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REVIEW

Comparative Efficacy of Nutritional Supplements in Modulating Lung Function and Exercise Capacity in COPD Patients: A Network Meta-Analysis

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Objective: To compare the effects of nutritional supplements on lung function and exercise tolerance in chronic obstructive pulmonary disease (COPD).

Methods: We searched PubMed, Embase, Cochrane Library, and Web of Science for randomized controlled trials (RCTs) on nutritional supplements in COPD patients, with the search ending December 31, 2023. Two authors independently screened studies, extracted data, and assessed quality using the Cochrane risk of bias tool. Data were analyzed using RevMan 5.4 and R 4.2.3.

Results: Forty-eight studies with 2481 COPD patients were included. Network meta-analysis showed six supplements significantly improved the 6-minute walk distance (6MWD) (all p<0.05), with the top three being: Coenzyme Q10+ Creatine [MD=63, 95% CI (36, 90)], L-carnitine [MD=53, 95% CI (24, 82)], and anabolic steroids [MD=44, 95% CI (7.1, 82)]. Four supplements improved FEV_1% (all p<0.05): nanocurcumin [MD=13, 95% CI (7.7, 18)], Vitamin D [MD=7.5, 95% CI (5.1, 9.9)], probiotics [MD=7.1, 95% CI (5.2, 9.1)] and BSO [MD=4.9, 95% CI (1.6, 8.3)]. In pairwise comparisons, nanocurcumin outperformed BSO and Probiotics. Nanocurcumin [MD=12, 95% CI (4.6, 19), p<0.05] improved FEV_1/FVC, and nitrate [MD=26, 95% CI (9.7, 42), p<0.05] was effective for the Incremental Shuttle Walk Test (ISWT). Traditional Chinese Medicine (TCM) products [MD=−1.3, 95% CI (−1.9, −0.67)], melatonin (MLT) [MD=−0.9, 95% CI (−1.6, −0.21)] and Calcitriol [MD=−0.66, 95% CI (−0.93, −0.39)] improved the modified Medical Research Council(mMRC) dyspnea score (all p<0.05), with comparable efficacy among them.

Conclusion: Nutritional supplements improve lung function and exercise endurance in COPD. Coenzyme Q10+Creatine is most effective for endurance, while Nanocurcumin has the greatest impact on lung function.

Keywords: chronic obstructive pulmonary disease, nutritional supplements, network meta-analysis, lung function, exercise endurance

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide.[1] The hallmark of COPD is progressive lung function decline, often accompanied by extrapulmonary complications, including cardiovascular disease, osteoporosis, sarcopenia, anxiety, depression, and cancer. Decreased exercise tolerance is common, and severe dyspnea often limits daily activities. This restriction leads to reduced physical activity, muscle weakness, atrophy, and further declines in endurance, which may progress to sarcopenia or cachexia.[2] In COPD, increased oxygen consumption by respiratory and peripheral muscles during exercise worsens dyspnea and fatigue, creating a vicious cycle that reduces physical activity and heightens the risk of acute exacerbations.[3] Additionally, sarcopenia affects approximately 23%of COPD patients,[4] and reduced exercise is linked to a higher mortality risk in this population.[5] Although guidelines recommend at least 150 minutes of moderate-intensity exercise per week for all older adults, most COPD patients do not

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meet this target.[6] Additionally, reduced respiratory function and expectoration ability lead to recurrent infections and frequent hospitalizations, resulting in a lower quality of life and increased economic burden.[7] Moreover, global productivity losses due to decreased physical activity in COPD patients account for about 10%of total output.[8] Therefore, improving lung function and exercise endurance in these patients is essential.

COPD treatment includes both pharmacological and non-pharmacological approaches. While pharmacological treatment is central, long-term use of glucocorticoids or antibiotics can increase the risk of infections. Non-pharmacological treatments, such as pulmonary rehabilitation, physical exercise, oxygen therapy, and lung transplantation, are also essential. Malnutrition is common in COPD patients and can lead to muscle atrophy, respiratory muscle fatigue, reduced cough and expectoration ability, impaired lung infection clearance, and decreased exercise endurance and work capacity.[9] Compared to well-nourished COPD patients with similar disease severity, malnourished patients have reduced diffusion capacity and exercise endurance.[10] Malnutrition in COPD is associated with disease-specific factors such as symptoms (dyspnea, fatigue, anxiety, depression, dysphagia, poor chewing ability, etc). or social problems (living alone or eating alone, or poverty).[11] As a result, there is growing awareness of the impact of nutrition on COPD management. Commonly used supplements include protein, energy, vitamins, minerals, and antioxidant-rich foods. Oxidative stress and associated inflammation in the lungs and circulation due to exposure to air pollution, tobacco smoke, infection, or potential obesity are the main causative processes of COPD. Multiple epidemiological studies have shown that high levels of fruit and vegetable consumption are associated with lower levels of markers of oxidative stress and inflammation and higher levels of antioxidant markers.[12,13] A high intake of antioxidant nutrients (vitamin and non-vitamins) and foods rich in antioxidants are potentially beneficial for improving lung function and COPD symptoms.[14–19] Studies have shown that diets rich in vegetables, fruits, fiber, cereals, and fish may reduce the risk of morbidity in COPD patients.[20–22] Previous meta-analyses mostly focused on comparative analysis of a specific nutritional supplement, while cross-comparative studies on different types of nutritional supplements were lacking.[23–28] This study aims to reveal the advantages and disadvantages of different nutritional supplements in improving pulmonary function, exercise ability and quality of life in COPD patients through a network meta-analysis, so as to provide better guidance for the prevention, rehabilitation and prognosis of COPD patients.

Materials and Methods

This study was designed and conducted following the PRISMA guidelines.[29] The protocol was registered in the international prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO), registration number CRD42024507713.

Search Strategy

A systematic search was conducted in Cochrane, PubMed, Embase, and Web of Science databases for randomized controlled trials (RCTs) evaluating the effects of nutritional supplements on exercise endurance and lung function in COPD patients, with a search deadline of December 31, 2023. The search used a combination of subject and free-text terms, including “chronic obstructive pulmonary disease”, “pulmonary disease chronic obstructive”, “chronic obstructive airway disease”, “nutritional supplementation”, “dietary supplementation”, and “food supplementation”. The full search strategy is detailed in Table S1. Additionally, references from the included studies and recent literature were screened for relevant research.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) All patients included in this study met the diagnostic criteria of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD):[30] the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/ FVC) < 0.7, and the forced expiratory volume in the first second (FEV_1) accounted for less than 80% of the predicted value. (2) randomized controlled trials (RCTs); (3) any type of nutritional supplement as the intervention; (4) a placebo control group; (5) assessment using 6-minute walk distance (6MWD), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, incremental shuttle walk test (ISWT), and modified Medical Research Council (mMRC) dyspnea scale.

The exclusion criteria were as follows: (1) duplicate publications; (2) inaccessible full text or inability to extract necessary data; (3) inability to convert or merge effect indicators; and (4) patients with comorbidities of other organic diseases.

Data Extraction

Two authors independently screened the literature based on predefined inclusion and exclusion criteria. Disagreements were resolved through discussion or third-party consultation. Initial screening was based on titles and abstracts, followed by full-text review to confirm inclusion. Statistical data included study characteristics (eg, first author, publication year, sample size), demographic information (eg, gender, age), intervention details (eg, type, dosage, duration of supplements), and outcome measures. For missing data from the study, we first try to extrapolate from other information reported in the literature, such as charts, supplementary materials, or relevant statistics. If data is not directly available through the literature, we will contact the corresponding author of the respective study via Email to request missing data or further clarification of relevant information. If this is not available, we consider excluding the study from the analysis.

Quality Assessment

Two authors assessed the included RCTs for risk of bias using the Cochrane tool,[31] evaluating five areas: randomization, deviation in intervention measures, missing outcome data, outcome measurement, and selective outcome reporting. The risk was categorized as "low", "uncertain", or "high". Disagreements were resolved through discussion or third-party consultation.

Statistical Analysis

Statistical analyses were performed using R software version 4.2.3 (R Foundation for Statistical Computing). A Bayesian framework with a vague prior random-effects model was employed for network meta-analysis (NMA) of multiple trial datasets. For fixed-effect model parameters, a normal distribution $N(0, 100^2)$ was selected as the prior distribution; for the heterogeneity parameter (τ^2) of the random-effects model, a uniform distribution Uniform (0,5) was used as the prior distribution; and for treatment effects (eg, mean difference, MD), a normal distribution $N(0, 100^2)$ was chosen as the prior distribution. Model fitting was conducted using the Markov Chain Monte Carlo (MCMC) method,[32] with four Markov chains, each running 50,000 iterations, including a burn-in period of 20,000 iterations to ensure convergence. Posterior distributions were used to obtain the best combined estimates and probabilities for each treatment.

For model selection, a fixed-effects model was adopted when the total heterogeneity ($I^2 \leq 50\%$) was low; otherwise, a random-effects model was used. Treatment effects were expressed as MD with 95% confidence intervals (CI). To compare the effectiveness of interventions, the Surface Under the Cumulative Ranking Curve (SUCRA) was calculated to estimate the probability of each intervention being the best treatment. Additionally, network plots and funnel plots were generated using the pass-through macro in STATA 15.1, and cumulative probability plots were created using the ggplot2 package in R.

Results

Search results and Quality Assessment

A total of 1339 articles were retrieved from the preliminary search, with 7 additional articles sourced from other reviews and meta-analyses. After removing 440 duplicates, 819 articles were excluded based on titles and abstracts, and 39 were excluded after full-text review. Finally, 48 studies, involving 2481 COPD patients, were included (Figure 1).The basic characteristics of the included studies are summarized in Table 1. Twenty-five studies used low-risk randomization methods (eg, random number table, computer randomization), while 22 studies only mentioned random allocation. For allocation concealment, 1 study used opaque envelopes, 3 used open labels, and the rest were unspecified. Regarding blinding, 34 studies blinded both patients and experimenters, 3 did not, and the rest were unclear. All studies reported primary and secondary outcome indicators, with no significant baseline differences between the groups before intervention. The bias risk assessment of the included studies is shown in Figure 2.

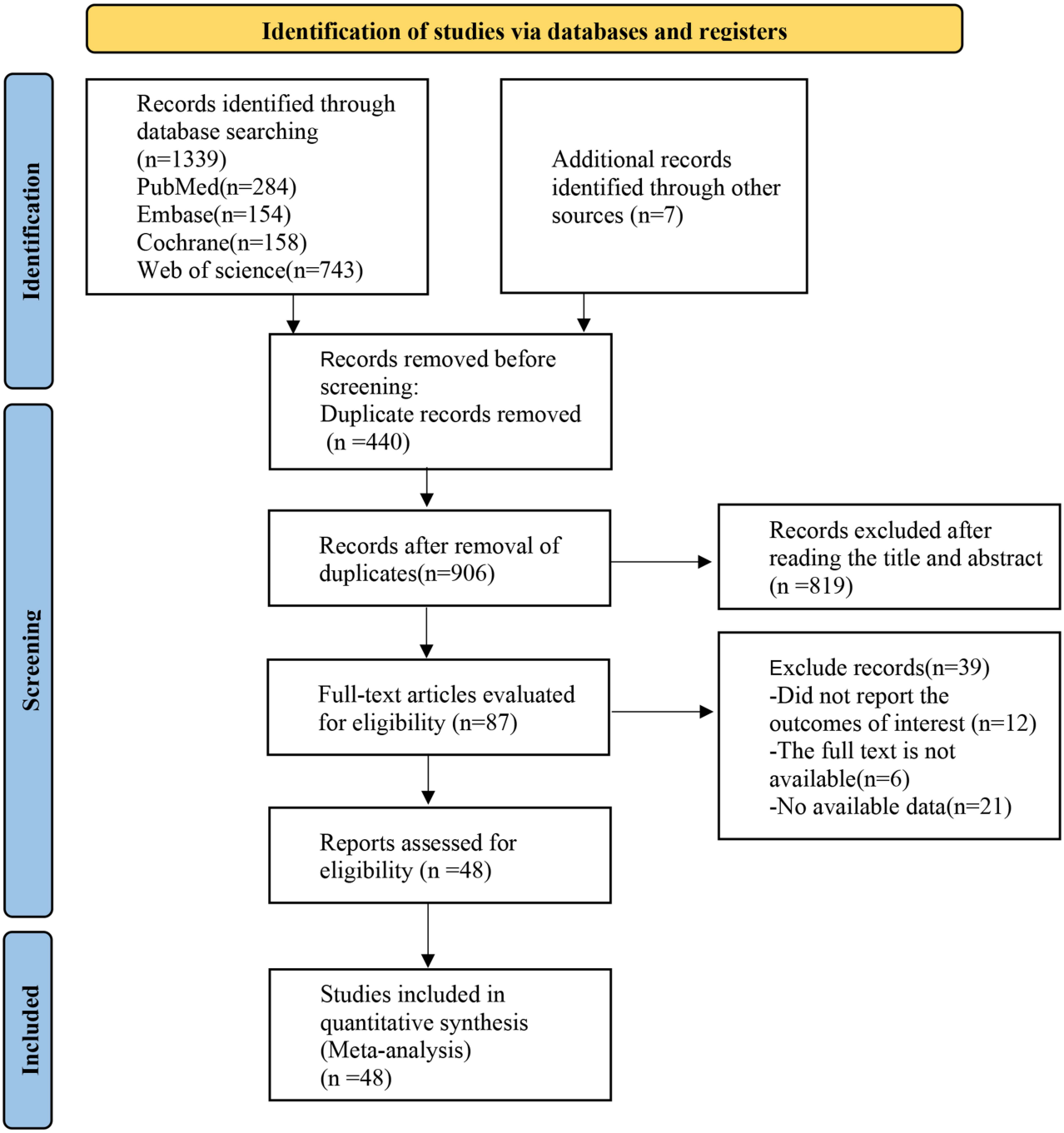

Figure 1 PRISMA flow diagram of the study process. PRISMA: Preferred Reporting Items for Systematic review and Meta-analysis. PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[33]

Network Meta-Analysis

Network Meta-Analysis of 6MWD

Twenty studies[34–54] (Figure 3a) reported 6MWD. Compared with placebo, Coenzyme Q10+ Creatine [MD=63, 95% CI (36, 90)], L-carnitine [MD=53, 95% CI (24, 82)], anabolic steroids [MD=44, 95% CI (7.1, 82)], MLT [MD=34, 95% CI (17, 52)], nitrate [MD=30, 95% CI (19, 41)], and protein [MD=19, 95% CI (10, 28)] (all $p<0.05$) significantly improved 6MWD in COPD patients (Figure 3c). Coenzyme Q10+Creatine was more effective than nitrate and protein, and

Table 1 Characteristics of the Studies Included in This Network Meta-Analysis

Study	Year	Country	Sample Size	Gender (M/F)	Mean Age, y	Intervention	Outcome
Steiner	2003	UK	High_CHO:42 UC:43	32/53	High_CHO:66 UC:68	High_CHO: 125mL tid for 7 weeks	F5;
Vermeeren	2004	Netherlands	High_CHO:23 UC:24	32/15	ONS:66 UC:65	High_CHO:125mL contains 60%CHO tid for 7days	F2;
Fuld	2005	UK	Creatine:18 UC:20	23/15	Creatine:61 UC:63	Creatine:5g tid for 2weeks	F5;
Silva	2006	Brasil	L_carnitine:8 UC:8	10/6	L_carnitine:69 UC:65	L_carnitine:1g bid for 6weeks	F1;
Cerdá	2006	Spain	Polyphenol:15 UC:15	30/0	Polyphenol:60 UC:63	Polyphenol:400mL/Day for 5weeks	F3;
Faager	2006	Solna	Creatine:13 UC:10	10/13	Creatine:67 UC:64	Creatine:0.3g/kg/day for 1week, and 0.07g/kg/day for 7weeks	F2;
Wu	2007	China	VE-400:9 VE-200:9 VC:9 UC:8	27/8	VE-400:71 VE-200:72 VC:68 UC:65.5	VE-400:400mg/day VE-200: 200mg/day VC250:250mg/day for 12weeks	F2;F3;
Nadeem	2008	India	VE:10 UC:14	24/0	VE:54.8 UC:60.1	VE:400IU bid for 8weeks	F2;
Deacon	2008	UK	Creatine:38 UC:42	50/30	Creatine:67.6 UC:68.3	Creatine:22g qd for 5days	F5;
Sharma	2008	Canada	Anabolic steroids:8 UC:8	9/7	Anabolic steroids:71 UC:64	Anabolic steroids: Man:50mg every 2 weeks for 16 weeks Women:25mg every 2 weeks for 16weeks	F1;
Ansari	2010	Pakistan	VC:23 UC:22	45/0	VC:53 UC:55	VC:500mg bid for 9 months	F3;
Sugawara	2010	Japan	Omega_3 andVA:17	NA	Omega_3 and VA:17 UC:78	Omega_3 and VA:omega_3 0.6g and VA 248mg qd for 12weeks	F1;
Laviolette	2010	Canada	Whey:12 UC:10	14/8	Whey:62.9 UC:67.6	Whey:20g qd for 16weeks	F2;
Sugawara	2012	Japan	Whey:17 UC:14	29/2	Whey:77.4 UC:77.1	NA	F1;
Hornikx	2012	Belgium	VD:24 UC:25	NA	VD:67 UC:69	VD:100IU/Month for 1years	F1;
Zhao	2012	China	TCM:26 UC:23	46/3	TCM:80.1 UC:80.8	TCM:Shan yao 30g and XianLingPi 12g bid for 3months	F1;F2;F4;
De Matos	2012	Brazil	MLT:18 UC:18	30/6	MLT:68 UC:65	MLT:3mg qd for 3months	F1;
Marinari	2013	Italy	Coenzyme Q10 _Creatine:30 UC:25	NA	Coenzyme Q10 _Creatine:73.2 UC:73.9	Coenzyme Q10 _Creatine:Creatine 170 mg+ 160 mg Coenzyme Q10 bid for 2 months	F1;
Gurgun	2013	Turkey	High_CHO:15 UC:15	28/2	High_CHO:64 UC:66	High_CHO:250mL tid for 8 weeks	F1;F5;
Daga	2014	India	Anabolic Steroids:20 UC:12	32/0	Anabolic Steroids:60 UC:56.7	Anabolic Steroids:25mg qd on days 1, 8, 15, 22, 29, and 35	F1;F2;F3;

(*Continued*)

Table 1 (Continued).

Study	Year	Country	Sample Size	Gender (M/F)	Mean Age, y	Intervention	Outcome
Kerley	2015	Ireland	Nitrate:7 UC:5	5/7	Nitrate:69 UC:69	Nitrate:12.9mmol once	F5;
Dal Negro	2015	Verona	EAAs:44 UC:44	61/27	EAAs:75 UC:73	EAAs:4g bid for 12weeks	F3;
Zendedel	2015	Iran	VD:44 UC:44	60/28	NA	VD:100000IU/month for 6 months	F2;
Sanjari	2015	Iran	VD:39 Calcitriol:39 UC:42	91/29	VD:55.8 Calcitriol:55.6 UC:58.4	VD:50000IU qd for 1week, Calcitriol:0.25ug qd for 1week	F2;F3;F4;
Khan	2016	India	Protein:30 UC:30	54/6	Protein:55 UC:53	Protein:10g qd for 12weeks	F1;F2;F3;
Van De Bool	2017	Netherlands	Leucine, omega_3, and VD:42 UC:39	41/40	Leucine, omega_3, and VD:62.8 Placebo:62.2	Leucine, omega_3 and VD: 125mL bid-tid for 4months	F1;
Rafiq	2017	Amsterdam	VD:24 UC:26	26/24	VD:64 UC:61	VD:1200IU qd for 6months	F1;F2;F3;
Hoang	2018	Vietnam	TCM:30 UC:30	37/23	TCM:63.2 UC:61.7	TCM:Bao Khi Khang 3 tablets bid for the first 10 days and reduced to 2 tablets bid for the next 20 days	F2;
De Benedetto	2018	Italy	Coenzyme Q10 _Creatine:45 UC:45	68/22	Coenzyme Q10 _Creatine:73 UC:73	Qter®_Creatine:160mg Coenzyme Q10 +170mg Creatine bid for 8weeks	F1;F2;F4;
Behnia	2018	USA	Nitrate:12 UC:13	13/12	Nitrate:67 UC:68	Nitrate:70mL qd for 8days	F3;
Lu	2018	China	OPC:13 UC:14	NA	OPC:71 UC:72	OPC:150mg qd for 8weeks	F2;F3;
Ogasawara	2018	Japan	Omega_3:24 UC:21	41/4	Omega_3:77 UC:79	EPA:1g/day during hospitalization	F4;
Pourrashid	2018	Iran	VD:30 UC:32	52/10	VD:62.7 UC:64	VVD:300000IU Once	F4;
Alavi Foumani	2019	Iran	VD:33 UC:33	60/6	VD:67.9 UC:68.4	VD:50000IU qw for 8weeks, 50000IU/month for 4months	F2;F3;
Gouzi	2019	France	VE and VC and zinc gluconate and selenium:31 UC:26	28/29	VE and VC and zinc gluconate and selenium:62 UC:61	VE and VC and zinc gluconate and selenium selenomethionine:VE30mg/day, VC180mg/day, zinc gluconate 15mg/day selenium 50ug/day for 28days	F1;
Kerley	2019	Ireland	Nitrate:5 UC:5	5/5	Nitrate:62.9 UC:62.9	Nitrate:12.9mmoL qd for 14days	F2;F5;
Dastan	2019	Iran	VD:33 UC:34	57/10	VD:64 UC:63	VD:300000IU Once	F4;
Ahmadi	2020	Iran	Whey and magnesium and VC:23 UC:23	NA	Whey and magnesium and VC:62 UC:63	Whey and magnesium and VC:15.9g whey and 625mg magnesium and 685mg VC daily for 8weeks	F2;
Azzawi	2020	Iraq	BSO:47 UC:44	63/28	BSO:54 UC:55	BSO:1g bid for 3weeks	F2;F3;
Pavitt	2020	UK	Nitrate:57 UC:65	53/69	Nitrate:70 UC:68	Nitrate:12.9mmol twice a week for 8 weeks	F5;

(*Continued*)

Table 1 (Continued).

Study	Year	Country	Sample Size	Gender (M/F)	Mean Age, y	Intervention	Outcome
De Bisschop	2021	France	EAAs:25 UC:29	36/18	EAAs:65 UC:64	EAAs:BCAA4.3g qd for 4weeks	F1;F4;
Kim	2021	USA	Omega_3:20 UC:20	22/18	Omega_3:67.5 UC:66	Omega_3:1 capsule daily for 1 week, 2 capsules daily for 1 week, followed by 3 capsules daily for 22weeks	F1;F2;F3;
Aldhahir	2021	UK	Protein:22 UC:22	28/16	Protein:75 UC:70	Protein:125mL contains 24%protein bid for 6weeks	F4;F5;
Karim	2022	United Arab Emirates	Probiotic:47 UC:53	100/0	Probiotic:66.9 UC:68.3	Probiotic:one capsule a day for 16 weeks	F2;
De Brandt	2022	Belgium	Beta_alanine:21 UC:19	30/10	Beta_alanine:66 UC:65	Beta_alanine:3.2g qd for 12weeks	F1;
Viana	2023	Brazil	MLT:18 UC:21	24/15	MLT:67 UC:66	MLT:3mg qd for 12weeks	F1;F4;
Alasmari	2024	UK	Nitrate:36 UC:34	48/22	Nitrate:63 UC:65	Nitrate:400mg qd for 3months	F1;
Zare'i	2024	Iran	Nanocurcumin:30 UC:30	29/31	Nanocurcumin: 61 UC:60	Nanocurcumin:80mg qd for 3 months	F2;F3;

Abbreviations: M/F, male/Female; qd, once a day; bid, twice a day; tid, three times a day; high_CHO, High Carbohydrate; UC, Unhandled Control Group; VE, Vitamin E; VC, Vitamin C; VD, Vitamin D; Omega_3and VA, Omega-3 Fatty Acids and Vitamin A; Whey, Whey Protein; TCM, Traditional Chinese Medicine; MLT, Melatonin; EAAs, Essential amino acid; OPC, Oligomeric proanthocyanidins; BSO, Black Seed Oil; Whey, Whey Protein; F1, Six-Minute Walk Distance (6MWD); F2, Forced Expiratory Volume in 1 second % predicted (FEV_1%); F3, Forced Expiratory Volume in 1 second/ Forced Vital Capacity (FEV_1/FVC); F4, modified Medical Research Council(mMRC); F5, Incremental Shuttle Walk Test (ISWT).

L-carnitine was more effective than protein; no significant differences were observed among the remaining interventions (Table S2). The cumulative ranking curve showed that Whey had the highest probability (85.8%), followed by TCM (84.9%), Coenzyme Q10+ Creatine (83.6%), with EAAs having the lowest (13.3%) (Figure 3b and Table S3).

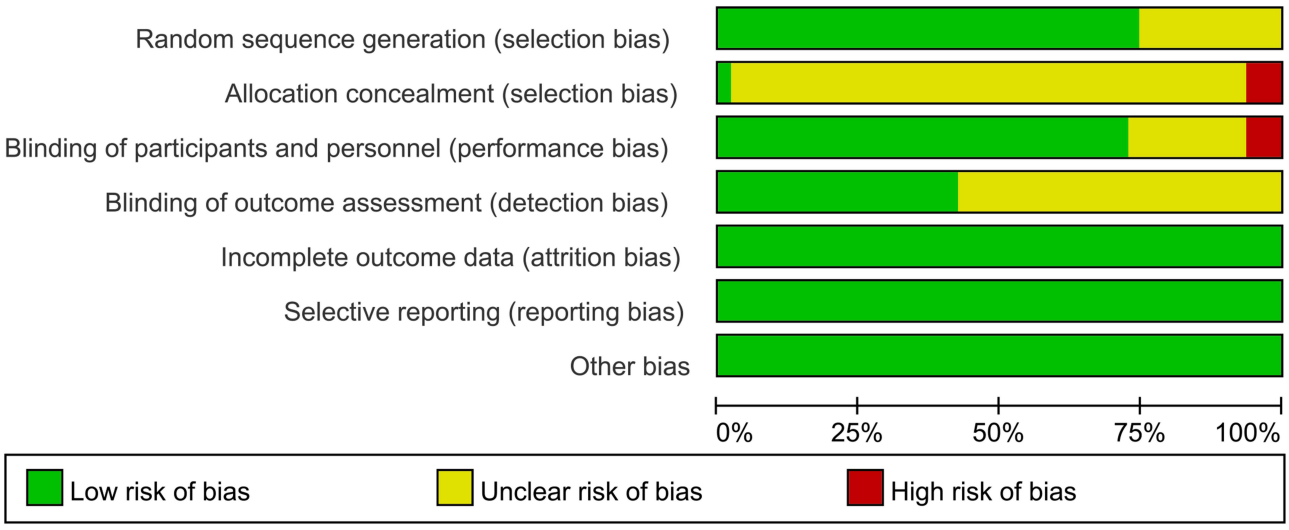

Figure 2 Risk of Bias for all studies included in this network Meta-analysis.

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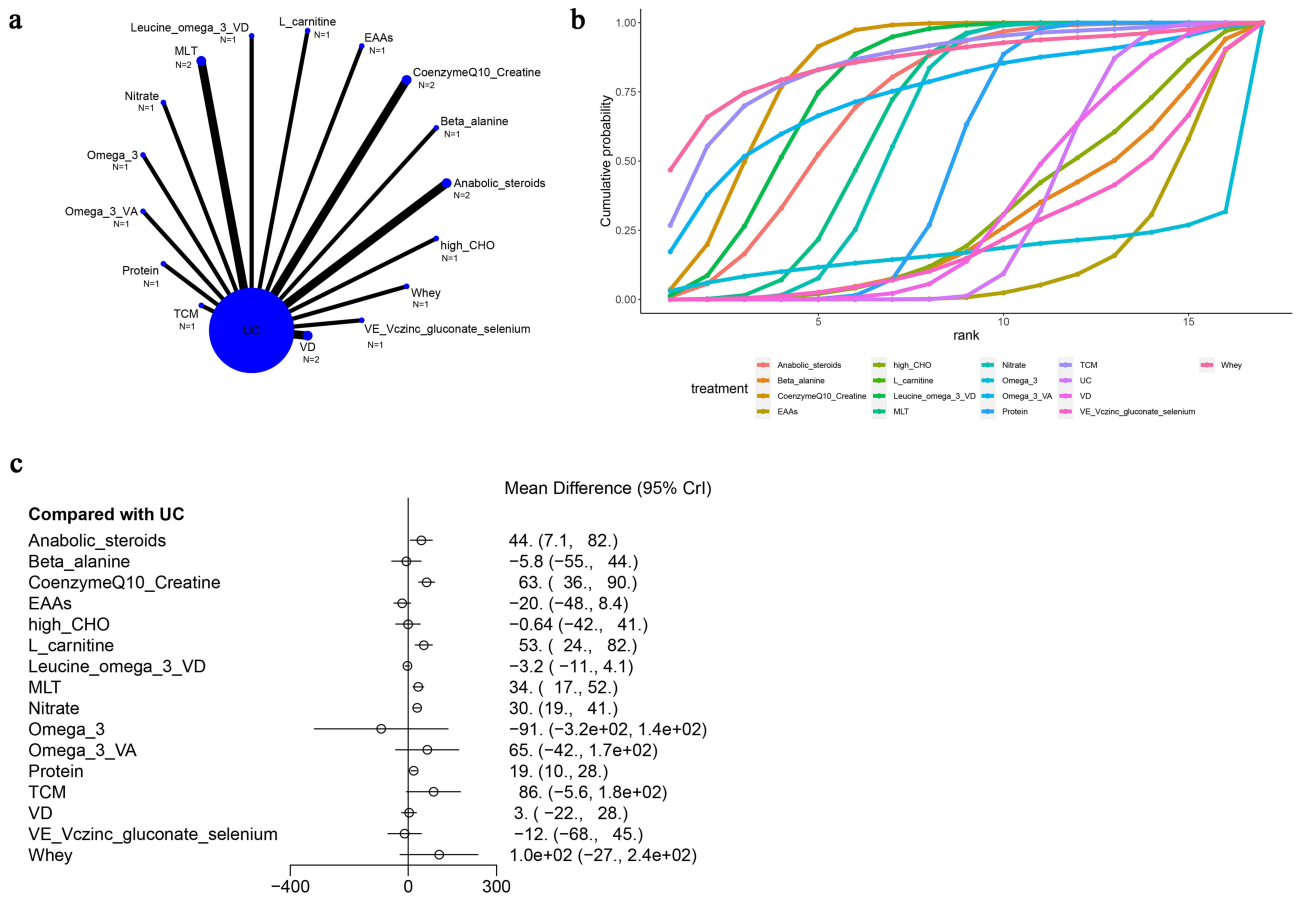

Figure 3 Meta analysis of 6MWD ((**a**) Network plot: (**b**) area under the cumulative probability curve: (**c**) forest plot) The number on each edge indicates the trials included in the direct comparison.

Abbreviations: UC, Unhandled Control Group; VD, Vitamin D; VE_Vczinc_gluconate_selenium, VE and Vc and zinc and gluconate and selenium; Coenzyme Q10 _Creatine, Coenzyme Q10 and Creatine; EAAs, Essential amino acid; Leucine_omega_3_VD, Leucine and omega-3 and VD; MLT, Melatonin; Omega_3and VA, Omega-3 Fatty Acids and Vitamin A; TCM, Traditional Chinese Medicine.

Network Meta-Analysis of FEV1%

Twenty-one studies[39,43,44,46,47,50,54–68] reported FEV_1% (Figure 4a). Compared with placebo, Nanocurcumin [MD=13, 95% CI (7.7, 18)], and vitamin D [MD=7.5, 95% CI (5.1, 9.9), p<0.05], Probiotics [MD=7.1, 95% CI (5.2, 9.1)] and BSO [MD=4.9, 95% CI (1.6, 8.3)](all p<0.05) significantly improved FEV_1%in COPD patients (Figure 4c). Pairwise comparisons showed that Nanocurcumin was more effective than BSO and Probiotics (Table S4). The cumulative ranking curve indicated that Nanocurcumin had the highest probability (97.5%), followed by vitamin D (84.5%), Probiotics (82.9%), and OPC (19.5%) (Figure 4b and Table S3).

Network Meta-Analysis of FEV1/FVC

Fourteen studies[43,44,46,50,56,60,62,63,66,68–72] reported FEV_1/FVC (Figure 5a). Compared with placebo, Nanocurcumin [MD=12, 95% CI (4.6, 19), p<0.05] significantly improved FEV_1/FVC in COPD patients (Figure 5c), while the other treatments had no significant effect. In pairwise comparisons, Nanocurcumin outperformed most supplements, except for nitrate, and vitamin C (Table S5). The cumulative ranking curve showed Nanocurcumin with the highest probability (97.7%), followed by BSO (81.8%), vitamin C (66.6%), and protein (26.5%) (Figure 5b and Table S3).

Network Meta-Analysis of mMRC

Nine studies[39,47,49,52,60,73–76] reported mMRC (Figure 6a). Compared with placebo, traditional Chinese medicine (TCM) [MD=−1.3, 95% CI (−1.9, −0.67)], Melatonin [MD=−0.9, 95% CI (−1.6, −0.21)] and calcitriol [MD=−0.66, 95% CI (−0.93, −0.39)] (all p<0.05) significantly improved mMRC scores in COPD patients (Figure 6c). However, no significant differences

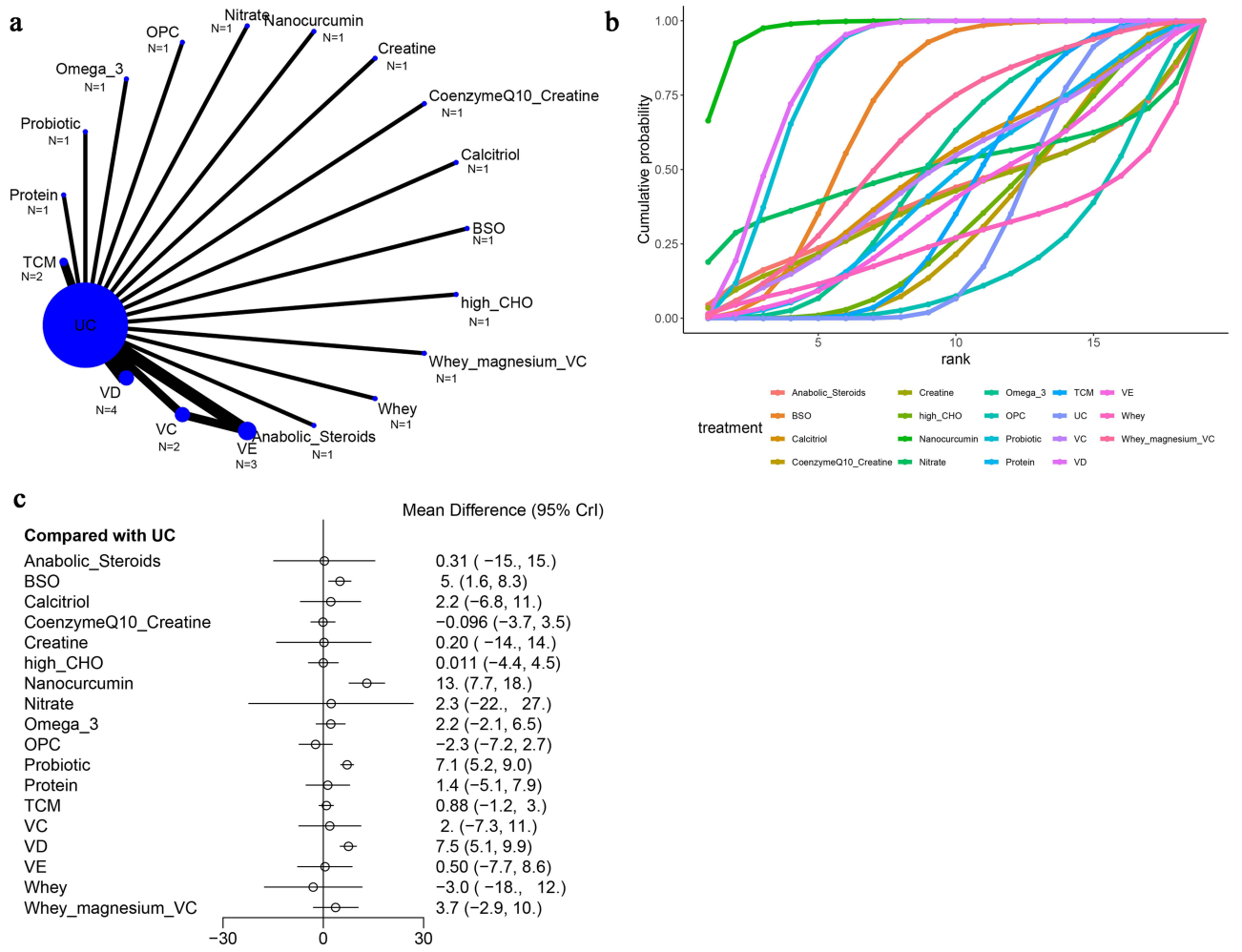

Figure 4 Meta analysis of FEV_1% ((**a**) Network plot: (**b**) area under the cumulative probability curve: (**c**) forest plot) The number on each edge indicates the trials included in the direct comparison.

Abbreviations, UC, Unhandled Control Group; VC, Vitamin C; VD, Vitamin D; VE, Vitamin E; Coenzyme Q10 _Creatine, Coenzyme Q10 and Creatine; Omega_3, Omega-3 Fatty Acids; TCM, Traditional Chinese Medicine; OPC, Oligomeric proanthocyanidins; BSO, Black Seed Oil; Whey_magnesium_VC, Whey and magnesium and Vitamin C.

were found between Calcitriol, Melatonin, and TCM (Table S6). The cumulative ranking curve showed TCM with the highest probability (96.9%), followed by Melatonin (84.8%), Calcitriol (76.9%), and UC (27.9%) (Figure 6b and Table S3).

Network Meta-Analysis of ISWT

Eight studies[41,64,68,76–81] reported ISWT (Figure 7a). Compared with placebo, nitrate [MD=26, 95% CI (9.7, 42), p<0.05] significantly improved ISWT in COPD patients (Figure 7c), while other treatments were ineffective. In pairwise comparisons, nitrate was more effective than UC (Table S7). The cumulative ranking curve showed nitrate with the highest probability (80.2%), followed by protein (68.6%), high-CHO (47%), and UC (14.3%) (Figure 7b and Table S3).

Results of Publication Bias in Studies

Funnel plots were used to assess publication bias for 6MWD, FEV_1%, FEV_1/FVC, and mMRC. The plots showed symmetrical distribution on the upper half, indicating low publication bias. However, some dispersion points at the bottom suggested a small sample effect (Figure S1-4).

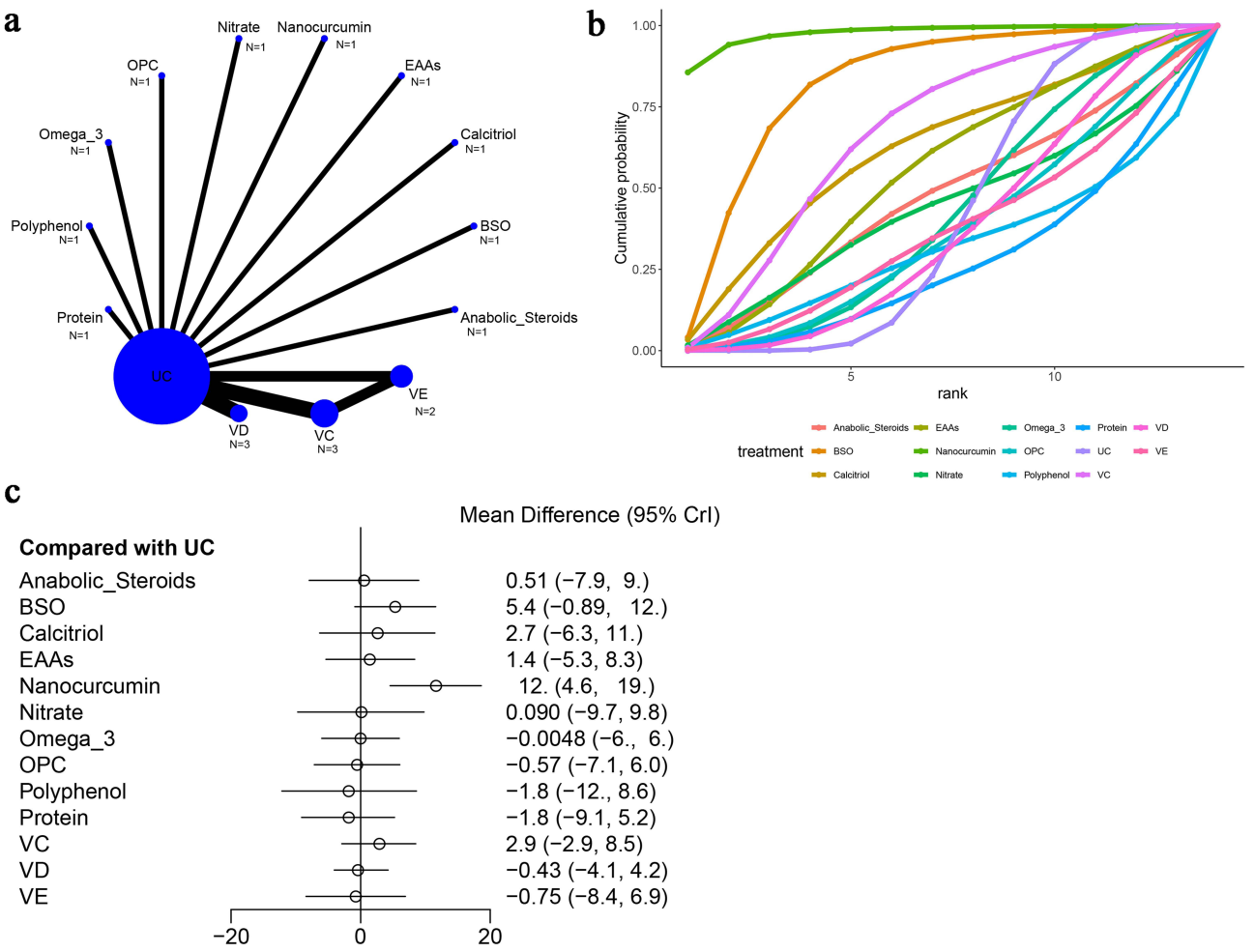

Figure 5 Meta analysis of FEV_1/FVC ((**a**) Network plot: (**b**) area under the cumulative probability curve: (**c**) forest plot) The number on each edge indicates the trials included in the direct comparison.

Abbreviations: UC, Unhandled Control Group; VC, Vitamin C; VD, Vitamin D; VE, Vitamin E; EAAs, Essential amino acid; Omega_3, Omega-3 Fatty Acids; high_CHO, High Carbohydrate; OPC, Oligomeric proanthocyanidins; BSO, Black Seed Oil.

Discussion

To our knowledge, this is the first network meta-analysis comparing different nutritional supplements to improve lung function and exercise endurance in COPD patients. Previous meta-analyses have examined nutritional supplementation in COPD patients,[23–28] but none have made direct comparisons. This network meta-analysis included 48 randomized controlled trials with 2481 participants. The results showed that the effects of nutritional supplements on lung function and exercise endurance in COPD patients were different. Coenzyme Q10+creatine increased 6MWD (mean 63m; 95% CI [37,82]), nitrate improved ISWT (mean 26m; 95% CI[9.7,42]), nanocurcumin improved FEV_1% (mean 13m;95% CI [7.7,18]) and FEV_1/ FVC (mean 12; 95% CI[4.6,19]), TCM[mean −1.3, 95% CI(−1.9,-0.67)] was the most effective in improving mMRC.

Coenzyme Q10, a key lipid-soluble compound in cell mitochondria, plays an essential role in the electron transport chain, facilitating cellular respiration and ATP synthesis. Research indicates that Coenzyme Q10 supplementation can significantly reduce oxidative stress in various clinical contexts.[82,83]

However, the effects of Coenzyme Q10 on exercise performance remain inconsistent in current research. Some studies have found that, compared to healthy individuals,[84] COPD patients have significantly lower high-energy phosphate levels in both skeletal and respiratory muscles. Coenzyme Q10 supplementation may improve exercise tolerance by enhancing these mechanisms. The typical daily dose ranges from 30mg to 60mg, which is generally

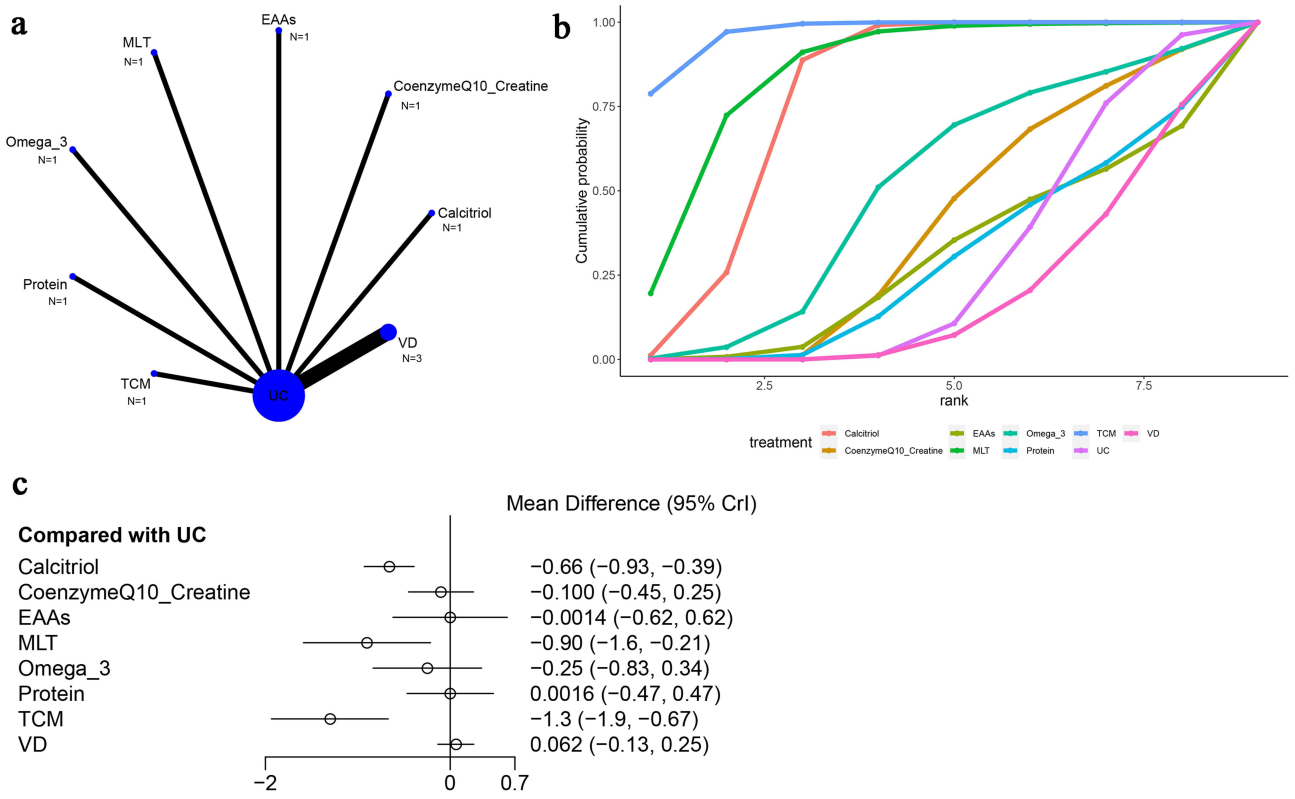

Figure 6 Meta analysis of mMRC ((**a**) Network plot: (**b**) area under the cumulative probability curve: (**c**) forest plot) The number on each edge indicates the trials included in the direct comparison.

Abbreviations: UC, Unhandled Control Group; VD, Vitamin D; Coenzyme Q10 _Creatine, Coenzyme Q10 and Creatine; EAAs, Essential amino acid; MLT, Melatonin; Omega_3, Omega-3 Fatty Acids; TCM, Traditional Chinese Medicine.

sufficient for most individuals. However, some studies have used higher doses of Coenzyme Q10, such as 90mg/day and 320mg/day, and observed positive effects.[42,47,85] Nonetheless, excessive doses may lead to side effects, including palpitations, insomnia, and gastrointestinal discomfort. Therefore, determining the optimal dosage is crucial to maximize benefits while minimizing potential risks.

On the other hand, Creatine, a widely used nutritional supplement, helps generate ATP substrates when phosphorylated, thereby supporting ATP circulation. A meta-analysis of Creatine supplementation in COPD patients found no significant improvement in exercise performance, such as 6MWD and ISWT.[23] This may be due to the influence of other treatments, such as pulmonary rehabilitation, or it could suggest that Creatine itself has limited impact on exercise performance in COPD patients.[79] We need to exercise caution when exploring the effects of Coenzyme Q10 combined with Creatine therapy. While some studies suggest that this combination may improve exercise performance in COPD patients, it remains unclear whether the improvement is due to the individual effects of Coenzyme Q10, Creatine, or their potential synergistic interaction. Therefore, larger prospective randomized controlled trials, both for individual and combined supplementation, are needed to further validate the efficacy and determine the optimal dosage of these two nutritional supplements.

In addition, although the results of the forest plot showed that Coenzyme Q10 + Creatine combination therapy had a statistically significant advantage, the SUCRA ranking suggested that they may have the best efficacy. Whey can improve muscle mass, exercise capacity and quality of life in patients with COPD, but the effect of Whey on 6MWD is still inconsistent. A meta-analysis suggested that although Whey improved muscle mass and nutritional status in COPD patients, the effect on 6MWD was not significant ($p>0.05$). This may be related to the intervention dose, course of treatment or the patient ‘s baseline nutritional status.[86] In addition, most of the studies included in this analysis had small sample sizes, which significantly reduces the confidence in ranking treatment effects.

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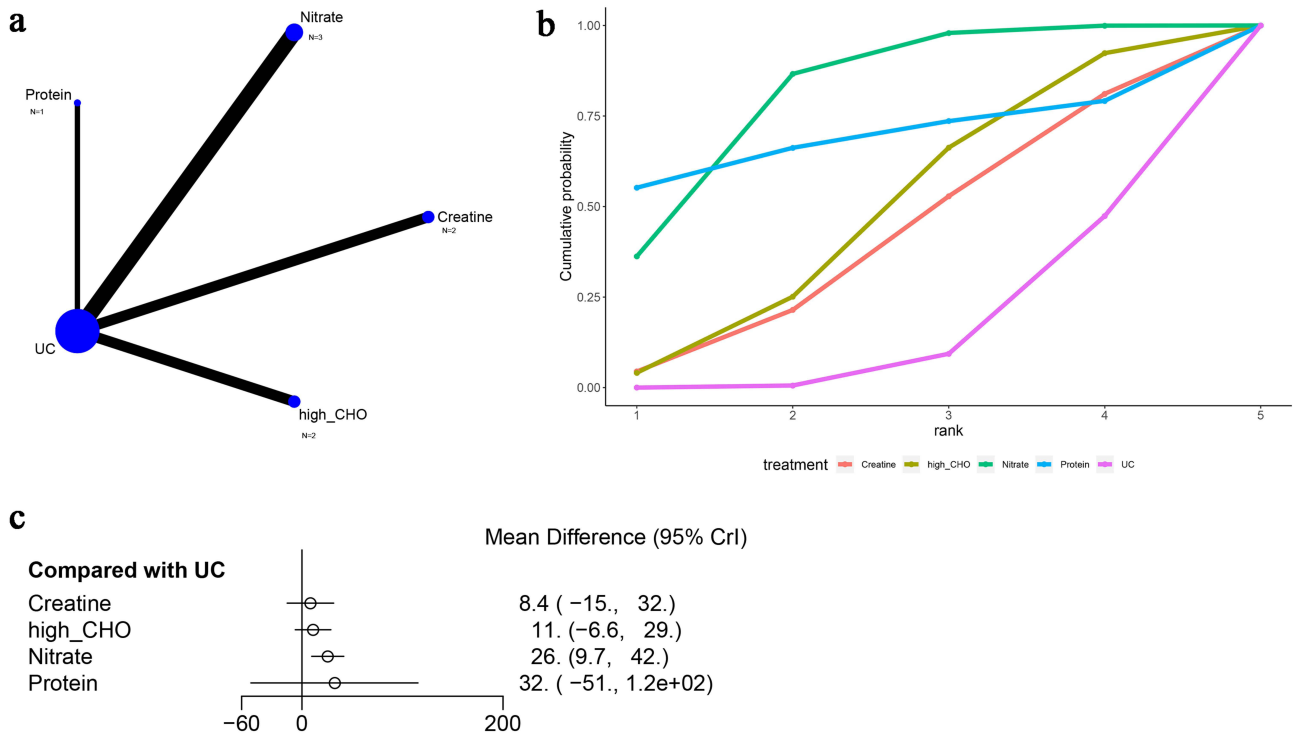

Figure 7 Meta analysis of ISWT ((**a**): Network plot: (**b**): area under the cumulative probability curve: (**c**): forest plot) The number on each edge indicates the trials included in the direct comparison.
Abbreviations: UC, Unhandled Control Group; high_CHO, High Carbohydrate.

Additionally, studies have shown that nitrate supplementation can increase blood nitrate/nitrite levels, thereby improving exercise endurance.[87] This is consistent with our findings-nitrate supplementation can increase 6MWD and ISWT in COPD patients. The underlying mechanism may involve nitrate entering the bloodstream, where it is converted into nitric oxide (NO). NO helps to dilate blood vessels, enhancing blood flow and improving the transport of oxygen to hypoxic regions or skeletal muscles.[88] This process increases the efficiency of mitochondrial oxidative phosphorylation, reduces oxygen consumption, and enhances the availability of nitric oxide synthase (NOS) substrates.[89,90] Nitrite has also been shown to reduce pulmonary artery pressure during hypoxia.[91] However, direct consumption of nitrite may lead to the formation of carcinogenic nitrosamines, which could have harmful effects. Despite this, two previous meta-analyses [26,27] indicated that nitrate supplementation was ineffective in improving 6MWD. However, a meta-subgroup analysis suggested that nitrate supplementation could improve ISWT in COPD patients.[26] These two meta-analyses included patients with acute exacerbations of COPD. During acute exacerbations, patients experience increased dyspnea and a sharp decline in exercise capacity, which may weaken or obscure the efficacy of nutritional supplementation. In contrast, the patients in our study were in the stabilization phase, with relatively better exercise tolerance. Additionally, due to differences in inclusion criteria, only one randomized controlled trial on Nitrate to improve 6MWD was included in this study, which was not part of the previous meta-analyses.[26,27] The quality of this trial was high, with Nitrate administered at higher doses and for a longer duration compared to earlier studies, which may have made it easier to observe efficacy. Therefore, further confirmation is needed through larger prospective randomized controlled trials that explore varying doses, treatment durations, and well-designed methodologies.

Among all the nutritional supplementation therapies, Nanocurcumin demonstrated the most significant improvement in lung function. COPD is characterized by chronic inflammation and oxidative stress in the airways and lungs, including infiltration of alveolar macrophages and neutrophils, protease-antiprotease imbalance, and increased apoptosis of lung epithelial cells and endothelial cells.[92] Curcumin is a polyphenolic compound with various biological activities such as anti-oxidation, anti-inflammation, immune regulation, anti-cancer and anti-mutagenesis.[93] The phenolic hydroxyl and β-diketone groups in its molecular structure can directly scavenge free radicals.[94] In addition, curcumin up-regulated the

expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) by activating the nuclear factor E2-related factor 2(Nrf2) signaling pathway.[95] In the resting state, Nrf2 binds to Keap1 and is degraded by ubiquitination; curcumin promotes the nuclear translocation of Nrf2 by modifying the cysteine residues of Keap1, thereby enhancing antioxidant defense. At the same time, curcumin prevents the degradation of IκB by inhibiting IKK activity, thereby inhibiting the nuclear translocation and transcriptional activity of nuclear factor-κB (NF-κB) and reducing the inflammatory response.[96,97]

In the pathological process of COPD, Th17 cells play a key role in COPD-associated pneumonia by promoting the production of pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and chemokines. Studies have shown that nano-curcumin can significantly reduce the number of Th17 cells and related inflammatory cytokines in patients with moderate to severe COPD, while promoting the differentiation of Treg cells and enhancing immune tolerance, thereby improving lung function by regulating the inflammatory environment.[98] A meta-analysis also showed that curcumin can inhibit the thickening and proliferation of alveolar epithelial cells in patients with COPD, reduce inflammation, reshape airway structure, reduce the production of reactive oxygen species, alleviate airway inflammation, delay the progression of emphysema, and prevent ischemic complications.[99]

In terms of lung function improvement, a previous meta-analysis of vitamin C supplementation in COPD patients[25] found that vitamin C can significantly improve FEV_1% and FEV_1/ FVC. The pairwise comparison results of this network meta-analysis showed that nano-curcumin was superior to vitamin C in improving $FEV_{1\%}$, further supporting the potential of curcumin in improving lung function. In addition, animal experiments showed that curcumin treatment for 10 days could significantly reduce airway inflammation and remodeling in COPD mice induced by vanilla smoke (LC), and inhibit the proliferation of BEAS-2B cells, suggesting that it had a preventive effect on airway remodeling and inflammatory response mediated by bronchial epithelial cells.[100] Nanocurcumin is encapsulated in nanocarriers (such as liposomes, nanoparticles, micelles, etc.) by nanotechnology to improve its bioavailability and therapeutic effect. However, COPD patients often use inhaled hormones, bronchodilators and other drugs. Curcumin may affect the efficacy through liver enzyme induction, so it is necessary to be alert to potential risks.[101] At present, most studies are still limited to animal experiments. In the future, more RCTs are needed to verify its clinical efficacy and promote its clinical application.

Limitation

There are some limitations to this study: First, most of the randomized controlled trials included had a sample size of less than 50 cases, and the contrast-corrected funnel plot showed publication bias, which may lead to high estimates of treatment effects. This bias is particularly prominent in small sample studies, which are more likely to produce extreme effect sizes. Methodological modeling studies suggest that the effect size may be overestimated by 30–50% in mesh meta-analyses consisting entirely of small sample studies.[102] Therefore, we suggest that future studies should focus on conducting large randomized controlled trials to validate the findings of this study.

Conclusion

In our analysis, Coenzyme Q10+Creatine had the most significant effect on improving exercise endurance, while nano-curcumin had the most effective effect on improving lung function. However, at present, the impact of single nutrients may be relatively limited, and comprehensive nutrition assessment and personalized intervention are gradually becoming an important part of COPD management. Personalized nutrition intervention can provide accurate nutritional support according to the patient ‘s metabolic status, nutritional needs and disease characteristics. For example, supplementation with antioxidants (such as nanocurcumin, vitamin C, vitamin E) and anti-inflammatory nutrients may help to reduce oxidative damage and inflammatory response, thereby improving lung function and quality of life. Therefore, future research should pay more attention to the development and optimization of comprehensive nutrition intervention strategies, combined with the synergy of multiple nutrients, to provide more effective personalized treatment options for COPD patients.

Data Sharing Statement

All data generated or analyzed in the course of this study are included in this published article.

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Disclosure

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