Annals of Nutrition and Metabolism

Pediatric Issues in Time of Pandemia: From Infection to Nutritional Strategies

Ann Nutr Metab
DOI: 10.1159/000522093

Received: October 8, 2021
Accepted: January 19, 2022
Published online: March 10, 2022

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-

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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-

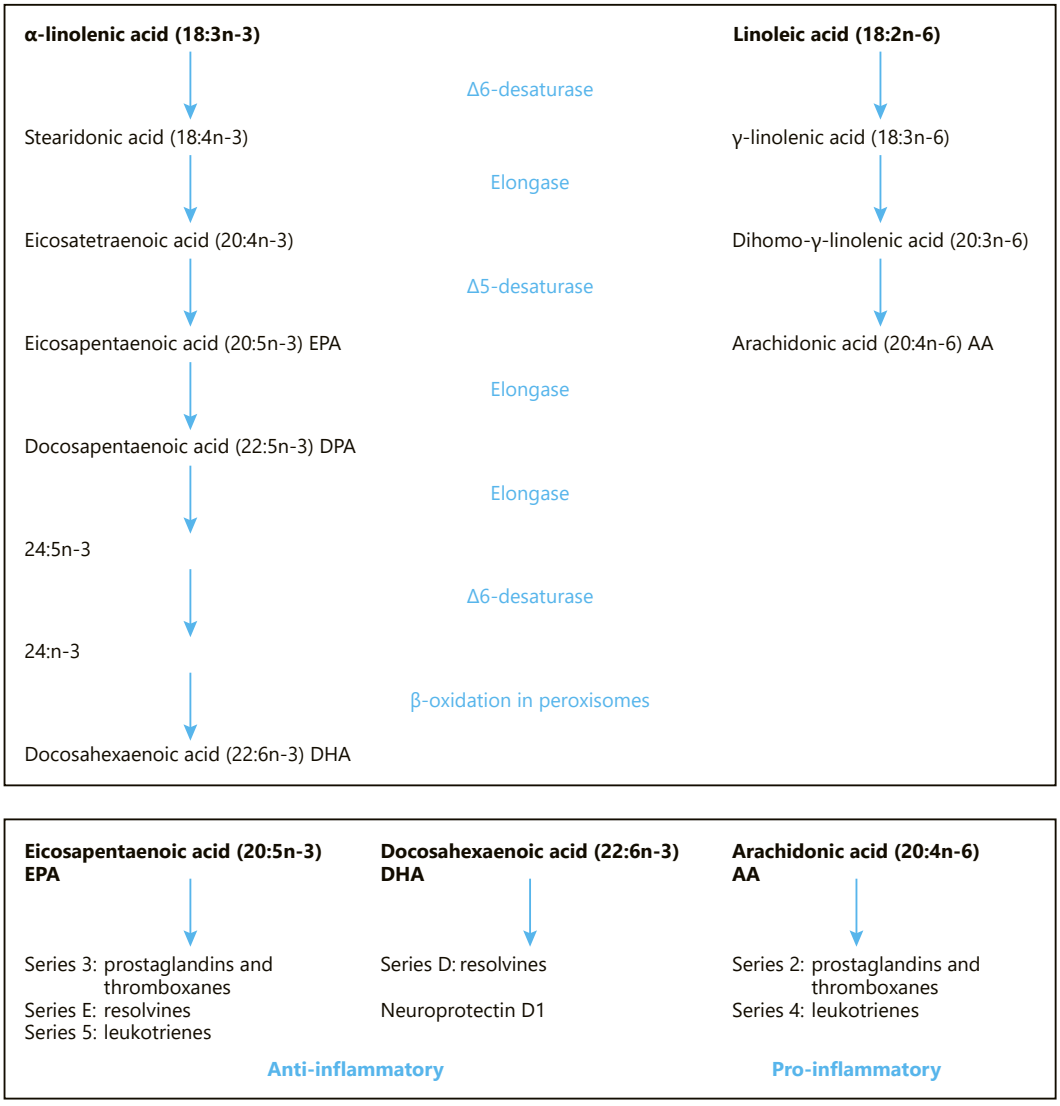

Fig. 1. ω3 and ω6 fatty acids metabolism pathways.

gration of various lymphoid-derived cell types [14]. TXA2 inhibits naïve 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-

taenoic acid, and DHA are the precursors of several oxygenated lipids. The resulting compounds have been collectively described as a novel genus of specialized pro-resolving lipid mediators and are endowed with potent anti-inflammatory, pro-resolution activities within the immune system. This molecular family includes D- and E-series resolvins, protectins, maresins [18, 19], and maresin conjugates in tissue regeneration, which have been proved effective in limiting inflammation and accelerating the physiological resolution of the inflammatory response [18, 20].

Methods

A nonsystematic 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.

The authors observed a reduced number of infectious episodes, days of fever, and absence from school at 120–180 days from intervention

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 (scGOS/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 et al. [26]	Mexico	1,094 women	Pregnant women in gestational week 18–22, aged 18–35 years	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
Peterson et al. [28]	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	Cold symptoms recorded by subjects	Supplementation did not reduce the frequency of infection or illness after experimental HRV inoculation
Bisgaard et al. [27]	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
Children								
Lapillonne et al. [24]	France	325 infants	Healthy term infants Less than 60 days of age at enrollment Exclusively fed with one of the study formulas for at least 24 h before enrollment	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)
Chatchatee et al. [25]	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 added scGOS/lcFOS (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/lcFOS (9:1) and 19.2 mg/100 mL of n-3 LCPUFAs (EPA + DHA, 4:6) Comparison group: growing up milk without scGOS/lcFOS/n-3 LCPUFAs	Subject's illness symptoms reported by the parents during the intervention period	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
Birch et al. [21]	USA	89/179 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	Medical diagnosis	Lower odds for developing URI: OR: 0.22; 95% CI: 0.08–0.58 in DHA/ARA group

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.

ied 736 pregnant women supplemented with 2.4 g/day of ω3 LCPUFA (55% EPA and 37% DHA) in the third trimester and concluded that the infants of supplemented mothers had a reduced risk of both wheeze or asthma and of infections of the lower respiratory tract. Lastly, only 1 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.

Discussion and Conclusion

There are few clinical trials on LCPUFA supplementation to prevent and manage respiratory tract infections, but available results point out a potential role of LCPUFA supplementation in preventing respiratory tract infections. This positive impact on reducing diseases of the respiratory tract is highlighted also by data from observational studies as reported by Pastor et al. [29]. They found a decreased incidence of bronchiolitis/bronchitis, upper airway infection, and rhinitis in infants fed a formula supplemented with DHA/ARA compared with infants fed with lower levels of DHA/ARA supplementation or no supplementation at all [29]. The mechanisms underlying the effect of LCPUFAs remain largely unknown. On the one hand, it is possible that the reduction of inflammation of the respiratory airways might prevent symptomatic disease. In that case, subjects such as those with allergic asthma might have a significant benefit from supplementation with LCPUFA [21]. On the other hand, the effect of LCPUFA supplementation was also observed in other subjects at risk of infections, such as those receiving chronic iron supplementation [23].

Finally, the potentially beneficial effect was confirmed in healthy subjects, too. These data point out that the benefit of LCPUFA supplementation is not limited to subjects with chronic inflammation and might represent a promising strategy for preventing viral diseases. However, we could not identify any trial investigating the effect of LCPUFA in the prevention or treatment of respiratory tract infection due to SARS-CoV-2 infection. It is important to note that the strength of available evidence is also limited by important factors. The included trials are heterogenous with respect to the cohorts considered, the type of supplementation, and the duration. While the current results add to the understanding of the potential health benefits of LCPUFAs in infants' diet, our review has some important limitations. First, the results are poorly comparable, and a formal evaluation of the studies' quality was not performed. For instance, the lack of positive conclusions in Chatchatee et al.'s [25] study is probably due to the nonhomogeneous cohort with significantly different diet attitudes. Another limitation is the small cohort size of 2 studies:

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.

Funding Sources

This study was supported by a contribution from the Italian Ministry of Health (IRCCS grant).

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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