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3rd International Immunonutrition Workshop

Session 5: Early programming of the immune system and the role of nutrition
Is there a role for fatty acids in early life programming of the immune system?

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There may be a causal relationship between *n*-6 PUFA intake and allergic disease and there are biologically plausible mechanisms, involving eicosanoid mediators of the *n*-6 PUFA arachidonic acid, that could explain this. There is some evidence that high linoleic acid intake is linked with increased risk of atopic sensitisation and allergic manifestations. Fish and fish oils are sources of long-chain *n*-3 PUFA and these fatty acids act to oppose the actions of *n*-6 PUFA. It is considered that *n*-3 PUFA will protect against atopic sensitisation and against the clinical manifestations of atopy. All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations. Epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants or children are inconsistent, although the majority of the studies (9/14) showed a protective effect of fish. Fish oil provision to pregnant women is associated with immunologic changes in cord blood. Provision of fish oil during pregnancy may reduce sensitisation to common food allergens and reduce the prevalence and severity of atopic dermatitis in the first year of life. This effect may persist until adolescence with a reduction in prevalence and/or severity of eczema, hayfever and asthma. Fish oil supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but whether this benefit persists as other factors come into play remains to be determined.

Atopy: Immune function: Eicosanoid: Fish oil: Pregnancy

Epidemiological and animal studies suggest that besides genetic factors, environmental exposures early in life are important determinants of health and disease later in life[1]. Since the effects of the early exposures can be long-lasting, even persisting until adulthood, this phenomenon has been termed 'early life programming', 'early life origins of health and disease' or 'developmental origins of heath and disease'[2]. Nutrition has been identified as one source of early exposures that might influence early development and later phenotype[3]. There is substantial immune development in human subjects *in utero* and in the weeks and months after birth[4–6], and it is possible that such development can be influenced by nutritional factors[7]. However, relatively little attention has been devoted to the potential for early life programming of the immune system by dietary factors. Nevertheless a body of mainly epidemiological literature has developed, which associates temporal changes in the patterns of intake of *n*-6 and *n*-3

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; COX, cyclooxygenase; LA, linoleic acid; LOX, lipoxygenase; LT, leucotriene; Th2, T-helper 2; TX, thromboxane.

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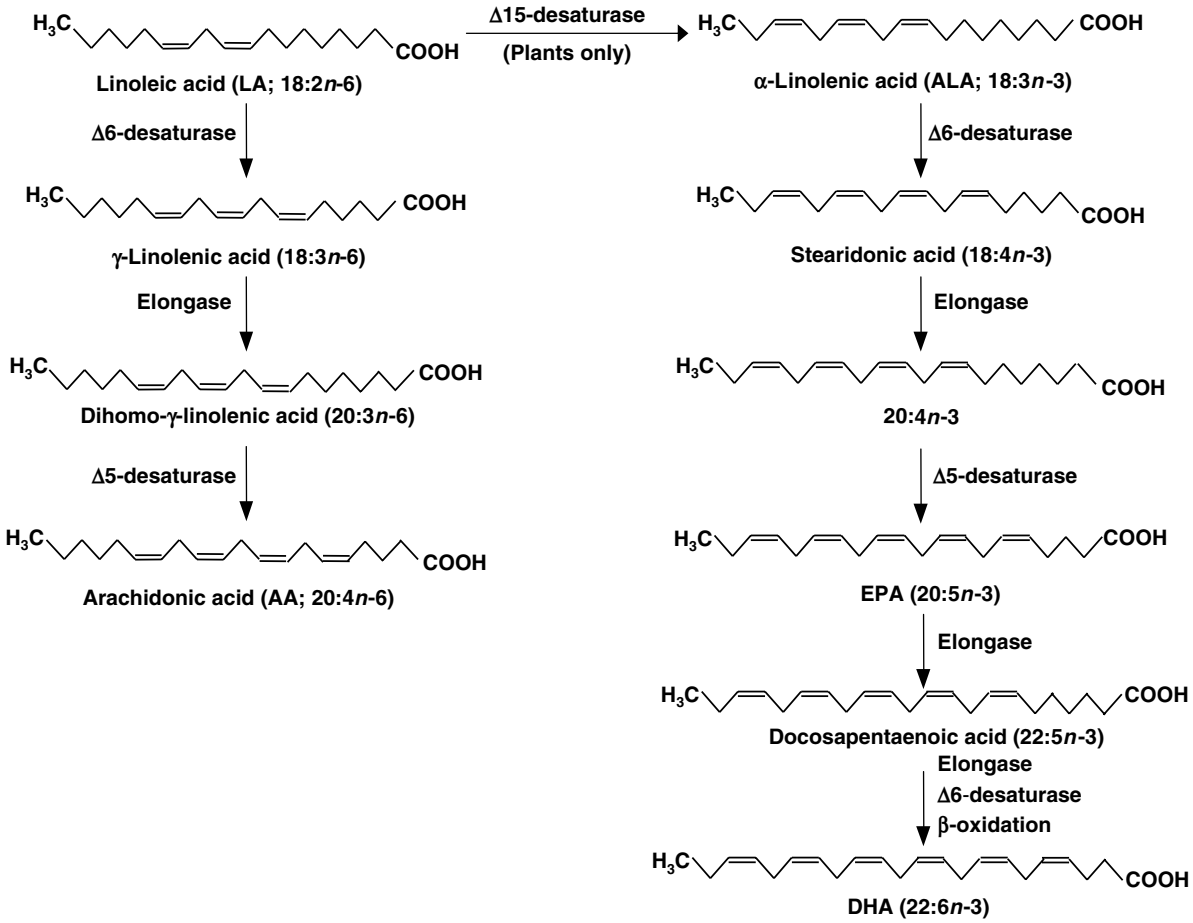

Fig. 1. Biosynthesis of *n*-6 and *n*-3 PUFA.

PUFA with temporal changes in the incidence and prevalence of atopic sensitisation or its clinical manifestations (allergies, atopic eczema, hayfever and allergic asthma), and there is a proposed molecular and cellular mechanism to explain the observed association[8,9]. In this article, the proposed mechanism that relates early exposure to *n*-6 or *n*-3 PUFA to increased or decreased risk of developing atopy will be described as will the literature relating early exposure to *n*-6 or *n*-3 PUFA or their main dietary sources to atopy or its manifestations or immune outcomes relevant to atopy.

Fatty acids: nomenclature, sources and intakes

Fatty acid structure and nomenclature have been described elsewhere[10]. There are two principal families of PUFA, the *n*-6 and the *n*-3 families. The simplest members of each family, linoleic acid (LA; 18:2*n*-6) and α-linolenic acid (ALA; 18:3*n*-3), cannot be synthesised by mammals. LA is found in significant quantities in many vegetable oils, including corn, sunflower and soyabean oils, and in products made from such oils, such as margarines. ALA is found in green plant tissues, in some common vegetable oils, including soyabean and rapeseed oils, in some nuts, and in flaxseed (also known as linseed) and flaxseed oil. Between them, LA and ALA contribute over 95%, and perhaps as much as 98% of dietary PUFA intake in most Western diets,[10] with LA intake being in excess of that of ALA. The intake of LA in Western countries increased greatly over the second half of the 20th century, following the introduction and marketing of cooking oils and margarines[10,11]. ALA intake probably changed little over this time. Typical intakes of both essential fatty acids are in excess of requirements. However, the changed pattern of consumption of LA has resulted in a marked increase in the ratio of *n*-6 to *n*-3 PUFA in the diet. This ratio is currently between 5 and 20 in most Western populations[10,12].

Although LA and ALA cannot be synthesised by human subjects they can be metabolised to other fatty acids (Fig. 1). This is achieved by the insertion of additional double bonds into the acyl chain (i.e. unsaturation) and by elongation of the acyl chain. Thus, LA can be converted via γ-linolenic acid (18:3*n*-6) and di-homo-γ-linolenic acid (20:3*n*-6) to arachidonic acid (AA; 20:4*n*-6) (Fig. 1). By an analogous set of reactions catalysed by the same enzymes, ALA can be converted to EPA (20:5*n*-3). Both AA and EPA can be further metabolised, EPA giving rise to docosapentaenoic acid (22:5*n*-3) and DHA (22:6*n*-3) (Fig. 1). Dietary intakes of the longer-chain, more unsaturated PUFA are much lower than those of LA and ALA[10,11,13]. AA is found in meat and offal and intakes are estimated at 50–500 mg/d. EPA and DHA are found in

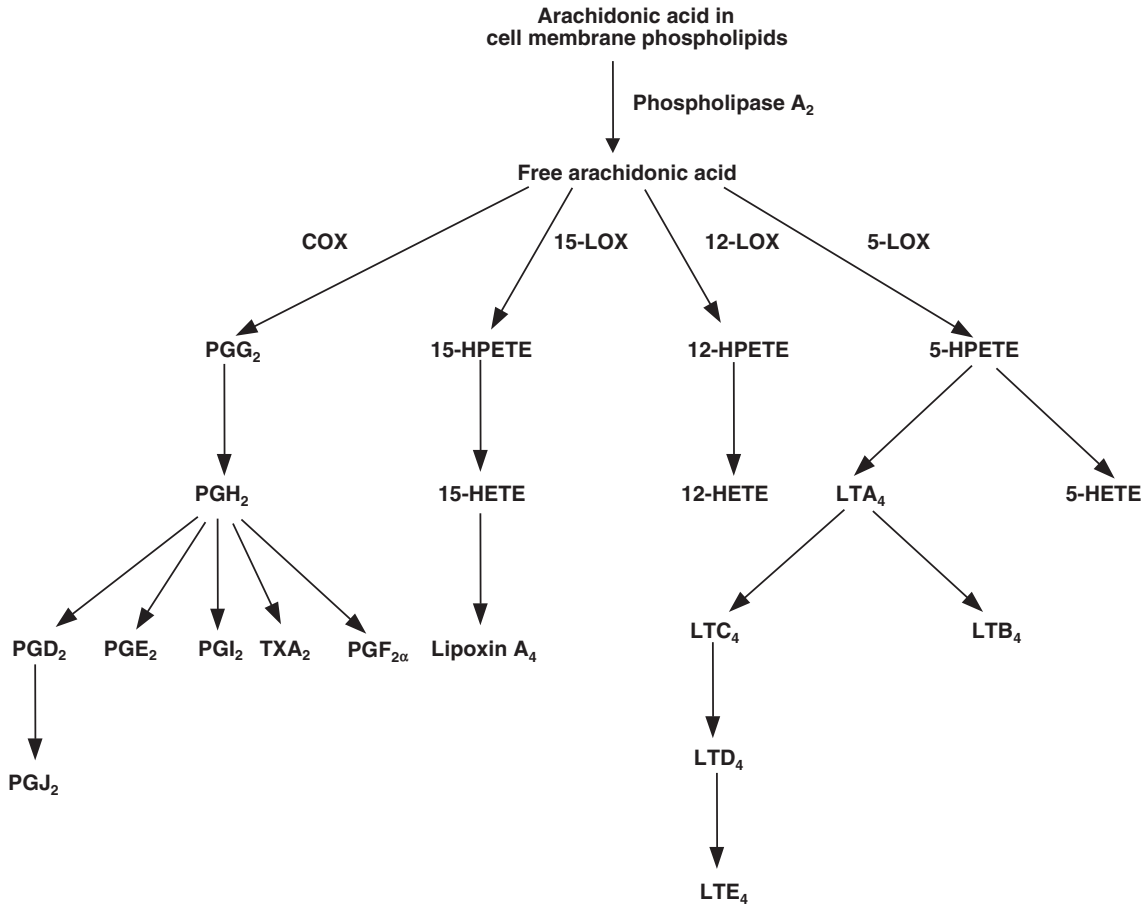

Fig. 2. Outline of the pathway of eicosanoid synthesis from arachidonic acid. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; LT, leucotriene; TX, thromboxane.

fish, especially so-called 'oily' fish (tuna, salmon, mackerel, herring and sardine). One oily fish meal can provide between 1·5 and 3·5 g of these long-chain *n*-3 PUFA[13]. Commercial products known as fish oils also contain these long-chain *n*-3 PUFA, which typically will contribute about 30% of the fatty acids present. Thus, consumption of a typical one gram fish oil capsule per day can provide about 300 mg of these fatty acids. In the absence of oily fish or fish oil consumption, intake of long-chain *n*-3 PUFA is likely to be <100 mg/d[10,11,13], although foods fortified with these fatty acids are now available in many countries.

n-6 PUFA, eicosanoids, inflammatory processes and atopy

PUFA play roles ensuring the correct environment for membrane protein function, maintaining membrane fluidity and regulating cell signalling, gene expression and cellular function[10]. Through these actions PUFA can influence the functioning of immune cells[14–16] and so could impact on the development and manifestations of atopy[17,18]. However, the key link between PUFA and immunological processes related to atopy is that the eicosanoid family of mediators is derived from 20-C PUFA. Because immune cells typically contain a high proportion of the *n*-6 PUFA AA and low proportions of other 20-C PUFA, AA is usually the major substrate for eicosanoid synthesis. Eicosanoids, which include PG, thromboxanes (TX), leucotrienes (LT) and other oxidised derivatives, are generated from AA by the action of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes (Fig. 2). These enzymes are expressed in inflammatory and epithelial cells and give rise to a mix of mediators, depending upon the nature of cell types present and the nature, timing and duration of the stimulus[19,20–22]. Eicosanoid mediators are involved in modulating the intensity and duration of inflammatory responses. Through actions on dendritic cells, T cell differentiation and Ig class switching in B cells, some eicosanoids (e.g. PGE_2) are believed to play a role in promoting sensitisation to allergens. Through their actions on inflammatory cells, smooth muscles and epithelial cells, some eicosanoids are strongly implicated in different immunologic features and clinical manifestations of atopic disease. Indeed, allergic inflammation in animal models is associated with increased PG and LT production. However, inhibition of COX-1 or COX-2 or knockout of either COX results in augmented allergic inflammation with increased T-helper 2 (Th2)-type cytokine production and increased airway reactivity (see Moore *et al.*[23] and Park & Christman[24]). This suggests that the overall effect of PG

is to restrain allergic inflammation. However, individual PG might enhance or inhibit allergic inflammation, depending upon their specific action. One current view is that PGD_2, $PGF_{2\alpha}$ and thromboxane A_2 increase allergic inflammation, whereas PGE_2 and PGI_2 inhibit it (see Moore *et al.*[23] and Park & Christman[24]). PGD_2 is produced mainly by mast cells and activated macrophages. It is a potent bronchoconstrictor, promotes vascular permeability, and activates eosinophils and a Th2-type response. Thromboxane A_2 is a bronchoconstrictor and stimulates acetylcholine release. PGE_2 is a vasodilator, increases vascular permeability, inhibits the production of T-helper 1-type cytokines and primes naïve T cells to produce IL-4 and IL-5. PGE_2 also promotes Ig class switching in uncommitted B cells towards the production of IgE. Despite these effects of PGE_2, it is now considered that this eicosanoid is protective towards airway inflammation[23,24]. It is possible that PGE_2 promotes sensitisation via its effects on T cell phenotype and B cells, but is protective against the subsequent manifestations of inflammation upon re-exposure to allergen. PGI_2 appears to suppress Th2 lymphocyte activity and eosinophil recruitment. LTB_4 is chemotactic for leucocytes, increases vascular permeability, induces the release of lysosomal enzymes and reactive oxygen species by neutrophils and of inflammatory cytokines (e.g. TNF-α) by macrophages, and promotes IgE production by B cells. The cysteinyl LT (LTC_4, D_4 and E_4) may be either vasoconstrictors or vasodilators, depending upon the situation and the location of their synthesis. They cause smooth muscle contraction and bronchoconstriction, increase vascular permeability and eosinophil recruitment, and promote mucus secretion. PGE_2 inhibits 5-LOX activity, so down-regulating LT production[25]. Furthermore PGE_2 induces 15-LOX leading to production of lipoxin A_4, which is anti-inflammatory[26–28]. These effects highlight the antagonist nature of eicosanoids and may underlie, at least in part, the protective effect of PGE_2 in allergic inflammation.

The foregoing discussion has led to suggestions that there is a causal link between the increased intake of the *n*-6 PUFA LA over the second half of the 20th century and the incidence and prevalence of atopy and its clinical manifestations and that the link is mediated via increased potential to produce pro-atopic and pro-allergic eicosanoids from AA[8,9]. This link is shown in Fig. 3.

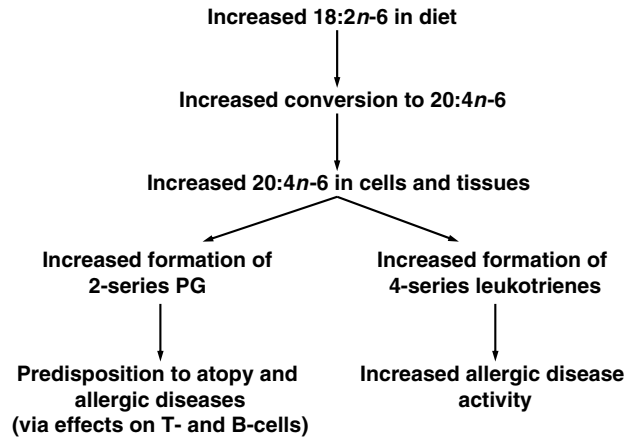

Fig. 3. Proposed relationship between increased LA exposure and increased atopic disease.

Evidence relating high early *n*-6 PUFA exposure to increased risk of atopic outcomes in infancy or childhood

There is some ecological, epidemiological and case *v.* control evidence associating high LA intake with atopy or its manifestations. Differences in the prevalence of asthma and allergic rhinitis and in blood concentrations of allergen-specific IgE between former East and West Germany accorded with differences in butter and margarine consumption[29]. Differences in the prevalence of bronchial asthma, allergic rhinitis and atopic dermatitis among Finnish schoolchildren were related to levels of LA in plasma cholesteryl esters, an indicator of dietary LA intake[30]. Margarine consumption among German schoolchildren was associated with a greater risk of hayfever compared with not consuming margarine (OR = 2·0 after adjustment for other factors)[31]. Margarine consumption was higher in Australian schoolchildren with atopic dermatitis or with other manifestations of atopic disease compared with controls[32]. High PUFA consumption was associated with increased risk of recent asthma compared with low PUFA consumption among Australian schoolchildren (OR = 2·03)[33]. Margarine consumption was associated with increased risks of allergic sensitisation and of allergic rhinitis *v.* no margarine, although this effect was seen in boys only[34]. Polyunsaturated oil consumption was associated with increased risk of wheeze in Swedish children (OR = 1·91)[35]. A high dietary ratio of *n*-6 to *n*-3 PUFA was associated with increased risk of asthma in Australian schoolchildren (OR = 1·93; after adjustment for other factors = 2·89)[36]. These studies all associate dietary intake and disease at the same point in time and none attempt to associate early LA exposure with later disease. However, some studies report that LA is higher in breast milk consumed by infants who go on to develop atopy in infancy, although not all such studies have found this (reviewed in Sala-Vila *et al.*[37]). Umbilical cord lipids from neonates who go on to develop atopy in early childhood contain a higher amount of LA than normal (see Sala-Vila *et al.*[37]). Thus there is some evidence to support some aspects of the chain of events shown in Fig. 3.

n-3 PUFA eicosanoids and inflammatory processes

Increased consumption of long-chain *n*-3 PUFA such as EPA and DHA (usually given as fish oil) results in increased proportions of those fatty acids in inflammatory cell phospholipids[38–40]. The incorporation of EPA and DHA into human inflammatory cells occurs in a dose–response fashion and is partly at the expense of AA[38–40]. Since there is less substrate available for synthesis of eicosanoids from AA, fish oil supplementation of the human diet has been shown to result in decreased production of AA-derived eicosanoids by inflammatory cells (see Calder[41] for references) (Fig. 4). EPA is also able to act as a substrate for COX and LOX enzymes, giving rise to eicosanoids with a slightly different structure to those

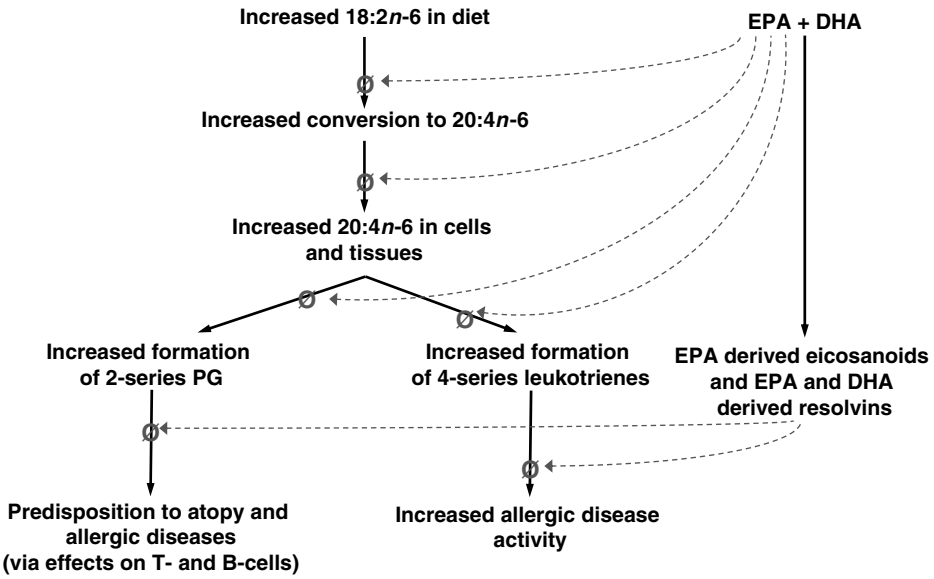

Fig. 4. Actions by which marine *n*-3 fatty acids can decrease production of eicosanoid mediators from arachidonic acid (AA). EPA + DHA can inhibit (∅) synthesis of AA, incorporation of AA into membrane phospholipids and metabolism of AA to eicosanoids. In addition, eicosanoids and resolvins derived from EPA and DHA can interfere with or antagonise the actions of eicosanoids produced from AA.

formed from AA. Thus, fish oil supplementation of the human diet has been shown to result in increased production of 5-series LT by inflammatory cells[41]. The functional significance of this is that the mediators formed from EPA are believed to be less potent than those formed from AA. For example, LTB_5 is 10- to 100-fold less potent as a neutrophil chemotactic agent than LTB_4 (see Calder[41]). In addition to long-chain *n*-3 PUFA modulating the generation of eicosanoids from AA and to EPA acting as substrate for the generation of alternative eicosanoids, recent studies have identified a novel group of mediators, termed E- and D-series resolvins, formed from EPA and DHA, respectively, that appear to exert anti-inflammatory and inflammation-resolving actions (see Serhan *et al.*[42] and Serhan[43] for reviews). In recent studies in ovalbumin-sensitised Balb/C mice, administration of resolvin E1 was found to decrease airway eosinophil and lymphocyte recruitment, production of the Th2 cytokine IL-13, circulating ovalbumin-specific IgE and airway hyper-responsiveness to inhaled methacholine[44] and to promote the resolution of inflammatory airway responses by directly suppressing the production of IL-23 and IL-6 in the lung[45].

The above considerations have led to the idea that while a high exposure to *n*-6 PUFA (or low exposure to *n*-3 PUFA) will promote atopy (both sensitisation and manifestations), a high exposure to *n*-3 PUFA will be protective[8,9].

Evidence relating high early *n*-3 PUFA exposure to decreased risk of atopic outcomes in infancy or childhood

A small number of studies report that EPA and DHA are lower in breast milk consumed by infants who go on to develop atopy in infancy, although not all studies find this (reviewed in Sala-Vila *et al.*[37]). Umbilical cord blood lipids from neonates who go on to develop atopy in early childhood appear to contain lower than normal amounts of EPA and DHA (see Sala-Vila *et al.*[37]). All five studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations[46–50]. The protective effect varied between 25 and 95%, which might be attributed to differences in study design, exposure and outcome measure classification and assessment. Nine studies observed a beneficial effect of fish intake during infancy/childhood and atopic outcomes in those infants/children[32,35,51–57]. The reduction in atopy/allergy risk among these studies ranged between 22 and 80%. It is important to note that two studies observed a negative effect of fish intake on childhood atopy[58,59], and three studies observed no associations[60–62].

Studies of maternal fish oil supplementation during pregnancy report effects on umbilical cord blood immune markers (blood cytokine mRNA[63], plasma cytokines[64], LTB_4 production from neutrophils[65], cytokine production by mononuclear cells[66]) and an altered cord blood haemopoietic progenitor phenotype[67]. These immunologic effects might be expected to impact on allergic sensitisation and on the development of atopic disease. Indeed, Dunstan *et al.*[66] reported beneficial effects on atopic outcomes in one-year-old infants as a result of maternal fish oil supplementation during pregnancy (less severe atopic dermatitis, lower risk of positive skin prick test to egg). Olsen *et al.*[68] identified that fish oil supplementation in late pregnancy is associated with a marked reduction in atopic manifestations in the offspring at age 16 years, suggesting a long-term effect of any immunologic changes that occurred in pregnancy and early life of those children. A study of fish oil supplementation during both pregnancy and lactation

showed expected effects on *n*-3 PUFA status and these were associated with differences in PGE_2 production by stimulated maternal blood[69]. The latter might be expected to influence Th2 polarisation. Indeed, infants from mothers in the fish oil group had a reduced risk of developing allergic sensitisation to egg, IgE-associated eczema and food allergy during the first year of life[70]. A study of maternal fish oil supplementation during lactation[71] is the only one of these studies investigating immune outcomes in the offspring beyond birth. Infants of lactating mothers who received fish oil supplements had a higher *n*-3 PUFA status at 4 months of age and interferon-γ production at 2·5 years of age was higher in the fish oil group, an observation that may reflect faster maturation of the immune system. This study did not assess clinical outcomes.

One study has examined the long-term effect of fish oil supplementation of infants on atopy and its manifestations[72–76]. Fish oil supplementation from 6 months of age increased plasma *n*-3 PUFA status and decreased *n*-6 PUFA status at 18 months, 3 years and 5 years of age. At 18 months of age there was a decreased prevalence of wheeze in the fish oil group and higher plasma *n*-3 PUFA levels were associated with lower bronchodilator use[72,73]. Follow-up at 3 years of age suggested that fish oil supplementation from infancy to childhood could reduce allergic sensitisation and airway disease at this early age, as the fish oil group had reduced cough, but not wheeze[74]. However, no effect of fish oil was seen on the other end points measured such as eczema, serum IgE concentration or doctor diagnosis of asthma. At 5 years of age there was no significant effect of fish oil on any of the clinical outcomes relating to lung function[75], allergy[75] or asthma[76]. Possible reasons for the lack of beneficial effects of long-chain *n*-3 PUFA at 5 years of age may be related to suboptimal adherence to and/or implementation of the intervention (50% and 56% compliance in the intervention and control group, respectively), as well as to the dose of fish oil used, loss to follow-up and lack of power.

Thus, there is quite good evidence that early exposure to *n*-3 PUFA induces immune effects that may be associated with reduced atopic sensitisation and with a reduction in allergic manifestations. However, data available from existing studies, which are of many different types, are not entirely consistent and so it is not possible to draw a firm conclusion at this stage. Clearly more studies in this area are needed and, where these are interventions, it is important that they be sufficiently powered, that they measure both immune and clinical outcomes where possible, and that the dose of *n*-3 PUFA and duration are carefully considered.

Conclusions

There are two main families of PUFA, the *n*-6 and the *n*-3 families. Intake of the *n*-6 PUFA LA increased over the second half of the 20th century, this increase coinciding with increased prevalence of atopy and its clinical manifestations. It has been suggested that there is a causal relationship between *n*-6 PUFA intake and allergic disease and there are biologically plausible mechanisms, involving eicosanoid mediators of the *n*-6 PUFA AA, that could explain this. There is some evidence from association studies that high LA intake is linked with increased risk of atopic sensitisation and allergic manifestations. However, there is little evidence that early exposure to LA increases later risk, although there are supportive observations using cord blood and later outcomes. Fish and fish oils are sources of long-chain *n*-3 PUFA and these fatty acids act to oppose the actions of *n*-6 PUFA. Thus, it is considered that *n*-3 PUFA will protect against atopic sensitisation and against the clinical manifestations of atopy. Evidence to examine this has been acquired from epidemiological studies investigating associations between fish intake in pregnancy, infancy and childhood and atopic outcomes in infants and children and from intervention studies with fish oil supplements in pregnancy, lactation and infancy and atopic outcomes in infants and children. All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations. The evidence from epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants or children is inconsistent, although the majority of the studies (9/14) showed a protective effect of fish intake during infancy or childhood on atopic outcomes in those infants/children. Fish oil provision to pregnant women is associated with immunologic changes in cord blood and such changes may persist. Studies performed to date indicate that provision of fish oil during pregnancy may reduce sensitisation to common food allergens and reduce the prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hayfever and asthma. Fish oil supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but this benefit may not persist as other factors come into play. Further studies of increased long-chain *n*-3 PUFA provision in pregnancy, lactation and infancy are needed to more clearly identify the immunologic and clinical effects in infants and children and to identify protective effects and their persistence.

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