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ORIGINAL RESEARCH

Effect of Omega-3 Fatty Acids on Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: Omega-3 fatty acid is an emerging hotspot on anti-inflammation and chronic obstructive pulmonary disease (COPD) is known as a chronic inflammatory disease. The effect of Omega-3 fatty acid supplement on patients with COPD remains mixed for insufficient evidence. This systematic review and meta-analysis is based on neat randomized controlled trials trying to give a clearer impression on the effect of Omega-3 on patients with COPD.

Methods: This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statements. Randomized clinical trials (RCTs) published in electronic databases including Medline, Embase, Cochrane Library, ClinicalTrials.gov and China National Knowledge Infrastructure (CNKI) by May 10, 2021 were searched. Data extracted from 6 predetermined domains (nutritional condition, lipid composition, inflammatory biomarker, lung function, physical endurance and quality of life [QoL]) were reviewed and analyzed.

Results: A total of 8 RCTs evaluating 418 patients (age, mean [SD] = 67.3 [10.2] years) were included. Statistical differences were found in 3 parameters of 3 domains – weight (Wt) (0.25 [95% CI, 0.02 to 0.48], $P = 0.03$) in nutritional condition, low-density lipoprotein (LDL) (0.70 [95% CI, 0.30 to 1.10], $P = 0.00$) in lipid composition and interleukin-6 (IL-6) level (−0.32 [95% CI, −0.60 to −0.05], $P = 0.02$) in inflammatory biomarker – while no significant difference was found in lung function, physical endurance or QoL.

Conclusion: Comparing with placebo, Omega-3 intake was associated with more weight-gaining, LDL increase and IL-6 reduction. These results should be interpreted cautiously for the quality and quantity of available evidence are limited.

Keywords: COPD, omega-3 fatty acids, systematic review and meta-analysis

Introduction

Around the globe, COPD is now a tremendous social and medical burden with a point prevalence of 3.92% and the third highest mortality of 41.9 deaths per 100,000 a year.[1,2] COPD is characterized by incompletely reversible limitation and chronic inflammation of the airway.[2] Chronic inflammation locally causes reconstruction of the airway and systematically leads to weight loss. Moreover, weight loss was confirmed as an independent risk factor of mortality in COPD patients.[3,4] Therefore, exerting intervention on COPD patients' nutritional and inflammatory condition is vital to improve patients' life quality and lighten the relative social burden.

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Omega-3 fatty acids, also named n-3 poly-unsaturated fatty acids (n-3 PUFAs), are a special kind of lipid found to be a weight promoter in cachexia cancer patients.[5,6] It is widely discussed as a potential anti-inflammatory factor,[7] and has become a potential therapy method on anti-acute /chronic inflammation. It has lots of pathways that Omega-3 may have to function as an anti-inflammation factor mainly including competitively inhibiting Omega-6's metabolism,[8] directly or indirectly downregulating nuclear factor kappa-B (NF-$\varkappa$B).[9] Theoretically, Omega-3 can reduce local or systemic inflammation to furthermore improve patients' body weight, muscle volume and responses of other medical interventions and finally promote QoL through these pathways.[7,10]

Omega-3 has been discussed in many studies but its reported results on several respiratory diseases were inconsistent. A 2019 meta-analysis about Omega-3 and acute respiratory distress syndrome (ARDS) indicates that Omega-3 enteral supplement may be associated with an improvement in partial arterial O_2 pressure (PaO_2) to fraction of inspiration O_2 (FiO2) ratio (PaO_2/FiO_2).[11] While results of a 2006 systematic review and a 2009 meta-analysis about Omega-3 and asthma show unignorable inconsistency to aforementioned theoretical deductions.[12,13]

Based on previous practices on other respiratory diseases and its theoretical potential, a hypothesis presented that Omega-3 intake may be beneficial in COPD patients.[14] Even though lots of observational studies reported results that seems to support the beneficial effect of Omega-3 on COPD patients, almost the same number of reports exist with contrary results, and a 2015 meta-analysis based on such studies concluded these evidences as "paucity".[15]

Recently, more randomized controlled trials (RCTs) about COPD have been published, but just as former observational studies, contradictions among them are still not able to be diminished. For instance, on body weight, a study indicates that Omega-3 intake can cause weight-gaining,[16] while another shows that no between-group differences can be observed in the Omega-3 group and the comparator group;[17] on QoL, Kim et al found that Omega-3 intake may somehow improve patients' QoL,[18] but other studies show that Omega-3 intake is ineffective on such domain.[17,19]

Hence, it is now of great necessity to re-evaluate the effect of Omega-3 on patients with COPD to provide a clearer and more comprehensive understanding.

Methods

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statements (full checklist in Supplementary Table S1: PRISMA 2009 checklist).[20] Protocol of this study was registered and artificially censored in the International Prospective Register of Systematic Reviews (PROSPERO #CRD42021249933).[21]

Search Strategy

Five databases including Medline, Embase, Cochrane Library, ClinicalTrials.gov and CNKI were searched for literatures published by May 10, 2021. To define the population, "chronic obstructive pulmonary disease" was combined by the Boolean operator "AND" with terms that potentially evaluated Omega-3 fatty acid supplementation such as "n-3 polyunsaturated fatty acid", "fish oil", etc. To limit the study design, the term "randomized controlled trials" was added to the search strategy with "AND" respectively. See detailed search strategy in Supplementary Data S2.

Study Selection

Only articles reporting RCTs written in English or Chinese were included. RCTs included must focus on the effect of Omega-3 intake (no matter how it was administered) on patients with spirometrically diagnosed COPD. All relevant publications were assessed separately by two researchers, and a third researcher re-assessed when there are different opinions about articles.

Data Extraction and Quality Assessment

A standardized data extraction chart was developed in advance. Two reviewers extracted the data separately and a third reviewer integrated if differences appeared. Risk of bias was evaluated by data-extractors utilizing Cochrane Collaboration risk of bias tool for RCTs.[22]

Outcome Measurements

At the stage of conception, we reviewed the hypothesis of the role Omega-3 may play in COPD, and roughly separated it into 2 groups: intrinsic one indicates the change that Omega-3 supplementation might cause in biochemical or pathophysiological aspects, including inflammation biomarker, lipid composition, lung function; extrinsic one presents the difference of clinical manifestation, including nutritional status, physical endurance, QoL. All of 6 domains in the 2 groups were considered as primary outcomes. In the actual

data extraction stage, firstly we summarized parameters provided by included studies, and a parameter would be meta-analyzed only when it had been reported by at least 3 studies. If no parameter in a domain could be statistically synthesized, such domain would be analyzed only in the manner of systematic review.

Statistical Analysis

Given that the sample size of relative studies is generally too small to ignore the influence of baseline deviation, we conducted data synthesis and analysis procedure based on the principle of "change from baseline". All data we extracted for pooling are continuous, so standardized mean difference (SMD) with 95% CI was utilized. The pooled effect size was calculated by the fixed-effects method in this study, but random-effects method would be chosen instead if the heterogeneity cannot be ignored. I^2 test was conducted to quantify the heterogeneity among studies. Sensitivity analysis would be exerted if substantive heterogeneity existed. Publication bias would be tested by Egger's test if the number of included studies is more than 10.[23] Only when two-tailed P values were smaller than 0.05 could it be deemed as statistically significant.

We used R (version 4.0.4, meta package [version 4.18-1]) to do all statistical analysis.

The Engauge Digitizer (version 4.1) graphical data extraction software was used to extract data that were only provided by images.

Results

The literature search identified 217 studies, from which we finally included 8 studies with a total population of 418 (age, mean [SD], 67.3 [10.2]) (see Figure 1). Administrations of Omega-3 vary, but all of the studies administered standardized mixture of Omega-3 (some with vitamin D or other components). Baseline characteristics of population and details of administration are managed in Table 1.

Overall risk of bias was graded moderate to low mainly because uncertainty of randomization and sequence allocation (see full assessment in Supplementary Figure S3: Risk of bias across studies and Supplementary Table S4: Risk of bias in individual studies). It is unavailable to evaluate the publication bias for the quantity of included studies is too small (<10).[23]

For 6 pre-decided domains, we analyzed every parameter to decide those synthesizable ones. The criterion of inclusion for meta-analysis is that the data were reported

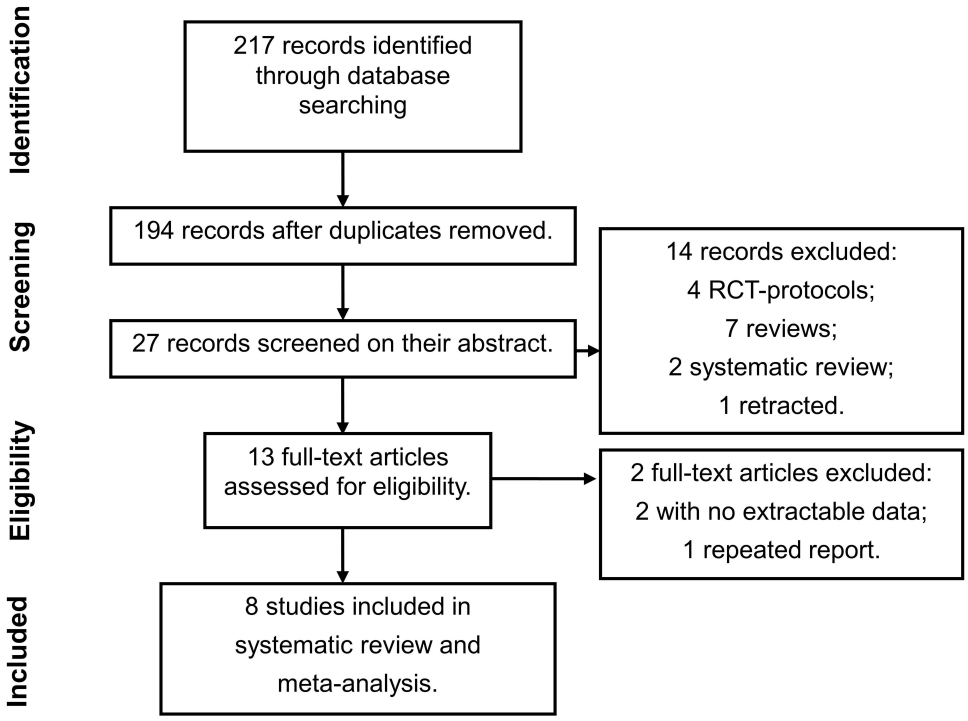

Figure 1 PRISMA flowchart.
Notes: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. Creative Commons.

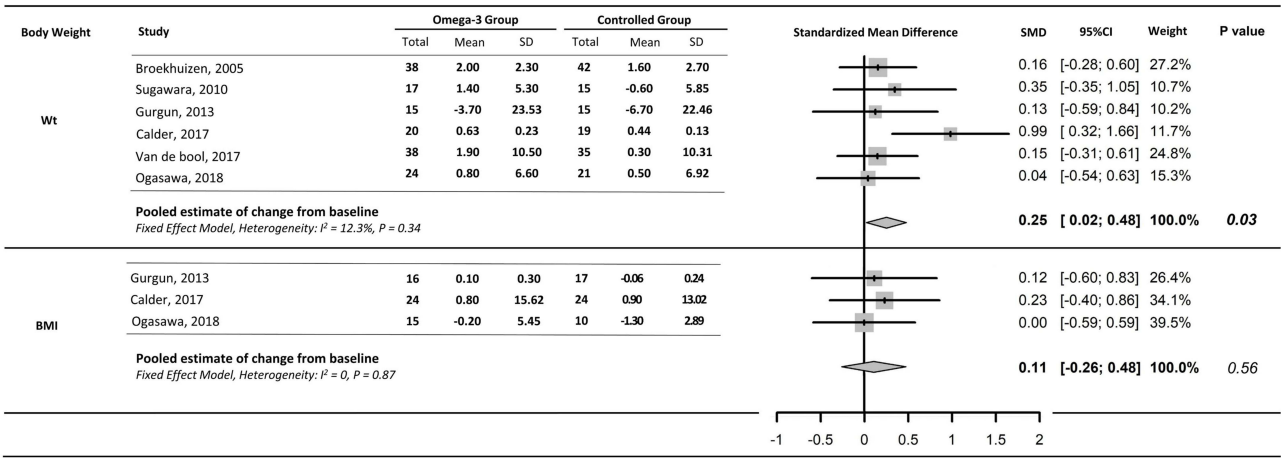

Figure 2 Pooled estimation of nutritional condition.

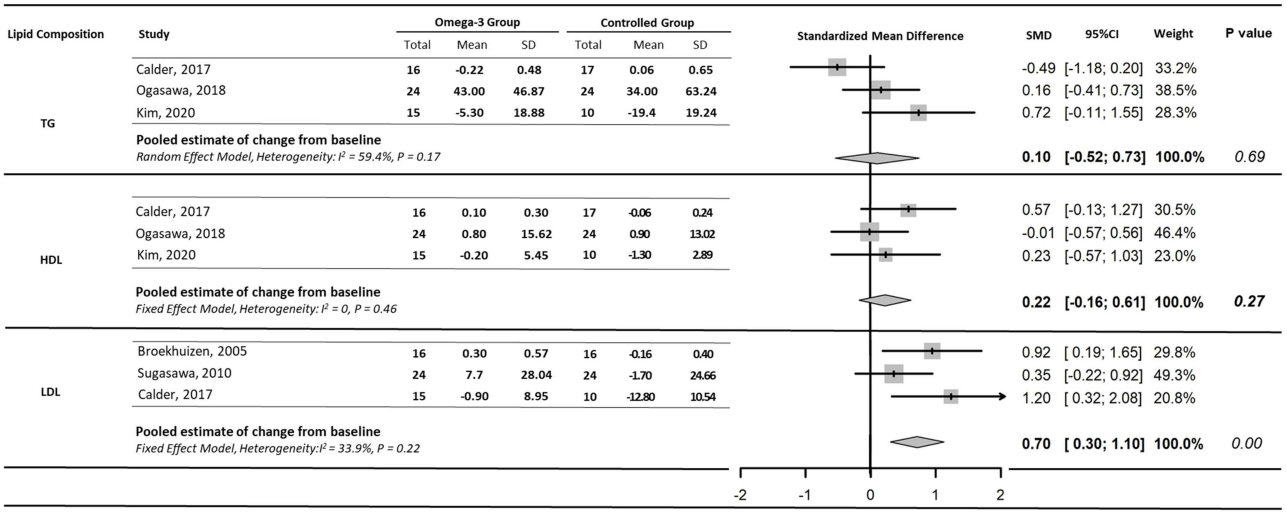

Figure 3 Pooled estimation of lipid composition.

by at least 3 studies and at the meantime extractable. Based on this criterion, we finally decided body weight and body mass index (BMI) in nutritional condition; blood concentrations of triglyceride (TG), high-density lipoprotein (HDL), LDL in lipid composition; blood concentration of C-reactive protein (CRP), IL-6, tumor necrosis factor-α (TNF-α) and white blood cell (WBC) in inflammatory biomarker; 6-minute walking distance (6MWD) in physical endurance; 2 scales including COPD assessment test (CAT) and St Georges' respiratory questionnaire (SGRQ) in QoL. Lung function relating parameters would be presented in a manner of systematic review for the insufficiency and inconsistency of reports.

Sensitivity analysis was performed to exclude possible influence of heterogeneity on pooling results in each domain one by one. Results remain stable in those parameters with significant differences (see in Supplementary Figure S7: Sensitivity analysis results).

Nutritional Condition

Six studies are available for meta-analysis of body weight,[17,19,24–27] and 3 for BMI.[17,19,25] In the body weight group, 5 studies provided the body weight of participants,[17,19,24,26,27] while the other LBM (Figure 2).[25] Before pooling estimating, only 1 study indicated that Omega-3 could increase the body weight of the COPD population with statistical significance.[17] Meta-analysis shows no statistical difference between Omega-3 supplemented population and controlled population in BMI (SMD, I^2 = 0%, fixed effects model, 0.11 [95% CI, −0.26 to 0.59]). However statistical significance can be found when it comes to the body weight (SMD, I^2 =

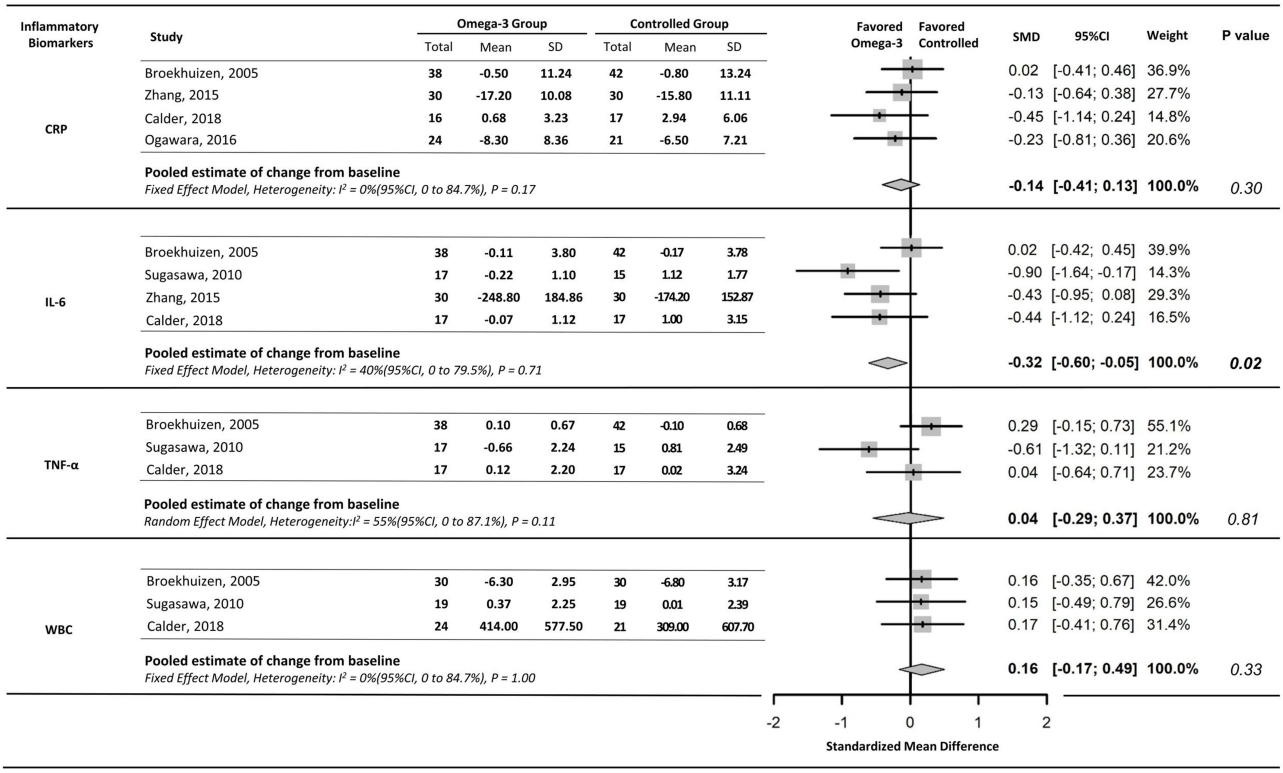

Figure 4 Pooled estimation of inflammatory biomarkers.

12.3%, fixed effects model, 0.25 [95% CI, 0.02 to 0.48], $P = 0.03$).

Lipid Composition

In this domain, TG, HDL and LDL were finally decided to be meta-analyzed for each of them was reported in 3 studies (Figure 3).[17,18,25] There is no difference in TG (SMD, $I^2 = 59.4\%$, random effects model, 0.10 [95% CI, −0.52 to 0.73], $P = 0.69$) and HDL (SMD, $I^2 = 0$, fixed effects model, 0.22 [95% CI, −0.16 to 0.61], $P = 0.27$) between 2 groups, but we found Omega-3 may be associated with higher concentration of blood LDL (SMD, $I^2 = 33.9\%$, fixed effects model, 0.70 [95% CI, 0.30 to 1.10], $P = 0.00$).

Inflammatory Biomarkers

CRP and IL-6 were separately reported in 4 studies,[17,24–26,28] meanwhile white blood cell count (WBC) and TNF-α were separately reported in 3 studies (Figure 4).[17,24–26,28] Between 2 groups of patients, no statistically significant difference was found in CRP (SMD, $I^2 = 12.6\%$, fixed effects model, −0.14 [95% CI, −0.41 to 0.13], $P = 0.30$), TNF-α (SMD, $I^2 = 55\%$, random effects model, 0.04 [95% CI, −0.29 to 0.37], $P = 0.81$) and WBC (SMD, $I^2 = 0$, fixed effects model, 0.16 [95% CI, −0.17 to 0.49], $P = 0.33$). However, it was found that comparing with the placebo intaking group, the Omega-3 intaking group had statistically significant reduction on IL-6 level (SMD, $I^2 = 40\%$, fixed effects model, −0.32 [95% CI, −0.60 to −0.05], $P = 0.02$).

Physical Endurance

Five studies evaluated the 6MWD and were included in the evaluation of this domain (see Supplementary Figure S5: Pooled estimation of physical endurance). Although other data like 6-minute walking test BORG scale[17–19] and steps per day[16,25] were also reported by other included studies, we considered 6MWD sufficient and respective for pooling. No significant statistical difference can be found in the pooled results between the Omega-3 supplement group and the control group (SMD, $I^2 = 0\%$, fixed effects model, −0.02 [95% CI, −0.29 to 0.26], $P = 0.90$).

QoL

Four studies with a total population of 203 were included in this domain for meta-analysis (see Supplementary Figure S6: Pooled estimation of Quality of Life),[17–19,25] all of them report no difference in both groups but Kim et al reports a 35% superiority ($P = 0.01$) of Omega-3 on

Table 1 Characteristics of Included Studies

(**A**) **Baseline Characteristics of Population**					
Author, Year	**Population**	**Age (Years)**	**Male, Female**	**Spirometry**	**BMI (kg/m^2)**
Broekhuizen, 2005	80, hospitalized sCOPD	63.0, 9.1	71, 31	37.0, 14.1 (FEV_1pred%)	22.3, 3.8
Calder, 2018	45, sCOPD, pre/overt cachexia	69.5, 7.3	23, 22	48.8, 9.5 (FEV_1/FVC, %)	23.0, 3.9
Gurgun, 2011	30, sCOPD, nutritional depletion	65.4, 10.2	NA	41.9, 12.1 (FEV_1pred%); 53.3, 24.8 (FEV_1/FVC, %)	18.9, 2.0
Kim, 2020	40, sCOPD, ex-smokers	66.9, 7.0	22, 18	43.9, 14.7 (FEV_1pred%); 42.0, 12.0 (FEV_1/FVC, %)	NA
Ogasawara, 2018	50, aeCOPD	78.2, 8.6	41, 4	66.1, 29.8 (FEV_1pred%)	19.2, 2.6
Sugawara, 2010	32, sCOPD, BMI<19	77.7, 6.8	NA	55.6, 26.0 (FEV_1pred%); 43.8, 15.1 (FEV_1/FVC, %)	18.3, 1.2
Van De Bool, 2016	81, COPD, low muscle mass	62.5, 1.3	41, 41	55.1, 19.6 (FEV_1pred%); 43.1, 12.2 (FEV_1/FVC, %)	22.8, 2.9
Zhang, 2015	60, aeCOPD, ICU-MV	64.2, 13.5	46, 14	NA	NA
(**B**) **Intervention and comparator**					
Author, Year	**Intervention**			**Comparator**	
Broekhuizen, 2005	Purified in standardized ONS, STA 400 mg|ALA 1200 mg|EPA 700 mg|DHA 340 mg per day, 8W			Palm oil & sunflower oil, 8W	
Calder, 2018	Mixed (in standardized ONS), 2000 mg DHA & EPA per day, 12W			Sunflower oil, 12W	
Gurgun, 2011	Mixed in standardized ONS, 8W			Undefined placebo, 8W	
Kim, 2020	Purified in standardized ONS, 3 g/d, 6M			Corn oil, 6M	
Ogasawara, 2018	Mixed in standardized ONS (ProSure®; Abbott), 1.1 g EPA per day, 36M			Placebo (ENSURE®H; Abbott), 36M	
Sugawara, 2010	Mixed in standardized ONS along with low intensity exercise, 0.6 g, 12W			No placebo, 12W	
Van De Bool, 2016	Mixed in standardized ONS, 4M			Placebo, 4M	
Zhang, 2015	Mixed in standardized ENS, 4W			Undefined placebo, 4W	

Abbreviations: BMI, body mass index; aeCOPD, acute exacerbating chronic obstructive pulmonary disease; sCOPD, stable chronic obstructive pulmonary disease; NA, not available; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1pred, percentage of FEV_1 in its prediction; ONS, oral nutritional supplement; ENS, enteral nutritional supplement; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; STA, stearidonic acid; W, week; M, month; MV, mechanical ventilated.

the population of decreased SGRQ points more than 4.[18] No significant difference can be found between the Omega-3 supplement group and the control group (SMD, I^2 = 83%, random effect model, −0.31 [95% CI, −1.15 to 0.53], P = 0.47) in this domain.

Lung Function

Three studies mentioned the change of lung function before and after the intervention,[17,18,24] but only 2 reported extractable data of different measurements,[18,24] so we can do only systematic review rather than meta-analysis in this domain. Broekhuizen et al reported that no effect was observed on FEV_1 and inspiratory strength without data shown in their article.[24] Calder et al reported that no effect was observed on forced expiratory volume in 1 second (FEV_1) (P = 0.37), while the intervention group exacerbated less than the controlled group (4.5% [n = 1] vs 13.6% [n = 3]).[17] Kim et al reported the change of spirometry, but no statistical difference between groups was found also (FEV_1, 0.002 [95% CI, −0.14 to 0.18]; FEV_1%pred, 0.8 [95% CI, –4.8 to 6.4]; forced vital capacity (FVC), 0.1 [95% CI, −0.2 to 0.5]; FEV_1/FVC, −0.01 [95% CI, −0.06, 0.04]; carbon monoxide diffusing capacity (DLCO),

0.2 [95% CI, −0.8 to 1.1], DLCO/VA (alveolar ventilation), 0.1 [95% CI, −0.1 to 0.3]).[18] Overall, up to now there is no sufficient evidence that can support that Omega-3 may have positive effect on lung function of patients with COPD.

Discussion

Results show that Omega-3 intake does have some effects on weight-gaining, LDL increase and IL-6 reduction. No more significant difference can be found in physical endurance, QoL. In the domain of lung function, a small number of studies existed and the disparity of their results disenabled us to analyze its relationship with Omega-3.

In the domain of nutritional condition, we found that Omega-3 may have weight-gaining effect on patients with COPD. Nutritional condition is an important factor influencing the quality of life and prognosis in patients with COPD. Unhealthy nutritional condition can impair the QoL of patients with COPD.[29] A Cochrane systematic review by Ferreira et al found that low BMI and fat-free mass index (FFMI) condition in a COPD population are related to a poor prognosis.[30] And the weight-losing process of COPD patients is caused multifactorially by chronic inflammation and oxidant stress.[10] It is shown in a study by Grimble et al that Omega-3 intake can inhibit the inflammatory process.[31] And a series of studies showed that the metabolism of Omega-3 can produce anti-oxidative derivatives.[32,33] The weight-gaining effect of Omega-3 on COPD patients found in our study indicates that the hypothesis that Omega-3 may improve COPD patients' nutritional condition is tenable.

In the domain of lipid composition, we found that Omega-3 supplementation may cause LDL increase in COPD population. An overall increasing tendency of lipid can be observed in our study, but only the increase of LDL is statistically significant. First reason of this phenomenon may be that even though existing studies about the relationship of Omega-3, LDL, and health remain mixed,[34] not few of them concluded the same result as us. For instance, Phillipson et al found that LDL decreased after 4 weeks of Omega-3 enriched diet.[35] However, Gries et al found that Omega-3 supplement did not make any difference to participants' concentration of blood lipid.[36] Harris et al found that though very low-density lipoprotein (VLDL) decrease is positively related to the dose of Omega-3 intake, but LDL increased no matter what the dose is.[37] The second reason may be the designs of included studies vary. For instance, Simopoulos suggests that LDL after Omega-3 supplement may increase if the intake of saturated fatty acids was not controlled,[38] and none of the studies we reviewed did control the intake of saturated fatty acids. The third reason may be that the analysis was based on a limited number of included studies and small population. In a word, it is well proved that lipid metabolism was closely associated with inflammation,[39] and HDL/LDL ratio may matter on COPD patients' comorbidity (pulmonary hypertension, for example) and prognosis.[40] Relationships of Omega-3 intake, different lipids and COPD are still confusing. More attention is needed on such problems.

In the domain of inflammatory biomarkers, our meta-analysis indicates that Omega-3 intake is significantly related to IL-6 reduction. COPD is characterized as a disease of chronic inflammation, and many studies strongly connect Omega-3 intake with lowering of inflammatory level.[7] High IL-6, TNF-α level was found related to cachexia in cancer patients,[41,42] and cachexia is not an uncommon condition in COPD patients. CRP and WBC are also confirmed as indicators of systemic inflammation in COPD patients.[43] IL-6 is widely seen as a hub of various inflammatory pathways. As we comprehensively investigated series of inflammatory biomarkers including IL-6, CRP, WBC, and TNF-α, only IL-6 shows significance. Hence, albeit we found IL-6 reduction in our pooled results, it is insufficient to conclude that Omega-3 is capable of downregulating the COPD patients' inflammatory level. More studies are needed to confirm the still-mixed Omega-3's anti-inflammatory effect on COPD.

In the left domains, including patients' physical endurance, lung function and QoL, although all of which were highly associated with the aforementioned 3 domains, we did not get enough evidence to support the relationship between Omega-3 and COPD.[44] In our study, no significant effect was observed based on the pooling results of physical endurance and QoL. However, in the study by Kim et al, the effect that the Omega-3 group has significantly more SGRQ score-decreasing cases is still unignorable for our statistical pooling results were based on limited studies and small population.[18] Future studies ought to pay extra attention to checking Omega-3's effect on QoL closely. As for lung function, no parameter is available of statistical synthetization, and it seems no superiority of Omega-3 exhibited based on the results of our systematic review.

The results of this systematic review and meta-analysis should be interpreted quite cautiously for the limited quality and quantity of available evidence. Existing RCTs were

limited by incomplete control (for instance, used regular vegetable oil instead of refined Omega-3 free oil to be the placebo), lacking detailed description of concealment approach (for example, Omega-3 and placebo ought to be encapsulated in the same nontransparent capsules), unbalanced follow-up, high dropout rates and the potential bias because of industrial funding. Additionally, most studies ignored to measure some fundamental clinical outcomes, such as change of lipid composition (especially the concentration if Omega-3, Omega-6 in the blood). Future studies may benefit from inclusion of clearly described concealment approach and comprehensive observation. More well-conducted RCTs are required to determine the comparative effectiveness of specific Omega-3 kinds (EPA vs DHA, for example) along with other treatment.

It ought to be noticed that a few limitations in this meta-analysis and systematic review itself can also impair the strength of evidence of our findings. The first point is that pooled results are all imprecise for the limited sample size and the majority of results did not show statistical significance. Second, though we excluded the potential effect by sensitivity analysis, heterogeneity related to outcome definitions, measurement tools (eg, different questionnaires to measure QoL) and administrations is still unignorable and therefore weakened the strength of evidence. Third, publication bias assessment was unable to be conducted for the small number of finally included studies.

Conclusion

In this systematic review and meta-analysis, we found that compared with placebo, Omega-3 intake was associated with weight-gaining, LDL increase and IL-6 reduction, while no significant difference in physical endurance, QoL or lung function was found. It should be emphasized that any interpretation based on the results of this study should be quite cautious for the quality of available evidence is limited, and the majority of outcomes was based on small numbers of studies.

Abbreviations

ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; CNKI, China National Knowledge Infrastructure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DLCO, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 second; FFMI, fat-free mass index; FVC, forced vital capacity; HDL, high density lipoprotein; IL-6, interleukin-6; LDL, low density lipoprotein; MV, mechanical ventilated; NF-ϰB, nuclear factor kappa B; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; QoL, quality of life; RCT, randomized controlled trial; SD, standard difference; SMD, standardized mean difference; TG, triglycerides; TNF-α, tumor necrosis factor-α; VA, alveolar ventilation; VLDL, very low-density lipoprotein; Wt, weight.

Consent for Publication

All details of any images, videos, recordings, etc presented in this article can be published, and all authors agree with the article contents to be published. All authors are able to provide copies of signed consent forms to the journal editorial office if requested.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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