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EAACI Position Paper: Influence of Dietary Fatty Acids on Asthma, Food Allergy and Atopic Dermatitis

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Abstract

The prevalence of allergic diseases such as allergic rhinitis, asthma, food allergy and atopic dermatitis has increased dramatically during the last decades, which is associated with altered environmental exposures and lifestyle practices. The purpose of this review is to highlight the potential role for dietary fatty acids, in the prevention and management of these disorders. In addition to their nutritive value, fatty acids have important immunoregulatory effects. Fatty acid-associated biological mechanisms, human epidemiology and intervention studies are summarized in this review. The influence of genetics and the microbiome on fatty acid metabolism is also discussed. Despite critical gaps in our current knowledge, it is increasingly apparent that dietary intake of fatty acids may influence the development of inflammatory and tolerogenic immune responses. However, the lack of standardized formats (i.e. food versus supplement), standardized doses and frequently a lack of pre-study serum fatty acid level assessments in clinical studies significantly limit our ability to

compare allergy outcomes across studies and to provide clear recommendations at this time. Future studies must address these limitations and individualized medical approaches should consider the inclusion of specific dietary factors for the prevention and management of asthma, food allergy and atopic dermatitis.

Abbreviations

AA - Arachidonic Acid; AD – Atopic Dermatitis; AERD - Aspirin-Exacerbated Respiratory Disease; ALA – alpha-linolenic acid; DGHA - Dihomo-γ-Linoleic Acid; DHA - Docosahexaenoic Acid; EETs - Epoxyeicosatrienoic acids; EPA - Eicosapentaenoic Acid; FA – Fatty Acid; GLA - γ-Linoleic Acid; GPCRs - G Protein-Coupled Receptors; HETEs - Hydroxyeicosatetraenoic acids; iNKTs - Invariant Natural Killer T cells; LA - Linoleic Acid; LC-PUFA – Long Chain Polyunsaturated Fatty Acid; MUFA - Monounsaturated Fatty Acid; n-6 - omega-6; n-3 - omega-3; SCFA - Short-Chain Fatty Acids; SFA - Saturated Fatty Acid; SPT – Skin Prick Test.

Introduction

Intensive research efforts and debate are focused on understanding the reasons for the rising prevalence of allergic diseases today. It is commonly thought that environmental exposures and lifestyle factors such as diet, infections, microbiome, pollutants, exercise, hygiene, vaccinations etc, may play a role. Among the many dietary factors that can influence immune mechanisms, we will focus specifically on one dietary component in this review, i.e. fatty acids. The search terms used to identify potentially relevant papers are indicated in supplementary appendix 1.

Fatty acids are carboxylic acids containing varying number of carbons with no double bonds between them (saturated – SFA), one double bond (monounsaturated - MUFA), more than one double bond (polyunsaturated - PUFA) .[1] Examples are illustrated in Figure 1. Fatty acids are the building blocks of all complex lipids within the human body; therefore, they are fundamental to several major physiological processes including: i) they are essential components of phospholipids, glycolipids and sphingolipids within cell membranes; ii) they are important energy sources; iii) they are required for intracellular trafficking of proteins following their covalent attachment; iv) their derivatives serve as hormones and important intracellular and extracellular mediators and messengers. Fatty acids are ingested in the diet and some can also be generated by either the gut microbiota or host cells. Certain fatty acids are classed as “essential” (e.g. linoleic (LA) and alpha linolenic (ALA)) because the body cannot synthesize them. Mammals lack the enzymes to introduce double bonds at carbon atoms beyond C-9;therefore, precursor unsaturated fatty acids or long chain polyunsaturated fatty acids (LC-PUFAs), need to be ingested. Certain lipid mediators promote inflammation, whereas others promote cellular homeostasis mechanisms and serve to dampen inflammatory responses.

Figure 1: Classification of fatty acids Mechanisms of immune regulation

Fatty acids impact and influence the immune system on multiple levels. Direct interactions between allergenic proteins and lipids can occur, impacting their allergenicity. For example, Pru p 3, the major peach allergen and a member of the non-specific lipid transfer protein (nsLTP) family, can bind to a range of lipids, which facilitates crossing of the intestinal epithelial barrier interacting with lipid rafts and caveolae formation, thus resulting in interaction with immune cells and polarizing a Th2 response.[2] In addition, certain lipids are presented via CD1 molecules expressed by DCs, macrophages and B cells, leading to activation of invariant natural killer T cells (iNKTs).[2 3] Interference with FA synthesis pathways exert therefore, profound effects on the metabolic programming of T cells. For example, the glycolytic-lipogenic axis is crucial for Th17 development, but not for Treg cells. Moreover, protein acetylation, *N*-myristoylation and palmitoylation, which depend on availability of the corresponding FA, are crucial for many T cell functions.[4]

Many of the lipid mediators that regulate inflammation are metabolites derived from omega-6 (*n*-6) or omega-3 (*n*-3) fatty acids, including arachidonic acid (AA; 20:4n-6), LA (18:2n-6), ALA (18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3) (Figure 2). In general, *n*-6 fatty acids are associated with proinflammatory responses, while *n*-3 fatty acids are associated with anti-inflammatory responses. Thus, the *n*-6:*n*-3 ratio in the diet is important in influencing host immunological activity. Foods typically high in *n*-3 fatty acids include fatty fish, algae, flax seeds, chia seeds and walnuts, while *n*-6 fatty acids are typically high in vegetable oils and seeds. AA and its metabolites are particularly involved in several pro- and anti-inflammatory mechanisms in the pathogenesis of asthma and allergy.[5] Once liberated, AA is a substrate for several enzymes including i) cyclooxygenase 1 and 2 (COX1 and 2) giving rise to prostaglandins D2, E2, prostacyclins, thromboxanes, lipoxins and other pro-resolving mediators; ii) 5-lipooxygenase, leukotriene C4 synthase and leukotriene hydrolase involved in production of leukotriene B4 and cysteinyl leukotrienes C4, D4 and E4; and iii) cytochrome P450, producing several hydroxyeicosatetraenoic acids (HETEs) and epoxyeicosatrienoic acids (EETs).[6-8] These active lipid mediators act intracellularly or in local extracellular microenvironments through several G protein-coupled receptors (GPCRs) such as DP1 and CRTH2 (DP2), EP1-4, cysLTR1-2, as well as through peroxisome proliferator-activated receptors (PPARs).

Figure 2: Immunomodulatory effect of fatty acids

EPA and DHA can be incorporated into membrane phospholipids of effector cells at the expense of AA. This results in alterations in membrane fluidity, which can affect lipid rafts essential for immune cell activation. In addition, changes in the AA:EPA ratio limits the production of inflammatory eicosanoids that can impact Th2 lymphocytes and ILC2 cells.[9] Moreover, lipid mediators produced from EPA and DHA show anti-inflammatory and inflammatory resolving potency, for example by limiting neutrophil infiltration or by inhibiting pro-inflammatory cytokine production. In addition, *n*-3 EPA and DHA directly inhibit production of pro-inflammatory cytokines through inhibition of the activation of the nuclear transcription factor NF-κB, which can result from disruption of lipid rafts that initiates inflammatory signaling (e.g. TLR4-Myd88 interactions), from induction of PPARγ that physically interacts with NF-κB, and/or from interaction with GPR120 receptors which interferes with the NF-κB activation pathway.

Essential fatty acids are incorporated into plasma membrane phospholipids of keratinocytes and lamella bodies - the contents of which form part of the lipid-rich extracellular matrix of the stratum corneum. However, reduced levels of ceramides have been observed in AD compared to healthy skin and differential expression of ceramide-processing enzymes have also been identified in AD skin. Notably, decreased gene expression of the PUFA-processing enzymes δ-6-desaturase and δ-5-desaturase have been observed in AD. Potentially impaired desaturase activity is further supported by findings of elevated levels of LA and significantly reduced levels of its downstream metabolites γ-linoleic acid (GLA), dihomo-γ-linoleic acid (DGHA) and AA in AD. Thus, defective essential fatty acid metabolism may lead to abnormal lipid composition of the stratum corneum, defective interactions with other elements of the epidermal structures and result in barrier disruption.[10]

Animal models

Multiple animal models have demonstrated the impact of dietary fatty acids on allergic outcomes in the gut, skin and lung. Dietary supplementation with fish oil from the start of weaning suppressed inflammatory responses to challenge with ovalbumin (OVA), whey or peanut in murine food allergy models.[11 12] Supplementation was shown to increase EPA and DHA levels in erythrocyte membranes at the expense of AA, and to decrease PGE2 levels in plasma. Erythrocytes are used as indicator cells and increased levels are expected also in other cell membranes. Moreover, a DHA-enriched diet led to modification in dendritic cell and T cell subpopulations in spleen or GALT. Notably, allergen-specific CD4+CD25+ cells were induced and were required for the protective effect. A direct effect of DHA-enriched diet on effector mast cells, independently of adaptive cells, was also shown. A α-linolenic acid (ALA)-rich diet resulted in a high content of ALA and its metabolites EPA and DHA in the lamina propria of the large intestine and in serum of mice. The cytochrome P450 EPA-derived metabolite 17,18-epoxyeicostetraenoic acid (17,18-EpETE) was identified as the active lipid mediator decreasing mMCP1 levels and the allergic diarrhea.[13 14] However, the conversion of ALA to DHA and EPA in humans has been shown to be much more limited than that observed in mice.[14]

The influence of dietary fatty acids on inflammation of the skin has long been studied in animal models, which show that a fatty acid (e.g. LA or ALA) deficient diet induced skin changes, including erythema, scaling and hyperkeratosis. One widely used mouse model to investigate the mechanisms of AD is the NC/Nga model.[15] Plasma levels of total IgE in NC/Nga mice are markedly elevated, correlating with increased numbers of mast cells and IL-4+ T cells in the skin. Oral administration of DGHA prevents development of the skin disease. An additional murine strain, termed Hairless mice, develop AD-like features when fed an unsaturated fatty acid deficient diet, which are reversed by supplementation with LA, ALA, GLA and AA.[16] DHA suppressed the development of hapten-induced dermatitis in mouse models by reducing serum IgE, histamine production, ear thickness, and lymph node size, associated with increased CTLA4+ regulatory T cells.[17] Similarly, fish oil feeding to rats reduced transepidermal water loss, increased skin hydration, alleviated the acetone induced skin barrier alteration, and eliminated itch-related scratching induced by dry skin.[18] Finally, a significant reduction in cyclosporine usage could be achieved by LC-PUFAs supplementation in dogs with AD.[19]

As described above for the gut and the skin, multiple animal studies have shown modulatory effects of dietary fatty acids on allergen-induced respiratory inflammation. In particular, *n*-3 fatty acids seem to function as protective molecules in murine models of respiratory inflammation.[20] Interestingly, DHA inhalation during the allergen challenge phase in mice was also effective in suppressing airway eosinophilic inflammation.[21] The pro-resolving lipid mediators protectin D1 (PD1) and resolvin E1 (RvE1) may play important roles in mediating *n*-3 fatty acid protective effects in the lung.[22]

Role of fatty acids in food allergy

Epidemiological evidence

Unfortunately, studies investigating the role of fatty acids in allergy seldom evaluate food allergy, particularly challenge-proven food allergy, as an outcome. Typically, studies make use of sensitization data as a proxy for potential food allergy (most commonly to cow's milk, egg and peanut).

(A) *Pregnancy and lactation*: Two observational studies have evaluated the relationship between maternal intake of butter (rich in saturated fats), margarine, vegetable oils (rich in parental *n*-6 and *n*-3 PUFA) and fish (rich in *n*-3 LC-PUFA) during pregnancy and food sensitization in their offspring. Sausenthaler *et al*. found no association between sensitization to cow's milk, egg and peanut at 2 years of age and maternal fat intakes during the last four weeks of pregnancy.[23] Similarly, Calvani *et al.* found that SPT reactivity to fresh cow's milk and egg white was not associated with maternal intake of butter and margarine in a group of children (median age 5 years). However, this study did observe a reduced risk of food sensitization by over a third associated with increased (2-3 times/week or more) maternal consumption of fish (white or fatty fish type was unspecified); this trend was significant in the whole study population (including both allergic and non-allergic mothers).[24]

Notenboom *et al.* measured maternal fatty acid status (*n*-3 and *n*-6 LC-PUFAS in maternal phospholipids) during the last trimester of pregnancy in atopic and non-atopic mothers. They reported no significant differences between the groups in the levels of individual fatty acids. Maternal fatty acid status was not associated with allergic sensitization to hen's egg, cow's milk, or peanut in the offspring at 24 months.[25] Pike *et al.* also measured maternal fatty acid status (phosphatidylcholine fatty acid composition) during the last trimester. In this study, a higher ratio of LA to unsaturated metabolic products was associated with a significantly reduced risk of sensitization in the offspring.[26]

Soto-Ramirez *et al.* measured *n*-3 and *n*-6 fatty acids in maternal colostrum and mature milk samples. No association was found between any of the fatty acids studied in human milk colostrum with atopy at age 12 months.[27] However, for mature breast milk (2 weeks after delivery), total *n*-3 fatty acids as well as individual *n*-3 fatty acids (EPA, DHA and DPA), were associated with reduced sensitization to food allergens (milk, egg, peanut) at 12 months. These findings are supported by those of a separate study.[28] A third study investigating the effects of maternal diet during lactation on the risk of sensitization to cow’s milk, egg, wheat and inhalant allergens in the offspring found none of the dietary variables investigated was significantly related to sensitization to milk or egg but was associated with sensitization to wheat. Risk of sensitization to wheat was lower with higher maternal intakes of total PUFA, *n*-3 and *n*-6 LC-PUFA during lactation.[29]

(B) Infants and children: Fish consumption by infants during the first year of life in the BAMSE Cohort was associated with reduced development of allergic disease including sensitization (specific IgE to milk, egg, fish, soy, peanut and wheat) by age 4 years. The effect was dose-dependent but significant only for children without any parental allergy history.[30] Introducing fish early during the first year of

life (age 3-8 months) was more beneficial than introducing fish later on (age >= 9 months). However, the fish type (white/fatty) was not specified.

(C) Adults: No studies investigating the role of fatty acids and food allergy prevention were identified.

Prevention trials (summarized in supplementary Table S1)

(A) *Pregnancy and lactation*: In a randomized double blind placebo controlled trial providing *n*-3 LC-PUFA supplements to atopic and non-atopic women during pregnancy continuing up to 3-4 months of breastfeeding, the prevalence of egg, milk or wheat sensitization and food allergy was significantly lower in the offspring at 1 year of age compared to placebo (soybean oil), particularly so for offspring of non-atopic mothers.[31] At 2 years of age, the cumulative incidence (0–24 months) of positive SPTs to food was lower in the *n*-3 group. [32] The effect was related to maternal and infant plasma proportions of *n*-3 LC-PUFA in a dose-dependent manner. A subgroup analysis found that the supplementation regimen also increased the proportions of *n*-3 LC-PUFA in breastmilk and that a high proportion of *n*-3 LC-PUFA in colostrum and early mature milk was associated with the absence of food allergy. [32 32 32 32,56] Another study suggested that egg sensitization at one and three years may be reduced in infants at high risk of allergy through maternal supplementation with *n*-3 LC-PUFA during pregnancy. [33 34] However, sensitization to other foods was not reduced and longer term follow up found the effect on egg sensitization was no longer significant at 3 years of age.[35]

In contrast, Bisgaard *et al*.[36] reported no reduction in the risk of sensitization to milk or egg allergens in infants at 6 months and 18 months of age following *n*-3 LC-PUFA supplementation given as a fish oil capsule to their mothers during pregnancy. Fish oil supplementation for up to 4 months during breastfeeding did not reduce the prevalence of food allergy.[37] Similarly for pre-term infants, consumption of expressed breastmilk from mothers taking either a high-DHA or standard-DHA supplement had no effect on incidence of parental reported food allergy.[38]

(B) Infants and children: Direct supplementation of infants at high risk of atopy from birth to 6 months improved their *n*-3 LC-PUFA status but did not reduce the prevalence of food allergy and sensitization at 12 months of age.[39] In children, *n*-3 PUFA supplementation was compared to a reduced *n*-6 PUFA diet and the intervention led to a significantly higher proportion of *n*-3 fatty acids and a lower proportion of *n*-6 fatty acids in plasma.[40] However, there were no differences in the prevalence of atopy defined as physician diagnosis of IgE-mediated food allergy, eczema, or asthma.

(C) Adults: No studies investigating the role of fatty acids and prevention of food allergy were identified.

Treatment studies

No human intervention studies have been identified that assessed the impact of fatty acids on patients with existing food allergy. However, one study found that food allergic children on elimination diets had significantly lower total plasma levels of LC-PUFAs, particularly EPA and DHA.[41] Due to the immunomodulatory role of *n*-3 and *n*-6 LC-PUFAs, future studies should examine supplementation in patients with food allergy.

Role of fatty acids in atopic dermatitis

Epidemiological evidence

(A) *Pregnancy and lactation*: Prenatal maternal fatty acid intake was not associated with the development of AD in the offspring.[29] An additional study also found that no specific fatty acid measured in maternal plasma at 12 weeks gestation was associated with AD in children at 14 months, except for a decreased risk of AD with increasing concentration of LC-PUFA.[42] In the same study, increasing concentrations of cord blood total *n*-3 PUFA, DHA, and total LC-PUFA reduced the risk of AD. Notenboom *et al*. found, an increasing ratio of maternal third trimester *n*-6 to *n*-3 LC-PUFA plasma levels decreased the risk of AD in 6-7-year old children; while an increasing concentration of AA increased the risk of AD at 7 and 12 months but not after 12 months.[25]

Low levels of *n*-3 LC-PUFAs in breast milk have been shown to be a risk factor for AD.[43-45] Another study showed a protective effect of high concentrations of *n*-3 fatty acids and ruminant fatty acids in breast milk at 1 month on the development of AD.[46] In contrast, in a high-risk birth cohort, measurements of fatty acids in colostrum and breast milk at 3 months showed that high levels of *n*-3 LC-PUFA were associated with an increased risk of AD.[47] Similarly, a Swedish study reported higher mean concentrations of cord serum *n*-3 PUFA and *n*-6 PUFA in AD cases compared to non-allergic 13-year old children; however, non-allergic children had higher cord serum concentrations of saturated and mono-unsaturated fatty acids.[48] Finally, another study showed no association between levels of LC-PUFA in breast milk and allergic diseases, such as AD.[49]

(B) Infants and children: A population-based epidemiological study reported a decreased intake of *n*-3 PUFA, reduced serum level of *n*-3 PUFA, and an increased intake of *n*-6 PUFA among patients with AD.[50] Higher levels of LA and lower levels of its metabolites were associated with an increased risk of AD; also higher levels of its metabolites decreased the severity of AD.[51] In a large Swedish cohort, introduction of fish before 9 months (unspecified white or fatty fish type) was protective against the development of AD in the first year of life.[52] However, in another Swedish study, fatty acid profiles measured at 13 years did not differ between AD cases and non-allergic children.[53] In a Spanish cross-sectional study, consumption of butter ≥3 times a week was associated with a decreased risk of AD in 6-7-year-old children, but not consumption of seafood/fish or margarine.[54]

(C) Adults: There is one epidemiological study on fatty acids and AD in adults. Solvoll *et al* reported that women with consumed diets that were low in vitamin D and *n*-3 LC-PUFAs.[55]

Prevention studies (summarized in supplementary Table S2)

(A) *Pregnancy and lactation*: In three studies[32 33 56 57] and one subgroup analysis[56] pregnant women received supplements ranging from 900 mg to 3.7 g *n*-3 LC-PUFA with varying amounts of DHA and EPA. IgE-associated diseases, including AD, were significantly reduced by *n*-3 LC-PUFA supplementation in the study by Furujelhm *et al* and in the subgroup analysis in the Warstedt *et al.* study.[32 57] Palmer *et al*. only observed an effect for AD in sensitized participants.[33]The final study by Dunstan *et al* observed no difference in the frequency of AD at one year, but AD severity was less in the supplemented group.[56]

(B) Infants and children: At 6 months, *n*-3 LC-PUFA levels were associated with lower risk of eczema following supplementation of high risk infants with fish oil; however, there were no differences in prevalence of allergic outcomes.[39] In a subgroup analysis, infants with higher plasma DHA levels were significantly less likely to develop eczema, while lower erythrocyte EPA levels also predicted eczema development.[58] Healthy infants who received DHA- and AA- supplemented formula had significantly lower odds for developing AD.[59] Supplementation with GLA during early life was not protective against AD development.[60 61] However, early life supplementation with blackcurrant seed oil had a transient protective effect at 12 months of age, which disappeared by 24 months.[62]

(C) Adults: No prevention studies were identified in adults.

Treatment studies

AD treatment studies are summarized in supplementary Table S3. The use of fish oil supplementation in adults, particularly rich in *n*-3 LC-PUFAs, have shown some benefit on the severity of AD in small randomized clinical trials.[63-65] Also, a small study on DHA supplementation showed a reduction in AD severity in adults after 8 weeks.[66] An open label small trial with children and adults showed improvement in SCORAD scores following LC-PUFA supplementation.[67] However, other RCTs using fish oil in adults and children did not show any benefit over placebo for AD.[68 69] Similarly to the prevention studies, clinical trials on the therapeutic effect of supplementation with GLA on AD were inconclusive.[70]

Role of fatty acids in asthma

Epidemiological evidence

(A) *Pregnancy and lactation*: Two studies showed that higher maternal PUFA levels during pregnancy were associated with a decreased risk of asthma or non-atopic persistent wheeze in offspring.[26 71] However, a different study showed no association between maternal fatty acids blood levels and offspring airway-related atopic manifestations at 7 months of age.[25] Maternal ALA, total *n*-3 LC-PUFA and palmitic acid intake may decrease, while AA intake may increase the risk of asthma in the offspring at 5 years of age.[72] In addition, fish (unspecified fish type) intake during pregnancy was shown to have protective respiratory effects in a number of studies.[73-75] A further study suggested that maternal intake of butter, the ratio of *n*-6:*n*-3 FA and intake of LC-PUFA and ALA during pregnancy may be potential determinants of allergic rhinitis in the offspring.[29] However, not all maternal fatty acids intake studies have shown consistent results.[76]

High levels of total *n*-6 PUFAs measured in breast milk were associated with an increased risk for asthma-like symptoms, whereas *n*-3 PUFAs decreased the risk of atopy.[27] Similarly, asthma is less prevalent in children of allergic mothers receiving breast milk with higher levels of *n*-3 LC-PUFA and more prevalent in children of non-allergic mothers receiving breast milk with higher levels of *n*-6 PUFA.[28] However, another study suggested that maternal fatty acid intake during lactation did not influence the risk of asthma by 5 years of age.[72]

(B) Infants and children: School age children adhering strictly to a Western diet, high in total and saturated fat and processed foods, have a higher risk of asthma.[77] High levels of low-density

lipoprotein cholesterol were associated with asthma in children and this association was amplified in overweight and obese children.[78 79] In contrast, adolescent asthma was associated with low serum high-density-lipoprotein cholesterol levels independent of childhood levels.[80] Increased intake of SFAs, myristic and palmitic acids was associated with current asthma in school children, while no relationship was seen with the intake of any other fatty acids or the *n*-6/*n*-3 ratio.[81] North American adolescents with the lowest dietary intakes of fruits and *n*-3 FAs had lower pulmonary function (lower FEV1) and increased respiratory symptoms (chronic bronchitic symptoms).[82] Total red blood cell n-3 PUFAs were lower in Korean preschoolers with atopy (including asthma) than controls, while *n*-6 PUFA and the *n*-6/*n*-3 PUFA ratio were greater.[83] Higher proportions of LA and total *n*-6 PUFAs were associated with an increased risk of atopic asthma, while higher proportions of EPA were associated with a decreased risk of nonatopic asthma.[84] Indeed, continuous farm milk consumption protects against asthma at school age potentially by means of higher intake of *n*-3 PUFAs.[85] However, daily *n*-3 and *n*-6 PUFA dietary intakes were not significantly different between sensitized wheezers compared with nonsensitized nonwheezy children.[86] Similarly, no association was seen for fatty acids with a reduced prevalence of asthma in preschool children.[87] Consumption of both *n*-3 and *n*-6 polyunsaturated fatty acids, especially LA, was associated with an increased prevalence of wheeze in Japanese children.[88]

(C) Adults: A high concentration of DHA in serum phospholipids may have a protective effect on lung function in adults.[89] Serum levels of palmitoleic acid, AA and DHA were significantly reduced in non-obese asthma patients with severe or uncontrolled disease, which was not observed in obese asthma patients. In addition, the serum desaturation index (palmitoleic:palmitic ratio) was significantly suppressed in severe asthma patients, suggesting that inhibition of desaturase activity might be associated with airway hyper-responsiveness.[90] Of note, this desaturation index is controlled by a δ-9-desaturase, which is unrelated to the δ-6- and δ-5-desaturase enzymes involved in the LC-PUFA pathways. However, reduced δ-9-desaturase activity may be driven by an excess of dietary *n*-6 fatty acids. Intakes of *n*-3 PUFAs have been inversely longitudinally associated with the

incidence of asthma in American young adults.[91] Higher intakes of *n*-3 LC-PUFA, ALA and SFA were associated with good asthma control, while the risk for uncontrolled asthma increased with a higher *n*-6:*n*-3 PUFA ratio.[92] Increased intake of *n*-3 fatty acids (g/day) in adult asthma patients was associated with an increase in FEV1.[93]

Fish consumption and the *n*-3 to *n*-6 ratio may be associated with a reduced prevalence of asthma in young female Japanese adults.[94] In older adults (>55 years), higher intake of antioxidant vitamins and *n*-3 PUFAs was associated with better pulmonary health.[95] A high intake of *n*-3 PUFAs does not appear to protect against asthma in Dutch adults, but a high intake of several *n*-6 PUFAs was associated with a significant reduction in FEV1. These findings indicate that high dietary intake of *n*-6 PUFAs, rather than reduced *n*-3 intake, may have an adverse effect on lung health.[96]

Prevention studies (summarized in supplementary Table S4)

(A) *Pregnancy and lactation*: Fish oil capsule supplementation during pregnancy reduced the probability of having asthma medication prescribed, an asthma discharge diagnosis or having been prescribed allergic rhinitis medication in adult offspring.[97] Similarly, a trend towards reduction in the incidence of parent-reported hay fever (p=0.06) and significant reduction in house dust mite sensitization following maternal supplementation with *n*-3 LC-PUFA fish oil was noted.[35] Maternal supplementation with *n*-3 LC-PUFA showed that at 5 year follow-up, there was a significant reduction in the risk of persistent wheeze or asthma and reduced lower respiratory tract infections (best effects seen in mothers with lowest EPA and DHA levels).[36] In addition, maternal *n*-3 LC-PUFA supplementation reduced cord blood plasma IL-13 levels.[98]

(B) Infants and children: Infants fed formula supplemented with DHA and ARA had a reduced incidence and delayed onset of upper respiratory infection and wheezing or asthma at 3 years of age.[59] In high risk infants, no difference in asthma prevalence was observed at 5 years, but wheeze

and cough were reduced at younger time points when comparing n-3 versus n-6 oils and spreads.[99] Similarly, *n*-3 LC-PUFA fish oil supplementation of high risk infants resulted in elevated plasma levels of DHA and total *n*-3 LC-PUFA at 6 months associated with a reduced risk of recurrent wheeze in the first 12 months of life.[39] Infant formula supplemented with *n*-3 and *n*-6 PUFA reduced the risk of respiratory allergic diseases in childhood with effects influenced by maternal allergies.[100] High dose DHA supplementation of preterm infants reduced bronchopulmonary dysplasia and hay fever in boys.[38]

(C) Adults: No prevention studies in adults were identified.

Treatment studies (summarized in supplementary Table S5)

(A) Children: In two small trials, LC-PUFA supplementation was associated with decreased asthma symptom scores or improvement in exhaled nitric oxide and FEV1.[101 102] However, an additional small study showed no clinical differences with LC-PUFA supplementation, although reduced TNF-α secretion and a trend towards lower blood eosinophils was observed.[103] Interestingly, a larger study combining multiple supplements (fish oil, fruit & vegetables and a probiotic) showed significant improvements in pulmonary function parameters.[104]

(B) Adults: In adults with exercise-induced bronchoconstriction, multiple studies examining supplementation with *n*-3 LC-PUFAs showed attenuation of hyperpnoea-induced bronchoconstriction and/or improved asthma symptoms.[105 106-108] However, one study showed no effect in this asthma group.[109] Compared to placebo, supplementation with n-3 and n-6 LC-PUFAs was associated with improvement in exhaled nitric oxide and serum eosinophils following a low dose allergen challenge.[110] Supplementation with LC-PUFAs generally showed no clinical benefits in adults with all other types of asthma (studies are summarized in supplementary Table S5).

Influence of genetics on fatty acid absorption, synthesis and signaling

Given the heterogeneity in responses to fatty acid supplementation described above, it is possible that gene-environment interactions may play a critical role, in addition to the type of fatty acid intervention, fatty acid dose and outcome studied. The *n* -5 and *n*-6 fatty acid desaturase (FADS) genes are involved in the desaturation of *n*-3 and *n*-6 PUFAs. Schaeffer *et al.* found that single-nucleotide-polymorphisms (SNPs) in the FADS gene cluster were associated with protection from allergic rhinitis and atopic eczema, but lost significance after correction for multiple testing.[111] However, the AA levels in serum phospholipids were associated with SNPs in the FADS genes. Rzehak *et al.* analyzed two cohorts in the Netherlands and Germany, and also found that SNPs in the FADS gene cluster were associated with LC-PUFAs in the blood and with eczema in Dutch, but not the German cohort.[112] However, the further analysis of these SNPs in a large cohort did not confirm any associations with eczema, asthma, hay fever or bronchitis.[113] Recent gene-nutrition interaction studies suggest that FADS genotypes might be indirectly implicated in atopic diseases. For example, Standl *at al.* found that the *n*-3/*n*-6 PUFA ratio and daily margarine intake were associated with an increased risk of hayfever and asthma, only in homozygous major allele FADS SNPs carriers.[114] Similarly, breast feeding had a protective effect against asthma development only for heterozygous and homozygous carriers of the minor SNPs alleles of the FADS gene cluster.[115] Minor FADs allele carriers also had decreased risk of developing atopic eczema, while FADS2 gene variants have been associated with asthma.[116,117] Phospholipase A2α cleaves AA from membrane phospholipids and its activity can be regulated on the transcriptional level by two microsatellite regions. One microsatellite fragment has been associated with a severe asthma phenotype.[118] There was no association between the genetic variants of PTGS1 or PTGS2 (encoding COX1 or COX2 respectively) and asthma, disease severity, atopy, or AIA in certain populations.[119] However, PTGS2 gene variants were associated with asthma only in females and resulted in significantly increased monocyte secretion of PGE2 and PGD2 or were associated with asthma, atopy and lung function parameters.[120] PTGS1 variants were also associated with AERD.[121]

PGD2 receptors DP1 and DP2 (CRTH2) are encoded respectively by PTGDR and PTGDR2 genes. Associations between PTGDR gene variants with asthma, allergy or NSAIDs-induced urticaria have been replicated in several studies.[122] However, the PTGDR gene variant associations can disappear in different ethnical backgrounds and age groups. PGE2 receptors EP1-4 are encoded by PTGER1- PTGER4 genes, while PTGIR and TBXA2R genes encode receptors for PGI2 and thromboxane A2, respectively. Genetic variants or SNPs in all of these genes have been linked with asthma and/or bronchial hyperesponsiveness.[123] Indeed, PTGER4 gene variants were associated with differential suppressive function of regulatory T cells.[124]

Several leukotriene metabolism pathway loci have been implicated in asthma or asthma pharmacogenomics studies.[125] ALOX5 polymorphisms were associated with asthma or asthma severity and responsiveness to leukotriene receptor antagonists in several but not all populations. Similarly, LTC4S polymorphic loci were associated with asthma, asthma exacerbations, NSAID-exacerbated respiratory disease (N-ERD) and urticaria.[126 127] PTGDR and LTC4S polymorphisms influence responsiveness to leukotriene receptor antagonists in Korean children with asthma.[128] CYSLTR1 promoter polymorphisms were associated with atopy and N-ERD in some populations and in a gender specific manner, while other variants of CYSLTR1 were associated with atopy, and/or asthma in some but not all studies.[129 130] CYSLTR2 gene variants also showed associations with asthma, N-ERD and atopy, but were not associated with AD or asthma in different genetic backgrounds.[131 132]

Thus, fatty acid synthesis, metabolism and signaling are significantly influenced by a wide range of genetic polymorphisms. Future studies examining dietary interventions with fatty acids should include genetic analyses of lipid metabolism genes to better define these gene-diet-disease interactions.

Interactions between fatty acids and the microbiota

The influence of the mucosal-associated microbiota on the innate and adaptive immune system has been well described, with changes in microbiota composition and/or metabolism affecting the development of asthma, AD and food allergy.[133-135] The composition and activity of the microbiota is influenced by many factors, including hygiene practices, antibiotics, medications, infections and most importantly, diet.[136] The influence of fat content on the composition of the gut microbiota has been shown in humans, where European children on a high fat, low fiber diet showed a higher abundance of *Shigella* and *Escherichia* and an overall lower microbial diversity compared to African children on a low fat, high fiber diet.[137] Gut bacterial enterotypes were strongly associated with long-term diets, particularly protein and animal fat (Bacteroides-dominated) versus carbohydrates (Prevotella-dominated).[138] The microbiota of obese individuals is significantly different to lean individuals and microbiota changes were linked to higher pro-oxidant and pro-inflammatory status.[139] Murine studies suggest that the high-fat content of the diet, rather than obesity itself, was responsible for influencing microbial functional changes.[140] Indeed, when animals were fed a high fat diet (HFD) enriched with *n*-6 (HFDn-6) or *n*-3 (HFDn-3) PUFAs, different dietary fat profiles led to distinct microbiota, intestinal and metabolic outcomes that were independent of obesity.[141] The HFD and HFDn-6 groups showed significant changes in the H2S-producing bacteria *Bilophila* and *Desulfovibrio*, which were associated with reduced gut integrity. The HFDn-3 group was free from all intestinal or metabolic dysfunctions and did not display elevated inflammatory cell numbers in mesenteric fat.

Short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate are produced in the colon following the fermentation of dietary fibers by intestinal microbes, or can be consumed in certain foods such as milk products containing significant amounts of butyrate. SCFAs influence dendritic cell and T cell responses, via their binding to GPCRs and their inhibition of histone deacetylases, thereby promoting epigenetic changes.[142] Deliberate administration of SCFAs, or dietary fibers that are metabolized to SCFAs, has repeatedly been shown to reduce airway inflammation in murine models.[143] A recently published study in humans suggests that high levels of butyrate and propionate at 1 year of age is associated with a reduced risk of later life atopic outcomes.[144] In addition to SCFAs, commensal microbes secrete lipid ligands that structurally mimic human signaling molecules, thereby binding to GPCRs such as prostaglandin receptors.[145] Finally, lipid metabolism by gastrointestinal microbes can modify host fatty acid composition.[146] Thus, the microbiota can directly or indirectly influence fatty acid levels and signaling processes in the host, suggesting that future fatty acid prevention or intervention studies should consider the impact of the microbiota in their trials.

Practical messages: Where science and food meet – what do we advise?

As outlined above, there are numerous inconsistencies in the allergic outcomes reported for studies examining the role of fatty acids in the prevention or treatment of food allergy, AD and asthma (as demonstrated in Supplementary tables S1- S5 and summarized in Supplementary Tables S6.1 [prevention] and S6.2 [treatment]). These inconsistencies can be partially explained by complicating factors such as variability in trial design, doses tested, different product formats, genetics, microbiota and lifestyle factors. However, it's important to note that the most significant protective effects in some studies were observed in individuals who had the lowest pre-existing levels of LC-PUFAs, suggesting that targeted supplementation of individuals with a low level of LC-PUFAs could be advised. In addition, LC-PUFA supplementation appears to be well tolerated, even during pregnancy. Despite the relatively small number of studies, and their inconsistencies, we have summarized our practical messages and recommendations in Box 1.

Box1: Current opportunities relating to fatty acids that may mitigate risk and be of benefit to treatment of allergic disease.

Maternal fatty acid intake during pregnancy: The European Food Safety Authority (EFSA) set recommendations for EPA and DHA of approximately 250 mg of EPA+DHA per day for adults plus an additional 100 – 200 mg of preformed DHA per day during pregnancy.[147] Current intervention trials have used much higher doses than these recommended amounts. Based on the current evidence we advise that pregnant women should adhere to the current recommendations from their respective countries regarding fatty acid intake, either by consuming it through their diet or as a supplement.

Maternal fatty acid intake during lactation: Maternal intake of LC-PUFAs will affect breast milk fatty acid content. Breast milk has been shown to be an important source of fat and in particular *n*-3 and *n*-6 LC-PUFAs.[148] Several cross-sectional and epidemiological studies described above suggest that a high *n*-3 LC-PUFA (EPA and DHA) or fish intake (usually unspecified fish type) during lactation reduces the risk of allergen sensitization in the offspring. However, the effects are not consistent across all studies and there are differences between allergic- and non-allergic mothers. We recommend adhering to the international recommendations on FA intakes, as summarized in Supplementary Table S7.

Fatty acids in infant formula: The current European Union (EU) Directive on infant formula [2006/141/EC] provides clear guidelines on the content of fatty acids in infant formula (total lipid content of 4.4 – 6 g/100 kcal). LC-PUFAs may be added to formula and when added they should not exceed 1% of total fat content for *n*-3 or 2% for *n*-6 LC-PUFAs. EPA content should not exceed that of DHA and the DHA content should not exceed that of n-6 LC-PUFAs. Several guidelines have suggested the addition of LC-PUFAs to infant formula as desirable, but the ideal levels of *n*-3 and *n*-6 LC-PUFAs are still debated.[149,150] EFSA has published adequate nutrient intakes of PUFAs for infant formulas from birth to the age of 6 months as 100 mg DHA/day and 140 mg AA/day.[147] Several studies have been published on the positive impact of LC-PUFAs in supplemented formula, including a potential influence on allergic disease.[100] Although the allergy prevention data are not conclusive, no studies have found PUFA supplementation harmful and as PUFAs are found in breast milk, it seems prudent to choose a formula (including hypoallergenic formulas) with LC-PUFAs.

Fatty acids in foods: The EFSA Panel has made recommendations on adequate intakes of *n*-3 LC-PUFAs of 100mg DHA per day for infants >6 months to 24 months of age, approximately 250 mg of EPA plus DHA per day for children aged 2-18 years and for adults (i.e., 1 to 2 fatty fish meals per week); and 250 mg DHA and EPA per day during pregnancy and lactation with an additional 100 - 200 mg per day of DHA. The Joint Food and Agriculture Organization (FAO) and World Health Organization (WHO) Expert Consultation on Fats and Fatty Acids in Human Nutrition provide a similar recommendation, namely 300 mg/day EPA and DHA, of which at least 200 mg/day should be DHA.[151] While there is limited scientific evidence to support specific recommendations regarding dietary intakes of fish for the purposes of prevention or treatment of allergic disease in infants and children, current recommended fatty fish intakes would achieve intakes above those that were effective in published epidemiological studies. However, certain populations such as women planning a pregnancy, and those who are pregnant or breastfeeding, as well as children are advised to limit their consumption of oily fish due to pollutants such as methylmercury which can build up in the body over time. EFSA has recommended national guidance is provided to balance the health benefits of regular fish and seafood consumption with risk of pollutants based on patterns of fish consumption in each country.[147]

Food allergy: Studies have reported inconsistent results but in general, increased maternal breast milk *n*-3 LC-PUFA (EPA and DHA) levels seem to have protective effects against the development of food allergy. The early introduction of fish to infants may be more beneficial than later introduction (i.e. later than 9 months of age). Supplementation studies are not conclusive but where successful, the effect was related to pre-treatment maternal and infant *n*-3 LC-PUFA levels. A recent systematic review also indicates that *n*-3 supplementation during pregnancy and lactation may reduce food allergen sensitization.[152]

Atopic dermatitis: In general, increased maternal and breast milk *n*-3 LC-PUFA (EPA and DHA) levels were associated with a reduced risk of AD in the offspring. A diet low in *n*-3 LC-PUFAs or fish was associated with an increased risk of AD during childhood in some studies, but not all. Similarly, prevention studies with *n*-3 LC-PUFA supplements were often, but not always, protective against the development of AD. Although results are contradictory, dosages and duration of supplementation were diverse, and because no adverse effects were found, supplementation with *n*-3 LC-PUFAs (EPA and DHA) could be recommended for the prevention and treatment of AD.

Asthma: A substantial number of studies have assessed the role of fatty acids in asthma prevention and treatment. In general, maternal and infant *n*-6 PUFA levels were associated with an increased risk of asthma-like symptoms, while *n*-3 PUFA levels were often associated with a decreased risk. Supplementation was most effective for the children of mothers with the lowest *n*-3 LC-PUFA status and those with a FADS genotype associated with low PUFA blood levels. This suggests that targeting of particular populations may be the most effective way to achieve the benefits of *n*-3 LC-PUFA supplementation for asthma prevention during pregnancy and infancy.

Treatment studies in adult asthmatics generally did not show any clinical benefits, other than the notable exception of exercise-induced bronchoconstriction.

Current gaps and future directions

Bioavailability and incorporation of n-3 LC-PUFAs: Inconsistent trial results with *n*-3 LC-PUFAs can, at least in part, be explained by differences in bioavailability and inter-individual variability in response to supplementation.[153] Bioavailability can be influenced by lipid structure and pancreatic lipase activity, but most important is the degree of emulsification, which is best when given as part of a meal rich in lipids. Thus, *n*-3 LC-PUFA bioavailability within different foods and supplements will influence subsequent incorporation into host cells and the pooling of trial results from different studies testing fixed PUFA dosages, but without incorporation data, is not reasonable. The biologically effective status can be assessed by analyzing the Omega-3 Index (the sum of EPA and DHA in erythrocytes). For optimal cardio-vascular health, the HS-Omega-3 Index® has been established with a target range of 8% to 11%. For future allergy and asthma trials, instead of giving a fixed dosage, a target range for the Omega-3 index should be defined and the required supplementation dose should be individually determined. In addition, future studies should use a standardized single formulation (i.e. supplement and not a food) to allow for a systematic review of multiple studies across multiple indications.

Conversion from ALA to n-3 PUFAs: EPA and DHA are derived directly from the diet or via conversion of their dietary precursor ALA. Although conversion of the plant-derived *n*-3 PUFA ALA to the longer chain derivates, particularly DHA, is theoretically possible it appears to be limited in humans.[154] Intake of foods fortified with ALA does not alter erythrocyte fatty acid composition, while competition between the plant-derived *n*-6 PUFA LA and ALA is thought to negatively impact on the capacity to convert ALA. Thus, supplementation with preformed *n*-3 derivatives or consumption of foods rich in *n*-3 LC-PUFAs (e.g. fatty fish, certain microalgae and meat from ruminants reared with adequate exercise and a grass-based diet) are likely to be more beneficial than intake of ALA.

Can some trans-fatty acids be beneficial: Trans-fatty acids derived by partial dehydrogenation of vegetable oils are known to have detrimental health effects.[155] However, naturally occurring trans-fatty acids, which differ markedly from their industrially derived counterparts, seem to possess protective health effects. Consumption of the ruminant milk trans-fatty acid Vaccenic acid (tVA) and conjugated linoleic acid (c9,t11-CLA) may reduce sensitization and allergic inflammation, possibly via a PPAR-gamma-related mechanism and by reducing eicosanoid precursors.[46 156] Future research needs to further examine the role for these ruminant-derived trans-fatty acids in the prevention and treatment of atopic disorders. In addition, possible synergies between *n*-3 LC-PUFAs and natural, trans-fatty acids should be explored.

An individualized approach to nutrition: The lack of consistent results across the different studies presented in this review may largely be influenced by the lack of a standardized approach to supplementation and individual host features that are difficult to compare across studies. Polymorphisms in genes associated with fatty acid synthesis, catabolism and utilization will influence fatty acid requirements and function. GWAS-led prevention and intervention studies, including functional microbiome, immunological, metabolomic and lipidomic assessments are required and will increase our understanding of the importance of fatty acids in the natural course of allergies and asthma. It is likely that a custom-individual-tailored approach to nutrition, including fatty acid supplementation, is required to observe the optimal benefits that can potentially be derived from fatty acids in the prevention and treatment of allergies and asthma. Future research and clinical efforts should be focused on large, adequately powered human studies, which are focused on identifying the key host characteristics (i.e. genetics, environmental factors, microbiome, biochemical and inflammatory parameters and functional clinical characterization) that influence responses, whilst also taking the composition of the total underlying diet and nutrient interactions into account. Furthermore, interactions between LC-PUFAs and concomitant allergy/asthma medications need to be evaluated.

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Figure 1: Classification of fatty acids

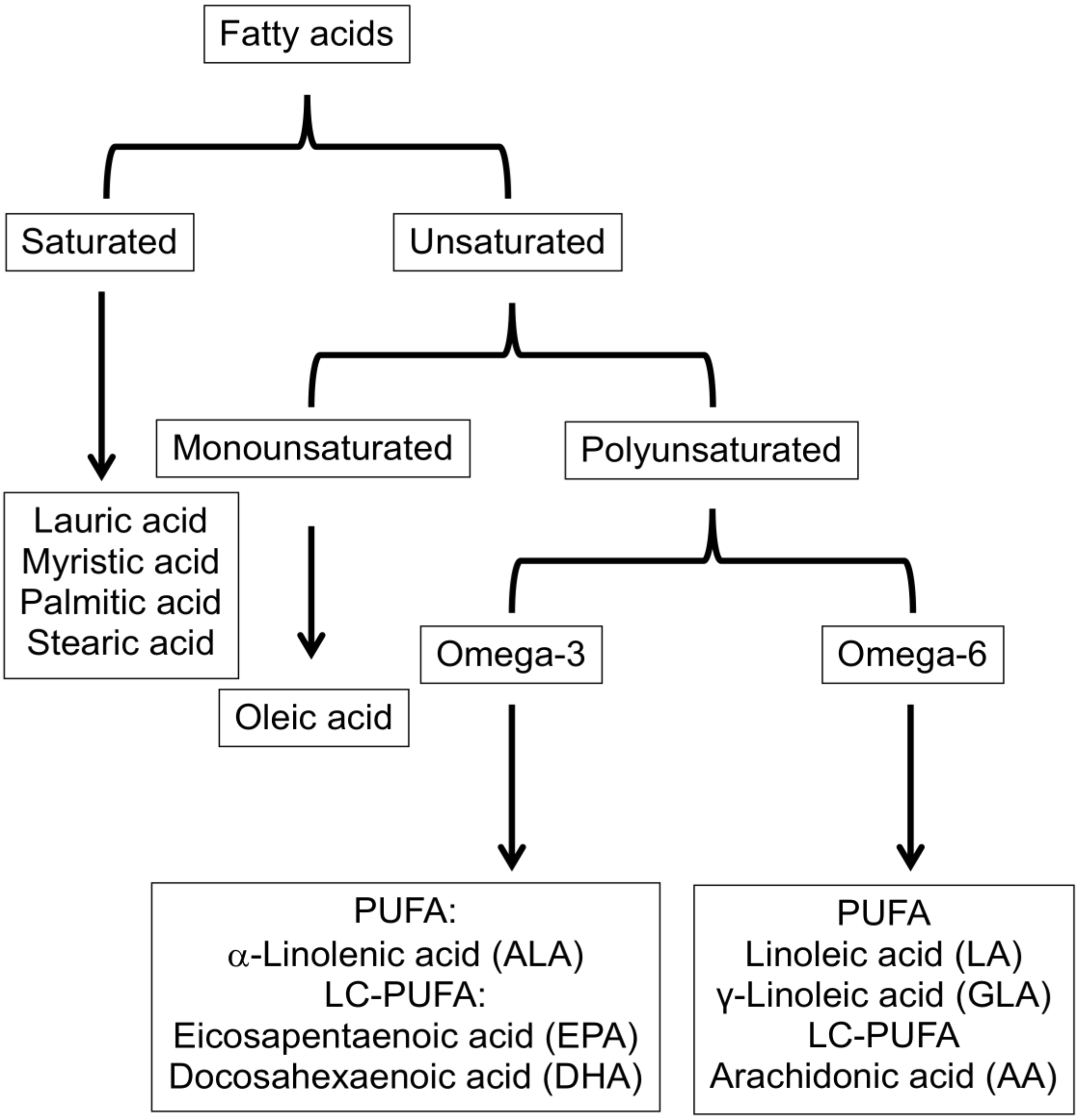
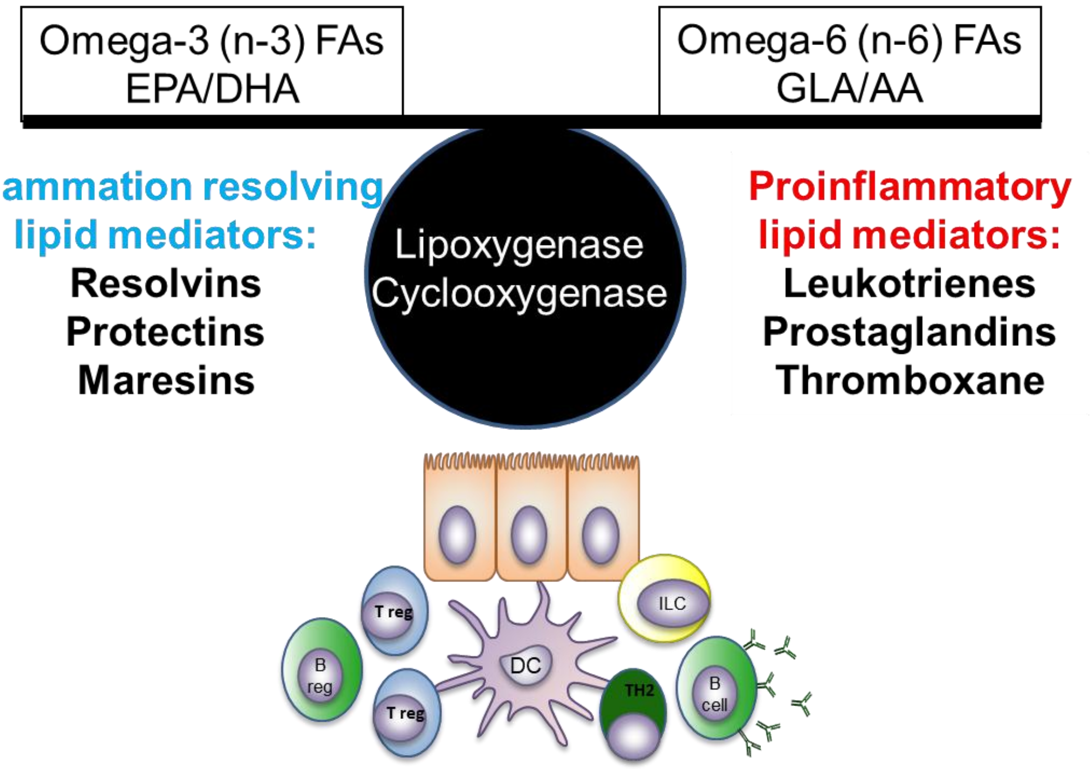


Figure 2: Immunomodulatory effect of fatty acids



Box1: Current opportunities relating to fatty acids that may mitigate risk and be of benefit to treatment of allergic disease.

Recommendation	Rationale
Optimize and disseminate public health dietary recommendations	Fatty acids are essential components of a healthy diet and deficiencies should be avoided. In addition, allergy prevention with LC-PUFA supplementation may be more effective in individuals with the lowest pre-existing levels of LC-PUFAs, particularly EPA and DHA.
PUFA-supplemented formulas	No studies have found LC-PUFA supplementation harmful. LC-PUFAs are found in breast milk in significant quantities. Infant formula constituents should be as close as possible to that of human milk. Hence, if a formula is to be used, the LC-PUFAs constituents should be considered. .
Supplementation of at-risk populations (e.g. allergic children on food elimination diets)	Allergic children on elimination diets can be deficient in LC-PUFAs, particularly the *n*-3 series. Due to their immunomodulatory role and general health benefits, a dietary assessment of LC-PUFAs intake is advised and safe dietary expansion to include LC-PUFA rich foods or alternatively, PUFA supplementation may be required in these children.
Supplementation of pregnant and lactating mothers with low pre-existing EPA and DHA levels	A reduced risk of food allergy, atopic dermatitis and asthma was more consistently observed in supplementation studies when mothers had low pre-existing levels of EPA and DHA