Long-Chain Polyunsaturated Fatty Acids Supplementation and Respiratory Infections

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Key Messages

- Long-chain polyunsaturated fatty acids (LCPUFAs) and their metabolites are involved in the control of chronic and acute inflammations.
- No data were available on the role of LCPUFAs in COVID-19 disease.
- More focused randomized controlled trials are necessary to evaluate the effect of LCPUFA supplementation.

Keywords

Long-chain polyunsaturated fatty acid · Immunity · Respiratory disease · COVID-19 · Supplementation

Abstract

Background: Long-chain polyunsaturated fatty acids (LCPUFAs) can actively affect the maintenance and optimal functioning of immune cells. The metabolites of both omega-3 and omega-6 play an important role in the synthesis of different mediators, such as prostaglandins, leukotrienes, thromboxanes, protectins, and resolvins, that can interfere with the virus and modulate inflammation. Summary: In this narrative review, we aim to identify whether LCPUFA supplementation may be effective in protecting the population against respiratory tract infections. We included only randomized controlled trials performed in both pediatric and adult subjects. Eight papers were selected: five trials were conducted in a pediatric population and three in adults. Different concentrations of fatty acids supplementation were associated with a lower incidence of common respiratory symptoms, except for two studies that did not provide significant results. Most of the studies are of low quality, and respiratory infections were assessed as secondary or even safety outcomes. Key Messages: No data were available on the role of LCPUFAs in coronavirus disease 2019 (COVID-19). Although these data showed that LCPUFAs may be effective in preventing respiratory tract infections, future studies are still needed to clarify their possible co-adjuvant role in the prevention and treatment of respiratory infections.

Introduction

It is well known that nutrients can actively affect the maintenance and optimal functioning of immune cells [1]. Long-chain polyunsaturated fatty acids (LCPUFAs) have a very spe-
cial role in this process because they participate in controlling chronic and acute inflammations. The metabolites of both omega-3 (ω3) and omega-6 (ω6) play an important role in the synthesis of different mediators, such as prostaglandins, leukotrienes, thromboxanes, protectins, and resolvins [1]. Particularly ω3 LCPUFAs could notably help improve the resolution of the inflammatory process and may also interact at different stages of viral infections. In this narrative literature review, we provide information on LCPUFAs and the possible effects of these dietary compounds in promoting better immune function and, therefore, as a co-adjuvant treatment to decrease the severity of disease among those who have been diagnosed with respiratory tract infections.

Among the respiratory viruses, particular attention has been paid to coronavirus disease 2019 (COVID-19), identified for the first time in December 2019 in Wuhan, China. Because of its rapid spread worldwide and the increased infection rate, the WHO declared it a pandemic in March 2020 [2]. In 10–15% of all cases, COVID-19 is complicated by severe pneumonia requiring hospitalization, with a high risk of developing acute respiratory distress syndrome, which can lead to intensive care unit placement of the patient and is often lethal. Other patients may remain asymptomatic even if they test positive for the virus [3]. In this context, due to its highly infectious nature and alarming mortality rate, every effort is focused on prevention and treatment to alleviate the suffering of COVID-19 patients, including the immune response.

The Immune System and LCPUFAs

The immune system is a network of biological processes with the main aim to protect the organism from pathogenic organisms and, therefore, from disease. Overactivity of the immune system can display many forms, including an excessive reaction to allergens or autoimmunity, while underactivity of the immune system (immunodeficiency) can be due to primary immunodeficiency diseases or can be the result of other conditions, such as cancer, immunosuppressants, and HIV/AIDS. These conditions increase the susceptibility to other infections.

LCPUFAs are an essential component of immune cells, and their relationships are an ongoing matter of research. It has been reported that in lymphocytes, monocytes, and neutrophils, arachidonic acid (ARA) constitutes about 20% of total fatty acids, while ω3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) constitute 1 and 2.5%, respectively [4].

ω6/ω3 Equilibrium

LCPUFAs are synthesized by elongation and desaturation of the carbon chain from the essential PUFAs: linoleic acid (LA) for the ω6 series and alpha-linolenic acid (ALA) for the ω3 series [5]. The metabolic pathway consists of successive carbon chain elongation and desaturation steps as illustrated in Figure 1. Due to the different roles and effects of the ω6 and ω3 series, it is important to understand the effect of the ω6 to ω3 ratio on the immune system, in particular the ratio of LA/ALA.

LA, defined as an essential fatty acid in mammals because of their inability to synthesize it, is common in the human diet, being widely distributed in foods [6]. In many vegetable oils, it represents more than 50% of the lipid content; high amounts of LA are also present in nuts, while lower levels are found in cereals (more in whole grains), legumes, some meats, eggs, and dairy products [6]. LA has been reported to be the substrate for CYP450 enzymes, leading to the formation of linoleic epoxides 9,10-epoxyoctadecenoic acid (9,10-EpOME), and 12,13-epoxyoctadecenoic acid (12,13-EpOME) known as leukotoxin and isoleukotoxin [7]. The epoxides are then metabolized by the soluble epoxide hydrolases into the dihydroxy derivatives 9,10-DiHOME and 12,13-DiHOME. DIHOMEs may play a dual role in inflammation, stimulating neutrophil chemotaxis at low concentrations, while inhibiting neutrophil respiratory burst at higher concentrations [8]. Like LA, ALA is defined as an essential fatty acid in mammals [9], and its principal diet sources are nuts, leafy vegetables, and seed oils. After absorption, it can be catabolized into longer-chain and more unsaturated fatty acids, such as EPA and DHA, but, like LA conversion into ARA within the ω6 series, the endogenous production of ALA derivatives is low in humans.

Arachidonic Acid and Its Metabolites and the Immune System

ARA is the main ω6 product and is present esterified to the 2-position in membrane phospholipids [10]. Upon release from membrane phospholipids by the activity of the cytosolic phospholipase A2 (PLA2), ARA is enzymatically metabolized by several oxygenases into eicosanoids, a large family of mostly proinflammatory molecules. The main ARA metabolites involved in the immune system are prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and thromboxane A2 (TXA2). PGE2 inhibits T-cell and NK-cell proliferation, as well as interferon-γ (IFN-γ) and interleukin-12 (IL-12) production after binding cell surface receptors [11, 12]. PGE2 also inhibits B-cell activation secondary to IL-4 stimulation in a specific manner and enhances IgE and IgG1 production [13]. LTB4 enhances T-cell recruitment, inhibits de novo induced Tregs generation, and increases IL-17 cytokine production during T-cell differentiation. Also, it regulates the mi-
The incorporation of various lymphoid-derived cell types [14]. TXA2 inhibits naive T-cell proliferation. Moreover, it inhibits T-cell interaction with dendritic cells and increases mature T-cell proliferation and activation [11].

Regarding the role of ARA and SARS-CoV-2, two recent reviews resume some pivotal points. Ripon et al. [15] describe the role of the ARA metabolic cascade during the cytokines storm due to virus infection, concluding with the recommendation to use bioactive lipids, nonsteroidal anti-inflammatory drugs, steroids, cell phospholipase A2 (cPLA2) inhibitors, and specialized pro-resolving mediators to treat COVID-19 disease, while Das [16] explains and supports the use of ARA to counteract SARS-CoV-2 due to its active role against viruses and to reduce inflammation.

**ω3 EPA, DHA, and Their Metabolites and the Immune System**

ω3 LCPUFAs act to inhibit the inflammatory response both in a direct and indirect pathway. DHA reduces endoplasmic reticulum stress and reactive oxygen species production in mitochondria, inhibits Toll-like receptor activation, and upregulates cytoprotective proteins, intracellular antioxidants, and anti-inflammatory and detoxifying enzymes via the activation of nuclear factor erythroid 2-related factor 2 (NRF2). Both DHA and EPA regulate the inflammation response acting on the expression of oxidized low-density lipoprotein receptor 1, plasminogen activator inhibitor 1, TXA2 receptor, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and intercellular adhesion molecule 1 [17]. EPA, docosapen-
Fatty Acids Supplementation and Respiratory Infections

Methods

A non-systematic review of the literature was initially performed in May 2021 and then updated in November 2021. The search was carried out via PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (www.emabase.com), Web of Science (www.isiknowledge.com), and the Cochrane library (www.cochranelibrary.com). In this narrative review, we aim to identify whether LCPUFA supplementation may be effective in protecting the population against respiratory tract infections. Only human studies reported in English were considered. Letters to the editor, abstracts, and proceedings from scientific meetings were excluded from the analysis. Two authors (V.C. and A.M.) independently selected the articles, retrieved and assessed the potentially relevant ones. Eligible were clinical trials on LCPUFA supplementation (intervention) and respiratory tract infection (outcome), including participants of all ages and from any region of the world. Secondary references of identified papers were also screened.

Results

A total of 8 RCTs were identified [21–28], which are detailed in Table 1. They included 4,107 subjects. Five trials were performed in a pediatric population (age 0–11 years) and 3 studies in adults (age 18–45 years). One study was conducted in Italy, 1 in Mexico, 1 in Denmark, 1 in France, 1 in Africa, 2 in the USA, and 1 multicenter study was conducted in Malaysia, the Netherlands, Poland, Portugal, and Thailand. A wide range of LCPUFA dosages and types was used for supplementation. The duration of the intervention was 4–9 months. Three studies showed a reduced incidence of upper respiratory tract infections or infective episodes in children when fed with DHA, ARA or ALA/LA, or EPA/DHA, respectively, in the first year of life [21–23].

First, Birch et al. [21] reanalyzed data from two cohorts to investigate the incidence of allergic and respiratory diseases in children with a DHA/ARA-supplemented formula (DHA/ARA as 0.32–0.36% and 0.64–0.72% of total fatty acids, respectively) during infancy. They found lower odds of developing upper respiratory infection in the DHA/ARA-supplemented group for 1 year. Second, Venuta et al. [22] designed an interventional study in children between 36 and 49 months of age to evaluate the impact of supplementation of LA (596 mg/day) and ALA (855 mg/day) on respiratory tract infections. The authors observed a reduced number of infectious episodes, days of fever, and absence from school at 120–180 days from intervention in children receiving supplementation. Malan et al. [23] supplemented 321 children aged 6–11 years with 50 mg Fe ++ , 420 mg DHA, and 80 mg EPA given on 4 days/week. The supplementation was associated with a 3-fold lower odds of school absence (OR: 0.30, 95% CI: 0.11, 0.82), but no associations with other outcomes were found.

Two more studies analyzed LCPUFA supplementation in formula milk. Specifically, Lapillonne et al. [24] observed that infants fed with formula containing 17 mg DHA and 34 mg ARA/100 kcal had a lower incidence and delayed onset of respiratory illnesses (bronchitis/bronchiolitis) and of their symptoms (croup, nasal congestion, cough), as well as less diarrhea requiring medical attention, when compared to infants who received formula without DHA and ARA. On the contrary, Chatchatee et al. [25] in an international multicenter interventional study failed to demonstrate a reduced risk of infection in 767 healthy children fed with growing-up milk with the addition of 1.2 g/100 mL of short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides (sc-GOS/lcFOS) (9:1) and 19.2 mg/100 mL of ω3 LCPUFAs (EPA + DHA, 4:6).

Two studies involved pregnant women. Imhoff-Kunsch et al. [26] studied the effect on infant morbidity of 400 mg of DHA taken daily by mothers in the prenatal period. This double-blind randomized placebo-controlled trial demonstrated a lower occurrence of cold symptoms in the DHA group with respect to placebo at 1 and 3 months of age (37.6 vs. 44.6% and 37.8 vs. 44.1%, respectively). Moreover, a shorter duration of nasal secretion, fever, and difficulty breathing at 6 months (RR: 0.87, 95% CI: 0.77–0.98; RR: 0.80, 95% CI: 0.66–0.98; and RR: 0.46, 95% CI: 0.24–0.87, respectively) was reported. Another trial with the same design by Bisgaard et al. [27] stud-
### Table 1. Summary of the studies addressing the effects of LCPUFAs supplementation on respiratory symptoms

| Authors [ref.] | Location | Number of participants | Study population | Study design | Study aim | Supplementation | RTI diagnosis | Results |
|----------------|----------|------------------------|------------------|--------------|-----------|----------------|---------------|---------|
| Adults         |          |                        |                  |              |           |                |               |         |
| Imhoff-Kunsch  | Mexico   | 1,094 women            | Pregnant women   | Double-blind randomized placebo-controlled trial | To investigate the effects of prenatal DHA supplementation on infant morbidity (cough, nasal congestion) at 1, 3, and 6 months of life | Treatment group: DHA: 400 mg/day; Comparison group: capsule with corn and soy oil blend with no added antioxidants | Numbers of infective episodes reported by women | DHA group: lower occurrence of cold symptoms than the placebo group (37.6% vs. 44.6% and 37.8 vs. 44.1%, respectively) at 1 and 3 months shorter duration of nasal secretion, fever, difficulty breathing at 6 months: RR: 0.87 (95% CI: 0.77–0.98); RR: 0.80 (95% CI: 0.66–0.98); and RR: 0.46 (95% CI: 0.24–0.87), respectively |
|                | et al. [26] |       | Mexico, Pregnant women in gestational week 18–22, aged 18–35 years | Double-blind randomized placebo-controlled trial | To assess the frequency of colds among participants supplemented with CLA | Supplemented group: CLA: 2 g/day; Comparison group: high oleic sunflower oil | Clinical visit | Risk of persistent wheeze or asthma: treatment group 16.9% vs. 23.7% in control (hazard ratio, 0.69; 95% CI: 0.49–0.97; 30.7% of relative reduction) Reduced risk of infections of the lower respiratory tract: 31.7% vs. 39.1% hazard ratio, 0.75; 95% CI: 0.58–0.98 |
|                |           |                        | Study population |               |           |                |               |         |
| Peterson       | USA       | 60 subjects            | 18–45 years of age | Double-blind randomized placebo-controlled trial | To assess the frequency of colds among participants supplemented with CLA | Supplemented group: CLA: 2 g/day; Comparison group: high oleic sunflower oil | Clinical visit | Supplementation did not reduce the frequency of infection or illness after experimental HRV inoculation |
|                | et al. [28] |       | 60 subjects | Double-blind randomized placebo-controlled trial | To assess the frequency of colds among participants supplemented with CLA | Supplemented group: CLA: 2 g/day; Comparison group: high oleic sunflower oil | Clinical visit | Supplementation did not reduce the frequency of infection or illness after experimental HRV inoculation |
| Bisgaard       | Denmark   | 736 pregnant women and 695 children | Pregnant women between 22 and 26 weeks of gestation | Double-blind randomized placebo-controlled trial | To assess the effect of supplementation on the risk of persistent wheeze and asthma in offspring | Supplemented group: 2.4 g/day of n-3 LCPUFA (55% EPA and 37% DHA); Comparison group: olive oil, containing 72% n-9 oleic acid and 12% n-6 linoleic acid | Clinical visit | Risk of persistent wheeze or asthma: treatment group 16.9% vs. 23.7% in control (hazard ratio, 0.69; 95% CI: 0.49–0.97; 30.7% of relative reduction) Reduced risk of infections of the lower respiratory tract: 31.7% vs. 39.1% hazard ratio, 0.75; 95% CI: 0.58–0.98 |
|                | et al. [27] |       | Denmark, Pregnant women between 22 and 26 weeks of gestation | Double-blind randomized placebo-controlled trial | To assess the effect of supplementation on the risk of persistent wheeze and asthma in offspring | Supplemented group: 2.4 g/day of n-3 LCPUFA (55% EPA and 37% DHA); Comparison group: olive oil, containing 72% n-9 oleic acid and 12% n-6 linoleic acid | Clinical visit | Risk of persistent wheeze or asthma: treatment group 16.9% vs. 23.7% in control (hazard ratio, 0.69; 95% CI: 0.49–0.97; 30.7% of relative reduction) Reduced risk of infections of the lower respiratory tract: 31.7% vs. 39.1% hazard ratio, 0.75; 95% CI: 0.58–0.98 |
| Children       |          |                        |                  |              |           |                |               |         |
| Lapillonne     | France   | 325 infants            | Healthy term infants | Observational, multi-center, prospective study | To compare the frequency of common illnesses in infants who received formula with or without added LCPUFAs | Formula with 17 mg DHA and 34 mg ARA/100 kcal | Clinical visit | Supplemented infants: lower incidence of bronchitis/bronchiolitis (p = 0.004), croup (p = 0.044), nasal congestion (p = 0.001), cough (p = 0.014), and diarrhea requiring medical attention (p = 0.034); OR of having at least one episode of bronchitis/bronchiolitis (0.41, 95% CI: 0.24–0.70); croup (0.23, 95% CI: 0.05–0.97); nasal congestion (0.37, 95% CI: 0.20–0.66); cough (0.52, 95% CI: 0.32–0.86) |
| et al. [24]    |          |                        |                  |              |           |                |               |         |
| Chatchatee     | Malaysia, The Netherlands, Poland, Portugal, Thailand | 767 healthy children | 11–29 months of age | Randomized double-blind controlled, parallel, multi-country intervention study | To investigate the effect of growing-up milk with the addition of scGOS/scFOS (9:1) and n-3 LCPUFAs on the occurrence of infections in healthy children attending day care centers | Supplemented group: growing-up milk with the addition of 1.2 g/100 mL of scGOS/scFOS (9:1) and 19.2 mg/100 mL of n-3 LCPUFAs (EPA + DHA, 4:6); Comparison group: growing up milk without scGOS/scFOS (9:1) and n-3 LCPUFAs | Clinical visit | Supplemented group: decreased risk of developing at least 1 infection: 299/388 (77%) vs. 313/379 (83%), respectively; RR: 0.93, 95% CI: 0.87–1.00 |
| et al. [25]    |          |                        |                  |              |           |                |               |         |
| Birch          | USA       | 89/79 children from 2 previously published cohorts: 38 fed DHA/ARA formula | 3-year-old children | Randomized, placebo-controlled | To investigate the incidence of allergic and respiratory diseases in children fed DHA/ARA supplemented formula during infancy | Supplemented group: DHA/ARA in formula as 0.32–0.36% and 0.64–0.72% of total fatty acids, respectively; Comparison group: similar unsupplemented formula | Clinical visit | Supplemented group: decreased risk of developing at least 1 infection: 299/388 (77%) vs. 313/379 (83%), respectively; RR: 0.93, 95% CI: 0.87–1.00 |
| et al. [21]    |          |                        |                  |              |           |                |               |         |
Table 1 (continued)

| Authors (ref.) | Location | Number of participants | Study population | Study design | Study aim | Supplementation | RTI diagnosis | Results |
|----------------|----------|------------------------|------------------|-------------|-----------|----------------|--------------|---------|
| Venuta et al. [22] | Italy | 20 children | Children aged between 36 and 49 months, affected by RRI | Randomized crossover double-blind study | To evaluate the impact of supplementation on RRI | Supplemented group: linoleic acid: 596 mg/day and alpha-linolenic acid: 855 mg/day; Comparison group: olive oil | Not specified | Reduced number of infective episodes, days' fever, and days' absence from school at the end of supplementation period (T120) and at 2 months later (T180) in children receiving supplementation |
| Malan et al. [23] | Africa | 321 children | 6- to 11-year-old children with iron deficiency | Double-blind, randomized placebo-controlled study | To evaluate the effect of iron and DHA/EPA supplements on school absenteeism and illness | Supplemented group: 1 iron tablet and 2 DHA/EPA capsules given 4 days/week: 50 mg Fe as iron sulfate and, in total, 420 mg DHA and 80 mg EPA; Comparison group: capsules with medium-chain triglycerides with the same total fat content as that of DHA/EPA capsules | Subject's illness symptoms reported by the children, asking them the symptoms they experienced as soon as they were back at school after being absent | Supplementation with iron and DHA/EPA: significant OR interaction (p = 0.019) attenuated the increased odds of being absent by 3 times (OR: 0.30, 95% CI: 0.11, 0.82) |

RTI, respiratory tract infections; DHA, docosahexaenoic acid; ARA, arachidonic acid; OR, odds ratio; CI, confidence interval; URI, upper respiratory tract infections; EPA, eicosapentaenoic acid; RR, relative risk; LCPUFA, long-chain polyunsaturated fatty acids; CLA, conjugated linoleic acid; RRI, recurrent respiratory infections; scGOS, short-chain galacto-oligosaccharides; lcFOS, long-chain fructo-oligosaccharides.

Discussion and Conclusion

There are few clinical trials on LCPUFA supplementation to prevent and manage respiratory tract infections. The results point out a potential role of LCPUFA supplementation in reducing diseases of the respiratory tract. This positive impact is also by data from observational studies as reported by Pastor et al. [29]. They found a decreased incidence of bronchiolitis, upper airway infection, and rhinitis in infants fed a formula supplemented with DHA/ARA compared with infants fed a formula supplemented with ARA alone [29]. They also found that LCPUFA intake at all levels was associated with a reduced risk of both wheeze or asthma and of infections of the lower respiratory tract. Lastly, only RCT investigated the effect of 2 g/day of conjugated LA in a population aged 18–45 years and showed no consistent effects on subjects affected by human rhinovirus colds.

There are no significant differences in the occurrence of respiratory tract infections in the study by Pastor et al. [29]. They found a significant reduction in the frequency of respiratory tract infections in infants fed a formula supplemented with DHA/ARA compared with infants fed a formula supplemented with ARA alone [29]. The mechanisms underlying the effect of LCPUFA supplementation are not fully understood. It is possible that the reduction of inflammation of the respiratory tract is mediated by the effects of DHA on the production of inflammatory mediators, including cytokines, chemokines, and prostaglandins. The lower respiratory tract. Lastly, only RCT investigated the effect of 2 g/day of conjugated LA in a population aged 18–45 years and showed no consistent effects on subjects affected by human rhinovirus colds.
38 subjects fed with DHA in the study of Birch et al. [21], and 20 subjects considered by Venuta et al. [22]. Different definitions of respiratory illness were used in the trials, and the incidence of upper respiratory tract infection was measured at different time points. Moreover, the methods to ascertain respiratory infections were not consistent among studies. In 4 studies, the respiratory illness was a secondary outcome, so that the sample size estimates for respiratory tract infection differences between the groups were not calculated. No adjustments for potential confounders were performed in most of the trials, and because multiple secondary outcomes were tested, the type II error rate could have been inflated. The study of Lapillonne et al. [24] was observational and not randomized. Moreover, in the same study regarding milk formula, the use of DHA/ARA formula may have been more prevalent in families who were of a higher socioeconomic status, which may have introduced a recruitment bias. A further weakness concerns the presence of small study effects, including, but not limited to, publication bias, which was not possible to assess.

The possibility to reduce the impact of diseases like COVID-19, and other future similar diseases, with a dietary change and/or nutritional supplementation may be useful for several reasons: less stress on the national health system and the possibility to avoid drugs’ side effects. It is also difficult to translate these considerations, also if positive, to the COVID-19 scenario, since it is a complex disease that involves several biochemical and physiological mechanisms [29]. This review highlights the potential association of LCPUFAs with respiratory infection, possibly in infants, children, and adults. The immunological scientific evidence is compelling, but it is difficult to draw firm conclusions from the few clinical studies. Due to the narrative nature of this review, it is not possible to draw conclusions on whether different supplementations of fatty acids, derived from either infant formulas or supplementation of the infant’s mother during pregnancy, may provide a protective effect on the incidence of respiratory infections or on symptoms. On the other hand, this review highlights that new randomized controlled trials designed to address the impact of LCPUFAs on respiratory infections are needed. In particular, the influence of perinatal ω3 PUFA nurture on infant immune function should be studied. Finally, additional studies including infants exposed to the same supplementation of fatty acids from birth might allow to drive firm conclusions on the role of LCPUFAs in the immune function of infants.

Conflict of Interest Statement

The writing of this article was supported by Nestlé Nutrition Institute and the authors declare no other conflicts of interest.

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Author Contributions

V.C., S.T., and A.M. drafted the manuscript; C.A. and G.P.M. supervised the work and gave technical support on data interpretation; V.C. arranged the references; A.M. and M.L.S. proofread the manuscript. All authors contributed significantly to the paper and agreed on the manuscript in its current form. All authors have read and agreed on the published version of the manuscript.

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