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REVIEW

The Inflammatory Roles of n-3 and n-6 Polyunsaturated Fatty Acids in COPD: Clinical Implications and Underlying Mechanisms

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Abstract: Chronic obstructive pulmonary disease (COPD) ranks among the leading causes of global mortality, with chronic inflammation as its primary pathogenic mechanism. Developing effective therapeutic strategies to attenuate this inflammatory response is crucial for reducing the prevalence, mortality, and overall burden of COPD. Polyunsaturated fatty acids (PUFAs) are recognized for their role in modulating inflammation and may influence inflammation-driven diseases. This narrative review evaluates observational and interventional studies on PUFAs in COPD and explores their potential mechanisms in modulating inflammation. The synthesis of the literature reveals limited and inconsistent evidence linking PUFAs to COPD. Robust data are lacking to conclusively demonstrate the biological benefits and clinical efficacy of n-3 PUFAs in COPD. Therefore, we systematically assess current research and recommends extensive and rigorous future clinical trials. Furthermore, PUFAs and their derivatives play roles in initiating and resolving inflammation in COPD through direct involvement, macrophage polarization regulation, and effects on membrane biophysics and signal transduction. Despite the current inconclusive evidence, we emphasize the necessity for intensified clinical trials and drug development efforts targeting PUFAs in COPD to develop new therapeutic strategies.

Keywords: n-3 PUFAs, n-6 PUFAs, COPD, inflammation, specialized pro-resolving lipid mediators, eicosanoid

Introduction

Chronic obstructive pulmonary disease (COPD) is a diverse respiratory disorder characterized by chronic respiratory symptoms, such as cough, sputum production and dyspnoea, accompanied with persistent and progressive airflow obstruction.[1] According to the Global Burden of Disease Study 2019, COPD affects 212.3 million individuals globally, contributing to 74.4 million disability-adjusted life years and 3.3 million deaths.[2] Given its high prevalence, mortality and substantial economic impact, COPD has emerged as a significant global public health concern.[3]

The pathogenesis of COPD is complex, with chronic airway and systemic inflammation as its key underlying mechanism.[4] Long-term exposure to harmful stimuli such as cigarette smoke and environmental particulate matter can trigger abnormal inflammatory responses in the respiratory system. Overactivated inflammatory cells, including macrophages and neutrophils, release excessive inflammatory mediators, which exacerbate inflammation and tissue damage. This process results in chronic bronchitis and/or emphysema.[5,6] Beyond localized lung damage, these inflammatory mediators can spill over into the circulatory system, leading to increased systemic inflammatory levels, which are further elevated during COPD exacerbations.[4] Sustained systemic inflammation in COPD contributes to complications like cardiovascular diseases, diabetes,

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osteoporosis and muscle dysfunction, thereby diminishing exercise capacity, quality of life and overall health status.[7,8] Therefore, targeting local and systemic inflammatory responses is pivotal in the treatment and management of this disease.[9]

Dietary interventions may present an alternative to mitigate inflammation associated with COPD, given the limited therapies available to prevent its onset and progression.[10] Polyunsaturated fatty acids (PUFAs) have been reported as dietary elements capable of regulating inflammation. PUFAs and their derivatives, such as eicosanoids and specialized pro-resolving mediators (SPMs), are pivotal in inflammatory-driven conditions like COPD, heart disease, and rheumatoid arthritis.[11–13] PUFAs mainly include n-3 and n-6 types. n-6 PUFAs are crucial in facilitating allergic reactions and modulating inflammation, whereas n-3 PUFAs exhibit anti-inflammatory, anti-aggregatory, vasodilatory and bronchodilatory properties.[14] Thus, n-3 and n-6 PUFAs appear to have conflicting effects in inflammatory diseases. The available evidence suggests that n-3 PUFAs and their metabolites can mitigate chronic airway inflammation through anti-inflammatory mechanisms.[15,16] A high dietary intake of n-3 PUFAs may protect smokers from developing COPD.[17,18] Conversely, n-6 PUFAs and their pro-inflammatory derivatives contribute to airway remodelling and alveolar damage.[5,19] A high intake of n-6 PUFAs is correlated with reduced lung function and an elevated COPD risk, potentially counteracting the anti-inflammatory benefits of n-3 PUFAs.[20,21] However, some studies highlight the positive impact of n-6 PUFAs on various chronic diseases without promoting inflammation.[22,23] A high ratio of n-6 to total PUFAs might reduce the risk of pneumonia, and substantial n-6 PUFA consumption appears to reduce COPD and dyspnea risk.[24,25] Given the conflicting evidence, further research is necessary to clarify the complex relationship between PUFA intake and COPD.

This manuscript presents a comprehensive review of published research and review articles to elucidate the role of PUFAs in the chronic inflammation associated with COPD. We detail the structure and sources of PUFAs and examine the potential links between PUFAs, their metabolites and inflammation from multiple perspectives. It also critically examines observational and interventional studies on the association between PUFAs and COPD, as well as the hypothesised pathways by which PUFAs may modify COPD-related inflammation. The findings of this review offer clinically relevant evidence and novel insights that could inform the prevention and treatment of COPD.

Potential Relationship Between PUFAs and Inflammation

n-3 and n-6 PUFAs are critical in numerous physiological and pathological processes and are essential in the human diet.[26] n-3 PUFAs include eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), stearidonic acid (SDA) and α-linolenic acid (ALA). These fatty acids are commonly found in diets through vegetable oils, flaxseeds, walnuts and fishes.[27,28] Although ALA can convert to EPA and DHA via desaturases and elongases, the endogenous synthesis of n-3 PUFAs is inefficient, fulfilling only 10% of daily PUFA needs, which may be inadequate for health benefits.[29] EPA and DHA must be sourced externally through diet, such as sardines and tuna or supplements.[30,31] Notable examples of n-6 PUFAs include linoleic acid (LA), γ-linolenic acid (GLA) and arachidonic acid (AA), which are primarily derived from sources such as vegetable oils, grain-fed animals, dairy products and eggs; their intake is crucial due to the limited endogenous biosynthesis of n-6 PUFAs.[32]

Proportion of PUFAs Consumed

Inflammation serves as a vital defence mechanism in the human body. n-6 PUFAs are implicated in modulating immune and inflammatory responses, whereas n-3 PUFAs are recognized for their anti-inflammatory properties.[33] Balancing n-3 and n-6 PUFAs is crucial for inflammation management and overall health. An intake ratio of 1:1 to 1:4 is recommended for health maintenance and infant brain development.[34–36] An elevated n-6/n-3 ratio may exacerbate chronic inflammation and increase the risk of cardiovascular disease, cancer and autoimmune disorders.[34,35] Research links a high prenatal n-6/n-3 ratio to attention-deficit and hyperactivity disorder symptoms in children.[37] A study identified a high n-6/n-3 PUFA ratio as a predictive marker for type 2 diabetes, underscoring the importance of maintaining balance for effective diabetes management.[38] However, current dietary patterns exhibit a deficiency in n-3 PUFAs and an excess of n-6 PUFAs, with consumption ratios typically ranging from 10:1 to 20:1.[27] The Western diet, for instance, has a ratio of 15.9:1, significantly surpassing the 1:1 ratio characteristic of the Palaeolithic era.[39] This disparity is primarily attributed to industrial food production practices, the prevalent use of n-6 PUFA-rich vegetable oils and the increased incorporation of grains in animal feed.[40] Although enzymes involved in PUFA biosynthesis favour the synthesis of n-3 PUFAs, diets

high in n-6 PUFAs lead to excessive AA production, thereby disrupting the balance between AA and n-3 PUFAs.[41] Foods high in n-3 PUFAs, such as flaxseeds, chia seeds and rapeseeds, are absorbed by intestinal cells and transported through the bloodstream for metabolism. This absorption process reduces the n-3/n-6 PUFA ratio, thereby diminishing the potential health benefits associated with their conversion into long-chain forms.[42] Therefore, external environmental factors and internal absorption and metabolism elevate n-6 PUFA levels, resulting in an imbalanced n-3/n-6 PUFA ratio and promoting inflammation-related diseases.

Eicosanoids and SPMs From PUFAs

When exposed to harmful or infectious stimuli, immune cells activate pattern recognition receptors like Toll-like and Nod-like receptors, promptly relaying "danger signals" to cells and tissues.[43] These signals stimulate immune cells to release pro-inflammatory cytokines and chemokines, attracting leukocytes and macrophages to the inflammatory site, thereby amplifying the immune response and protecting the body.[44–46] After the immune response is initiated, acute inflammation gradually diminishes. Phagocytes, including macrophages and neutrophils, are activated to eliminate apoptotic and necrotic cells, promoting tissue repair and sustaining homeostasis by generating pro-resolving mediators.[47,48]

Notably, upon cellular activation, n-3 and n-6 PUFAs are released from cell membrane phospholipids and converted through specific enzymatic reactions into bioactive substances, such as eicosanoids and SPMs, which are vital for the progression and resolution of inflammation.[49,50] Eicosanoids, a class of highly active lipids, can influence the functions of granulocytes and macrophages by upregulating the expression of complement and immunoglobulin receptors, thereby enhancing phagocytosis and cell-killing abilities.[51] The well-known mediators of inflammation, thrombosis, vasoconstriction and bronchoconstriction are classic eicosanoids such as prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs).[52] Three enzymatic pathways synthesise eicosanoids from n-3 and n-6 PUFAs: lipoxygenase (LOX), cytochrome P450 (CYP450) and cyclooxygenase (COX). EPA and DHA can be converted into 3-series PGs, 3-series TXs, 5-series LTs, resolvins (Rvs) and neuroprotectin, whereas AA can be transformed into 2-series PGs, 2-series TXs and 4-series LTs.[53] Eicosanoids derived from AA are commonly associated with inflammation; they can induce inflammatory responses at elevated levels and regulate vascular and bronchial constriction.[42] By contrast, eicosanoids from EPA and DHA have unique characteristics; they are prevalent in the lungs, acting as potent vasodilators and bronchodilators and possessing anti-inflammatory properties.[53,54] Furthermore, as a result of similar enzymatic pathways, ALA may reduce cellular and tissue levels of AA by outcompeting LA for metabolism and incorporation into cell membrane phospholipids, thereby reducing the synthesis of pro-inflammatory AA-derived eicosanoids.[55,56] The entire process of enzymatic generation of eicosanoids from n-3 and n-6 PUFAs and the effects of eicosanoids are shown in Figure 1.

The SPM family primarily governs the resolution of inflammation and originates from n-3 and n-6 PUFAs through enzymatic processes.[57,58] These endogenous SPMs are produced by immune cells such as T and B lymphocytes, as well as structural cells like airway and alveolar epithelial cells, endothelial cells and fibroblasts. They play critical roles in modulating immune responses, resolving inflammation and facilitating tissue repair.[59–61] The SPM family includes lipoxins (LXs), Rvs, protectins (PDs), maresins (MaRs) and novel cysteinyl-SPMs (Cys-SPMs). Lipoxins, the first identified pro-resolving lipids, such as lipoxin A4 (LXA4) and lipoxin B4 (LXB4), are derived from AA via the sequential action of 5-LOX, 12-LOX and 15-LOX.[62] With the advancement of research, additional SPMs derived from DHA, EPA and DPA have been identified. The synthesis of these mediators involves enzymes like COX, LOX and CYP450, with LOX being pivotal.[63,64] Given that most SPMs are derived from n-3 PUFAs, they are considered crucial molecules in the resolution of inflammation and in protecting organisms from the harmful effects of unregulated inflammatory processes.[48]

DHA is the precursor for various pro-resolving mediators, including D-series Rvs (RvD1 to RvD6), protectin D1 (PD1), protectin DX (PDX), maresin 1 (MaR1) and Cys-SPMs. Cys-SPMs are peptide-lipid conjugates that include resolvin conjugates in tissue regeneration (RCTRs), PD conjugates in tissue regeneration (PCTRs) and MaR conjugates in tissue regeneration (MCTRs).[65–67] The D-series Rvs and RCTRs are mainly formed by 15-LOX and 5-LOX. PDs and MCTRs are derived from DHA via 15-LOX, whereas MaRs and MCTRs are synthesised through 12-LOX.[68] Epoxyeicosatrienoic acids (EETs) are produced from AA by CYP450, and hydroxyeicosatetraenoic acids (HETEs) are formed by 12- and 15-LOX. HETEs and EETs have independent pro-resolution activities and act as precursors for other SPMs.[69,70] Although not officially classified as SPMs, they exhibit pro-resolution or anti-inflammatory properties.

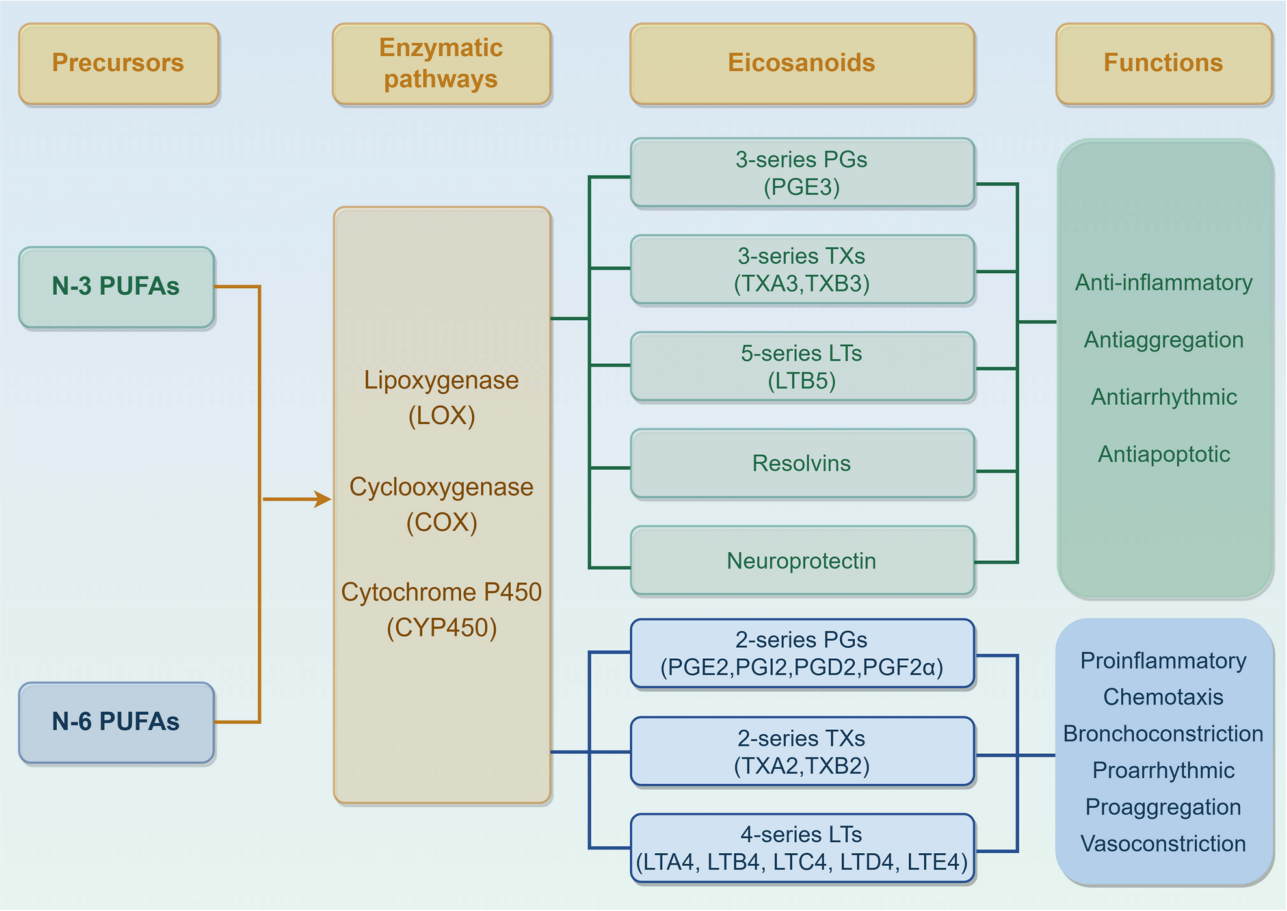

Figure 1 The process of enzymatic generation of eicosanoids from n-3 and n-6 PUFAs and their functions.
Abbreviations: PGs, prostaglandins; TXs, thromboxanes; LTs, leukotrienes.

E-series Rvs (RvE1 to RvE4) are derived from EPA, with COX-2 and CYP450; upon acetylation, they enhance RvE production via 5-LOX/15-LOX.[63,71] Over the past decade, SPMs from DPA have been increasingly identified, including RvDn-3 DPA (RvD1, RvD2 and 5n-3 DPA), PDn-3 DPA (PD1, PD2 and 3n-3 DPA) and MaRn-3 DPA (MaR1, MaR2 and 3n-3 DPA), as well as a new series of 13 Rvs (RvT1 to RvT4).[72,73]

SPMs enhance phagocytosis by combining with G protein-coupled receptors (GPCRs) to regulate neutrophil infiltration and modulate cytokines and chemokines.[74] This interaction is essential for their anti-inflammatory and pro-resolution roles. Known SPM receptors include DRV1/GPR32 (binding RvD1, RvD3 and RvD5), DRV2/GPR18 (binding RvD2), FPR2/ALX (binding RvD1, RvD3 and LXA4), ERV1/CMKLR1/ChemR23 (binding RvE1), BLT1/LTB4R (binding RvE1 and RvE2), GPR37 (binding PD1), LGR6 (binding MaR1) and GPR101 (binding $RvD5_{n\text{-}3\ DPA}$).[75] Some receptors are specific to a SPM, such as LGR6, which specifically binds MaR1, modulating leukocyte recruitment and enhancing macrophage phagocytosis.[11] PD1 plays an anti-inflammatory role in the immune system through its GPR37 receptor.[76] Some receptors can bind to various SPMs, which is crucial for understanding the therapeutic potential of SPMs and their analogues.[74] For example, RvD1 and LXA4 can bind to DRV1/GPR32 or FPR2/ALX, allowing RvD1 to exhibit anti-inflammatory and pro-resolving properties.[77] By contrast, FPR2 also binds to serum amyloid A (SAA), which can induce a pro-inflammatory response.[78] Similarly, RvE1 binds to ERV1/ChemR23 or BLT1/LTB4R. Binding to ERV1/ChemR23 activates intracellular signalling, whereas BLT1/LTB4R triggers the classical pro-inflammatory pathway.[28] Thus, different ligands binding to the same GPCR can produce varied downstream effects, highlighting the importance of understanding ligand structure and GPCR signalling pathways. As shown in Figure 2, SPMs are obtained from n-3 and n-6 PUFAs through a series of enzymatic reactions and exert their effects by binding to GPCRs.

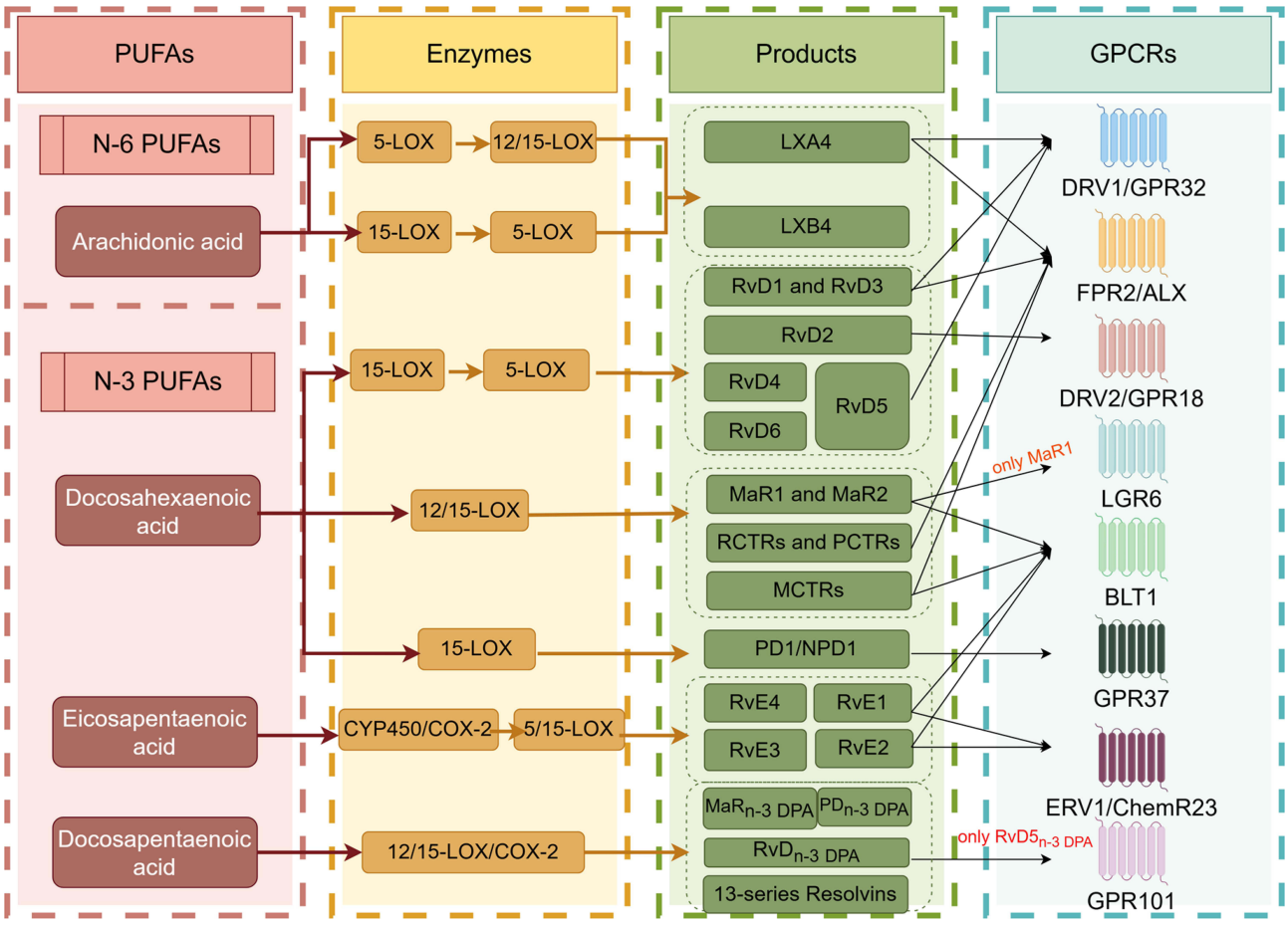

Figure 2 The synthetic pathway of SPMs from n-3 and n-6 PUFAs and their GPCR signaling network.
Abbreviations: LOX, lipoxygenase; CYP450, cytochrome P450; COX, cyclooxygenase; LXs, lipoxins; Rvs, resolvins; PDs, protectins; MaRs, maresins; RCTRs, resolvin conjugates in tissue regeneration; PCTRs, protectin conjugates in tissue regeneration; MCTRs, maresin conjugates in tissue regeneration; DPA, docosapentaenoic acid; GPCRs, G protein-coupled receptors.

Other Mechanisms for Regulating Inflammation

Research suggests that n-3 PUFAs exhibit anti-inflammatory effects by directly interacting with proteins and membrane channels. For example, DHA initiates anti-inflammatory processes by activating the DHA-specific cell membrane receptor GPR120, thereby inhibiting nuclear factor kappa-B (NF-κB) activation and reducing inflammation.[79] DHA also attenuates the activity of the pro-inflammatory Toll-like receptor 4 (TLR4) and disrupts membrane raft formation in inflammatory cells via its interaction with myeloid differentiation factor 88, facilitating the resolution of inflammation.[80] Additionally, n-3 PUFAs regulate ion channels and alter cell structure and signalling by modifying lipid configurations within the cell membrane. When integrated into the cell membrane, n-3 PUFAs influence ion channels such as L-type calcium and sodium, affecting inflammation-related signalling pathways and promoting inflammation resolution.[81] Furthermore, n-3 PUFAs serve as endogenous ligands for various nuclear receptors, including liver X receptors and retinoid X receptors, across different tissues. The interaction between these nuclear receptors and n-3 PUFAs is mediated by cytoplasmic lipid-binding proteins that transport fatty acids into the nucleus. n-3 PUFAs also affect transcription factors like sterol regulatory element binding proteins, affecting inflammatory pathways.[82]

In conclusion, the regulation of immune inflammation is a complex process. Emerging research on PUFAs has shed light on the relationship between n-3 and n-6 PUFAs and inflammation. The crucial factor in inflammation regulation is the ratio of n-3 to n-6 PUFAs. An elevated n-6/n-3 PUFA ratio escalates inflammation, potentially leading to disease. Although n-3 and n-6 PUFAs can generate eicosanoids and SPMs, their metabolites have distinct effects. They compete in the same enzymatic reactions, leading to varying inflammation levels following complex physiological transformations. Eicosanoids

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derived from n-3 PUFAs exhibit anti-inflammatory properties, whereas those from AA are crucial in the initial phase of inflammation. In contrast to lipoxins, marine n-3 PUFAs serve as precursors for numerous SPMs, which can impede inflammatory cell activation and recruitment, facilitating swift inflammation resolution and homeostasis restoration by binding to GPCRs. Hence, maintaining a balance between n-3 and n-6 PUFAs is essential for regulating inflammation and promoting overall health.

Roles of n-3 PUFAs and n-6 PUFAs in COPD

Extensive observational and interventional studies have investigated the relationship between PUFAs and COPD, given the regulatory role of PUFAs in various inflammatory conditions and the impact of chronic inflammation on COPD pathogenesis.

Observational Study

Several studies have investigated the impact of dietary PUFA intake, PUFA concentrations and inflammation in the airways and circulation on the risk, severity and health outcomes of patients with COPD. Dietary intake assessment commonly involves 24-hour recall and food frequency questionnaires. Studies have reported low n-3 PUFA intake in patients with COPD, which declines with disease severity.[83] Increased n-6 PUFA consumption is linked to an elevated COPD risk.[84] Two large US cohort studies found that high fish consumption (≥4 servings/week) is correlated with reduced newly diagnosed COPD risk, independent of PUFAs. However, this association disappeared when considering the overall dietary pattern, suggesting that fish's benefits may stem from the overall diet. Notably, high plant-based n-3 PUFA intake may lower COPD risk in both genders when fish consumption is high. Thus, diverse sources of n-3 PUFAs may offer greater COPD benefits than individual foods or nutrients.[85] This conclusion was aligned with another study's findings, which observed that a high consumption of plant-derived n-3 PUFAs and a low intake of n-6 PUFAs are linked to a reduced risk of COPD.[20]

However, some studies have indicated a non-significant negative correlation between n-3 PUFA intake and COPD prevalence.[25] A 25-year prospective longitudinal study of 793 middle-aged Dutch men revealed a positive correlation between n-6 PUFAs intake and 25-year COPD incidence, with no significant association found for n-3 PUFAs.[86] Studies investigating the relationship between PUFA intake and COPD mortality have yielded diverse results. For instance, a study involving men from seven countries found a negative association between 25-year COPD mortality and fish consumption.[87] Conversely, a study reported no significant link between fish consumption among middle-aged men from three European countries and 20-year COPD mortality.[88]

Most studies examining the impact of dietary intake of PUFAs on outcomes related to COPD primarily concentrated on lung function and respiratory symptoms. Research indicates a significant positive relationship between lung function and the consumption of n-3 PUFAs and dietary fibre.[89] Increased consumption of n-3 PUFAs from fish is linked to enhanced ventilation function and a protective influence on lung function across various age groups.[90,91] Several studies have highlighted an inverse association between fish consumption and COPD-related outcomes, potentially mitigating smoking-induced lung damage.[18,92,93] Nonetheless, these studies did not account for other dietary factors, which may introduce confounding variables.

To assess the independent correlation between diet and lung function in COPD, most studies mitigated confounding bias by adjusting for various factors known to affect lung function or dietary habits, such as gender, age, body mass index, physical activity, other nutritional components, energy intake, educational attainment and occupational and tobacco exposure. A study conducted on 878 patients with COPD as part of the National Health and Nutrition Examination Survey revealed no significant correlation between n-3 PUFA intake and respiratory symptoms. However, upon considering potential confounding variables, reduced levels of n-6 PUFA intake and increased intake of n-3 PUFAs were found to be linked to a decreased likelihood of chronic cough and wheezing. Notably, the beneficial impact of EPA + DHA on symptom alleviation was specifically observed in current smokers with low educational attainment. The protective relationship between n-3 PUFAs intake and respiratory symptoms was particularly evident in subgroups vulnerable to COPD, such as smokers and individuals with limited educational backgrounds.[94] Another study involving 13,820 individuals in the Netherlands demonstrated an inverse association between DHA and FEV1, with higher n-6 PUFA intake generally linked to lower FEV1 levels. Furthermore, a notable

interaction between smoking status and the correlation between n-6 PUFAs and FEV1 was identified, indicating a pronounced negative association among smokers.[84] A recent cross-sectional investigation revealed that higher overall n-3 PUFAs intake is associated with a reduced risk of COPD exacerbation, enhanced health-related quality of life and fewer respiratory symptoms among former smokers diagnosed with moderate to severe COPD. Conversely, elevated total n-6 PUFA intake yields contrasting outcomes. The patterns observed when analysing the n-6/n-3 ratio were aligned with the individual effects identified in the study.[95] Increased consumption of n-3 PUFAs, n-6 PUFAs and total PUFAs has been linked to enhanced quality of life, encompassing mobility, self-care and daily activities, among individuals with COPD. This relationship may be linked to improvements in mobility, self-care and daily activities.[96]

Nevertheless, conflicting findings have been reported, with some studies failing to establish a connection between PUFAs and COPD.[97,98] For instance, a cross-sectional analysis in 1990 involving 9074 American adults aged over 30 revealed that dietary fish intake was no longer correlated with COPD wheezing symptoms after adjusting for other dietary variables.[99] Conversely, a dietary investigation in Japan identified a positive correlation between PUFA intake and lung function in patients with COPD. Notably, high intake of PUFAs and n-6 PUFAs appears to mitigate the risk of COPD and dyspnoea symptoms.[25] This finding contradicts some earlier research results but also underscores the potential significance of n-6 PUFAs in managing COPD.

PUFA levels in the circulation and airways of patients with COPD are correlated with systemic inflammation and clinical outcomes. A two-year dietary survey study examined inflammatory biomarkers in patients with COPD, finding a negative association between ALA intake and tumour necrosis factor-α (TNF-α), a positive correlation between AA intake and interleukin-6 (IL-6)/C-reactive protein (CRP) and a relationship between the DHA/AA ratio and serum TNF-α levels.[100] Studies have reported elevated AA levels in the plasma of patients with COPD, inversely linked to lung function, whereas elevated DHA concentrations in serum phospholipids are positively associated with lung function, suggesting a protective role for marine-derived PUFAs.[101,102] In severe COPD cases, serum n-3 and n-6 PUFA levels are closely related to lung function and disease progression.[103] Additionally, COPD prevalence is inversely correlated with levels of DHA, not EPA, in plasma lipids after adjusting for confounding factors.[104] Regular n-3 PUFA supplementation in patients with COPD reduces inflammation, dyspnoea episodes and exacerbations and improves exercise capacity.[105]

In addition, the development of COPD is linked to alterations in the fatty acid composition of erythrocyte membranes and an imbalance between pro-inflammatory and anti-inflammatory eicosanoid precursors. Compared with individuals without COPD, patients with COPD exhibit a 41% increase in AA levels in erythrocyte membranes, along with elevated levels of LTB4 and PGD2 precursors, indicating heightened inflammation and bronchospasm. Conversely, EPA levels in patients with COPD are halved, leading to a threefold increase in the AA/EPA ratio. These changes in membrane composition correspond to elevated levels of circulating inflammatory mediators.[106] Furthermore, PGD2 and EPA levels in bronchoalveolar lavage fluid of patients with COPD exhibit a significant linear correlation with lung function.[107] Studies on the response of lung cell inflammation and remodelling markers to dietary PUFAs have shown that AA is associated with the stimulation of lung cell inflammatory mediators. Individuals with COPD exhibit a diminished response to AA compared with healthy counterparts.[19] Although there is an antagonistic effect between n-3 and n-6, their contents do not show a trend of increase or decrease. Nevertheless, the body can counteract the pro-inflammatory effects of n-6 PUFAs by enhancing the presence of n-3 PUFAs.[103] Consequently, further exploration is warranted to elucidate the specific fluctuations of PUFAs and their derivatives across various stages of COPD. These findings are summarised in Table 1.

In summary, existing observational studies on the relationship between PUFAs and COPD offer limited and conflicting evidence, characterised by substantial methodological variations. Even systematic analyses yield inconsistent conclusions.[108,109] Notably, a recent systematic review suggested a potential benefit from reducing daily PUFA intake in patients with COPD, with lower n-3 PUFA levels and higher n-6 PUFA levels correlating with an elevated COPD risk.[110] High-quality longitudinal studies suggest that elevated circulating n-3 PUFAs, especially DHA, have a protective effect on lung function, though no significant link to airway obstruction has been found.[111] However, a Mendelian study reported no significant correlations.[24] These discrepancies may be affected by factors such as gender, race and smoking habits. Therefore, large prospective cohort studies and clinical trials are essential to confirm this association.

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Table 1 The Effects of Dietary PUFA Intake, PUFA Concentrations, and Inflammation in the Airways and Circulation on the COPD Risk, Severity, and Health Outcomes

Ref.	Study Design, Study Population, Country	Duration (years)	N	Sex (Age)	Diet Assessment Method	Outcome	Main Results
Ahmadi et al, 2012[83]	Case-control study, individuals in therapeutic centers, Iran	1	COPD 93 Controls 108	F, M (55–75 years)	24-h dietary recall	n-3 PUFA intake	n-3 PUFA intake↓with disease severity; M'n-3 PUFA intake was lower than F'n-3 PUFA intake.
McKeever et al, 2008[84]	Cross-sectional study, individuals in 3 towns, Netherlands	3	Adults 13,820	F, M (20–59 years)	FFQ	FEV1, respiratory Symptoms and COPD odds	No association between n-3 PUFA intake and FEV1; n-3 PUFA intake was associated with risk of wheeze; n-6 PUFA intake↑ was associated with FEV1↓, being strongest in current smokers.
Varraso et al, 2015[85]	Cohort study, health professionals, United States	16	Adults 120,175	F, M (30–75 years)	FFQ	Intakes of fish, n-3 PUFAs, n-6 PUFAs, and the n-3: n-6 ratio; COPD odds	Fish intake (≥4 servings/wk) was inversely associated with risk of COPD (NS after adjusting); when ALA intakes↑, fish intake was negatively associated with risk of COPD.
Varraso et al, 2015[20]	Prospective cohort study, health professionals, United States	16	Adults 120,254	F, M (30–75 years)	FFQ	Food intake; COPD odds	Higher plant-derived n-3 PUFA and n-6 PUFA intake were linked to risk of COPD↓.
Hirayama et al, 2010[25]	Case-control study, Outpatients, Japan	4	COPD 278 Controls 340	F, M (50–75 years)	FFQ (recall 5 years ago)	FEV1, FVC, breathlessness and COPD odds	PUFA intake, n-6 PUFA intake, n-3 PUFA intake↓; Increased PUFA and n-6 PUFA intake were positively correlated with lung function, COPD odds and breathlessness.
Miedema et al, 1993[86]	Prospective cohort study, individuals in Zutphen, Netherlands	25	Adults 793	M (40–59years)	Cross-check dietary history method	Diet and incidence of chronic nonspecific lung diseases	A positive correlation between n-6 PUFA intake and the 25-year incidence, while there was no association for n-3 PUFA intake.
Tabak et al, 1998[87]	Cohort study, individuals in 16 cohorts, 7 Countries	25	Adults 12,763	M (40–59years)	Separate collection of data	Baseline diet and the COPD mortality rate	Independent inverse associations between 25-year COPD mortality and fish intake.

Walda et al, 2002[88]	Prospective cohort study, individuals in 5 population-based cohorts, 3 Countries	20	Adults 2917	M (50–69years)	Cross-check dietary history method	Baseline diet and the COPD mortality rate	No association between fish intake and 20-year COPD mortality.
Root et al, 2014[89]	Cohort study, individuals in 4 communities, United States	5	Adults 15,567	F, M (45–64 years)	Semiquantitative FFQ	FEV1/FVC, PUFA intake, n-3 PUFA intake	Positive correlation between PUFAs, n-3 PUFAs and FEV1/FVC.
Larsen et al, 2015[90]	Cross-sectional study, individuals in Hospital of Limache, Chile	3.25	Adults 1232	F, M (22–28 years)	FFQ, PCA	FEV1, FVC, n-3 PUFA intake	n-3 PUFA intake was positively associated with a higher FEV1 and FVC.
Ng et al, 2014[91]	Cross-sectional study, individuals in communities, Singapore	1.25	Older adults 2478	F, M (55 years and above)	Semiquantitative FFQ	FEV1, FVC, n-3 PUFA intake	n-3 PUFA intake was positively associated with a higher FEV1 and FVC.
Sharp et al, 1994[92]	Cross-sectional study, individuals in the Honolulu Heart Program, United States	3	Japanese-American adults 8006	M (45–68 years)	FFQ	FEV1, smoking status and fish intake	At > or = 40 yr of smoking and < or = 30 cigarettes/d, predicted FEV1 was higher in the high fish group; no difference at < or = 35 yr and and > 30 cigarettes/d.
Shahar et al, 1994[18]	Cross-sectional study, individuals in 4 communities, United States	3	Adults 15,800	F, M (45–64 years)	FFQ	FEV1, FVC, n-3 PUFA intake and COPD odds	EPA and DHA intake was inversely related to the risk of COPD in a quantity-dependent fashion.
Schwartz et al, 1994[93]	Cross-sectional study, individuals in 90 locations, United States	5	Adults 3478	F, M (30 years and above)	FFQ, 24-h dietary recall	FEV1, fish intake	Positive correlation between fish intake and FEV1.

(*Continued*)

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Table 1 (Continued).

Ref.	Study Design, Study Population, Country	Duration (years)	N	Sex (Age)	Diet Assessment Method	Outcome	Main Results
Lemoine S et al, 2019[94]	Cross-sectional study, individuals in NHANES, United States	5	Adults 878	F, M (40 years and above)	24-h dietary recall	Diet and respiratory symptoms	LA↓and ALA↑was associated with odds of chronic cough and wheeze↓; EPA + DHA, but not ALA, was associated with symptoms↓only among current smokers who did not complete high school.
Lemoine et al, 2020[95]	Cross-sectional study, individuals in Maryland, United States	4.25	COPD 112	F, M (40 years and above)	FFQ	n-3 PUFA and n-6 PUFA intake, respiratory symptoms and COPD odds	Total n-3 PUFA intake↑, n-6 PUFA intake↓and n-6 PUFA/n-3 PUFA ratio↓were associated with less COPD morbidity (risk of severe exacerbations↓, health-related quality of life↑, and respiratory symptoms↓).
Choi et al, 2020[96]	Cross-sectional study, individuals in KNHANES, Korea	2	COPD 573	F, M (40 years and above)	24-h dietary recall	HRQoL, lung function and diet	No association between PUFA intake and lung function; n-3, n-6, and total PUFA intake are associated with HRQoL.
Tabak et al, 1999[97]	Cohort study, individuals in 3 European countries	5	Adults 3325	M (40–59 years)	Cross-check dietary history method	Lung function and fish intake	No association between fish intake and lung function.
Tabak et al, 2001[98]	Cross-sectional study, individuals in Dutch, Netherlands	3	Adults 13,651	F, M (20–59 years)	Semiquantitative FFQ	Lung function, respiratory symptoms, fish intake and COPD odds	No independent beneficial associations between fish intake and COPD.
Schwartz et al, 1990[99]	Cross-sectional study, individuals in NHANES II, United States	4	Adults 9074	F, M (30 years and above)	24-h dietary recall	Respiratory symptoms and fish intake	No associations between fish intake and wheezing symptoms.
Batlle et al, 2012[100]	Cross-sectional study, inpatient, Spain	2	COPD 250	F, M (40 years and above)	FFQ	Systemic inflammation and diet	A negative association between ALA intake, DHA/AA ratio and TNF-α; a positive correlation between AA intake and IL-6/CRP.
Wada et al, 2012[101]	Case-control study, Japan	/	COPD 18 Controls 20	F, M (40 years and above)	/	AA in plasma and FEV1	AA↑; A negative association between AA% and FEV1 (%pred).

Kompauer et al, 2008[102]	Cross-sectional study, individuals in Erfurt, Germany	2	Adults 1282	F, M (20–64 years)	FFQ	Lung function and fatty acids in serum phospholipids	A positive correlation between percentage predicted FEV1 and FVC and DHA. No association between other fatty acids and lung function.
Xue et al, 2020[103]	Retrospective case-control study, individuals in hospital, China	2.75	COPD 82 Controls 29	F, M (70–80 years)	/	Lung function and fatty acids in serum	The concentrations of n-3 and n-6 PUFAs↑over time along with the progression of COPD; LA, GLA, AA, EPA and DHA were closely correlated with FEV1% predicted and FEV1/FVC.
Shahar et al, 1999[104]	Cross-sectional study, individuals in 4 communities, United States	3	Adults 2349	F, M (45–64 years)	/	Lung function, fatty acids in plasma and COPD odds	A negative association between DHA and the prevalence odds of COPD, not EPA.
Fekete et al, 2022[105]	Cross-sectional study, Hungary	1	COPD 400	F, M (40 years and above)	Questionnaire	Lung function, 6MWD, quality of life, COPD exacerbation, blood tests	n-3 PUFA intake↓in COPD; in the group with n-3 PUFA supplementation, CRP↓, quality of life↑, inhaled short-acting bronchodilators use↓, number of exacerbations in the previous half year↓, 6MWD↑.
Novgorodtseva et al, 2013[106]	Case-control study, Russia	/	COPD 15 chronic bronchitis 15 Healthy subjects 10	F, M (23–57 years)	/	Systemic inflammation and fatty acids in the erythrocyte membranes	Compared with healthy persons, the amount of AA↑(41%) in COPD; n-6 PUFAs↑LTB4 and PGD2↑; EPA↓(2-fold) and AA/EPA ratio↑(3-fold) in COPD; TNF-α and TGF-β↑in COPD.
Csanky et al, 2009[107]	Case-control study, Hungary	/	COPD 5 smoking control subjects 4	/ (40 years and above)	/	Lipid metabolite in bronchoalveolar lavage fluid and lung function	PGD2 and EPA show a remarkable linear correlation with lung function.
Rutting et al, 2018[19]	Case-control study, Sydney	/	COPD 32 Controls 50	F, M (Mean age 61 years)	/	The response to dietary fatty acids upon markers of inflammation and remodelling in pulmonary fibroblasts	IL-6 and CXCL8 release↓in COPD, not n-3 PUFAs; AA-induced cytokine release was partially mediated by COX-2 in both COPD and non-COPD; TNF-α-induced IL-6 and CXCL8 release was similar in COPD and non-COPD; AA, but not n-3 PUFAs reduced the basal deposition of fibronectin, type I collagen, tenascin and perlecan into the ECM in COPD fibroblasts.

Notes: Legend: /=not investigated; ↓significant decrease; ↑significant increase.

Abbreviations: COPD, chronic obstructive pulmonary disease; PUFA, polyunsaturated fatty acid; FFQ, food frequency questionnaire; F, female; M, male; FEV1, forced expiratory volume in one second; NS, not significant; FVC, forced vital capacity; PCA, principal component analysis; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NHANES, The National Health and Nutrition Examination Survey; LA, linoleic acid; ALA, alpha-linolenic acid; KNHANES, Korea National Health and Nutrition Examination Survey; HRQoL, health-related quality of life; AA, arachidonic acid; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; CRP, C-reactive protein; GLA, γ-linoleic acid; 6MWD, 6-minute walking distance; LTB4, leukotriene B4; PGD2, prostaglandin D2; CXCL8, C-X-C motif chemokine ligand 8; COX-2, cyclooxygenase 2; ECM, extracellular matrix.

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Interventional Research

n-3 PUFAs are known for their anti-inflammatory properties in various inflammatory diseases, yet evidence supporting their efficacy in COPD treatment remains limited. Few studies have specifically examined the effects of n-3 PUFA supplements on the lung health of patients with COPD. A protocol from Australia, published before 2013,[112] outlined a 16-week parallel, double-blind trial involving 40 participants who were randomly assigned to receive either 6 g/day of fish oil or placebo. Measurements included inflammatory biomarkers, n-3 PUFA levels, respiratory function and exercise capacity. However, results from this study are unavailable, and recruitment challenges were noted.[113] Recently, another research team published results from an randomized controlled trial (RCT) involving patients with moderate to severe stable COPD, demonstrating significant improvement in respiratory symptoms after 6 months of n-3 PUFA supplementation compared with placebo.[114] These findings suggested that n-3 PUFAs may enhance respiratory symptoms in COPD, supporting their potential therapeutic application in this condition.

All other RCTs involving n-3 PUFAs in COPD utilised combined interventions, precluding isolation of n-3 PUFA-specific effects. Nonetheless, research confirmed that combined interventions yield positive outcomes for COPD. Dietary strategies, particularly the Mediterranean diet rich in n-3 PUFAs, vitamin D, high-quality proteins and vegetables, are well-tolerated and safe, positively impacting blood pressure, blood lipids and dyspnoea.[115,116] However, long-term follow-up is necessary to assess the sustained effects of dietary interventions in patients with COPD.

Numerous studies have highlighted the benefits of combining n-3 PUFAs with exercise to enhance exercise tolerance. Four months of high-intensity exercise training significantly boosts lower limb muscle strength and exercise capacity in patients with COPD, low muscle mass and moderate airflow obstruction. Compared with a placebo, supplementation with n-3 PUFAs, vitamin D and leucine further improves nutritional status, inspiratory muscle strength and physical activity.[117] Additionally, low-intensity exercise with n-3 PUFAs aids COPD recovery. Specifically, 12 weeks of pulmonary rehabilitation training combined with different nutritional combinations containing n-3 PUFAs can increase body weight, exercise capacity and quality of life and reduce the systemic inflammatory response (CRP, IL-6, IL-8 and TNF-α) in patients with COPD.[118,119] Although both COPD patient groups experienced increased maximum exercise load and duration following 8 weeks of pulmonary rehabilitation with PUFAs or placebo supplementation, the improvement in exercise capacity was significantly greater in the PUFA group than in the control. Nevertheless, PUFA supplementation did not significantly impact muscle strength, lung function or inflammation, presumably due to varying intervention durations.[120] Recent gene-level research revealed a high incidence of COPD in individuals with elevated polygenic risk scores, suggesting that n-3 PUFA intake and exercise may influence COPD risk.[121] Thus, n-3 PUFAs might offer beneficial biological and clinical effects. Further RCTs are essential to assess the specific relationship between n-3 PUFAs and COPD progression and inflammation, focusing on the isolated effects of n-3 PUFAs rather than combined interventions. These findings are summarised in Table 2.

Potential Mechanisms of PUFAs on COPD Inflammation

COPD is a chronic inflammatory disease characterised by elevated levels of neutrophils, macrophages and lymphocytes, alongside an increased release of chemokines and pro-inflammatory cytokines.[122,123] This chronic inflammation results from an imbalance between pro-inflammatory and pro-resolving pathways.[124] Smoking, a known risk factor for COPD, disrupts lipid homeostasis in the respiratory system, exacerbating this imbalance and contributing to COPD pathogenesis.[125] PUFAs and their metabolites play a role in initiating and resolving inflammation in COPD through various pathways.

Directly Participate the Inflammation in COPD

The imbalance between pro-inflammatory and pro-resolution pathways is a hallmark of COPD. PUFAs and their metabolites directly influence COPD-related inflammation. Studies have demonstrated that an increased DHA/AA ratio can significantly reduce the release of pro-inflammatory cytokines and increase the release of anti-inflammatory cytokines in human alveolar cells stimulated by endotoxin.[126] AA serves as the substrate for prostaglandins and leukotrienes, which are key mediators in the initiation of acute inflammation.[127,128] However, AA is also the precursor of LXA4, an important

Table 2 Summary of RCTs Addressing the Impact of n-3 PUFAs on COPD

Ref.	Sample Size	Duration	Control	Time of Measures	Dose	Outcomes	Results
Kim et al, 2021[114]	20 COPD with high-dose fish oil capsules, 20 COPD with placebo	6 months	3 soft gel capsules of placebo (corn oil, Prevention Pharmaceuticals, Inc).	2, 4, and 6 months from baseline	3 soft gel capsules that contained 650 mg of EPA and 182 mg of DHA for a total daily dose of 3 grams of n-3 PUFAs	Percentage change in brachial artery FMD, peripheral arterial tonometry, EMPs, 6MWD, respiratory symptoms, and lung function	Improvement in respiratory symptoms and CD31+ EMPs; No difference in other outcomes.
Calder et al, 2018[115]	22 COPD with TMN, 23 COPD with comparator	3 months	~200 kcal; a milk-based comparator that contained no 25-hydroxy-vitamin D3, milk protein, and sunflower oil per 200 mL, drink two 200 mL daily	Screening (days −14 to −1), baseline (day 1), and every 3 weeks thereafter (weeks 3–12)	~230 kcal; 10 g whey protein concentrate, minimum 2.0 g DHA + EPA, and 10 μg 25-hydroxy-vitamin D3 per 200 mL, drink two 200 mL daily	Adverse events and changes in vital signs, laboratory parameters, and concomitant medications, weight, body composition, exercise tolerance, metabolic biomarkers, and systemic inflammation	TMN was well tolerated; Adverse events were similar; good compliance; weight↑; more fat mass↑, SBP↓ triglycerides↓, exercise-induced fatigue↓, dyspnoea↓, and HDL-C↑in TMN group.
Bool et al, 2017[117]	42 COPD with nutrition and PR, 39 COPD with placebo and PR	4 months	A flavoured non-caloric aqueous solution; standardized outpatient PR program	4 months from baseline	187.5 kcal in a distribution of 20 energy percent (EN%) protein, 60EN% carbohydrate (CHO), and 20EN% fat, and was enriched with leucine, n-3 PUFA, and vitamin D; standardized outpatient PR program	QMS, body composition, CET, IMS, and daily steps, dietary history, fasting plasma levels of vitamin D, BCAAs, and fatty acid profile in phospholipids; lung function, 6MWD and HADS	Body mass↑, plasma vitamin D↑, EPA↑, DHA↑, steps/day↑muscle mass↑, QMS↑, CET, and IMS↑in nutrition group.
Sugawara et al, 2010[118]	17 COPD with nutrition and low-intensity exercise, 15 COPD control	3 months	45-min education program; once every 4 weeks	3 months from baseline	400 kcal per day; Two 200 mL packages of nutritional drink consisted of 60% energy from carbohydrates, 25% energy from fat, and 15% energy from protein. This drink contains n-3 PUFAs 0.6 g and vitamins A 248 μg in total ingredients; low-intensity exercise	Lung function, maximum inspiratory and expiratory muscle force, CRQ, 6MWD, and the Borg scale, and systemic inflammation	Body weight and FFM↑; the dietary intake energy↑; REEpred ratio↓; IMS↑, QMS↑, 6MWD↑; improved in the domains of dyspnea; hsCRP, IL-6, IL-8, and TNF-α↓.

(*Continued*)

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Table 2 (Continued).

Ref.	Sample Size	Duration	Control	Time of Measures	Dose	Outcomes	Results
Sugawara et al, 2012[119]	18 COPD with nutrition and low-intensity exercise, 18 COPD control	3 months	Normal meals alone with dietary instruction	3 months from baseline	200 kcal/pack of nutritional supplement twice a day in addition to normal meals and dietary instruction (mineral, aminoacid composition, fattyacid composition)	The body composition, skeletal muscle strength, exercise tolerance, HRQOL, and inflammatory cytokines	The body weight↑, %IBW↑, FM↑, energy intake↑, %AC↑, Albumin↑, PImax↑, PEmax↑, 6MWD↑, WBI↑, emotional function↑, and CRQ total↑, and the levels of hsCRP, IL-6, IL-8, and TNF-α↓.
Broekhuizen et al, 2005[120]	38 COPD with PUFA and PR, 42 COPD with placebo and PR	2 months	9g per day; the placebo capsules contained 80% palm oil and 20% sunflower oil	2 months from baseline	9g per day; the daily dosage of PUFA consisted of 3.4 g active fatty acids, a blend of 400 mg STA, 760 mg GLA, 1200 mg ALA, 700 mg EPA, and 340 mg DHA	Body composition, lung function, incremental cycle ergometry test, submaximal cycle test, isokinetic quadriceps strength and inflammatory markers	Weight↑, FFM↑, and muscle strength↑in both groups; peak load and the duration of the constant work rate test↑more in PUFA group.

Note: ↓significant decrease; ↑significant increase.

Abbreviations: PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FMD, flow-mediated dilation; EMPs, endothelial microparticles; 6MWD, 6-minute walk distance; TMN, targeted medical nutrition; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; PR, pulmonary rehabilitation; QMS, quadriceps muscle strength; CET, cycle endurance time; IMS, inspiratory muscle strength; BCAAs, branched-chain amino acids; HADS, Hospital Anxiety and Depression scale; CRQ, Chronic Respiratory Disease Questionnaire; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; hsCRP, High-sensitivity C-reactive protein; IL-8, interleukin 8; REE, resting energy expenditure; HRQOL, health-related QOL; FM, fat mass; %IBW, %ideal body weight (= body weight (kg)/height $(m)^2$×22×100); AC, Mid-upper arm circumference; PImax, maximum inspiratory pressure; PEmax, maximum expiratory pressure; WBI, weight-bearing index; STA, stearidonic acid; GLA, gamma-linoleinic acid; ALA, alpha-linolenic acid; FFM, fat-free mass.

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participant in the resolution of inflammation.[129,130] Therefore, AA plays a dual role in inflammation, acting as a precursor for pro-inflammatory and anti-inflammatory signalling molecules. Substantial evidence suggests that the pathogenesis of COPD involves the dysregulation of lipid mediator pathways. Compared with healthy individuals, patients with COPD exhibit increased levels of leukotrienes and PGE2, as well as decreased levels of lipoxins in bronchoalveolar lavage fluid, sputum and exhaled breath condensate.[131–133] Additionally, COPD lung fibroblasts demonstrate reduced release of the pro-inflammatory cytokines IL-6 and CXCL8, partially mediated by the COX-2 pathway, suggesting that AA metabolism has complex effects on COPD inflammation.[19] SPMs, metabolites of PUFAs, play a key role in the resolution of inflammation, and multiple studies have focused on the relationship among LXA4, RvD1, their receptor FPR2/ALX and COPD inflammation.[134] SAA and LXA4, which both bind to the ALX/FPR2 receptor, play opposing roles in inflammation. In patients with COPD, SAA levels are elevated in serum and bronchoalveolar lavage fluid. During acute COPD exacerbations, SAA levels rise significantly more than LXA4 levels.[132,135]

RvD1 demonstrates strong anti-inflammatory and pro-resolving effects. In patients with COPD, levels of RvD1 in sputum, serum and exhaled breath are significantly reduced, whereas pro-inflammatory factors are notably elevated.[131,136] Compared to stable COPD patients, D-Rvs were downregulated and linked to an increased future risk of severe exacerbations during the follow-up period.[137] Animal model studies have highlighted RvD1's essential role in COPD.[138] RvD1 mitigates smoking-induced emphysema by reducing inflammation and promoting tissue regeneration.[139] Exogenous RvD1 administration significantly decreases neutrophil counts triggered by cigarette smoke, reducing inflammation, oxidative stress and cell death.[136,140] Additionally, RvD1 administered concurrently for 3 days during cigarette smoke exposure markedly diminishes acute inflammation, neutrophil recruitment and pro-inflammatory signalling. RvD1 alleviates airspace enlargement in mice subjected to chronic cigarette smoke exposure, reduces neutrophil infiltration and pro-inflammatory cytokine production, enhances the expression of the anti-inflammatory cytokine IL-10 and accelerates the resolution of inflammation.[141] Further research demonstrated that RvD1 administration post-smoking cessation facilitates lung repair in mice. RvD1 attenuates oxidative stress by activating the Nrf2/Keap1 pathway, augments IL-10 expression and aids in the restoration of pulmonary elastin fibres and lung morphology.[142] The administration of RvD1 after smoking cessation is equally effective as its administration during the final 6 weeks of smoke exposure.[139] These findings suggested that RvD1 has potential for the prevention and treatment of COPD.

In summary, the imbalance between pro-inflammatory and pro-resolution pathways in the respiratory system is a key mechanism underlying chronic inflammation in COPD. PUFAs and their metabolites can directly modulate chronic inflammation, thereby reducing COPD incidence.

Regulation of Macrophage Polarisation in COPD Inflammation

COPD's inflammatory process is closely associated with an imbalance in macrophage phenotypes. Cigarette smoke triggers the classical polarisation pathway (M1 type) in alveolar macrophages, resulting in the substantial secretion of pro-inflammatory factors like TNF-α and IL-6. Conversely, M2 macrophages, activated via the alternative pathway, facilitate the resolution of inflammation by eliminating apoptotic cells and secreting anti-inflammatory mediators such as IL-10.[143,144] Rvs derived from n-3 PUFAs modulate macrophage phenotype imbalances via dual pathways. D-series Rvs enhance anti-inflammatory cytokines, decrease inflammatory factors, promote M2 macrophage differentiation and correct cigarette smoke-induced phagocytic defects. These effects are partly mediated through the regulation of the NF-κB signalling pathway.[136] Specifically, RvD1 inhibits the NF-κB signalling pathway, significantly reducing IL-8 secretion in human bronchial epithelial cells exposed to cigarette smoke extract (CSE).[145] RvD1 stimulates IL-10 production in lung fibroblasts, facilitating M2 macrophage differentiation, neutrophil secretion and the resolution of pulmonary inflammation.[141] RvE1 reduces ROS production in macrophages exposed to CSE, reinstates macrophage phagocytic activity towards apoptotic neutrophils and mitigates CSE-induced macrophage mortality.[140]

Macrophages can convert DHA into 13S,14S-epoxy-maresin and MaR1. Notably, 13S,14S-epoxy-maresin inhibits LTB4 production by selectively blocking LTA4 hydrolase activity. It also decreases AA conversion via human macrophage 12-lipoxygenase and facilitates the shift from M1 to M2 macrophage phenotypes.[146] In the lungs, macrophages modulate the lipidome via DHA, suppressing eicosanoid production, including prostaglandins, leukotrienes,

thromboxanes and pro-inflammatory cytokines.[147] Thus, MaRs may significantly influence macrophage polarisation and contribute to COPD inflammation.

Regulation of Membrane Biophysics and Signal Transduction in COPD Inflammation

The role of PUFAs in inflammation extends beyond their biochemical properties, as they also regulate membrane biophysical dynamics, which influence the disease process. n-3 PUFAs modulate ion channel activity by altering membrane fluidity, typically enhancing the activation of the mechanosensitive cation channel, transient receptor potential vanilloid 4 (TRPV4), via lipid bilayer reconstruction.[148] TRPV4 plays a crucial role in lung homeostasis by maintaining epithelial/endothelial barrier integrity, regulating bronchial smooth muscle contraction and coordinating mucosal ciliary clearance.[149] TRPV4 knockout mice exhibit structural changes similar to emphysema, confirming the importance of this channel in protecting lung parenchyma.[150] Recent research indicates that n-3 PUFAs can enhance TRPV4-mediated endothelial nitric oxide release, which is the core mechanism for maintaining endothelium-dependent vasodilation under physiological conditions.[151]

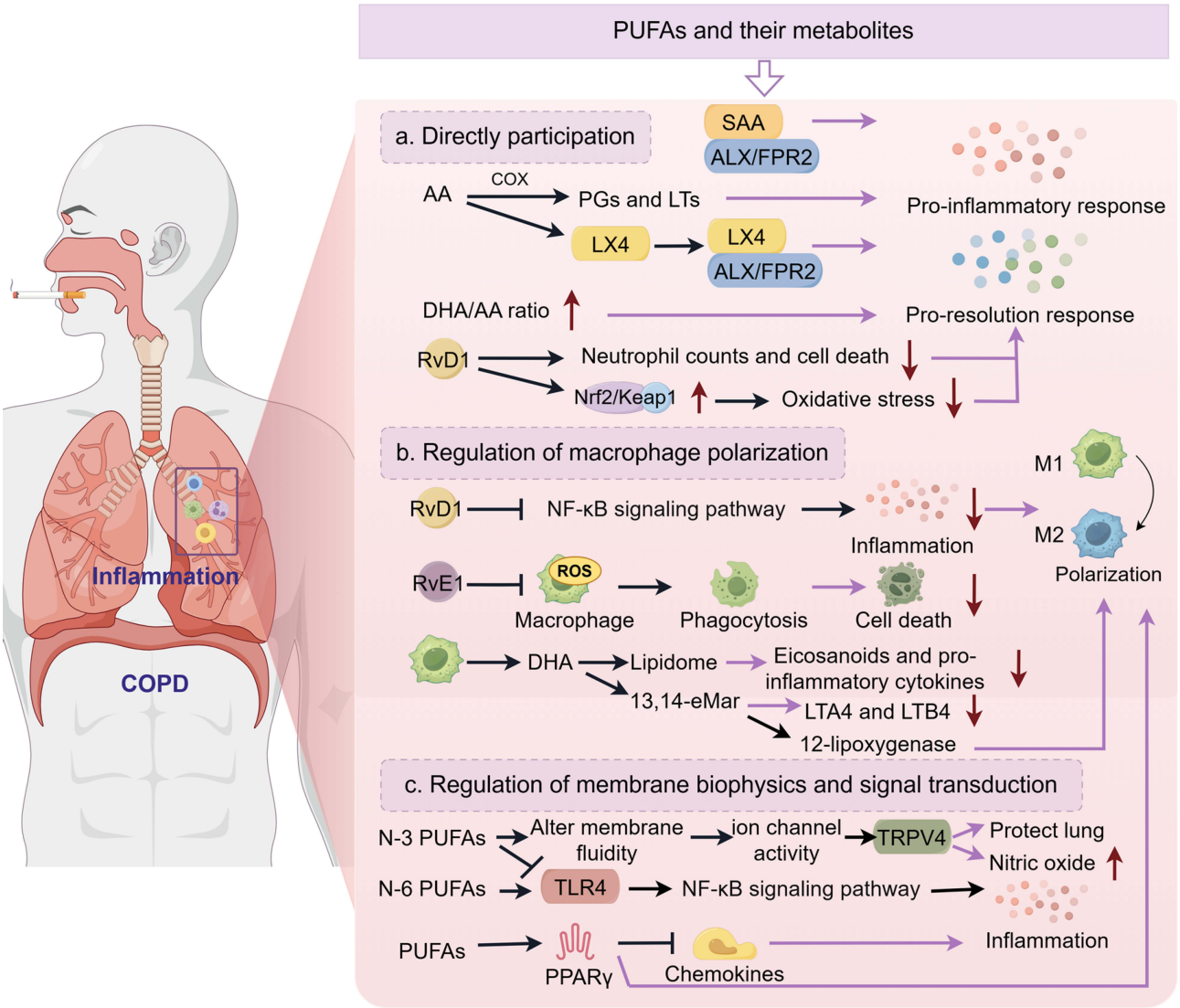

Figure 3 The mechanisms of PUFAs on COPD inflammation. PUFAs and their metabolites are mainly involved in COPD inflammation through the following ways: a. direct participation; b. regulation of macrophage polarization; c. regulation of membrane biophysics and signal transduction. ↑, significant upregulation; ↓, significant downregulation. **Abbreviations**: AA, arachidonic acid; COX, cyclooxygenase; PGs, prostaglandins; LTs, leukotrienes; LXs, lipoxins; DHA, docosahexaenoic acid; Rvs, resolvins; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species; 13S,14S-epoxy-maresin, 13,14-eMar; TRPV4, transient receptor potential vanilloid 4; TLR4, toll-like receptor 4; PPARγ, peroxisome proliferator-activated receptor gamma.

Conversely, cigarette smoke exposure significantly reduces the membrane fluidity of alveolar macrophages by inducing lipid peroxidation of unsaturated fatty acids in membrane phospholipids.[151–153] These findings suggest an antagonistic effect between the membrane-protective action of n-3 PUFAs and smoking-induced lipid peroxidation damage. Targeting membrane biophysical properties may offer a promising avenue for addressing COPD inflammation.[11]

In addition to regulating signalling pathways through the biophysical properties of the membrane, fatty acids can directly interact with pattern recognition receptors, such as cell surface receptors, TLR4 and intracellular receptors, to modulate the inflammatory response. These interactions activate NF-κB signalling, resulting in the release of pro-inflammatory mediators like TNF-α, IL-6 and IL-8.[4] n-3 PUFAs inhibit TLR4 signalling to exert anti-inflammatory effects, whereas n-6 PUFAs, such as AA, promote inflammation via a TLR4-independent pathway.[154] AA primarily enhances inflammation via its conversion to PGE2 by COX, affecting immune and lung epithelial cells, but showing no significant difference in fibroblasts between patients with and without COPD.[19,155] Non-selective COX inhibitors and COX-2 selective inhibitors only partially reduce AA-induced IL-6 and CXCL8 secretion, with no variation in efficacy between COPD and non-COPD cells, suggesting that AA also promotes inflammation via a COX-2-independent mechanism.[19]

The regulation of COPD by PUFAs is closely linked to the key transcription factor peroxisome proliferator-activated receptor gamma (PPARγ). Notably, the expression of PPARγ is significantly downregulated in the lung tissue, airway epithelial cells, lung myeloid dendritic cells and plasma of patients with COPD. Activation of PPARγ by its agonists can inhibit the expression of the chemokines CXCL10 and CXCL15 induced by cigarette smoke, reduce the abnormal aggregation of alveolar macrophages and reverse the pathological changes of emphysema.[156,157] Furthermore, the activation of PPARγ can promote the polarisation of M2 macrophages, enhance the phagocytic and clearance ability of apoptotic neutrophils and up-regulate the secretion of anti-inflammatory mediators to promote tissue repair.[158,159] The potential mechanisms of PUFAs on COPD inflammation are summarised in Figure 3.

Conclusions and Perspectives

This review evaluated the evidence linking PUFAs to chronic inflammation in COPD. Numerous observational studies have investigated the impact of dietary PUFAs on airway and circulatory inflammation in patients with COPD, considering disease prevalence, severity and outcomes. However, the findings remain inconclusive due to variability in study designs, populations and results. Even comprehensive analyses, such as meta-analyses, are limited by inconsistencies and contradictions in the research on n-3 and n-6 PUFAs in COPD. Thus, definitive conclusions cannot yet be drawn. Recent studies have provided evidence of a significant link between PUFAs and COPD development. Future research should also consider focusing on the n-6/n-3 PUFA ratio rather than individual fatty acid intakes. Notably, only one recent RCT demonstrated respiratory function benefits from n-3 PUFAs, whereas combined interventions show limited effects. Currently, the dearth of a more accurate biomarker for PUFA intake, such as the n-3 PUFA index, and the distinct inflammatory profiles and the role of PUFAs in COPD subtypes warrant further investigation. Overall, large, well-controlled clinical trials are urgently needed to elucidate the roles and efficacy of PUFAs in COPD.

We examined the potential mechanisms by which PUFAs influence inflammation in COPD, highlighting the roles of PUFAs and their derivatives in direct involvement, macrophage polarisation, membrane biophysics and signal transduction during the onset and resolution of COPD inflammation. Notably, SPMs derived from PUFAs can promote the resolution of COPD inflammation through multiple mechanisms. Targeting SPMs in drug development may provide therapeutic advantages for COPD. However, the roles of many SPMs in COPD remain underexplored. Specifically, the dynamic changes of SPMs in COPD and their levels following n-3 PUFA supplementation have not been investigated. Future research should focus on exploring the application of PUFAs and their metabolites in developing treatments for COPD.

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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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