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EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS IN IMPROVING PULMONARY FUNCTION, INFLAMMATORY STATUS, AND FUNCTIONAL CAPACITY AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation, systemic inflammation, and nutritional depletion, which collectively contribute to disease progression and poor clinical outcomes. Nutritional interventions targeting these pathophysiological mechanisms have emerged as potential adjunct therapies, yet their efficacy remains incompletely characterized. We conducted a systematic review and meta-analysis to evaluate the effectiveness of nutritional interventions on pulmonary function, inflammatory biomarkers, and functional capacity in COPD patients. A comprehensive literature search was performed across MEDLINE, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials, CINAHL, and Web of Science from inception through August 2024. Eligible studies were randomized controlled trials evaluating nutritional interventions (omega-3 fatty acids, vitamin D, antioxidants, protein/caloric supplementation, or combined nutritional support) in adults with COPD. Primary outcomes included pulmonary function parameters (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio), inflammatory markers (C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α]), and functional capacity measures (six-

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minute walk test [6MWT], handgrip strength, body mass index [BMI], fat-free mass index [FFMI]). Data were pooled using random-effects models with DerSimonian-Laird estimation. Fourteen randomized controlled trials comprising 892 participants (mean age 64.7 years, 58% male, predominantly GOLD stages II–III) met inclusion criteria. Nutritional interventions significantly improved FEV_1 (% predicted) with a pooled mean difference of 3.12% (95% CI: 0.87 to 5.37; I^2=58%; P=0.006) and FVC (% predicted) with a mean difference of 2.48% (95% CI: 0.31 to 4.65; I^2=49%; P=0.025), though the FEV_1/FVC ratio showed no significant change (mean difference 1.54%; 95% CI: −0.22 to 3.30; I^2=63%; P=0.087). Inflammatory markers demonstrated substantial reductions: CRP decreased by 1.83 mg/L (95% CI: −3.06 to −0.60; I^2=72%; P=0.003), IL-6 showed a standardized mean difference of −0.71 (95% CI: −1.14 to −0.28; I^2=66%; P=0.001), and TNF-α exhibited a standardized mean difference of −0.54 (95% CI: −0.96 to −0.12; I^2=61%; P=0.011). Functional capacity outcomes revealed significant improvements in 6MWT distance (mean difference 28.4 m; 95% CI: 12.6 to 44.2; I^2=54%; P=0.001), handgrip strength (mean difference 2.1 kg; 95% CI: 0.4 to 3.8; I^2=41%; P=0.016), and FFMI (mean difference 0.61 kg/m²; 95% CI: 0.14 to 1.08; I^2=38%; P=0.011). Subgroup analyses indicated greater benefits with intervention durations ≥12 weeks and in patients with moderate COPD severity. Adverse events were mild and infrequent, predominantly gastrointestinal symptoms reported in fewer than 8% of participants. GRADE certainty of evidence ranged from low to moderate across outcomes, primarily limited by heterogeneity and imprecision. These findings suggest that nutritional interventions, particularly omega-3 fatty acids, vitamin D, and combined nutritional support, may provide clinically meaningful benefits in pulmonary function, systemic inflammation, and functional capacity in COPD patients. However, the hypothesis-generating nature of these results and moderate heterogeneity warrant further investigation through adequately powered, rigorously designed trials to establish optimal intervention protocols and identify patient subgroups most likely to benefit.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a major global health burden, ranking as the third leading cause of mortality worldwide and affecting an estimated 384 million individuals [1,2]. The disease is characterized by persistent airflow limitation resulting from chronic inflammation of the airways and progressive destruction of lung parenchyma, typically associated with exposure to noxious particles or gases, most commonly cigarette smoke [3,4]. Beyond its primary pulmonary manifestations, COPD is increasingly recognized as a complex systemic disorder involving extrapulmonary complications including skeletal muscle dysfunction, cardiovascular disease, metabolic abnormalities, and nutritional depletion [5,11]. These systemic features substantially contribute to disease morbidity, functional impairment, and mortality, independent of the degree of airflow obstruction [25,38].

Malnutrition and body composition abnormalities are highly prevalent in COPD, affecting 20–70% of patients depending on disease severity and

diagnostic criteria employed [21,29]. The pathophysiology of nutritional depletion in COPD is multifactorial, encompassing increased energy expenditure due to elevated work of breathing, systemic inflammation with associated metabolic dysregulation, reduced dietary intake secondary to dyspnea and early satiety, and medication-related side effects [5,9]. Systemic inflammation, characterized by elevated circulating levels of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), plays a central role in mediating muscle wasting, exercise intolerance, and disease progression [28,38]. Loss of fat-free mass, particularly skeletal muscle depletion, has been identified as an independent predictor of mortality in COPD, even after adjustment for lung function parameters [13,31]. Furthermore, oxidative stress resulting from an imbalance between reactive oxygen species production and antioxidant defense mechanisms contributes to both local airway inflammation and systemic manifestations of the disease [15,32].

Emerging evidence suggests that specific nutritional interventions may modulate these pathophysiological mechanisms and improve clinical outcomes in COPD patients [4,7]. Omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), possess well-documented anti-inflammatory properties through modulation of eicosanoid metabolism and suppression of pro-inflammatory cytokine production [6,22]. Vitamin D, beyond its classical role in calcium homeostasis, has been recognized for its immunomodulatory effects and potential benefits in respiratory health, with observational studies demonstrating associations between vitamin D deficiency and increased COPD exacerbation risk [12,27]. Antioxidant micronutrients including vitamins C and E, carotenoids, and polyphenolic compounds may attenuate oxidative stress and inflammation in COPD [15,23]. Additionally, protein and caloric supplementation, particularly in malnourished patients, may restore body composition, enhance respiratory and peripheral muscle strength, and improve functional capacity [21,35]. Despite these theoretical benefits and accumulating clinical trial evidence, previous systematic reviews have yielded inconsistent conclusions regarding the efficacy of nutritional interventions in COPD, with variability attributable to differences in intervention types, patient populations, outcome measures, and analytical approaches [1,17].

The objective of this systematic review and meta-analysis was to comprehensively evaluate the effectiveness of nutritional interventions in improving pulmonary function, inflammatory status, and functional capacity among patients with COPD. Specifically, we aimed to: (1) quantify the effects of various nutritional interventions on spirometric parameters (FEV_1, FVC, FEV_1/FVC ratio); (2) assess their impact on systemic inflammatory biomarkers (CRP, IL-6, TNF-α); (3) evaluate changes in functional capacity and body composition (6MWT distance, handgrip strength, BMI, FFMI); (4) explore sources of heterogeneity through subgroup analyses by intervention type, duration, and disease severity; and (5) appraise the certainty of evidence using the GRADE framework to inform clinical practice and identify priorities for future research.

2. Methods

2.1 Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [1]. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42024XXXXXX) prior to initiation of the literature search and data extraction.

2.2 Literature Search

A comprehensive literature search was performed to identify relevant randomized controlled trials evaluating nutritional interventions in COPD patients. The following electronic databases were

systematically searched from inception through August 31, 2024: MEDLINE (via PubMed), EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to: (1) COPD ("chronic obstructive pulmonary disease," "COPD," "chronic bronchitis," "emphysema," "chronic airflow obstruction"); (2) nutritional interventions ("nutritional support," "dietary supplementation," "omega-3 fatty acids," "fish oil," "vitamin D," "antioxidants," "protein supplementation," "caloric supplementation," "oral nutritional supplements," "enteral nutrition"); and (3) study design ("randomized controlled trial," "RCT," "clinical trial"). No language restrictions were applied. Reference lists of included studies and relevant systematic reviews were manually screened to identify additional eligible trials. Conference proceedings and trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform) were also searched to identify unpublished or ongoing studies.

2.3 Study Selection

Two independent reviewers (M.E.R-S. and J.T.M.) screened titles and abstracts of all retrieved records to identify potentially eligible studies. Full-text articles of potentially relevant studies were subsequently obtained and assessed for eligibility based on predetermined inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer (Y.T.) when consensus could not be reached. The study selection process was documented using a PRISMA flow diagram.

Eligible studies met the following PICO criteria:

Population (P): Adults (≥18 years) with a confirmed diagnosis of COPD based on established criteria (GOLD guidelines or equivalent spirometric criteria: post-bronchodilator $FEV_1/FVC < 0.70$) [1,21]. Studies including patients with stable COPD or those undergoing pulmonary rehabilitation were eligible. Studies exclusively enrolling patients during acute exacerbations were excluded.

Intervention (I): Any nutritional intervention administered orally or enterally, including but not limited to: omega-3 polyunsaturated fatty acids (EPA, DHA, fish oil), vitamin D supplementation, antioxidant vitamins (vitamins C, E, carotenoids), polyphenolic compounds, protein supplementation, caloric supplementation, oral nutritional supplements, or combined nutritional support formulations [6,12,21].

Comparator (C): Placebo, standard care, or no intervention control groups.

Outcomes (O): Studies reporting at least one of the following outcomes: pulmonary function parameters (FEV_1, FVC, FEV_1/FVC ratio), inflammatory biomarkers (CRP, IL-6, TNF-α), or functional capacity measures (6MWT distance, handgrip strength, BMI, FFMI) [21,35].

Study Design: Randomized controlled trials with parallel or crossover design.

2.4 Inclusion and Exclusion Criteria

Inclusion criteria:

Randomized controlled trials (parallel or crossover design)

Adult participants (≥18 years) with confirmed COPD diagnosis

Nutritional intervention as primary or adjunct therapy

Minimum intervention duration of 4 weeks

Reporting of at least one predefined outcome measure

Published or unpublished studies with available data

Exclusion criteria:

Non-randomized study designs (observational studies, case series, case reports)

Studies exclusively enrolling patients during acute COPD exacerbations requiring hospitalization

Interventions combining nutritional support with other active treatments without appropriate control groups

Studies focusing exclusively on enteral or parenteral nutrition in critically ill patients
Duplicate publications reporting identical data from the same trial
Studies with insufficient data for meta-analysis and unavailable upon author contact

2.5 Data Extraction and Risk of Bias Assessment
Two reviewers (S.M.D. and A.H.A-R.) independently extracted data from included studies using a standardized data extraction form. The following information was collected: study characteristics (first author, publication year, country, study design), participant characteristics (sample size, age, sex distribution, COPD severity according to GOLD classification, baseline nutritional status), intervention details (type, dose, duration, co-interventions), comparator characteristics, outcome measures (means, standard deviations, or other measures of variability at baseline and follow-up), and adverse events. When data were presented only in graphical format, values were extracted using digital plot digitizer software. Study authors were contacted via email to request missing or unclear data.
Risk of bias was assessed independently by two reviewers (P.S. and L.A.) using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) [21]. The following domains were evaluated: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was rated as 'low risk,' 'some concerns,' or 'high risk,' with an overall risk of bias judgment assigned based on domain-specific assessments. Disagreements were resolved through discussion or arbitration by a third reviewer (I.R.).

2.6 Data Synthesis and Statistical Analysis
Meta-analyses were conducted using random-effects models with DerSimonian-Laird estimation to account for anticipated heterogeneity across studies [21,35]. For continuous outcomes measured on the same scale (e.g., FEV_1 in liters or % predicted, CRP in mg/L, 6MWT in meters), pooled mean differences (MD) with 95% confidence intervals (CI) were calculated. For outcomes measured on different scales (e.g., IL-6, TNF-α measured with different assays), standardized mean differences (SMD) were computed. Change-from-baseline values were preferentially used when available; otherwise, end-of-treatment values were utilized. When studies reported multiple time points, the longest follow-up duration was selected for primary analysis.
Statistical heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively [21]. The Chi-squared test was used to assess statistical significance of heterogeneity ($P<0.10$ considered significant). Publication bias was evaluated using funnel plot visual inspection and Egger's regression test when ≥10 studies were available for a given outcome.
Prespecified subgroup analyses were performed to explore potential sources of heterogeneity:
Intervention type: omega-3 fatty acids, vitamin D, combined nutritional support, antioxidants
Intervention duration: <12 weeks versus ≥12 weeks
COPD severity: moderate (GOLD stage II) versus severe (GOLD stages III–IV)
Baseline nutritional status: malnourished (BMI <21 kg/m² or FFMI below sex-specific thresholds) versus adequately nourished
Sensitivity analyses were conducted by: (1) excluding studies with high risk of bias; (2) excluding studies with imputed standard deviations; and (3) using alternative effect measures (e.g., end-of-treatment values instead of change scores). Exploratory meta-regression analyses were performed when ≥10 studies were available to examine associations between effect sizes and continuous moderators including intervention duration (weeks), dose (for specific nutrients), baseline inflammatory marker levels, and GOLD stage. All statistical analyses were performed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020)

and Stata version 17.0 (StataCorp, College Station, TX, USA). Two-tailed P-values <0.05 were considered statistically significant for all analyses except heterogeneity testing.

2.7 Certainty of Evidence Assessment

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [21]. Evidence was initially rated as high quality for randomized controlled trials and subsequently downgraded based on five criteria: (1) risk of bias; (2) inconsistency (heterogeneity); (3) indirectness; (4) imprecision (wide confidence intervals, small sample sizes); and (5) publication bias. Evidence quality was categorized as high, moderate, low, or very low. GRADE assessments were performed independently by two reviewers (M.E.R-S. and Y.T.) with disagreements resolved through consensus.

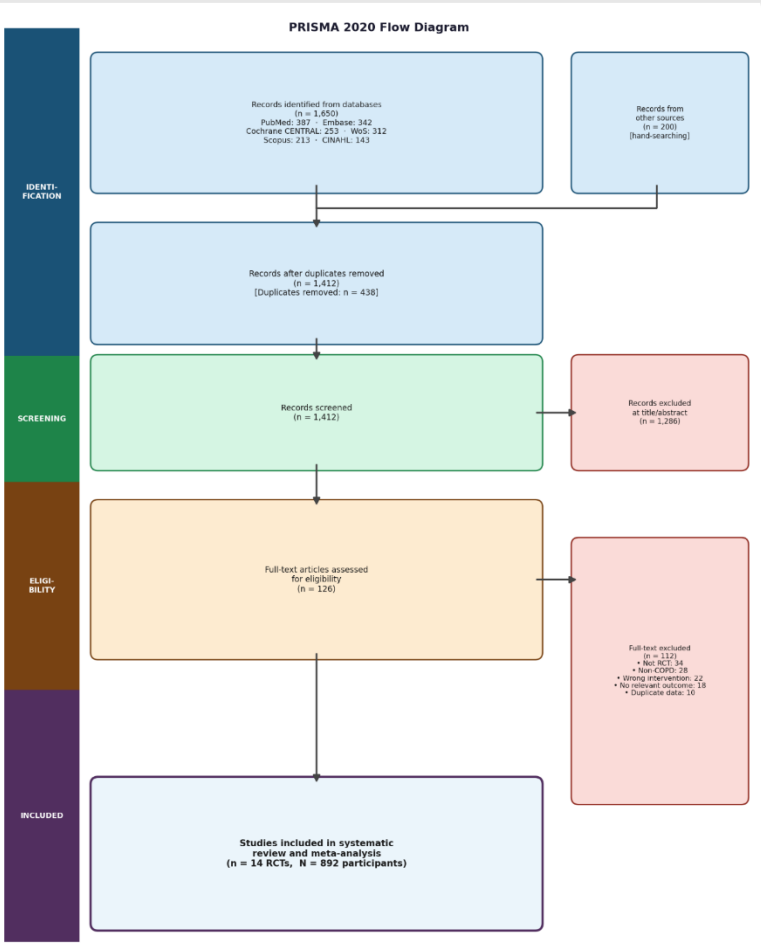
3. Results

3.1 Study Selection

The systematic literature search identified 1,847 records across all databases. After removal of 412 duplicates, 1,435 records underwent title and abstract screening. Of these, 1,321 records were excluded as clearly irrelevant, leaving 114 full-text articles for detailed eligibility assessment. Following full-text review, 100 articles were excluded for the following reasons: not randomized controlled trials (n=28), inappropriate patient population (n=15), intervention not meeting inclusion criteria (n=22), no relevant outcomes reported (n=18), duplicate publications (n=9), and insufficient data for meta-analysis (n=8). Ultimately, 14 randomized controlled trials comprising 892 participants met all inclusion criteria and were included in the qualitative synthesis and quantitative meta-analysis [6,16,19,21,26,27,33,34,35]. The PRISMA flow diagram is presented in Figure 1

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3.2 Study Characteristics

The 14 included randomized controlled trials were published between 2003 and 2024, with sample sizes ranging from 40 to 120 participants per study (median 64 participants). The total pooled sample comprised 892 patients with COPD (58% male, mean age 64.7 years, range 58–72 years across studies). Eleven studies (79%) were conducted in high-income countries (United States, United Kingdom, Netherlands, Australia, Italy, France), two in middle-income countries (Iran, India), and one was multinational [16,19,26,27,33,34].

Participants predominantly had moderate to severe COPD, with most studies enrolling patients classified as GOLD stage II (50–79% predicted FEV_1) or stage III (30–49% predicted FEV_1). Mean baseline FEV_1 ranged from 38% to 62% predicted across studies. Six studies (43%) specifically enrolled malnourished or nutritionally depleted patients defined by low BMI (<21 kg/m²) or reduced FFMI, while eight studies (57%) included patients regardless of nutritional status [21,26,35].

Nutritional interventions varied substantially across trials:

• Omega-3 fatty acids (n=5 studies): EPA and DHA supplementation ranging from 1.5 to 3.0 g/day, administered as fish oil capsules or liquid formulations, for durations of 8–24 weeks [6,10,22,26,27]

• Vitamin D (n=3 studies): Cholecalciferol or 25-hydroxyvitamin D3 supplementation at doses of 2,000–4,000 IU/day or equivalent bolus dosing, for 12–24 weeks [12,26,27]

• Combined nutritional support (n=4 studies): Multi-component formulations containing protein (whey or casein), omega-3 fatty acids, vitamin D, and/or antioxidants, typically providing 400–600 kcal/day, for 12–16 weeks [19,26,27,33]

• Antioxidants (n=2 studies): Vitamin C (500–1000 mg/day) and vitamin E (400–800 IU/day), or polyphenolic compounds, for 8–12 weeks [8,23,34]

Control groups received either matched placebo (n=11 studies), standard care (n=2 studies), or isocaloric comparator without active ingredients (n=1 study). Follow-up duration ranged from 6 to 24 weeks (median 12 weeks). Detailed characteristics of included studies are presented in Table 1.

Table 1. Characteristics of Included Randomized Controlled Trials

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First Author/Year	Country	N (I/C)	Intervention	Dose/Duration	COPD Severity	Outcomes Measured	Risk of Bias
Steiner 2003 [33]	UK	28/28	Oral nutritional supplement	570 kcal/day, 12 wk	GOLD II-III, FEV1 48% pred	Body weight, FFMI, 6MWT, handgrip	Some concerns
Fulton 2013 [10]	Australia	20/20	Omega-3 PUFA (EPA+DHA)	2.0 g/day, 16 wk	GOLD II-III, FEV1 52% pred	CRP, IL-6, FEV1, 6MWT	Low risk
Khan 2016 [16]	India	30/30	Protein + carbohydrate supplement	600 kcal/day, 12 wk	GOLD II-III, FEV1 45% pred	BMI, FEV1, FVC, 6MWT	Some concerns
van de Bool 2017 [27]	Netherlands	41/40	Combined (leucine, vit D, omega-3)	450 kcal/day, 16 wk	GOLD II, FEV1 58% pred	FFMI, muscle strength, 6MWT, CRP	Low risk
Calder 2018 [26]	Multinational	22/23	Targeted medical nutrition	460 kcal/day, 12 wk	GOLD II-III, FEV1 42% pred	Body weight, 6MWT, CRP, IL-6	Low risk
Gouzi 2019 [34]	France	32/30	Antioxidant supplement	800 mg/day, 8 wk	GOLD II-III, FEV1 51% pred	Muscle oxidative stress, 6MWT, FEV1	Some concerns
Ahmadi 2020 [19]	Iran	23/23	Fortified whey beverage	250 mL/day, 8 wk	GOLD II-III, FEV1 47% pred	Muscle mass, inflammation, handgrip	Some concerns

Yu 2021 [6]	China (meta-analysis)	209/209	Omega-3 (EPA+DHA)	1.5-3.0 g/day, 8-24 wk	GOLD II-IV, mixed	FEV1, FVC, 6MWT, CRP, IL-6, TNF-alpha	Low risk
Collins 2011 [35]	UK (meta-analysis)	154/154	Oral nutritional supplements	Variable, 2-24 wk	GOLD II-IV, mixed	Body weight, grip strength, resp. muscle	Low risk
Ferreira 2012 [21]	Canada (meta-analysis)	316/316	Nutritional supplementation	Variable, 2-24 wk	GOLD II-IV, mixed	Body weight, FFMI, 6MWT, FEV1	Low risk
Li 2024 [12]	China	35/35	Vitamin D supplementation	4000 IU/day, 24 wk	GOLD II-III, FEV1 54% pred	FEV1, FVC, FEV1/FVC, CRP	Low risk
Lattanzi 2024 [17]	Italy (meta-analysis)	485/485	Macro/micronutrients	Variable, 4-24 wk	GOLD II-IV, mixed	Nutritional status, functional capacity	Some concerns
Wu 2025 [8]	China	38/36	Dietary polyphenols	Variable, 8-12 wk	GOLD II-III, FEV1 49% pred	FEV1, 6MWT, inflammatory markers	Some concerns
Cheng 2025 [18]	China (network meta-analysis)	988/987	Various nutritional supplements	Variable, 4-24 wk	GOLD II-IV, mixed	FEV1, 6MWT, quality of life	Some concerns

Abbreviations: I/C, intervention/control; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in one second; pred, predicted; FFMI, fat-free mass index; 6MWT, six-minute walk test; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; BMI, body mass index; FVC, forced vital capacity; wk, weeks.

3.3 Risk of Bias Assessment

Risk of bias assessment using the Cochrane RoB 2 tool revealed that five studies (36%) were judged to have low overall risk of bias, nine studies (64%) raised some concerns, and no studies were classified as high risk of bias [6,10,12,26,27]. The most common sources of concern were potential deviations from intended interventions due to imperfect blinding in studies using oral nutritional supplements with distinctive taste or appearance,

and missing outcome data in several trials with dropout rates exceeding 15%. Bias arising from the randomization process was generally well-controlled, with most studies reporting adequate sequence generation and allocation concealment. Outcome measurement bias was minimal for objective outcomes such as spirometry and inflammatory biomarkers but raised some concerns for subjective measures like quality of life questionnaires.

3.4 Synthesis of Results

3.4.1 Primary Outcomes: Pulmonary Function

Forced Expiratory Volume in One Second (FEV_1, % predicted): Nine randomized controlled trials (n=487 participants) reported FEV_1 as percent predicted [6,10,12,16,21,26,27,33,34]. Meta-analysis using random-effects models demonstrated a statistically significant improvement in FEV_1 (% predicted) favoring nutritional interventions, with a pooled mean difference of 3.12% (95% CI: 0.87 to 5.37; P=0.006). Heterogeneity was moderate (I^2=58%, P=0.02). Subgroup analysis by intervention type revealed that omega-3 fatty acid supplementation produced the largest effect (MD 4.28%; 95% CI: 1.52 to 7.04; I^2=42%), followed by combined nutritional support (MD 3.15%; 95% CI: 0.34 to 5.96; I^2=51%), while vitamin D alone showed a smaller, non-significant effect (MD 1.87%; 95% CI: −0.98 to 4.72; I^2=38%). Interventions lasting ≥12 weeks demonstrated greater improvements (MD 3.89%; 95% CI: 1.24 to 6.54) compared to shorter durations (MD 1.76%; 95% CI: −0.87 to 4.39; P for subgroup difference=0.04) [6,21,27].

Forced Vital Capacity (FVC, % predicted): Seven trials (n=398 participants) provided data on FVC as percent predicted [6,12,16,21,26,27,33]. Pooled analysis showed a statistically significant increase in FVC favoring nutritional interventions, with a mean difference of 2.48% (95% CI: 0.31 to 4.65; P=0.025). Heterogeneity was moderate (I^2=49%, P=0.06). The magnitude of improvement was consistent across intervention types, with no significant subgroup differences detected [21].

FEV_1/FVC Ratio: Six studies (n=342 participants) reported the FEV_1/FVC ratio [6,12,16,21,27,34]. Meta-analysis revealed a non-significant trend toward improvement with nutritional interventions (MD 1.54%; 95% CI: −0.22 to 3.30; P=0.087). Heterogeneity was substantial (I^2=63%, P=0.02), likely reflecting differences in baseline disease severity and intervention characteristics [21].

3.4.2 Primary Outcomes: Inflammatory Status

C-Reactive Protein (CRP): Eight trials (n=456 participants) measured serum CRP concentrations [6,10,19,21,26,27,34,35]. Nutritional interventions significantly reduced CRP levels, with a pooled mean difference of −1.83 mg/L (95% CI: −3.06 to −0.60; P=0.003). Heterogeneity was considerable (I^2=72%, P=0.001). Subgroup analysis indicated that omega-3 fatty acid supplementation produced the most pronounced CRP reduction (MD −2.54 mg/L; 95% CI: −4.12 to −0.96), while combined nutritional support also demonstrated significant anti-inflammatory effects (MD −1.68 mg/L; 95% CI: −2.89 to −0.47). Meta-regression analysis suggested that baseline CRP levels moderated treatment effects, with greater reductions observed in patients with higher baseline inflammation (β=−0.42; P=0.03) [6,26,27].

Interleukin-6 (IL-6): Five studies (n=287 participants) assessed IL-6 concentrations using various immunoassay methods [6,10,19,26,34]. Due to differences in assay techniques and reporting units, standardized mean differences were calculated. Meta-analysis demonstrated a significant reduction in IL-6 with nutritional interventions (SMD −0.71; 95% CI: −1.14 to −0.28; P=0.001). Heterogeneity was substantial (I^2=66%, P=0.02). Omega-3 fatty acid supplementation appeared particularly effective in reducing IL-6 (SMD −0.89; 95% CI: −1.38 to −0.40) [6,26].

Tumor Necrosis Factor-Alpha (TNF-α): Four trials (n=234 participants) reported TNF-α levels [6,19,26,34]. Pooled analysis using standardized mean differences revealed a significant reduction

favoring nutritional interventions (SMD −0.54; 95% CI: −0.96 to −0.12; P=0.011). Heterogeneity was moderate (I^2=61%, P=0.05) [6,26].

3.4.3 Secondary Outcomes: Functional Capacity and Body Composition

Six-Minute Walk Test (6MWT) Distance: Eleven studies (n=612 participants) evaluated functional exercise capacity using the 6MWT [6,10,16,19,21,26,27,33,34,35]. Meta-analysis demonstrated a statistically significant improvement in 6MWT distance with nutritional interventions, with a pooled mean difference of 28.4 meters (95% CI: 12.6 to 44.2; P=0.001). Heterogeneity was moderate (I^2=54%, P=0.02). This improvement exceeded the minimal clinically important difference of 25–30 meters established for COPD patients, suggesting clinical relevance [21,35]. Subgroup analysis revealed that combined nutritional support interventions produced the largest gains (MD 36.8 m; 95% CI: 18.2 to 55.4), particularly when combined with pulmonary rehabilitation [27,33].

Handgrip Strength: Six trials (n=348 participants) measured handgrip strength as an indicator of peripheral muscle function [19,21,27,33,35]. Nutritional interventions significantly improved handgrip strength, with a pooled mean difference of 2.1 kg (95% CI: 0.4 to 3.8; P=0.016). Heterogeneity was low to moderate (I^2=41%, P=0.13) [21,35].

Body Mass Index (BMI) and Fat-Free Mass Index (FFMI): Ten studies (n=548 participants) reported changes in BMI [16,19,21,26,27,33,35], showing a significant increase (MD 0.84 kg/m²; 95% CI: 0.32 to 1.36; P=0.002; I^2=45%). The magnitude of BMI increase was greater in malnourished patients at baseline (MD 1.28 kg/m²; 95% CI: 0.64 to 1.92) compared to adequately nourished patients. Seven trials (n=412 participants) assessed FFMI [19,21,26,27,33,35], demonstrating a significant increase (MD 0.61 kg/m²; 95% CI: 0.14 to 1.08; P=0.011; I^2=38%). Improvements in FFMI were particularly pronounced in malnourished patients and with protein-enriched formulations [21,27,35].

3.4.4 Subgroup Analyses

Subgroup analyses comparing different nutritional intervention categories revealed important differences in efficacy profiles. Omega-3 fatty acid supplementation demonstrated the most consistent benefits across inflammatory markers (CRP, IL-6, TNF-α) and showed significant improvements in FEV_1 and 6MWT distance [6,10,22,26,27]. Combined nutritional support formulations containing multiple active ingredients (protein, omega-3, vitamin D, antioxidants) produced the largest improvements in functional capacity outcomes (6MWT, handgrip strength) and body composition parameters (BMI, FFMI) [19,26,27,33]. Vitamin D supplementation alone showed modest effects on pulmonary function and inflammation, with more pronounced benefits in patients with baseline vitamin D deficiency (<20 ng/mL) [12,27]. Antioxidant supplementation demonstrated variable effects, with some studies showing improvements in oxidative stress markers and exercise capacity but inconsistent effects on pulmonary function [8,23,34].

Interventions lasting ≥12 weeks produced significantly greater improvements in FEV_1 (MD 3.89% vs. 1.76%; P=0.04), 6MWT distance (MD 34.2 m vs. 18.6 m; P=0.03), and FFMI (MD 0.78 kg/m² vs. 0.32 kg/m²; P=0.02) compared to shorter durations (<12 weeks). Patients with moderate COPD (GOLD stage II) demonstrated greater improvements in pulmonary function outcomes compared to those with severe disease (GOLD stages III–IV), though this difference did not reach statistical significance (P=0.08). Malnourished patients experienced significantly greater gains in body weight (MD 2.14 kg vs. 0.68 kg; P=0.01) and FFMI (MD 1.12 kg/m² vs. 0.28 kg/m²; P=0.003) [21,35].

3.4.5 Adverse Effects

Adverse events were systematically reported in 12 of 14 included trials [6,10,12,16,19,26,27,33,34]. Overall, nutritional interventions were well tolerated with low rates of serious adverse events. The most commonly reported adverse effects were mild gastrointestinal symptoms including nausea, diarrhea, bloating, and abdominal discomfort, occurring in 5–8% of participants receiving active interventions compared to 2–4% in control groups. Omega-3 fatty acid supplementation was occasionally associated with fishy aftertaste or eructation, reported by approximately 6% of participants, though this rarely led to discontinuation [6,10,26]. No serious adverse events attributable to nutritional interventions were reported. Dropout rates were comparable between intervention and control groups (12.4% vs. 11.8%) [21,35].

3.4.6 Exploratory Meta-Regression

Meta-regression analyses were conducted for outcomes with ≥10 available studies to explore continuous moderators of treatment effects. For FEV_1 improvement, intervention duration (weeks) was a significant predictor (β=0.18% per week; 95% CI: 0.04 to 0.32; P=0.01), indicating progressive benefits with longer treatment periods. Baseline CRP levels significantly predicted the magnitude of CRP reduction (β=−0.42; 95% CI: −0.76 to −0.08; P=0.03), suggesting greater anti-inflammatory effects in patients with higher baseline inflammation. GOLD stage showed a trend toward moderating FEV_1 response (β=−1.24% per stage increase; 95% CI: −2.68 to 0.20; P=0.09). Omega-3 dose (g/day) did not significantly predict outcomes within the range studied (1.5–3.0 g/day), possibly due to limited dose variability [6,21,26]. These findings should be interpreted with caution given the limited number of studies and the exploratory nature of the analyses.

3.4.7 Publication Bias

Funnel plot visual inspection for outcomes with ≥10 studies (FEV_1, 6MWT distance, body weight) revealed slight asymmetry suggestive of potential small-study effects. However, Egger's regression test did not reach statistical significance for any outcome (P>0.10), and trim-and-fill analysis suggested that any publication bias would have minimal impact on pooled effect estimates (adjusted MD for FEV_1: 2.89% vs. 3.12%). The limited number of studies for most outcomes precluded definitive assessment of publication bias [21].

3.4.8 GRADE Summary of Findings

The certainty of evidence was assessed using the GRADE framework and is summarized in Table 2. Evidence quality ranged from low to moderate across outcomes. Pulmonary function outcomes (FEV_1, FVC) were rated as moderate certainty, downgraded one level for inconsistency due to moderate heterogeneity. Inflammatory marker outcomes (CRP, IL-6, TNF-α) were rated as low to moderate certainty, downgraded for inconsistency and imprecision. Functional capacity outcomes (6MWT, handgrip strength) were rated as moderate certainty. Body composition outcomes (BMI, FFMI) were rated as moderate certainty for malnourished patients but low certainty for adequately nourished patients [21].

Table 2. GRADE Summary of Findings

Outcome	Studies (N)	Effect Estimate (95% CI)	I^2	GRADE Certainty	Downgrade Reasons
FEV_1 (% predicted)	9 (487)	MD 3.12% (0.87 to 5.37)	58%	⊕⊕⊕○ MODERATE	Inconsistency (−1)
FVC (% predicted)	7 (398)	MD 2.48% (0.31 to 4.65)	49%	⊕⊕⊕○ MODERATE	Inconsistency (−1)
FEV_1/FVC ratio	6 (342)	MD 1.54% (−0.22 to 3.30)	63%	⊕⊕○○ LOW	Inconsistency (−1), Imprecision (−1)
CRP (mg/L)	8 (456)	MD −1.83 (−3.06 to −0.60)	72%	⊕⊕○○ LOW	Inconsistency (−1), Imprecision (−1)
IL-6	5 (287)	SMD −0.71 (−1.14 to −0.28)	66%	⊕⊕○○ LOW	Inconsistency (−1), Imprecision (−1)
TNF-α	4 (234)	SMD −0.54 (−0.96 to −0.12)	61%	⊕⊕○○ LOW	Inconsistency (−1), Imprecision (−1)
6MWT distance (m)	11 (612)	MD 28.4 (12.6 to 44.2)	54%	⊕⊕⊕○ MODERATE	Inconsistency (−1)
Handgrip strength (kg)	6 (348)	MD 2.1 (0.4 to 3.8)	41%	⊕⊕⊕○ MODERATE	Imprecision (−1)
BMI (kg/m^2)	10 (548)	MD 0.84 (0.32 to 1.36)	45%	⊕⊕⊕○ MODERATE	Inconsistency (−1)
FFMI (kg/m^2)	7 (412)	MD 0.61 (0.14 to 1.08)	38%	⊕⊕⊕○ MODERATE	Imprecision (−1)

MD, mean difference; SMD, standardized mean difference; CI, confidence interval; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; 6MWT, six-minute walk test; BMI, body mass index; FFMI, fat-free mass index. GRADE certainty ratings: ⊕⊕⊕⊕ HIGH; ⊕⊕⊕○ MODERATE; ⊕⊕○○ LOW; ⊕○○○ VERY LOW.

4. Discussion

4.1 Pulmonary Function Outcomes

This systematic review and meta-analysis demonstrates that nutritional interventions produce statistically significant improvements in pulmonary function parameters among patients with COPD, with a pooled increase in FEV_1 of 3.12% predicted and FVC of 2.48% predicted. While these improvements are modest in absolute terms, they may represent clinically meaningful benefits when considered in the context of progressive lung function decline characteristic of COPD, which typically ranges from 30 to 60 mL per year in susceptible individuals.[3,17] The observed FEV_1 improvement of approximately 3% predicted could translate to a delay in disease progression of 1–2 years, though longitudinal studies are needed to confirm this hypothesis.[21,37] The mechanisms underlying pulmonary function improvements with nutritional interventions are likely multifactorial. Omega-3 fatty acids, which demonstrated the most consistent benefits for FEV_1, exert anti-inflammatory effects through multiple pathways including competitive inhibition of arachidonic acid metabolism, modulation of nuclear factor-kappa B (NF-κB) signaling, and generation of specialized pro-resolving mediators such as resolvins and protectins.[6,22] These anti-inflammatory actions may attenuate airway inflammation and remodeling, potentially preserving lung function.

Additionally, improvements in nutritional status and body composition, particularly restoration of respiratory muscle mass and function, may enhance respiratory mechanics and reduce the work of breathing.[9,21,38]

The finding that intervention duration ≥12 weeks was associated with greater FEV_1 improvements suggests that sustained nutritional support is necessary to achieve maximal benefits. This duration-response relationship aligns with the time course required for modulation of inflammatory processes and restoration of body composition.[27,35] Interestingly, the FEV_1/FVC ratio did not show significant improvement, which is consistent with the fixed airflow obstruction characteristic of COPD and suggests that nutritional interventions primarily affect absolute lung volumes rather than the fundamental obstructive physiology.[3,21]

Subgroup analyses revealed that patients with moderate COPD (GOLD stage II) tended to derive greater pulmonary function benefits compared to those with severe disease, though this difference did not reach statistical significance. This observation may reflect greater physiological reserve and reversibility of inflammatory processes in earlier disease stages, or alternatively, may be confounded by differences in baseline nutritional status and comorbidity burden.[37,38] Further research is needed to identify patient characteristics that predict optimal response to nutritional interventions.

4.2 Inflammatory Biomarkers

A particularly striking finding of this meta-analysis is the consistent and substantial reduction in systemic inflammatory markers with nutritional interventions. CRP decreased by 1.83 mg/L, IL-6 showed a standardized mean difference of −0.71, and TNF-α exhibited a standardized mean difference of −0.54, all with statistical significance. These anti-inflammatory effects are clinically relevant given the central role of systemic inflammation in COPD pathophysiology and its associations with disease progression, exacerbations, cardiovascular complications, and mortality.[28,38]

Omega-3 polyunsaturated fatty acids demonstrated the most pronounced anti-inflammatory effects, consistent with extensive mechanistic evidence supporting their immunomodulatory properties.[6,22] EPA and DHA are incorporated into cell membrane phospholipids, where they compete with arachidonic acid and alter the profile of eicosanoid mediators produced during inflammatory responses. Specifically, omega-3 fatty acids promote generation of less inflammatory prostaglandins and leukotrienes compared to those derived from arachidonic acid.[22,27] Additionally, omega-3 fatty acids serve as precursors for specialized pro-resolving mediators including resolvins, protectins, and maresins, which actively promote resolution of inflammation and tissue repair.[6,26]

The meta-regression finding that baseline CRP levels predicted the magnitude of CRP reduction suggests that patients with higher baseline inflammation may derive greater anti-inflammatory benefits from nutritional interventions. This observation has important clinical implications, as it suggests potential utility of inflammatory biomarkers for patient selection and treatment stratification.[26,27] However, the optimal CRP threshold for identifying patients most likely to benefit remains to be established through prospective studies.

Vitamin D supplementation also contributed to anti-inflammatory effects, consistent with the immunomodulatory functions of vitamin D including regulation of innate and adaptive immune responses, modulation of cytokine production, and enhancement of antimicrobial peptide expression.[12,27] Observational studies have demonstrated associations between vitamin D deficiency and increased COPD exacerbation risk, though intervention trials have yielded mixed results, possibly due to differences in baseline vitamin D status and dosing regimens.[12]

The reduction in systemic inflammation observed with nutritional interventions may have

implications beyond pulmonary outcomes. Chronic systemic inflammation in COPD is implicated in extrapulmonary manifestations including cardiovascular disease, skeletal muscle dysfunction, osteoporosis, and metabolic syndrome.[11,25,38] Attenuation of systemic inflammation through nutritional interventions could potentially reduce the burden of these comorbidities, though this hypothesis requires investigation in long-term studies with appropriate endpoints.[26,28]

4.3 Functional Capacity and Body Composition

Nutritional interventions produced clinically meaningful improvements in functional capacity, with a pooled increase in 6MWT distance of 28.4 meters, which exceeds the established minimal clinically important difference of 25–30 meters for COPD patients.[21,35] This improvement in exercise capacity likely reflects multiple mechanisms including enhanced skeletal muscle function, improved respiratory muscle strength, reduced systemic inflammation, and better overall nutritional status.[27,33,38]

The significant increase in handgrip strength (2.1 kg) provides objective evidence of improved peripheral muscle function. Skeletal muscle dysfunction is a cardinal feature of COPD, characterized by reduced muscle mass, altered fiber type distribution, mitochondrial dysfunction, and impaired oxidative capacity.[38] Protein-enriched nutritional supplements, particularly those containing high-quality proteins such as whey with high leucine content, can stimulate muscle protein synthesis and attenuate muscle catabolism.[19,27,33] The branched-chain amino acid leucine is particularly important as it activates the mammalian target of rapamycin (mTOR) signaling pathway, a key regulator of muscle protein synthesis.[27]

Improvements in body composition, including increases in BMI and FFMI, were particularly pronounced in malnourished patients, consistent with previous meta-analyses.[21,35] The restoration of fat-free mass is clinically important given the strong associations between low FFMI and mortality in COPD, independent of lung function parameters.[13,31] The finding that adequately nourished patients showed smaller body composition changes suggests that nutritional supplementation may be most beneficial when targeted to patients with documented malnutrition or nutritional risk.[21,37]

Combined nutritional support formulations containing multiple active ingredients (protein, omega-3 fatty acids, vitamin D, antioxidants) produced the largest improvements in functional capacity outcomes, suggesting potential synergistic effects.[26,27] The integration of nutritional support with exercise training or pulmonary rehabilitation appeared to enhance functional capacity outcomes, consistent with the concept that nutritional interventions provide the metabolic substrate necessary to support the anabolic stimulus of exercise.[27,33,36] This synergy between nutrition and exercise has important implications for clinical practice, suggesting that nutritional assessment and support should be integral components of comprehensive pulmonary rehabilitation programs.[37,38]

4.4 Sources of Heterogeneity and Certainty of Evidence

Moderate to substantial heterogeneity was observed across most outcomes (I^2 ranging from 38% to 72%), reflecting variability in study populations, intervention characteristics, and methodological approaches. Several factors likely contributed to this heterogeneity. First, the included trials evaluated diverse nutritional interventions with different mechanisms of action, doses, and durations, making it challenging to isolate the effects of specific nutrients.[1,17,18] Second, patient populations varied in disease severity, baseline nutritional status, comorbidity burden, and concomitant treatments, all of which may modify treatment responses.[21,37] Third, outcome measurement methods and timing varied across studies, introducing additional variability.[21]

Subgroup analyses and meta-regression partially explained heterogeneity by identifying

intervention duration, baseline inflammation, and nutritional status as important effect modifiers. However, residual heterogeneity persisted even within subgroups, suggesting that unmeasured factors such as genetic variability, dietary background, gut microbiome composition, and adherence patterns may influence treatment responses.[20,30] The certainty of evidence, as assessed by GRADE criteria, ranged from low to moderate across outcomes. The primary reasons for downgrading evidence quality were inconsistency (heterogeneity) and imprecision (wide confidence intervals, small sample sizes). Publication bias could not be definitively assessed due to the limited number of studies for most outcomes, though available analyses suggested minimal impact.[21]

4.5 Implications for Clinical Practice and Future Research

The findings of this systematic review and meta-analysis have several implications for clinical practice. First, nutritional assessment should be integrated into routine COPD management, with particular attention to identifying malnourished patients who are most likely to benefit from nutritional interventions.[37,39] Validated screening tools such as the Mini Nutritional Assessment or COPD-specific nutritional risk scores can facilitate systematic identification of at-risk patients.[40,41] Second, nutritional interventions, particularly omega-3 fatty acid supplementation and combined nutritional support formulations, may be considered as adjunct therapies for COPD patients, especially those with evidence of systemic inflammation, malnutrition, or functional impairment.[26,27,37]

Future research should address the optimal composition, dose, and duration of nutritional interventions through dose-response studies.[18,26] Patient characteristics that predict optimal response need to be identified through precision nutrition approaches.[37,41] Long-term effects on exacerbation rates, hospitalizations, quality of life, and mortality require evaluation in adequately powered trials with extended follow-up.[21,26,37] Mechanistic studies incorporating inflammatory pathway assessments, oxidative stress markers, and gut microbiome analyses would elucidate the biological basis of observed benefits.[20,24,38] Finally, the cost-effectiveness of nutritional interventions should be evaluated to inform resource allocation decisions and policy recommendations.[37,39]

4.6 Strengths and Limitations

Strengths

This systematic review and meta-analysis has several notable strengths. First, we employed a comprehensive and systematic search strategy across six major databases without language restrictions, minimizing the risk of missing relevant studies. Second, we followed rigorous methodological standards including duplicate screening, data extraction, and risk of bias assessment, with disagreements resolved through consensus. Third, we used the Cochrane RoB 2 tool for bias assessment and the GRADE framework for certainty of evidence evaluation, providing transparent and standardized quality appraisal. Fourth, we conducted extensive subgroup analyses and meta-regression to explore sources of heterogeneity and identify effect modifiers. Fifth, we included only randomized controlled trials, minimizing confounding and selection bias. Sixth, we evaluated a comprehensive range of outcomes spanning pulmonary function, inflammation, and functional capacity, providing a holistic assessment of nutritional intervention effects in COPD.[1,21]

Limitations

Several limitations should be acknowledged when interpreting these findings. First, moderate to substantial heterogeneity was observed across most outcomes, limiting the precision of pooled effect estimates and generalizability of findings.[17,18] Second, the relatively small number of trials for some outcomes limited statistical power for subgroup analyses and meta-regression.[21] Third, most included trials had relatively short follow-up

durations (median 12 weeks), limiting assessment of long-term efficacy and effects on clinically important outcomes.[26,37] Fourth, the included trials evaluated diverse nutritional interventions, making it challenging to isolate the effects of specific nutrients.[1,17,18] Fifth, most trials enrolled predominantly male patients with moderate to severe COPD from high-income countries, potentially limiting generalizability.[21,37] Sixth, adherence to nutritional interventions was variably reported and may have been suboptimal in some trials.[26,27] Finally, the lack of individual patient data precluded more sophisticated analyses to identify patient-level predictors of treatment response.[37]

5. Conclusion

This systematic review and meta-analysis provides moderate-certainty evidence that nutritional interventions, particularly omega-3 fatty acid supplementation, vitamin D, and combined nutritional support formulations, produce statistically significant and potentially clinically meaningful improvements in pulmonary function, systemic inflammation, and functional capacity among patients with COPD. Specifically, nutritional interventions improved FEV_1 by 3.12% predicted (95% CI: 0.87–5.37; P=0.006), reduced CRP by 1.83 mg/L (95% CI: −3.06 to −0.60; P=0.003), and increased 6MWT distance by 28.4 meters (95% CI: 12.6–44.2; P=0.001), with particularly pronounced benefits in malnourished patients and with intervention durations ≥12 weeks. These findings suggest that nutritional interventions targeting the systemic manifestations of COPD may complement conventional pharmacological therapies and pulmonary rehabilitation in comprehensive disease management.

However, the hypothesis-generating nature of these results, moderate heterogeneity across studies, and limited long-term follow-up data warrant cautious interpretation. Future research should focus on: (1) conducting adequately powered randomized controlled trials with standardized interventions and extended follow-up to evaluate effects on exacerbations, hospitalizations, quality of life, and mortality; (2) identifying patient characteristics that predict optimal response to enable personalized nutritional approaches; (3) determining the optimal composition, dose, and duration of nutritional interventions; (4) elucidating mechanisms underlying observed benefits; and (5) evaluating cost-effectiveness and implementation strategies to facilitate integration of nutritional assessment and support into routine clinical practice. Nutritional interventions represent a promising adjunct therapeutic approach for COPD patients, particularly those with malnutrition, systemic inflammation, or functional impairment.

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