 3·47]
Efthimiou, 1988	1·50	1·60	7	−0·10	1·60	7	41·2%	1·60 [−0·08, 3·28]
Knowles, 1988	0·12	4·77	25	−0·80	4·57	25	17·3%	0·92 [−1·67, 3·51]
Fuenzalida, 1990	2·66	4·76	5	0·20	3·95	4	3·6%	2·46 [−3·23, 8·15]
Entrenas Costa, 1991	0·20	5·20	16	0·10	4·06	21	12·2%	0·10 [−2·98, 3·18]
Rogers, 1992	0·20	5·20	15	−0·20	4·06	12	9·5%	0·40 [−3·09, 3·89]
Total (95% CI)			78			80	100·0%	1·09 [0·01, 2·16]

Heterogeneity: $Tau^2 = 0$; $\chi^2 = 1·19$, df = 5 ($P = 0·95$); $I^2 = 0\%$
Test for overall effect: $P = 0·05$

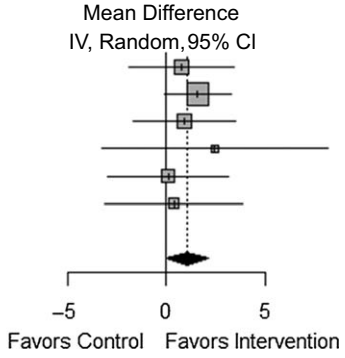

Fig. 6. Forest plot diagrams for triceps skinfold.

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std· Mean Difference IV, Random, 95% CI
Lewis, 1987	0·82	5·92	13	0·23	11·47	10	7·3%	0·07 [−0·76, 0·89]
Efthimiou, 1988	1·90	2·10	7	−0·30	2·10	7	5·1%	0·98 [−0·15, 2·11]
Rogers, 1992	2·10	2·20	15	−0·70	2·20	12	7·2%	1·23 [0·40, 2·07]
Saudny-Unterberger, 1997	−0·87	3·43	13	0·38	2·72	10	7·2%	−0·38 [−1·21, 0·45]
Steiner, 2003	0·64	1·72	25	−0·05	2·20	35	10·3%	0·34 [−0·18, 0·85]
Vermeeren, 2004	0·00	3·00	20	0·00	3·00	22	9·4%	0·00 [−0·61, 0·61]
Fuld, 2005	2·95	4·50	14	0·61	2·57	11	7·4%	0·60 [−0·21, 1·41]
Faager, 2006	0·69	7·19	12	1·70	11·08	10	7·2%	−0·11 [−0·95, 0·73]
Weekes, 2009	−0·80	2·34	22	−1·10	2·34	18	9·2%	0·13 [−0·50, 0·75]
Dal Negro, 2012	1·60	1·49	44	−0·60	1·81	44	10·9%	1·32 [0·85, 1·78]
Degirmenci, 2018	0·71	7·59	20	−0·14	6·07	20	9·2%	0·12 [−0·50, 0·74]
Ahmadi, 2020	3·06	7·08	23	0·25	7·36	21	9·5%	0·38 [−0·21, 0·98]
Total (95% CI)			228			220	100·0%	0·39 [0·07, 0·71]

Heterogeneity: $Tau^2 = 0·19$; $\chi^2 = 28·57$, df = 11 ($P < 0·01$); $I^2 = 62\%$
Test for overall effect: $P = 0·02$

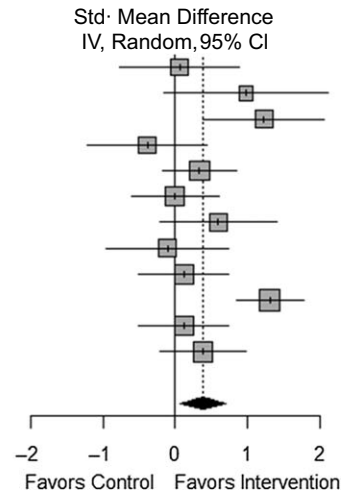

Fig. 7. Forest plot diagrams for handgrip strength.

No evidence of publication bias was found based on the funnel plot inspection and a non-significant Egger's test (intercept: 0·83, (CI 95 % −2·00, −3·65); $P = 0·58$) (online Supplementary Fig. S5). There was low-quality evidence (risk of bias and imprecision) (Table 4).

Discussion

In this systematic review with meta-analysis of RCT, we evaluated the effect of energy and/or protein ONS or food fortification (FF) on nutritional outcomes of COPD patients. The review identified thirty-two studies (1680 participants) and showed that

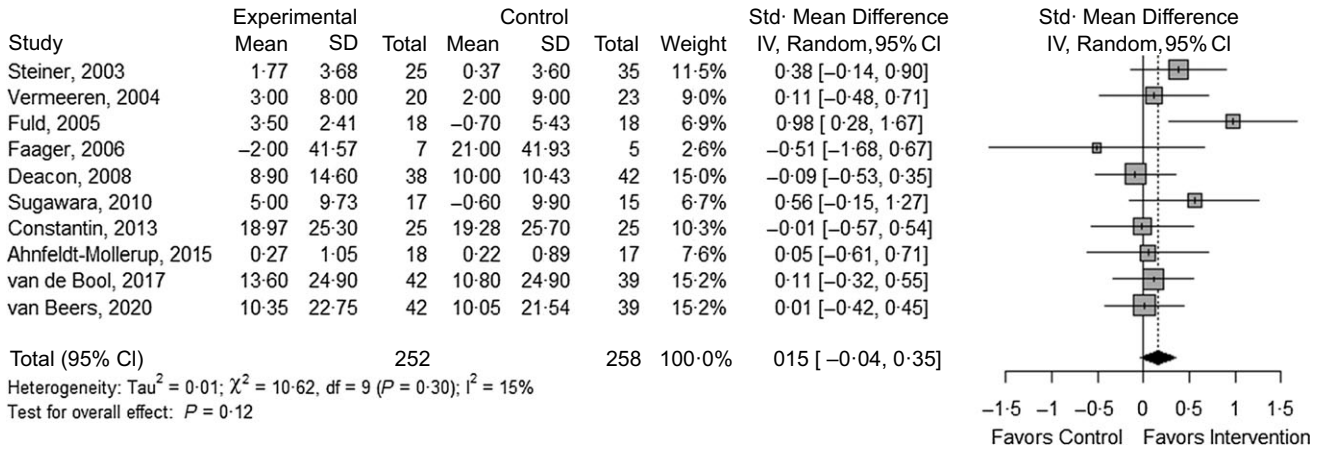

Fig. 8. Forest plot diagrams for quadriceps strength.

these nutritional interventions compared with control (placebo or usual care or dietary instruction) resulted in a significantly positive impact in several nutritional parameters. It is necessary to highlight that we identified a high risk of bias in most of the primary studies, and the certainty of the evidence was very low/low for all outcomes.

Our findings are consistent with most of the results from three meta-analyses[27–29] published between 2012 and 2013, limited to stable COPD patients, in which nutritional support, mainly in the form of ONS (for more than two weeks) compared with placebo or usual diet also revealed significant improvements in BW[27–29], midarm muscle circumference[27,29], skinfold thickness[27,29] (especially in malnourished patients) and handgrip strength[28], as well as a lack of benefit from nutritional interventions for free-fat mass[28] and quadriceps strength[28,29]. Notwithstanding, we observed methodological differences between the present meta-analysis and the previous ones[27–29], including intervention selection criteria (administration route, nutritional composition and duration) and the absence of information about protocol study registration.

The current review also provides a comprehensive analysis of the body of evidence by applying proper methodological safeguards to several limitations, compared with the previous ones[27,28], which used a tool (Jadad scale) to assess the risk of bias explicitly discouraged by the Cochrane Handbook for Systematic Reviews of Interventions[31]. Furthermore, such reviews did not judge the certainty of the evidence, according to the GRADE system[34], and limited the selected studies to English only[27,28]. In this review, we also included an additional ten studies published since these meta-analyses publications[27–29].

The present meta-analyses detected substantial statistical heterogeneity for BW and handgrip strength and a moderate statistical heterogeneity for fat-free mass. The meta-regression and the subgroup analysis were unable to explain the statistical heterogeneity, with nonsignificant interaction tests. However, the subgroup analyses for BW revealed a significant increase in the magnitude of effect from nutritional intervention in patients with lower BMI and clinically stable. Likewise, although the test for subgroup differences indicates that there was no statistically significant subgroup effect between the three categories of nutritional interventions, we observed greater effect size for BW with protein-based supplementation, which, according to the individual evaluation of these studies, suggests that the benefits come from the supplementation of creatine and essential amino acids. Caution is necessary in the interpretation of results on fat-free mass, since a publication bias was identified and the adjustment for funnel asymmetry by trim-and-fill method pointed to the lack of four studies and an important change in the pooled effect of the intervention. It is expected that in the presence of publication bias the summary measure shows a higher effect than the real effect, as evidenced in our results. Maybe, studies with negative results were not published and we did not identify them in our broad literature search.

The better outcomes of nutritional interventions for BW in lower BMI patients can be explained by the potential for improving baseline food intake and for weight gain, compared with those with normal or higher BMI. The demonstration of benefit in clinically stable patients compared with a subgroup of exacerbated patients for BW could be explained by the fact that in the last there is a marked increase in local and systemic inflammation, along with the presence of limiting factors to food intake, that negatively impact the nutritional status[17]. The purported mechanism for the effect of creatine supplementation may be associated with its orexigenic activity (as observed in animal studies)[87] and increased water retention, a consequent stimulus to increase in myofibrillar mRNA and protein content[88], promoting gains in free-fat mass. With anabolic effects in the same direction, the essential amino acids supplementation promotes protein synthesis and the resulting hypertrophy by activating translation and retarding proteolysis and expression of various atrogenes[89].

Regarding nutritional interventions, the trial protocols generated some uncertainty about the overall contribution of additional energy or proteins from nutritional supplementation to the usual food intake during interventions. About 88 % of studies did not tailor the nutritional intervention based on individual estimative of the energy-protein requirements of the patients. Of the 56 % of the studies that reported total energy and protein intake during the experiment, in forty percent of them, food intake was

lower in the intervention group compared with the control group at the end of the follow-up. Almost 60 % of the studies reported the methodology applied to assess adherence to the protocol, but only 21 % of these revealed the referred level of patient adherence (with heterogeneous reporting this information). These limitations on the guarantee of the intended intervention make it impossible to recognise the true magnitude of the effect of energy and protein supplementation on the outcomes of interest. However, this brings USA pragmatic character and the need to identify strategies to facilitate patient adherence to nutritional interventions in clinical practice, resulting in an overall net benefit for outcomes relevant to the patient.

We conducted the present systematic review with meta-analysis under the latest Cochrane recommendations[31], following Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[32] after a prospectively registered protocol. We assessed the certainty of the evidence for each outcome of interest using the GRADE system[33]. We identified and included all studies relevant to our research question, regardless of language. We used random effects for all outcomes, regardless of the heterogeneity expressed by I^2, assuming that there is not one single true effect size across studies due to their clinical and methodological divergences. Our main limitation was the inability to access one Chinese publication [90], which probably could fulfill our eligibility criteria. Yet, we need to underline the limitations for the interpretation of our results. All the RCT included in this review had some concerns or high risk of bias, due to problems mainly related to the randomisation process (no information on the concealment of allocation sequence), due to deviations from interventions (unreported data or lack of blinding of participants and/or caregivers and/or people delivering the interventions and/or people assessing the outcomes) and due to missing outcome data (no information about follow-up loss or losses of follow-up higher than 13 %). Most included studies were small sample sized with highly variable intervention duration (1·29–48 weeks). The statistical heterogeneity remains high after subgroup analyses, suggesting the influence of other features between the studies, unexplored due to the impossibility to create subgroups (e.g. COPD severity, since it was unreported in the majority of the studies). Furthermore, the information unavailability about patients' GOLD stage in most of the studies precluded the subgroup analysis for the disease severity.

The certainty of the evidence ranged from very low to low. The most common reasons for downgrading it were the identification of high or some concerns risk of bias in the included studies, imprecision of effect estimates and the inconsistency from individual studies, unexplained by sensitivity analysis. For these reasons, the available evidence herein summarised is insufficient to provide clear recommendations for clinical practice due to the limited certainty of evidence and should therefore be interpreted with caution. The potential benefit of nutritional supplementation/fortification directs to protein-based nutritional supplementation particularly for COPD patients with reduced BMI and clinically stable, which should be addressed in pragmatic trials.

In future RCT, investigations must be designed with adequate power to detect significant but realistic differences in outcomes relevant to individuals living with COPD; in addition to exploring the best protein substrate for supplements and its effective dose, if any, considering the patient's nutritional needs, establishing strategies to optimise adherence; and effectively assess total food intake. Authors should also consider the intention-to-treat analysis and then perform subgroup and sensitivity analyses based on COPD metabolic phenotypes, pulmonary rehabilitation and adherence to the nutritional intervention, in addition to assessing the degree of maintenance of the identified benefits after treatment ends. When comparing the intervention to 'routine care', the latter should be clearly described to allow for transparent comparisons with other trials and appropriate inferences for real-life practice.

Conclusion

Based on limited evidence, this meta-analysis suggests that high-energy and/or high-protein intake improves anthropometric parameters and handgrip strength in COPD patients. Conversely, the nutritional interventions showed no benefit in fat-free mass.

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S. B. and F. M. S. designed the study; C. F. B. and S. B. performed the data extraction; F.M.S. was the third review author in case of disagreement; S. B. and F. M. S. were responsible for quality assessment; F. M. S., I. C. E. and S. B. analysed the data; F. M. S., I. C. E., P. Z. T. and S. B. drafted the manuscript, and all authors read and approved the final manuscript.

The authors have no conflict of interest to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522000976

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