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Omega-3 long-chain polyunsaturated fatty acids and their bioactive lipids: A strategy to improve resistance to respiratory tract infectious diseases in the elderly?

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Abstract. Age-related changes in organ function, immune dysregulation, and the effects of senescence explain in large part the high prevalence of infections, including respiratory tract infections in older persons. Poor nutritional status in many older persons increases susceptibility to infection and worsens prognosis. Interestingly, there is an association between the amount of saturated fats in the diet and the rate of community-acquired pneumonia. Polyunsaturated fatty acids, particularly omega-3 long chain polyunsaturated fatty acids (ω-3 LC-PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have well-known anti-inflammatory, immunomodulatory, and antimicrobial effects, which may, in theory, be largely induced by PUFAs-derived lipids such as specialized pro-resolving mediators (SPMs). In adults, preliminary results of studies show that ω-3 LC-PUFAs supplementation can lead to SPM generation. SPMs have a crucial role in the resolution of inflammation, a factor relevant to survival from infection independent of the pathogen's virulence. Moreover, the immune system of older adults appears to be more sensitive to ω-3 PUFAs. This review explores the effects of ω-3 LC-PUFAs, and PUFA bioactive lipid-derived SPMs in respiratory tract infections and the possible relevance of these data to infectious disease outcomes in the older population. The hypothesis that PUFAs have beneficial effects via SPM generation will need to be confirmed by animal experiments and patient-derived data.

Keywords: Fatty Acids, Omega-3, respiratory tract infections, aging

1. Introduction

Excess mortality and morbidity secondary to respiratory tract infections (RTIs) are mainly observed in persons aged 65 years and older [1, 2]. In Europe, influenza is the disease with the highest burden (81.8 disability-adjusted life years per 100,000 population), followed fourth place by invasive pneumococcal disease (53.5 disability-adjusted life years per 100,000 population) [1]. Of 13 368 cases in the European dataset of patients admitted to intensive care units with influenza, 46 % were 60 years and older, of which 25,6% were fatal [3]. These two diseases were among the top 10 leading causes of death in the United States in 2020 [4]. Multiple interrelated factors explain the greater susceptibility to infectious diseases with age. For example, swallowing disorder, a clinical condition prevalent among older persons, represents a risk factor for

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RTIs [5]. Older adults are not only exposed to a higher rate of RTIs but also to more adverse outcomes after community-acquired pneumonia, such as cardiovascular events [6]. In addition, the strength of the respiratory muscles and chest-wall compliance gradually decrease with aging resulting in reduced ventilatory response in case of infection [7]. Thereby, patients aged 80 years and older have been disproportionally affected by coronavirus disease 2019 (COVID-19) [8]. Moreover, disease severity and progression to acute respiratory distress syndrome in COVID-19 could be predicted by levels of pro-inflammatory cytokines and chemokines, particularly in older people [9, 10]. RTIs in older adults thus represent an important healthcare burden and new impetus to developing therapeutic strategies is needed.

This review explores the effects of ω-3 LC-PUFAs, and SPMs in RTIs, highlights some promising results of pre-clinical studies using various pathogens and the possible relevance of these data to infectious disease outcomes in the older population.

2. Older subjects and nutritional status

There is considerable heterogeneity among available publications in this field, and the reported prevalence of malnutrition in nursing homes or long-term and rehabilitation care facilities varies between 17.5 % to 29.4% [11]. The interplay of numerous factors, including sensory (e.g., decreased senses of smell and taste), functional (e.g., dental problems, higher level of dependency), socio-economic, psychological (e.g., depression), and endogenous (e.g., increased pro-inflammatory cytokines, impaired production of peptides and hormones regulating appetite), contributes to lower nutritional intake [12–18]. In addition, a low intake of nutrient-dense foods leads to nutritional deficiencies associated with an impaired immune response [19, 20]. Moreover, nutritional status can be altered if the diet is unbalanced, even if the caloric intake is sufficient or even high.

Dietary lipids are fundamental, energy-providing nutrients, structural components of cells that significantly impact immune cell function [21]. In this context, a regular diet high in saturated-fats led to an impaired capacity to resist acute induced infections in mice [22]. In humans, a relationship between fatty acid consummation and RTIs has been observed in two cohorts. First, in a cohort of 83,165 women in the Nurses' Health Study II, subjects with the highest quintile of palmitic acid intake (saturated fatty acid) had a greater risk of community-acquired pneumonia than those in the lowest quintile [23]. Second, in 38,378 male U.S. health professionals, Merchand et al. noted that those with the highest quintile intake of linoleic and alpha-linolenic acid (polyunsaturated fatty acids ω-6 et -3 respectively), present in vegetable oils, had fewer cases of pneumonia than those in the lowest quintile [24]. Despite these considerations, the average daily intake of ω-3 PUFAs in nursing-home residents is 100 mg, which is below recommended values [25, 26].

3. Older subjects and immunity

Various changes in innate and adaptive immunity with age enhance the risk of infection in animals and humans [27]. Altered production of cytokines and reactive nitrogen species upon stimulation of monocyte-derived macrophages and alveolar macrophages from aged subjects weakens the capacity to kill some pathogens, such as *Streptococcus pneumoniae (S. pneumoniae)* [28, 29]. A reduced population of naïve T-cells because of slower output from the bone marrow and involution of the thymus also limits the antibody response to foreign antigens [30, 31]. Fewer antigen-specific B cells associated with impaired CD4 + T cell responses strongly reduced antibody titers in the elderly during vaccine administration [32]. Moreover, the expression of bacterial ligands of *S. pneumoniae*, the leading cause of death from RTIs, increases in lung senescent cells, particularly in older adults [33, 34]. Age-associated inflammation also primes the lungs for infection through an increased surface expression of proteins regulated by NF-kB and Toll-like receptor (TLR) dysfunction [35]. Even never-smoking healthy older individuals showed low-grade inflammation in bronchoalveolar lavage fluid (BALF) as illustrated by increased concentrations of interleukin (IL)-8 and expression of $CD^{+}4$ T cell activation markers [36, 37]. Crucially, survival after infection will depend not only on the pathogen's virulence and subsequently on the extent of the host's immune response, but also on the ability of that response to be self-limited [38, 39]. However, a decreased anti-inflammatory cytokine IL-10 response in the lungs of aged rats exposed to a carrageenan challenge (a proinflammatory polysaccharide used to induce inflammation) negatively impacted the resolution of inflammation, resulting in increased parenchy-

mal lung damage and dysfunction as assessed by nitrosative stress and lipid peroxidation [40]. Resolution of inflammation, called "catabasis", is biologically represented by a switch from pro-inflammatory mediators, such as prostaglandins and leukotrienes, to anti-inflammatory mediators [41]. Arnardottir et al. demonstrated, using lipid mediator quantification in a model of peritonitis, that aged mice had an increased acute polymorphonuclear (PMN) influx and a temporal dysregulated lipid mediator level compared to young mice [42]. The delayed resolution of acute inflammation was associated with lower levels of mediators derived from endogenous PUFAs, like lipoxins, resolvins, protectins, and maresins, collectively termed "specialized pro-resolving mediators" (SPMs) [43]. Of interest, age influences resolvin D1 production in mice, as demonstrated by Dufour et al. [44].

It is now well-established that SPMs are largely responsible for the immunomodulatory actions of PUFAs, even in older subjects [42, 45]. Functions of cells that are part of the innate and adaptive immune response are either promoted or attenuated after exposure to ω-3 PUFAs [46]. Supplementation with even small doses of ω-3 LC-PUFAs, equivalent to consumption of two portions of fatty fish weekly (0.4 g /day), results in gene expression changes in the polymorphonuclear cells (PBMC) involved in inflammation among healthy elderly subjects [47]. These aspects deserve further exploration of the relationship between ω-3 LC-PUFAs, mediator-derived ω-3 LC-PUFAs, and resistance to RTIs, especially in older subjects.

4. Older subjects and ω-3 LC-PUFAs

PUFAs are lipids distinguished by the presence of a double bond located at the third carbon atom from the methyl end group (ω-3 PUFA) or a double bond at the sixth carbon atom (ω-6 PUFA) [48]. The ω-3 PUFA family comprises alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), and the ω-6 PUFA family, linoleic acid (LA), gamma-linolenic acid (GLA), and arachidonic acid (AA) [48] (Fig. 1). This review will focus on EPA and DHA (ω-3 LC-PUFAs) rather than ALA.

After administration, EPA and DHA rapidly appear in local inflammatory exudates within two hours [49]. By activating various enzymes, such as phospholipase A2, cyclooxygenase-2, and 5-,12-, and 15-lipoxygenase, SPMs are generated from the PUFAs and represent the leading players in the resolution phase of infection [50]. Lower concentrations of SPMs have been observed in pathological conditions, such as Alzheimer's disease, peripheral artery disease and aspirin intolerant asthma [51–53]. Concentration of SPMs could be significantly improved with fish oil or ω-3 LC-PUFAs supplementation in adults, opening a field of exploration of new therapeutic strategies. Of interest, the ability of older subjects to incorporate EPA into plasma and peripheral blood mononuclear cell phospholipids after EPA-rich oil supplementation is significantly greater than that of younger people [54]. In addition, EPA metabolism is different in older than in younger men, inducing higher concentrations of DHA after EPA administration by increased conversion of EPA into DHA [55]. The significance and impact of this distinct metabolic functioning between older and younger participants has yet to be explained.

In the presence of invading microbes, pathogen-associated molecular patterns, such as TLR-4, induce signal transduction of cytokine expression initiated in membrane platforms called lipid rafts [56]. However, modification of lipid raft structure and subsequently of activated T cell functions with age may suggest a higher immune sensitivity of older subjects to ω-3 PUFAs than of younger ones through the actions of this molecule on lipid rafts [57, 58]. Taking these considerations into account, we will develop in this review the interplay between fatty acids and lipid-derived mediators, and their impact on lung pathogens and infectious disease.

5. ω-3 LC-PUFAs in RTIs: Pre-clinical studies

5.1. Animal models

Some studies have shown positive results of ω-3 LC-PUFAs on pathogen clearance and host survival, enabling resolution of inflammation caused by infection. Table 1 resume effects of ω-3 LC-PUFAs administration in animal models. Sharma et al. compared infection induced by *Klebsiella pneumoniae (K. pneumoniae)* in mice supplemented with cod liver oil, flaxseed oil, and olive oil and mice fed with standard chow [59]. Six weeks of ω-3 PUFA administration decreased the lung bacterial load. The severity of the acute pneumonia was also reduced. Moreover, survival among the mice fed fish oil for 6 weeks was better than among those fed a diet supplemented with corn oil [60]. Saini et al. tested sea-cod oil contain-

Table 1
In vivo experimental studies on animal model of effects of ω-3 LC-PUFAs enriched diet on the outcome of respiratory infectious diseases

Authors, year (References)	Model type, challenge	Interventions Daily dose of ω-3 LC-PUFAs	Effects
Sharma et al., 2013 [59]	BALB/c mice *K. pneumoniae* induced lung infection	cod liver oil (150 mg EPA/DHA), Maxigard (150 mg EPA/DHA), flaxseed oil (0.5 ml), versus standard chow for 6 weeks	↓ lung bacterial load ↓ severity of tissue damage with cod liver oil, Maxigard, and flaxseed
Thors et al., 2004 [60]	Mice *K. pneumoniae* and *S. pneumoniae.* induced lung infection	fish oil enriched diet or corn oil enriched diet (10% w/w of the diet daily) for 6 week	↓ mortality in mice infected with *K. pneumoniae* in group fish oil (ns *S. pneumoniae* group)
Saini et al., 2011 [62]	6–8 weeks old BALB/c mice, intra-tracheal *S. pneumoniae* D39 serotype 2	sea-cod oil (0,5 ml) versus standard chow for 60 days	↓ pulmonary bacterial load ↓ tissue injury ↓ mortality
Hinojosa et al., 2020 [63]	Three-month old C57BL/6J mice, *S. pneumoniae* serotype 4	5% corn oil (5%) or corn oil (1%) combined with fish oil (4%) for 2 months. Fish oil contain EPA/DHA at a ratio of 18/12.	↓ mortality ↓ lung bacterial titers ↓ tissue injury ↓ lung apoptotic cells ↓ pro-inflammatory cytokines
Freedman et al., 2002 [66]	30 days of age Cftr -/- mice and WT mice, repeated administration of aerosolized Pseudomona LPS	Peptamen containing 40 mg/day of DHA daily for 7 days	↓ neutrophils in bronchoalveolar lavage in mice cftr -/- treated with DHA,
Pierre et al., 2007 [67]	5 weeks of age Male C57BL/6 mice, bacterial inoculum of *P. aeruginosa*	3 isocaloric fatty acid mixtures: ω-3 PUFA (containing 10.5 and 5.1 g/100 g lipids of EPA and DHA respectively), ω-6 PUFA, or a control diet for 5 weeks	no change in lung bacterial load, ↑ distal alveolar fluid clearance ↓ mortality in ω-3 LC-PUFA group
Tiesset et al., 2009[68]	5 weeks of age male C57BL/6 mice, *P. aeruginosa*	EPA and DHA (DHA constituted 4.7% of the total fat content and EPA 11.4%) versus control diet for 5 weeks	↓ alveolar-capillary barrier permeability (↓ pulmonary injury) ↑ bacterial clearance in the late stage of infection ↓ mortality during the first 24 h in ω-3 LC-PUFA group
Caron et al., 2015 [69]	5 weeks of age male C57BL/6 mice, *P. aeruginosa*	control, DHA/EPA (2:1) and alkylglycerol diets for 5 weeks	↑ bacterial clearance ↓ lung injury ↓ mortality in ω-3 LC-PUFA group
McFarland et al., 2008 [71]	Male and female guinea pigs, aerosolized virulent *M. tuberculosis*	Corn oil (CO) and Menhaden FO (9.5 g and 10 g/100 g lipids of EPA and DHA respectively) for 3 weeks	↑ bacterial load in the lungs in ω-3 LC-PUFA group ↓ tuberculin skin test
Jordao et al., 2008 [72]	10 weeks old female BALB/c mice, intranasally *M. tuberculosis*	3 groups: - 0% safflower oil (ω-6, linoleic acid content 7.50%) - 10% Ropufa (ω-3, EPA content 1.5% and DHA 1.1%) - control for 2 weeks	↓ bacterial numbers in ω-3 LC-PUFA group no change in mortality
Seki et al., 2010 [91]	Six-to-8-wk old male C57BL/6J mice, Aspiration pneumonia wit sequential administration of hydrochloric acid followed by bacterial instillation of *E. Coli*	EPA (100 ng) compared to vehicule	↑ clearance of *E. coli* from the lung (↓ Bacterial Growth Index below 0.1)
Byleveld et al., 1999 [77]	6 weeks old BALB/c mice, *Influenza A* virus, H3N2 administered into the nostril	Fish oil for 2 weeks	↑ pulmonary viral load
Schwerbrock et al., 2009 [78]	6 weeks old male C57BL/6J, *Influenza A* virus Puerto Rico/8/34	Fish oil 4 g or corn oil 1 g for 2 weeks	↑ pulmonary viral load ↓ lung neutrophils ↓ degree of lung pathology (reduced inflammation) ↑ mortality in group with fish oil

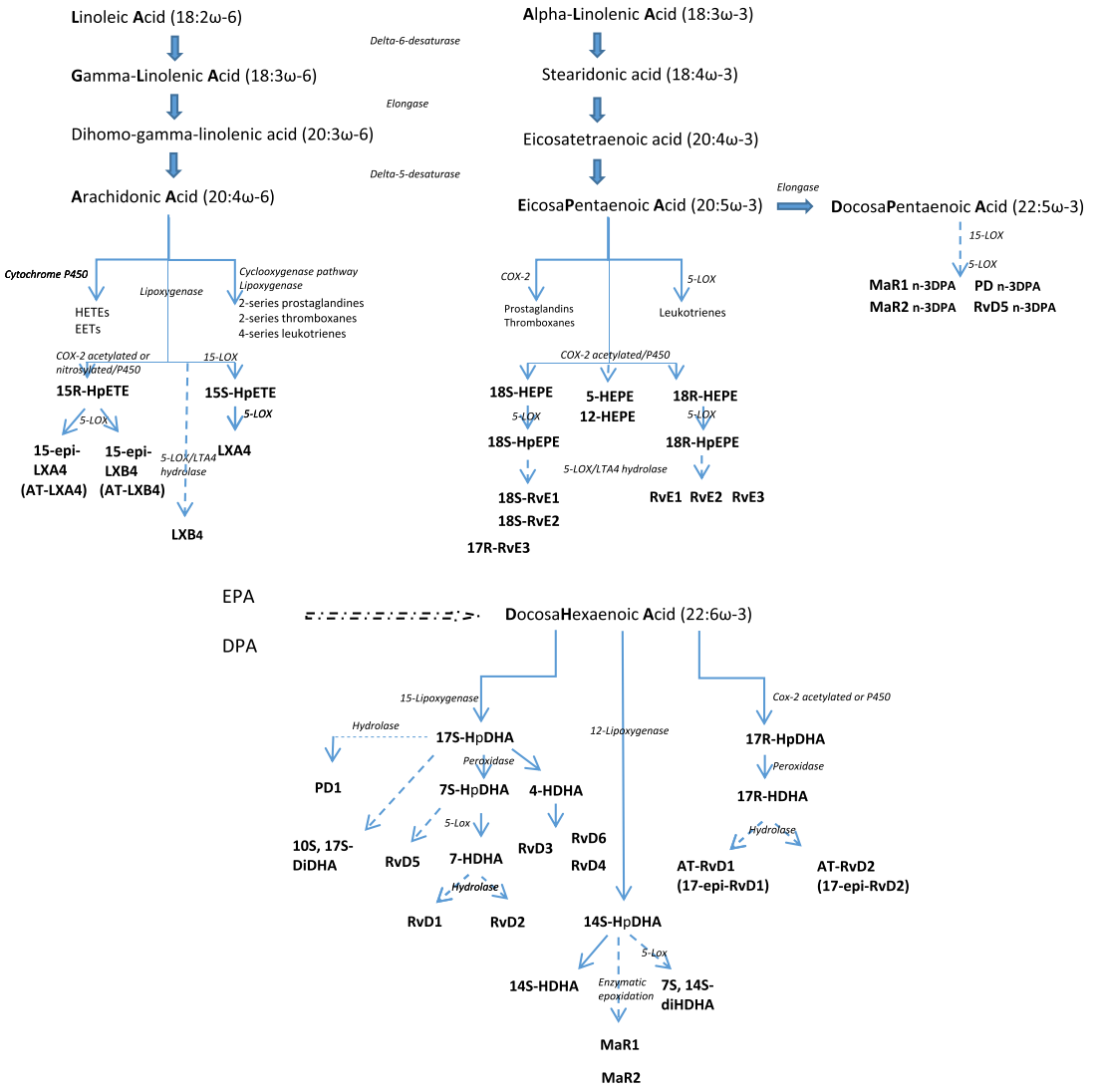


Fig. 1. The anabolic processing of the principal polyunsaturated fatty acids. LA and ALA are essential fatty acids obtained from the diet. LA and ALA are converted to long chain PUFA sharing the same enzymatic pathway but this conversion is not complete and also variable with individuals. Stearidonic acid, eicosatetraenoic acid, GLA, and DGLA are intermediates to synthesize EPA, DHA and AA. AA and EPA are substrates for the synthesis of eicosanoid products including prostaglandins, thromboxanes, and leukotrienes that mediate inflammatory processes. EPA and DHA are metabolized to resolvins, protectins and maresins that promote the resolution of inflammation.

ing ω-3 LC-PUFAs on the course of *S. pneumoniae* D39 serotype 2 in mice and showed a favorable immunomodulatory effect of ω-3 PUFAs against bacterial colonization of the lungs [61, 62]. Finally, ω-3 PUFA and ω-6 PUFA enriched diets were recently compared by Hinojosa et al.. Mice fed with an ω-3 LC-PUFAs diet (ratio 18:12 for EPA:DHA) had reduced bacterial titers in their lungs and blood associated with lower concentrations of pro-inflammatory cytokines and lower numbers of lung apoptotic cells [63]. In summary, long-term administration of ω-3 LC-PUFAs improves survival by reducing histopathological lesions of lung tissue and by modulating pro- and anti-inflammatory cytokines.

Pseudomonas aeruginosa (P. aeruginosa) is an opportunistic pathogen involved in respiratory tract infections. This Gram-negative aerobe/facultative anaerobe is responsible for many chronic infections commonly found in patients with chronic obstructive pulmonary disease and plays a significant role in the pathogenesis of cystic fibrosis-induced lung disease [64]. Human subjects with cystic fibrosis,

independent of pancreatic insufficiency and acute lung infection, showed an imbalance in essential fatty acid membrane composition compared to healthy control subjects [65]. The lower DHA and higher AA tissue concentrations observed in cystic fibrosis stimulated exploration of the effects of ω-3 LC-PUFAs in animal cystic fibrosis models. Indeed, oral administration of high doses of DHA suppressed the increase in bronchoalveolar neutrophil and eicosanoid concentration after pseudomonas lipopolysaccharide-induced pneumonia in CFTR knockout (CFTR-/-) mice but not in wild-type mice [66]. In addition to effects in cystic fibrosis, ω-3 LC-PUFAs have been shown to have a beneficial effect in wild-type animal models. In this context, Pierre et al. worked on a murine model of chronic *P. aeruginosa* infection [67]. An ω-3 LC-PUFAs enriched diet (EPA/DHA 2:1 ratio) given prior to *P.aeruginosa* infection improved distal alveolar fluid clearance (DAFC) and was associated with higher survival of animals compared with isocaloric control ω-6 PUFA diets. Using the same EPA/DHA ratio, Tiesset et al. observed the impact of ω-3 LC-PUFAs on kinetic modulation of inflammation, and showed heightened and overlapped pro and anti-inflammatory responses after *P.aeruginosa*-induced lung infection [68]. Finally, Caron et al. tested the impact of a mixture enriched with a reverse EPA/DHA ratio extracted from rays and chimeras given for five weeks [69]. EPA/DHA (1:2 ratio) supplementation was associated with faster bacterial clearance than in control mice and improved survival rate. In addition, a lower neutrophil count was detected in the lung 36 hours after the onset of infection in parallel with higher levels of the pro-inflammatory cytokine, tumor necrosis factor (TNF)-α, and the anti-inflammatory cytokine, Il-10. These observations suggest an accelerated resolution of infection with ω-3 PUFAs, predominantly DHA.

Intracellular pathogens such as *Mycobacterium tuberculosis (M. tuberculosis)* are also a part of the infectious disease burden in older individuals [70]. Unlike actions on the pathogens mentioned earlier, administration of high doses of ω-3 LC-PUFAs was associated with a larger bacterial load in mice lungs compared with an ω-6 PUFA diet rich in AA [71]. However, other experiments in mice showed that an EPA/DHA-enriched diet increased pathogen killing [72]. Despite the lower organ *M. tuberculosis* load in ω-3 LC-PUFA groups, there was no difference in survival between the interventions. In the context of intracellular infections, some authors have recommended caution with long-term, high-dose supplementation ω-3 LC-PUFA [73]. The Inuit population, well known for its high intake of ω-3 LC-PUFAs, despite signs of a nutritional transition [74], has the highest incidence rate of active tuberculosis among Canadian-born Aboriginals [75]. Nevertheless, epidemiologic data from a prospective study in Singapore showed a reduced risk of active tuberculosis with PUFA dietary intake [76]. The inconsistencies among pre-clinical and population studies evaluating the association between ω-3 LC-PUFAs and tuberculosis infection makes it difficult to draw definitive conclusions.

The effects of ω-3 LC-PUFA supplementation on influenza infections are also conflicting. Indeed, a fish oil-enriched diet for two weeks increased the susceptibility of mice to influenza viral infection and led to delayed viral clearance and an impaired antibody response and lung interferon-γ production [77]. In another experiment, an ω-3 LC-PUFA diet increased the severity of influenza-induced infection [78]. By contrast, administration of a bioactive lipid derived from DHA, protectin D1, improved survival of influenza-infected mice [79] (see later).

5.2. *Ex vivo studies*

Sharma et al. demonstrated that the phagocytic ability of murine alveolar macrophages, evaluated by lung myeloperoxidase production, against *K. pneumoniae* was increased after six weeks of ω-3 PUFA administration [59]. However, reduced lymphoproliferative response in splenocyte cultures from guinea pigs was observed after enriched ω-3 LC-PUFAs [71].

According to these studies whatever the type of model used, the effects of ω-3 LC-PUFAs in preventing infectious disease require further studies.

6. SPMs in RTI: Pre-clinical studies

The active process of resolution of inflammation mediated by bioactive pro-resolving molecules or SPMs works in concert and in an ordered manner with other anti-inflammatory processes to limit lung injury [80]. In cell cultures and *ex vivo* studies, SPMs counter-regulate the chemoattraction of polymorphonuclear cells to an inflamed site, stimulating monocyte recruitment and activation of macrophage efferocytosis of apoptotic granulocytes, pathogen,

and tissue debris [81–83]. Since the discovery of the first SPM, studies have been conducted to evaluate the mechanisms of action of these molecules, including receptor expression, signalization, and intercellular communication in murine lungs [84]. Moreover, in response to inflammation, SPMs are produced during interactions between neutrophils and lung cells, including bronchial epithelial cells, alveolar epithelial type II cells, alveolar macrophages, and mesenchymal stem cells [85–87]. In murine model, SPMs enhance bacterial clearance such that lower antibiotic doses are required [88]. SPM concentrations are positively correlated with increased phagocytosis in whole blood, whether endogenously produced or generated after PUFA supplementation. Interestingly, various SPMs have been shown to have a marked effect on the evolution of lung infection (e.g. resolvin E1, aspirin-triggered resolvin D1, resolvin D1, maresin 1, protectin D1). The major pre-clinical studies in this field are summarized in Fig. 2 and Table 2.

6.1. Animal models

In baboon, pneumonia influences the level of SPM production as demonstrated by Dalli et al [89]. These authors reported that inoculation of *S. pneumoniae* into baboons significantly reduced levels of plasma D-series, E-series, and lipoxins at 48 and 168 hours, demonstrating a temporal shift in the plasma lipid mediator profiles after infection.

Aspiration of gastric acid is a frequent clinical event that can lead to increased susceptibility to pneumonia and acute lung injury/acute respiratory distress syndrome (ALI/ARDS) [90]. In line with these data, Seki et al. used an experimental murine model of aspiration pneumonia with sequential administration of hydrochloric acid followed by bacterial instillation of *E. coli* to study the effects of SPMs and their precursors, ω-3 LC-PUFAs, on infection and inflammation [91]. EPA-derived resolvin E1 (RvE1) was injected prior to the insult and was associated with a dramatic reduction in pro-inflammatory cytokines and chemokines in the lung (i.e., IL-1β, IL-6, high-mobility group box [HMGB]-1 protein, macrophage inflammatory protein [MIP]-1α, MIP-1β, keratinocyte-derived chemokine, and monocyte chemoattractant protein [MCP]-1). Moreover, RvE1 administration also decreased neutrophil infiltration by 55% compared to vehicle. This experiment showed the anti-inflammatory effect of RvE1 combined with maintained clearance of *E. coli* pneumonia. By contrast, EPA decreased the Bacterial Growth Index (BGI) of *E. coli* in lung homogenate of animals and dampened the severity of bacterial pneumonia. However, RvE1 displayed more potent action during resolution of the infectious challenge than EPA.

Aspirin-triggered resolvin D1 (AT-RvD1), also known as 17-epi-RvD1, is a DHA-derived lipid mediator generated from an intermediate 17*R*-HDHA by COX-2 ASA and by oxygenation by 5-LOX [92]. This compound, 17R-HDHA, resists rapid degradation by oxidoreductase and has a longer *in vivo* half-life than RvD1 because of the conformation change of a hydrogen molecule from (S) to (R) around the seventeenth carbon. *E. coli* infection induced

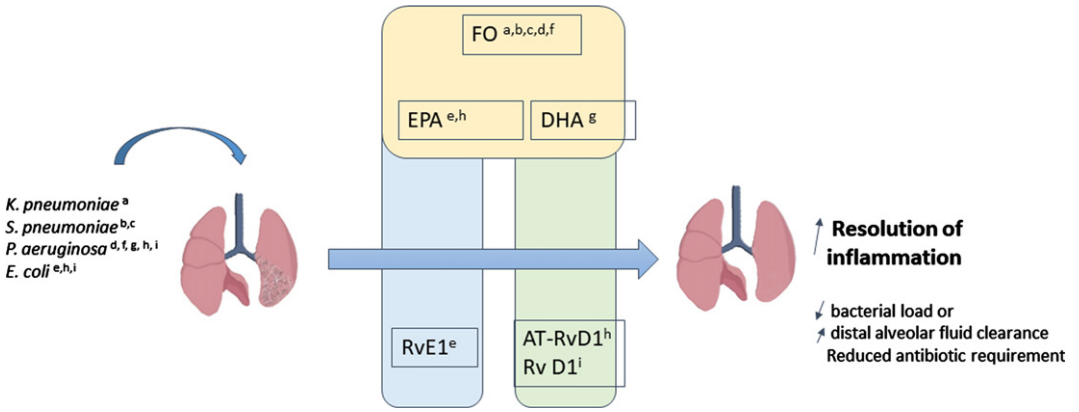


Fig. 2. Pre-clinical studies using and derived bioactive lipids ω-3 LC-PUFAs. Summary of results from experimental studies in mice using bacterial induced respiratory tract infections and interventions with fish oil (FO), EPA, DHA or SPM: [a]Sharma et al.; [b]Saini et al.; [c]Hinojosa et al.; [d]Pierre et al.; [e]Seki et al.; [f]Tiesset el al.; [g]Caron et al.; [h]Abdoulnour et al.; [i]Codagnogne et al.

Table 2
In vivo experimental studies on animal model of effects of SPM derived from ω-3 LC-PUFA on the outcome of respiratory infectious diseases

Authors, year (References)	Model type, challenge	Interventions	Effects
Seki et al., 2010 [91]	6-to-8-wk old male C57BL/6J mice, Aspiration pneumonia wit sequential administration of hydrochloric acid followed by bacterial instillation of *E. Coli*	administration of RvE1 (EPA-derived resolving at 100 ng) prior to acid injury compared to vehicle	↓ lung neutrophil accumulation by 55% ↑ clearance of *E. coli* (↓ Bacterial Growth Index)
Abdulnour et al., 2016 [93]	8–10 wk old C57BL/6 male mice, high dose of intra-bronchial *E.coli* or *P.aeruginosa*	AT-RvD1 (100 ng, IB) or vehicle via a repeat tracheostomy surgery 24 and 36 h after challenge	↓ lung *E.coli* at 6 h and 24 h ↑ lung *P.aeruginosa* bacterial clearance
Sekheri et al., 2020 [95]	Female C57BL/6 mice, intratracheal instillation of *E. coli*	Bolus injection 17-Epi-RvD1 (DHA-derived resolvin) 6 h post challenge	↑ bacterial clearance, ↓ in BAL fluid total leukocyte and PMN numbers
Codagnone et al., 2018 [96]	Mice, intratracheal instillation of *P. aeruginosa*	single oral administration of RvD1, a DHA-derived resolvin (100 ng/ mouse) or RvE1, a EPA-derived resolvin (100 ng/mouse) by intragastric gavage 3 h post intratracheal inoculum and every 48 h starting from day 5 post inoculum	↓ bacterial load and leukocyte infiltration in acute and chronic lung infection ↓ mortality with RvD1 but not RvE1 additional benefit of RvD1 in combination with ciprofloxacin (200 mg, ip)
Morita et al., 2013 [79]	wild-type mice subjected to intratracheal instillation of *influenza 2009 H1N1*	PD1 (Protectin D1, a bioactive lipid derived from DHA) 1 mg/mouse i.v. 12 h before and immediately after challenge (prophylactic model) or 48 h after challenge (therapeutic model) RvD1 or RvD2 (Resolvin derived from DHA)	↓ Mortality (additional benefit with PD1 plus peramivir treatment) ↓ nuclear export of viral mRNA from lung cells ↓ influenza virus replication no change in macrophage and neutrophil numbers in bronchioalveolar lavage (BAL) fluid 48 h after infection (completely rescued) no change with RvD1
Walker et al., 2021 [100]	6–8 week old C57BL/6 male mice, *Respiratory Syncytial Virus* (RSV) pneumonia	Intranasal PD1 or PCTR1 (bioactive lipids derived from DHA) 100 ng or vehicle on days 3, 4, 5 post infection (p.i.)	↓ lung eosinophils and lung macrophage ↓ lung neutrophils and Natural Killer (NK) with PCTR1 ↓ RSV N gene RNA 6 days after challenge with PD1 and PCTR1
Wang et al., 2017[94]	8–10 weeks old C57BL/6J male mice, Coinfected intranasally with *Influenza A* virus and *S. pneumoniae*	Intranasal AT-RvD1 (bioactive lipid derived from DHA) 100 ng or vehicle once daily on day 4 and 6	↓ Pneumococcal load in BALF no change in viral titer ↓ lung neutrophil numbers ↓ myeloperoxidase activity ↓ antimicrobial activity

AT-RvD1 release in mouse lung [93]. AT-RvD1 significantly reduced bacterial lung load and severity of pneumonia in coinfected mice with *influenza A* virus and *S. pneumoniae* [94]. Moreover, administration of AT-RvD1 enhanced macrophage phagocytosis of *E. coli* particles and efferocytosis in the lung, promoting bacterial clearance [93]. In contrast to combined use of ciprofloxacin and AT-RvD1, antibiotic administration alone did not decrease BALF neutrophils despite a lower concentration of *E. coli*. These results indicate a pivotal role of AT-RvD1 in bacterial clearance and pathogen-initiated lung inflammation. The same investigators observed increased bacterial clearance *in vivo* and lung macrophage phagocytosis *ex vivo* by early treatment with exogenous AT-RvD1 in *P. aeruginosa*-induced pneumonia.

AT-RvD1 may restore impaired phagocytosis and facilitate resolution of acute inflammation via the receptor ALX/FPR2, a potential therapeutic target [95]. Similarly, RvD1 administration enhances bacterial clearance by an additive effect with ciprofloxacin, suggesting that RvD1 may potentiate the efficiency of antibiotics [96].

P. aeruginosa represented 20.8% of isolated microorganisms in ICU-acquired pneumonia in 2016 and has a high level of resistance to multiple antibiotics in Europe [97]. *P. aeruginosa* is found in the airways of patients with cystic fibrosis, bronchiectasis, and chronic bronchitis [98]. Non-antibiotic strategies have therefore been evaluated in mice using resolvin D1 and an endogenous SPM enzymatically synthesized from DHA [41]. Recently, Codagnone et al. examined different actions of RvD1 in acute and chronic lung infection induced by a multi-drug resistant clinical strain of *P. aeruginosa* [96]. The authors first analyzed lipid mediators and precursors in lung homogenates from mice with long-term infection with *P. aeruginosa* RP73 at 0, 5, and 21 days after inoculation and determined defects in SPM production using metabololipidomics and proteomics. An intragastric dose of RvD1 reduced lung bacterial titer and BALF total leukocyte accumulation compared to vehicle and increased survival.

Severe influenza infection dramatically decreases the bioactive lipid-derived DHA or protectin D1 (PD1) levels in infected lung [99]. However, the administration of PD1 restores levels to pre-infection values and was associated with increased survival of virus-infected mice [79]. In addition, PD1 inhibits the nuclear export of viral mRNA from lung cells and thus reduces replication of the influenza virus. A decrease in genomic viral load in lung tissue secondary to respiratory syncytial virus (RSV) infection was also observed after intranasal PD1 administration [100].

6.2. Ex-vivo human studies

A pilot study analyzing plasma from patients with newly-diagnosed active tuberculosis infection showed higher levels of D-series resolvins (i.e., RvD1 and RvD2) and aspirin-triggered resolvin D1 (AT-RvD1) compared to asymptomatic and presumably uninfected controls, indicating that these resolvins are likely involved in the host response to infection [101]. The authors suggested the use of high-resolution metabolomic profiling of plasma to evaluate general response to TB by dosing D-series resolvins [101]. Ruiz et al. evaluated the effects of exogenous administration of SPMs on human monocytes-macrophages infected with *M. tuberculosis* [102]. All SPMs tested reduced tuberculosis-induced TNF-α production, but RvD1 and another DHA lipid-derived mediator, maresin R1 (MaR1), specifically limited *M. tuberculosis* growth. This study thus showed a potential therapeutic effect of pro-resolving lipids against *M. tuberculosis* [103].

Taken together, pre-clinical studies using SPMs seem to offer more encouraging results for infection outcomes than their parent molecules, the ω-3 LC-PUFAs [104].

7. Older subjects and severity of RTI

The mortality rate from sepsis, an infectious condition caused by a dysregulated immune system response associated with organ dysfunction, is 25–30% and is higher in older patients [105]. About half of sepsis cases have a respiratory site origin [105]. The hyperinflammatory response present in the initial stage of sepsis often leads to progressive development of immunosuppression responsible for late mortality [38]. Sepsis is characterized by modified metabolism of essential fatty acids, which is associated with the severity of sepsis and clinical outcome [106]. Some argue that the essential fatty acid deficiency seen in sepsis may be partly due to TNF-α in the same way as in chronic malnourished states [107].

Considering this imbalance in fatty acid levels, 146 patients with ARDS as a result of pneumonia, trauma, or aspiration injury were randomized to a high-fat enteral diet combining EPA and GLA or a standard diet for at least 4–7 days in a interventional multicenter trial [108]. The group receiving the high-fat diet required significantly fewer days of ventilatory support and had a decreased ICU length of stay compared with controls. Similarly, in a systematic review, Dushianthan et al. reported a significant improvement in blood oxygenation, reduced ventilator days, and shorter ICU length of stay in patients with ARDS who received nutrition enriched with EPA and DHA [109]. Moreover, in a pooled analysis of 40 randomized controlled trials, PUFAs had some beneficial effects on survival in sepsis-induced ARDS in the enteral nutrition subgroup [110]. Conflicting data on pulmonary outcomes have been observed in some randomized controlled trials, suggesting possibly harm with PUFA administration [111]. Among

these studies, daily combined enteral doses of EPA and DHA in a study by Rice et al. were more than 10 g, which is higher than doses considered safe [112]. Globally, trials that have evaluated PUFA in ALI or ARDS have been of low-quality [109].

By contrast with the population studies using PUFA, pre-clinical investigations with SPMs support their action in host immune response in severe inflammatory states, as suggested by a review of Fullerton et al. [113]. During lung injury, MaR1, a member of the SPM family, had a protective effect and may represent a potential new therapeutic approach for the treatment of ALI/ARDS [114]. This SPM, generated from DHA, is known to enhance macrophage phagocytosis [115]. Of interest, high doses of MaR1 mitigated LPS-induced lung injury by limiting neutrophil influx and pro-inflammatory cytokine/chemokine (TNF-α, IL-1β, IL-6, keratinocyte chemokine, monocyte chemoattractant protein-5, macrophage inflammatory protein MIP-1α and MIP-1γ) release [114]. In addition, MaR1 promoted generation of the anti-inflammatory cytokine, IL-10 [114]. RvE1 facilitates the resolution of inflammation and could prevent ALI/ARDS by promoting phagocytosis-induced neutrophil apoptosis [116]. These experiments highlight the evident link between neutrophil apoptosis in enhancing the resolution of inflammation and, conversely, the numbers of neutrophils in sustained deleterious inflammatory response [117, 118].

8. ω-3 LC-PUFAs intake and secondary SPM levels

The biosynthesis of SPMs partly depends on the availability of their precursor, the ω-3 LC-PUFAs. To analyze this relation, we reviewed all interventional studies combining ω-3 LC-PUFAs administration and detecting SPMs in blood samples of adult participants. We searched the Medline databases from May 2021 to March 2022 to identify relevant studies. The search terms were "Fatty Acids Omega-3, n3 PUFA, n3 Polyunsaturated Fatty acid, docosahexaenoic, eicosapentaenoic" and other related combined with the terms "resolvin, specialized pro-resolving lipid mediator." The search identified 818 articles that assessed SPMs after ω-3 PUFAs administration, and 26 studies were included in the table following the screening process. The details of search strategies and the flow chart of studies selected are described in Fig. 3. Various doses of ω-3 LC-PUFAs and durations of administration were tested in different populations. Concentrations of intermediate precursors of SPMs, such as 18-HEPE, 15-HEPE, 14-HDHA, 17-HDHA, were often increased after combined of EPA and DHA administration. Concentration of resolvin D1, resolvin E1, and maresin 1 were higher with intakes of ω-3 LC-PUFAs greater than 1 g. Interventions included single administration of ω-3 LC-PUFAs [119–121] or administration for a short period of time such as one week [122–124]. Population samples from healthy and chronically ill individuals older than 65 years were studied [124–131]. Methods of SPM measurement differed, with for example two studies assessing SPMs in stimulated neutrophils [132, 133]. It is difficult to interpret the results of studies that do not provide baseline levels of SPMs, no comparator control group or no correction of the results for multiple tests. Although the effect of age on SPM production deserves further investigation and evaluation of duration and dose-response relationships, these preliminary results are encouraging.

9. ω-3 LC-PUFAs and SPMs: A matter of debate

Despite some data showing plasma and local generation of SPM from EPA and DHA, interventional pre-clinical studies have mainly used direct bioactive lipid-derived SPMs instead of analyzing SPM production by the parent molecules. In addition, ω-3 LC-PUFAs are considered by some authors as immunosuppressive, describing absent or deleterious effects on the proliferation of certain pathogens *in vitro* [134]. Heterogeneity of experimental design in terms of ω-3 LC-PUFA doses, infectious challenge pathways, and inflammation-dampening strategies explain this mixed evidence base. Additionally, intake of ω-3 LC-PUFAs represents a considerable percentage of the total energy provided in animal studies, whereas in humans, the total amount of ω-3 LC-PUFAs rarely exceeds 3% [135]. In some cases, mice fed fish oil had less total food intake than controls, possibly secondary to a less palatable diet [77]. These discrepancies in studies concerning the immunomodulatory effects of ω-3 LC-PUFAs are challenging and should be explored in light of secondary SPM production.

Profiling of lipid mediators and their derivatives has recently been considered for its prognostic value [136, 137]. In healthy volunteers, early and delayed "resolvers" were described as two phenotypes in the resolution of inflammation [138]. Studies mentioned

Table 3
Interventional studies evaluating ω-3 LC-PUFA supplementation in adults and older participants on ω-3 LC-PUFA derived mediators production with related immunomodulatory effects

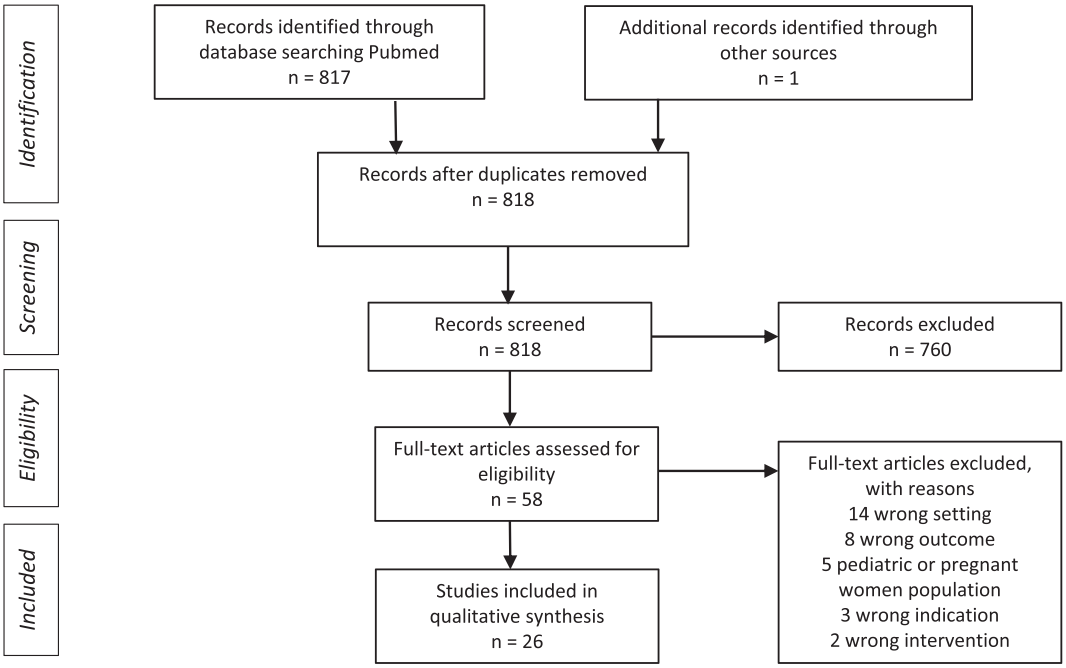
Authors, year, study design (References)	Total participants	Intervention Daily dose of ω-3 LC-PUFAs	Plasma SPMs, EPA-derived, n-3 DPA, DHA-derived precursors	Additional laboratory analysis, *ex-vivo* results and clinical outcome
Barden et al., 2014, one arm [122]	21 healthy participants, 53.7 (6.9) years old,	1.4 g EPA and 1 g DHA, for 5 days	↑ 18-HEPE ↑ 14-HDHA ↑ 17-HDHA ↑ **RvE1**	No additional benefit of aspirin in SPM production
Barden et al., 2015, two arms [142]	43 participants in total, 57.3 (2.1) in healthy group and 59.9 (1.1) years old in metabolic syndrome group	1.4 g EPA and 1 g DHA for 21 days	↑ 18-HEPE ↑ 14-HDHA ↑ 17-HDHA ↑ **RvE1**, RvE2, ↑ RvE3 ↑17R-RvE3	Concentration of 18-HEPE, 17-HDHA and 14-HDHA higher in women
Barden et al., 2016, single arm [143]	72 participants, 57.3 (2.4) years old, in arthritis patients	1.4 g EPA and 1 g DHA for 28 days	* ↑ 10 S,17S-diHDHA, ↑ RvE2, ↑ **AT-RvD1**, ↑ **RvD1**, ↑ RvD2, ↑ PD1 ↑ 14-HDHA, ↑ MaR1 adjusted *p*-value for comparison between healthy and arthritis patients	Level of plasma SPMs more elevated in arthritis patients
Barden et al., 2018, RCT [132]	74 participants with chronic renal impairment, 56.5 (1.4) years old	1.84 g EPA + 1.52 g DHA + 0.152 DPA g (ethyl ester formulation) for 56 days,	* ↑ 18-HEPE ↑ 17 HDHA ↑ **RvE1**, ↑ RvE2, ↑ RvE3, ↑ RvD5 (in stimulated neutrophils)	↓ plasma myeloperoxidase No effect of Coenzyme Q_{10}
Capo et al., 2016, controlled [133]	15 healthy participants (male footballers), 19.7 (0.4)	1.4 g DHA (drink beverage) for 56 days	↑ **RvD1** (LPS-stimulated PBMC) post-exercise	Synergistic effects of acute exercise and DHA supplementation in induction of anti-inflammatory response, ↓inflammatory response induced by PAMPs as LPS.
Colas et al., 2014, single arm [120]	10 healthy participants, 34 (2) years old	0.5 g EPA and 0.2 g DHA, one oral administration with ASA 81 mg 2 hours later	↑ RvE2, ↑ RvE3, ↑ **RvD1**, ↑ RvD2, ↑ 17-epi-PD1 (4 h after n-3 PUFA intake)	Whole blood phagocyte ingestion of *E.Coli* positively correlated with increased levels of Rv D1, Rv D2, Rv E2, Rv E3 and 17-epi-PD1
Dawczynski et al., 2013, RCT [144]	47 mildly hypertriglyceridemic participants, 61.6 (11.8) years old	3 groups: Yoghurt enriched with - 0.8 g ω-3 LC-PUFAs - 3 g ω-3 LC-PUFAs - control for 10 weeks	12 HEPE 15 HEPE 18 HEPE Not significantly elevated	↓ production of IL-2 by PMA/ionomycin-stimulated T cells in ω-3 LC-PUFAs groups
Elajami et al., 2016, controlled [145]	6 participants, 62.9 (11.8) years old, coronary artery disease	1.86 g EPA and 1.5 DHA for 1 year	↑ 17R-RvD3, ↑ RvD6, ↑ 17R-PD1	↑ macrophage phagocytosis of blood clots
Fischer et al., 2014, one arm [146]	20 healthy participants, 31.2 (2.5) years old for men and 38 (1.8) for women	460 mg EPA and 380 mg DHA (ethyl esters) for 28 days followed by 980 mg and 760 mg per day for 28 additional days	* ↑ 5-HEPE, ↑ 4-HDHA, ↑ 7-HDHA, ↑ 12-HEPE, ↑ 14-HDHA, ↑ 18-HEPE	Whole blood sample treated with calcium ionophore stimulated monohydroxy-metabolite formation via LOX enzymes

(*Continued*)

Table 3
(*Continued*)

Authors, year, study design (References)	Total participants	Intervention Daily dose of ω-3 LC-PUFAs	Plasma SPMs, EPA-derived, n-3 DPA, DHA-derived precursors	Additional laboratory analysis, *ex-vivo* results and clinical outcome
Grenon et al., 2015 [125]	80 participants, 68 (7) years old, with peripheral artery disease	2.6 g EPA and 1.8 g DHA for 30 days	↑ 5-HEPE, ↑ 15-HEPE, ↑18-HEPE ↑ 4-HDHA, ↑ 17-HDHA	
Lamon-Fava et al., 2021, RCT [147]	42 participants, adults, obese/overweight with major depressive disorder and chronic inflammation, 52 (13) years old in placebo group	3 groups tested, daily: - 1 g ω-3 LC-PUFAs - 2 g ω-3 LC-PUFAs - 3 g ω-3 LC-PUFAs	* ↑18-HEPE, ↑12-HEPE, 15-HEPE, ↑ 5-HEPE after 28 days of supplementation, ↑17-HDHA and ↑14-HDHA at 12 weeks	
Markworth et al., 2016, RCT crossover [123]	10 healthy participants (women), 25.5 (3.3) years old	8 g ω-3 LC-PUFAs for 7 days, 14 days	↑**RvD1**, ↑RvD2, ↑ RvD6, ↑ PD1, ↑ MaR1	divergent effects of EPA and n-3 DPA on human lipid mediator profile
Mas et al., 2012, one arm [148]	20 healthy participants, 59 (5) years old	1.4 g EPA and 1 g DHA with 81 mg ASA for 21 days	17 HDHA, **RvD1**, RvD2 detected (tests of significance not found)	
Mas et al., 2016, RCT [149]	85 participants with chronic kidney disease, 56.5 (1.4) years old	1.8 g EPA and 1.52 g DHA for 56 days with CoQ	↑ 18-HEPE, ↑ 17 HDHA, ↑ RvD1	Changes in 18-HEPE et 17-HDHA levels predicted by change in platelet EPA and DHA level. No effect of Coenzyme Q_{10}
Norris et al., 2018, RCT cross over [150]	9 healthy participants, 24 (0.3) years old	**Study A:** 2.7 g of ω-3 LC-PUFAs for 5 months (controlled design) **Study B:** 3.4 g of ω-3 LC-PUFAs for 8–12 weeks (crossover)	Study A (serum) and Study B (plasma): ↑**RvD1**, ↑**RvE1**, ↑17-HDHA, ↑18-HEPE after LPS challenge	
Oh et al., 2011, two arm [119]	3 healthy participants	1 g EPA + 80 mg aspirin, single administration	↑ 18-HEPE (serum) 3 h after administration	
Polus et al., 2016, controlled [151]	59 participants, 46.6 years old, women's moderate obese	0.45 g EPA and 1.29 g DHA for 3 months	* ↑ **RvD1**, ↑ RvD2, ↑ PDX	↓ hs-CRP, ↓ MCP-1, ↓ s-VCAM-1
Poreba et al., 2017, RCT [126]	74 participants, 65.6 (6.8) years old with type 2 diabetes, history of coronary artery disease or peripheral artery disease	1 g EPA and 1 g DHA (in a drink) for 3 months	No change in Rv D1	No change in inflammatory markers
Ramirez et al., 2019, RCT [127]	24 participants, 69 (8) years old with peripheral artery disease	2.6 g EPA and 1.8 g DHA for 3 months	↑ 18-HEPE, ↑ 15-HEPE, ↑ 5-HEPE, ↑ 12-HEPE, ↑ RvE3	No change in hs-CRP, IL-6, ICAM-1
Schaller et al., 2017, RCT [124]	80 participants, 68 (7) years old with peripheral artery disease	2.6 g EPA and 1.8 g DHA for 1 month	↑ 18-HEPE, ↑ 15-HEPE, ↑ 5-HEPE, ↑ 4-HDHA	
Schaller et al., 2020, arm for healthy and arm for patients with peripheral artery disease [128]	20 participants, 69.5 year old healthy and with peripheral artery disease	3 different groups tested: - 0.69 g EPA and 0.5 g DHA - 3 g EPA and DHA - 4.14 g EPA and 3 g DHA for 7 days with monohydroxylated SPM precursors and n-3 DPA	↑ 18-HEPE, ↑ 15-HEPE, ↑ 5-HEPE ↑ 17-HDHA, ↑ 14-HDHA, ↑ 7-HDHA, ↑ 4-HDHA 10 S,17S-diHDHA ↑ MaR2 n-3 DPA	↑ phagocytic activity of peripheral blood monocytes and neutrophils

(*Continued*)



Concept	MeSH	Synonymes
resolvin		("resolvin D5" [Supplementary Concept] OR "resolvin E2" [Supplementary Concept] OR "17,18-dihydroxyeicosapentaenoic acid" [Supplementary Concept] OR "resolvin D3" [Supplementary Concept] OR "resolvin D2" [Supplementary Concept] OR "resolvin D1" [Supplementary Concept] OR "5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid" [Supplementary Concept] OR "resolvin D4" [Supplementary Concept] OR "resolvin" [Title/abstract] OR “specialized pro-resolving lipid mediator”[Title/abstract] OR “specialized pro-resolving mediator” [Title/abstract] OR “specialized pro-resolving mediators” [Title/abstract] OR protectin*[Title/abstract] OR “SPM” [Title/abstract])
Omega-3	"Fatty Acids, Omega-3"[Mesh]	("Fatty Acids, Omega-3"[Mesh] OR "omega-3 fatty acids"[Title/abstract] OR "omega-3 fatty acid"[Title/abstract] "omega 3"[Title/abstract] OR n-3 oil*[Title/abstract] OR “n-3 fatty acid”[Title/abstract] OR “n-3 fatty acids”[Title/abstract] OR "n-3 PUFA"[Title/abstract] OR "n-3 PUFAs"[Title/abstract] OR "n 3 PUFA"[Title/abstract] OR “n3 fatty acid”[Title/abstract] OR “n3 Fatty Acids”[Title/abstract] OR "polyunsaturated fatty acids omega-3"[Title/abstract] OR "n3 PUFA" [Title/abstract] OR “n3 Polyunsaturated Fatty Acid”[Title/abstract] OR “n-3 LC PUFA” [Title/abstract] OR “docosahexaenoic” [Title/abstract] OR “eicosapentaenoic” [Title/abstract])

Fig. 3. PRISMA chart: Search strategy for studies evaluating plasma production of specialized pro-resolving mediators (SPM) from interventional studies using ω-3 PUFAs in adults and search terms.

Table 3
(*Continued*)

Authors, year, study design (References)	Total participants	Intervention Daily dose of ω-3 LC-PUFAs	Plasma SPMs, EPA-derived, n-3 DPA, DHA-derived precursors	Additional laboratory analysis, *ex-vivo* results and clinical outcome
Skarke et al., 2015, RCT [152]	6 healthy participants, 24.3 (4.3) years old	5.58 g EPA and 4.5 g DHA for 50 days followed by intravenous injection of 0.6 ng/kg endotoxin	↑ PD1, ↑ **RvE1** (tests of significance not found)	↑ cytokines and CRP after endotoxin challenge
	12 healthy participants, 30.8 (11.6) years old	9.7 g EPA and 7.9 g DHA for 24 days	PD1 (tests of significance not found)	
So et al., 2021, RCT crossover [129]	21 participants, between 50–75 years old, with chronic inflammatory disease	2 groups tested: 3 g of DHA and 3 g of EPA (ethyl ester) for 34 weeks	↑18-HEPE,↑ 15S-HEPE,↑ 12-HEPE, ↑11-HEPE, ↑ DPA-derived SPM ↑ 17-HDHA, ↑ 13-HDHA, ↑ 14-HDHA, ↑ 7-HDHA, ↑ 4-HDHA	Modulation of LPS-stimulated monocyte cytokine expression
Souza et al., 2020, RCT [121]	22 healthy volunteers aged between 19 and 37 years	3 different groups tested - 1.5 g ω-3 LC-PUFAs - 3 g ω-3 LC-PUFAs - 4.5 g ω-3 LC-PUFAs Analysis after 2 h, 4 h, 6 h, 24h	* ↑ 14-HDHA, ↑ 18-HEPE, ↑ 17-HDHA, ↑4 S,14S-diHDHA, ↑ Rv E3, ↑ Rv D5, ↑ Ma R1, ↑ Ma R2, ↑ DPA-SPM derived, for de two groups of higher dose received of ω-3 LC-PUFAs	↑ dose-dependent in neutrophil and monocyte phagocytosis of bacteria
Uno et al., 2016, control [130]	40 participants, 65.5 (1.9) years old in patients undergoing major hepatobiliary resection	oral supplementation containing EPA (immunonutrition)	↑ **RvE1** (after surgery)	↓ rate of infectious complications and severity of complication in group receiving immunonutrition
Wang et al., 2015, RCT [131]	15 participants with Alzheimer disease	0.6 g EPA and 1.7 g DHA for 6 months	↓ **Rv D1** in controlled group (released from PBMCs after Aβ40 exposure)	
Welty et al., 2021, RCT [136]	31 participants with stable coronary artery disease	1.86 g EPA and 1.5 g DHA for 30 months	↑ 18-HEPE, ↑ MaR1, ↑ **Rv E1**	

*Results adjusted for multiple tests. SPMs studies evaluated in animal model in Table 2 have been highlighted in bold in this Table.

earlier suggest an association between lower levels of ω-3 LC-PUFAs and their derivatives in case of infection [89]. However, in the recent DO-HEALTH randomized clinical trial, no significant effects of ω-3 LC-PUFAs on infections rate was found [139]. To explore the effect of SPM precursor on infectious disease burden, the choice of a more sensitive population, such as older patients at risk of immune dysregulation, seems important. Nevertheless, the use of ω-3 LC-PUFAs should take into account the impact of the aging process on their metabolism and age-related plasma metabolomic profile changes [55, 140]. ω-3 LC-PUFAs supplementation has diverse kinetic profiles depending on the formulation [141]. A growing understanding of the immunomodulatory effects of nutritional components and immunosenescence opens the field to complementary therapy to antibiotics. If generation of SPMs is a crucial mechanism of action of EPA and DHA in the prevention and treatment of inflammatory conditions, then it is important to understand more about the most effective strategies by which EPA and DHA can increase SPM concentrations.

10. Conclusions

Considering the impaired immune answer, increased risk of RTI, and low ω-3 LC-PUFAs intake of older subjects, there is an urgent need to examine

the potential effects of these molecules on infectious processes in light of secondary SPMs production. Indeed, outcomes from bioactive lipids derived seem to mitigate bacterial-induced pneumonia injury. However, the results of studies using ω-3 LC-PUFAs in the case of influenza and mycobacterial infections are conflicting.

Abbreviations

AA: Arachidonic Acid
ALA: Alpha linolenic acid
ALI: Acute lung injury
ARDS: Acute respiratory distress syndrome
AT-RvD1: Aspirin triggered- Resolvin D1
BGI: Bacterial Growth Index
BALF: Bronchoalveolar lavage fluid
CFTR: Cystic fibrosis transmembrane conductance regulator
CoQ: Coenzyme Q10
COVID-19: Coronavirus disease 20–19
COX-2 ASA: Cyclooxygenase-2 aspirin-acetylated
DHA: Docosahexaenoic acid
10S, 17S-di HDHA: 10S, 17S -dihydroxy hydroxydocosahexaenoic acid
EPA: Eicosapentaenoic acid
GLA: Gamma linolenic acid
HDHA: Hydroxydocosahexaenoic acid
HEPE: Hydroxyeicosapentaenoic acid
HETE: Hydroxyeicosatetraenoic acid
HMGB-1: High-mobility group box 1
ICU: Intensive care unit
IFN-γ: Interferon-γ
IL-1β: Interleukin -1β
IL-10: Interleukin 10
IL-6: Interleukin 6
KC: keratinocyte-derived chemokine
LA: Linolenic acid
LC-PUFA: Long chain polyunsaturated fatty acid
LOX: Lipoxygenase
LPS: Lipopolysaccharide
LTA4 hydrolase: leukotriene A4 hydrolase
LXA4: Lipoxin A4
LXB5: Lipoxin B5
MaR1: Maresin 1
MCP-1: Monocyte chemoattractant protein 1
MIP-1α: Macrophage inflammatory protein-1α
MIP-1β: Macrophage inflammatory protein-1β
MPO: Myeloperoxidase
NF-kB: Nuclear factor-kB
PAMP: pathogen-associated molecular pattern
PCTR1, Protectin conjugates in tissue regeneration 1
PD1: Protectin D1
PGE2: Prostaglandin E2
PMN: Polymorphonuclear neutrophil
PUFA: Polyunsaturated fatty acids
ω -3 PUFAs: n-3 polyunsaturated fatty acids
ω-6 PUFAs: n-6 polyunsaturated fatty acids
RCT: Randomized controlled trial
Ri: Resolution interval
RTI: Respiratory tract infection
RvD1: Resolvin D1
RvE1: Resolvin E1
SPMs: Specialized pro-resolving mediators
TB: Tuberculosis
TLR-4: Toll-like receptor-4
TNF-α: Tumor Necrosis Factor- α

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Conflict of interest

The author has no conflict of interest to report

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