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REVIEW

Fatty acid composition abnormalities in atopic disease: evidence explored and role in the disease process examined

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Summary

There is a hypothesis causally linking excess intake of n-6 polyunsaturated fatty acids (PUFAs) to atopic disease. Under most dietary conditions, the main precursor of eicosanoids is the n-6 PUFA arachidonic acid (AA). AA-derived eicosanoids play many roles in sensitization to allergens and in allergic inflammation. Long chain n-3 PUFAs inhibit AA incorporation into cell membranes and inhibit AA metabolism to eicosanoids. It is hypothesized that atopy is associated with a higher n-6 PUFA status and with a low n-3 PUFA status. However, measurements of fatty acid composition do not provide a clear picture that such fatty acid abnormalities exist in atopy with no really clear pattern of altered status of a particular fatty acid or a particular fatty acid family. There are few reports of elevated linoleic acid in atopy. Some studies report lower amounts of the n-6 PUFAs, including AA, and of long chain n-3 PUFAs in atopy, although observations on this are not consistent. Taken together these data clearly do not support the hypothesis that atopy is somehow associated with a high exposure to, and status of, n-6 PUFAs. Intervention studies with n-3 PUFAs in pregnant women, infants and children suggest some clinical benefits, although how long lasting these are remains to be determined. The observation that there may be low AA status in atopy suggests that fish oil intervention, which targets AA status and metabolism, may not be ideal and that a combination of fish oil with some longer chain n-6 PUFAs may be more efficacious.

Introduction

The human diet contains a wide range of fatty acids, consumed in differing amounts according to dietary patterns and food choices [1–3]. Among Western diets, polyunsaturated fatty acids (PUFAs) comprise 5–20% of dietary fatty acids. There are two main families of PUFAs, the ω-6 (or n-6) family and the ω-3 (or n-3) family. In most diets, intake of n-6 PUFAs exceeds that of n-3 PUFAs [3]. Linoleic and α-linolenic acids are the simplest and usually the most abundant dietary n-6 and n-3 PUFAs, respectively [3]. Derivatives of these fatty acids play a role as precursors of eicosanoids and similar mediators and hence can influence inflammatory processes. Under most dietary conditions, the main precursor of eicosanoids is the n-6 PUFA arachidonic acid (AA). AA-derived eicosanoids have roles in sensitization to allergens and in allergic inflammation. As a result of this, it has been hypothesized that there is a causal link between excess dietary intake of n-6 PUFAs and atopic disease [4, 5]. Long chain n-3 PUFAs, found in seafood, especially oily fish, inhibit AA incorporation into cell membranes and inhibit AA metabolism to eicosanoids. Thus, it is hypothesized that atopy is associated with a higher n-6 PUFA status and with a low n-3 PUFA status [4, 5]. The aim of this review is to examine this hypothesis in detail using available evidence from human studies that have reported the fatty acid composition of blood, breast milk and cell lipids in relation to atopic disease in children or that have reported the effects of increased dietary supply of n-3 PUFAs on atopic outcomes in children. Before considering and evaluating this evidence, the nature and sources of fatty acids in the human diet and aspects of their metabolism are described, as are the roles of AA-derived eicosanoids in sensitization to allergens and in allergic inflammation.

Fatty acids: structure, nomenclature, sources, roles and intakes

Fatty acids are hydrocarbon chains with a carboxyl group at one end and a methyl group at the other [3]. The carboxyl group is reactive and readily forms ester

links with alcohol groups, for example those on glycerol or cholesterol, in turn forming acylglycerols (e.g. triacylglycerols, phospholipids), and cholesteryl esters. The most abundant fatty acids have straight chains of an even number of carbon atoms. Fatty acid chain lengths vary from 2 to 30 or more and the chain may contain double bonds. Fatty acids containing double bonds in the acyl chain are referred to as unsaturated fatty acids; a fatty acid containing two or more double bonds is called a polyunsaturated fatty acid or PUFA. Saturated fatty acids do not contain double bonds in the acyl chain. The systematic name for a fatty acid is determined simply by the number of carbons and the number of double bonds in the acyl chain (Table 1). However, complications arise for the naming of unsaturated fatty acids. This is because there are multiple possibilities for the position of double bonds within the hydrocarbon chain and because each double bond may be in the *cis* or *trans* configuration. Therefore, when naming an unsaturated fatty acid it is important that the exact positions of double bonds and their configurations be clearly identified. Traditionally, the position of double bonds was identified by naming the carbon number [from carbon 1 (the carboxyl carbon)] on which each double bond occurs. Thus, octadecadienoic acid, an 18-carbon fatty acid with *cis* double bonds between carbons 9 and 10 and carbons 12 and 13 is correctly denoted as *cis*-9, *cis*-12-octadecadienoic acid or as *cis*, *cis*, 9,12-octadecadienoic acid. More recently, an alternative shorthand notation for fatty acids has come into frequent use. This relies upon identifying the number of carbon atoms in the chain, and the number of double bonds and their position. Thus, octadecanoic acid is notated as 18 : 0, indicating that it has an acyl chain of 18 carbons and does not contain any double bonds. Unsaturated fatty acids are named simply by identifying the number of double bonds and the position of the first double bond counted from the methyl terminus (with the methyl, or ω, carbon as number 1) of the acyl chain. The way the first double bond is identified is as ω-*x*, where *x* is the carbon number on which the double bond occurs. Therefore *cis*, *cis*, 9,12-octadecadienoic acid is also known as 18 : 2 ω-6. The ω-*x* nomenclature is sometimes referred to as omega *x* (e.g. 18 : 2 omega 6) or n-*x* (e.g. 18 : 2n-6). In addition to these nomenclatures, fatty acids are often described by their common names (Table 1). Figure 1 shows the structure of several 18-carbon fatty acids indicating the position of the double bonds in the chain and how this is reflected in their naming. Most common unsaturated fatty acids contain *cis* rather than *trans* double bonds. *Trans* double bonds do occur however as intermediates in the biosynthesis of fatty acids, in ruminant fats (e.g. cows' milk), in plant lipids and in some seed oils [3].

There are two principal families of PUFAs, the n-6 (or omega-6) and the n-3 (or omega-3) families. The simplest

Table 1. Fatty acid nomenclature

Systematic name	Trivial name	Shorthand notation
Octanoic	Caprylic	8 : 0
Decanoic	Capric	10 : 0
Dodecanoic	Lauric	12 : 0
Tetradecanoic	Myrsitic	14 : 0
Hexadecanoic	Palmitic	16 : 0
Octadecanoic	Stearic	18 : 0
cis-9-hexadecenoic	Palmitoleic	16 : 1n-7
cis-9-octadecenoic	Oleic	18 : 1n-9
cis-9, *cis* 12-octadecadienoic	Linoleic	18 : 2n-6
All *cis*-9,12,15-octadecatrienoic	α-Linolenic	18 : 3n-3
All *cis*-6,9,12-octadecatrienoic	γ-Linolenic	18 : 3n-6
All *cis*-8,11,14-eicosatrienoic	Di-homo-γ-linolenic	20 : 3n-6
All *cis*-5,8,11,14-eicosatetraenoic	Arachidonic	20 : 4n-6
All *cis*-5,8,11,14, 17-eicosapentaenoic	Eicosapentaenoic	20 : 5n-3
All *cis*-7,10,13,16, 19-docosapentaenoic	Docosapentaenoic	22 : 5n-3
All *cis*-4,7,10,13,16, 19-docosahexaenoic	Docosahexaenoic	22 : 6n-3

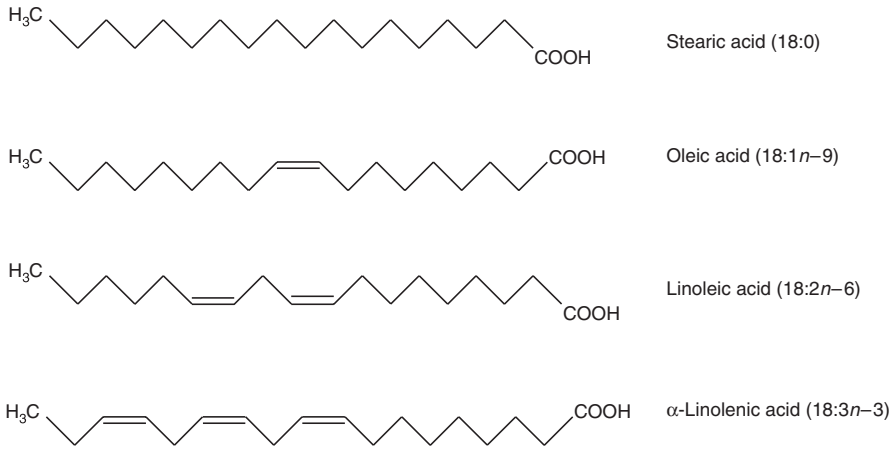

Fig. 1. The structure and naming of selected 18 carbon fatty acids.

members of each family, linoleic acid (18 : 2n-6, LA) and α-linolenic acid (18 : 3n-3; ALA), cannot be synthesized by mammals. LA is found in significant quantities in many vegetable oils, including corn, sunflower and soybean oils, and in products made from such oils, such as margarines [1, 3]. ALA acid is found in green plant tissues, in some common vegetable oils, including soybean and rapeseed oils, and in flaxseed (also known as linseed) and flaxseed oil [1, 3]. Between them, LA and ALA contribute over 95%, and perhaps as much as 98% of dietary PUFA intake in most Western diets [1, 3]. The intake of LA in Western countries increased greatly from about 1970, following the introduction and marketing of cooking oils and margarines [1, 2]. ALA intake probably changed little over this time. Typical intakes of both essential fatty acids are in excess of requirements [1]. However, the changed pattern of consumption of LA has resulted in a marked increase in the ratio of n-6 to n-3 PUFAs in the diet. This ratio is currently between 5 and 20 in most Western populations [1, 3].

Although LA and ALA cannot be synthesized by humans they can be metabolized to other fatty acids (Fig. 2). 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, linoleic acid can be converted via γ-linolenic acid (18 : 3n-6; GLA) and di-homo-γ-linolenic acid (20 : 3n-6; DGLA) to arachidonic acid (20 : 4n-6; AA) (Fig. 2). By an analogous set of reactions catalysed by the same enzymes ALA can be converted to eicosapentaenoic acid (20 : 5n-3; EPA). Both arachidonic acid and EPA can be further metabolized, EPA giving rise to docosapentaenoic acid (22 : 5n-3; DPA) and docosahexaenoic acid (22 : 6n-3; DHA) (Fig. 2). Dietary intakes of the longer chain, more unsaturated PUFAs are much, much lower than of LA and ALA [1–3]. Some plant oils contain GLA, DGLA and stearidonic acid (18 : 4n-3), but typical intakes of these fatty acids from the diet are likely to be < 10 mg/day [3]. AA is found in meat and offal and intakes are estimated at 50–500 mg/day [3]. EPA, DPA and DHA are found in fish, especially so-called 'oily' fish (tuna, salmon, mackerel, herring, sardine). One oily fish meal can provide between 1.5 and 3.5 g of these long chain n-3 PUFAs [2]. The commercial products known as fish oils also contain these long chain n-3 PUFAs, which typically will contribute about 30% of the fatty acids present. Thus, consumption of a typical 1 g 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 PUFAs is likely to be < 100 mg/day [1–3], although foods fortified with these fatty acids are now available in many countries.

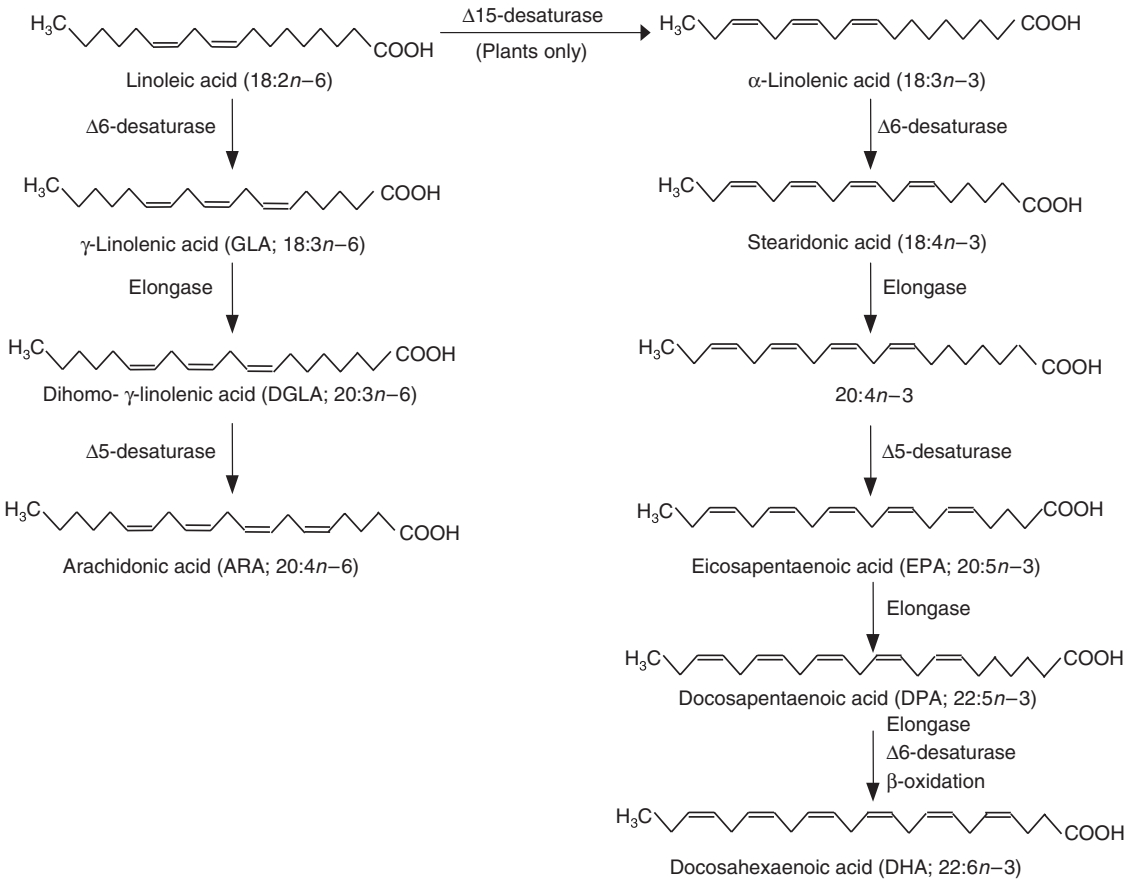

Fig. 2. The biosynthesis of polyunsaturated fatty acids.

PUFAs are important constituents of cells where they play roles assuring the correct environment for membrane protein function [6–8], maintaining membrane fluidity [6] and regulating cell signaling, transcription factor activation, gene expression and cellular function [9–11]. In addition, some PUFAs, particularly AA, act as substrates for synthesis of eicosanoids, which are involved in regulation of many cell and tissue responses [12, 13].

Polyunsaturated fatty acids, eicosanoids and inflammatory processes

The key link between PUFAs and inflammatory processes is that the eicosanoid family of mediators is derived from 20-carbon PUFAs [12, 13]. Because inflammatory cells typically contain a high proportion of the n-6 PUFA AA and low proportions of other 20-carbon PUFAs [14–17], AA is usually the major substrate for eicosanoid synthesis. Eicosanoids, which include prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs) and other oxidized derivatives, are generated from AA by the action of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes (Fig. 3). 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 [12, 13, 18, 19]. Eicosanoid mediators are involved in modulating the intensity and duration of inflammatory responses (see for reviews [18, 19]). Through actions on dendritic cells, T cell differentiation and Ig class switching in B cells, some eicosanoids [e.g. prostaglandin E2 (PGE_2)] are believed to play a role in promoting sensitization 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 (Table 2). 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 type-2 (Th2)-type cytokine production and increased airway reactivity [20, 21]. This suggests that the overall effect of PGs is to restrain allergic inflammation. However, individual PGs might enhance or inhibit allergic inflammation depending upon their specific action. One current view is that PGD_2, $PGF_{2\alpha}$ and TXA_2 increase allergic inflammation, whereas PGE_2 and PGI_2 inhibit it [20, 21]. 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. TXA_2 is a bronchoconstrictor and stimulates acetylcholine release. PGE_2 is a vasodilator, increases vascular permeability, inhibits the production of Th1-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

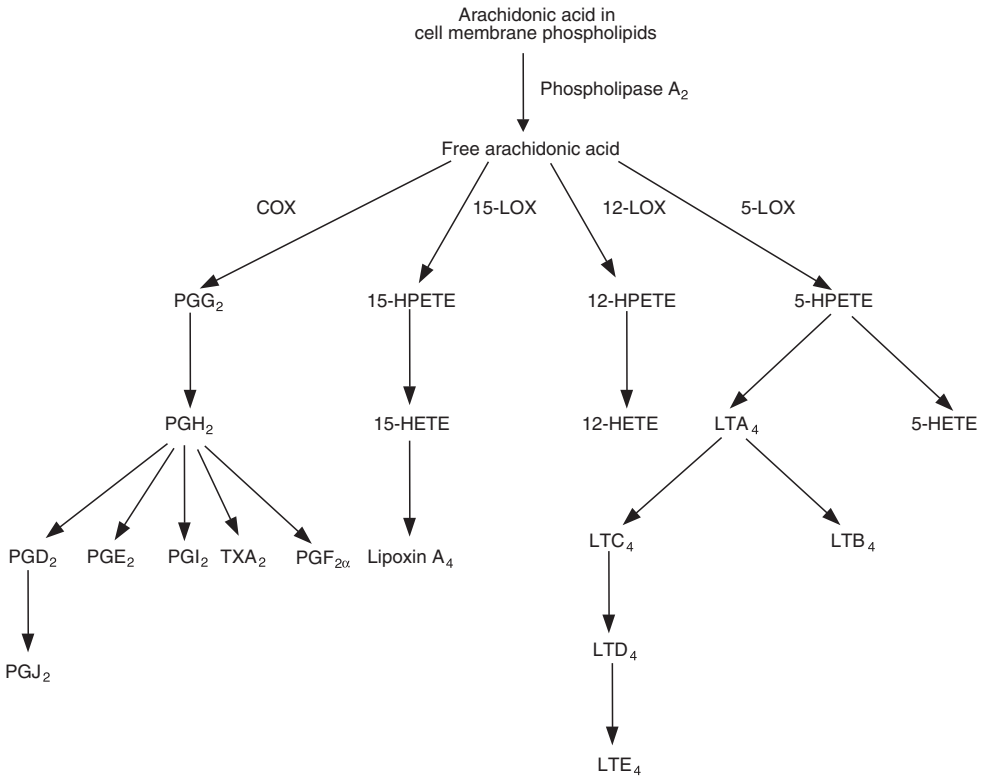

Fig. 3. Outline of the pathway of eicosanoid synthesis from arachidonic acid. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydrodoperoxyeicosatetraenoic acid; LOX, lipoxygenase; LT, leukotriene; PG, prostaglandin; TX, thromboxane.

Table 2. Selected effects of PGD_2, PGE_2, LTB_4 and cysteinyl leukotrienes

PGD_2	PGE_2	LTB_4	Cysteinyl LTs
Promotes bronchoconstriction	Increases vascular permeability	Increases vascular permeability	Vasodilation OR Vasoconstriction
Increases vascular permeability	Vasodilation	Enhances local blood flow	Promote smooth muscle contraction
Activates eosinophils	Inhibits Th1-type response	Chemotactic agent for leukocytes	Promote bronchoconstriction
Promotes Th2-type response	Promotes Th2-type response	Induces release of lysosomal enzymes	Increase vascular permeability
	Promotes IgE production by B cells	Induces release of reactive oxygen species	Promote mucus secretion
	Inhibits 5-lipoxygenase activity	Increases production of inflammatory cytokines (TNF-α, IL-1β)	
	Inhibits production of inflammatory cytokines (TNF-α, IL-1β)	Promotes IgE production by B cells	
	Inhibits T cell proliferation		
	Inhibits dendritic cell function		

LT, leukotriene; PG, prostaglandin; Th, T helper cell.

the production of IgE. Despite these effects of PGE_2 it is now considered that this eicosanoid is protective towards airway inflammation [20, 21]. It is possible that PGE_2 promotes sensitization 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 LTs (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 hence down-regulating LT production [22]. Furthermore, PGE_2 induces 15-LOX leading to production of lipoxin A_4, which is anti-inflammatory [23–25]. These effects highlight the antagonist nature of eicosanoids and may underlie, at least in part, the protective effect of PGE_2 in allergic inflammation.

Animal feeding studies have shown a strong positive relationship between the amount of AA in inflammatory cells and the ability of those cells to produce eicosanoids such as PGE_2 [26]. A recent human study also reported a strong positive correlation between the amount of AA in mononuclear cells and their ability to produce PGE_2 when stimulated by endotoxin [27].

Increased consumption of long chain n-3 PUFAs such as EPA and DHA (usually given as fish oil) results in increased proportions of those fatty acids in inflammatory cell phospholipids [14–17, 27]. The incorporation of EPA and DHA into human inflammatory cells occurs in a dose–response fashion [27, 28] and is partly at the expense of AA. Because 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, including PGE_2, TXB_2, LTB_4, LTE_4 and 5-HETE, by inflammatory cells (see for references [17]). EPA is also able to act as a substrate for both COX and LOX enzymes, giving rise to eicosanoids with a slightly different structure to those formed from AA. Thus, fish oil supplementation of the human diet has been shown to result in increased production of 5-series LTs by inflammatory cells [17]. 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 [17]. The reduction in generation of AA-derived mediators, which accompanies fish oil consumption has led to the idea that long chain n-3 PUFAs are anti-inflammatory.

In addition to long chain n-3 PUFAs 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 for reviews [29, 30]).

Dietary polyunsaturated fatty acids and risk of atopy

The notion that AA-derived eicosanoids are generally pro-inflammatory in nature, the view that PGE_2 promotes allergic sensitization, and the clear role played by some eicosanoid mediators (e.g. PGD_2, 4-series LTs) in allergic inflammation have led to the hypothesis that an increased intake of n-6 PUFAs in the diet has played a causal role in the increased incidence and prevalence of atopic diseases [4, 5]. This hypothesis assumes a higher content of n-6 PUFAs, especially AA, in cells involved in allergic sensitization and inflammation. Because long chain n-3 PUFAs

act to antagonize production of eicosanoids from AA, a second element of this hypothesis is that a low dietary intake of n-3 PUFAs, either in absolute terms or relative to n-6 PUFAs, is causally associated with atopic disease [4, 5]. There are epidemiologic, ecologic and case–control data linking high n-6 PUFA consumption with allergic sensitization and with increased risk of various manifestations childhood atopic disease [31–40] (see Table 3). Likewise there are data linking consumption of fish, especially oily fish, with lowered risk of childhood atopy [36, 41–45] (see Table 3). These associations accord with the hypothesis of Hodge et al. [4] and Black and Sharp [5] that n-6 PUFAs increase risk and that oily fish and n-3 PUFAs decrease risk.

Is atopy associated with abnormalities in fatty acid composition?

Because the fatty acid compositions of adipose tissue, plasma lipids, circulating erythrocytes and leucocytes, and breast milk partly reflect the dietary intake of n-6 and n-3 PUFAs, a causal role of altered intake of these fatty acids in atopic disease should be seen as a difference in fatty acid composition from that seen in non-atopic individuals. In order to identify all relevant literature reporting fatty acid composition in relation to childhood atopy, MEDLINE and SCIENCE CITATION INDEX searches were performed; the last search was performed on 27 April 2008. The keywords used were (atop* OR allerg*) AND fatty acids AND (breast milk OR serum OR plasma OR cord blood OR cell*). In addition, references cited in published original and review articles were examined until no further study was identified. Of all studies found in the literature search, only those performed in infants or children or in nursing women and including a group of non-atopic subjects as a control are included. In order to combine data of different types, from different sources and expressing fatty acid composition data in different ways, we have expressed the reported concentration of different n-6 and n-3 PUFAs as a difference, in percentage terms, from that seen in the control group.

Table 3. Summary of epidemiologic, ecologic and case control studies linking dietary intake of polyunsaturated fatty acids (PUFAs) or fish with manifestations of atopic disease in children

Reference	Location	Findings
[31–33]	Germany	Differences in 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
[34]	Finland	Differences in prevalence of bronchial asthma, allergic rhinitis and atopic dermatitis were related to levels of linoleic acid in plasma cholesterol esters, an indicator of dietary linoleic acid intake
[35]	Germany	Margarine consumption was associated with greater risk of hayfever compared with not consuming margarine (odds ratio = 2.0 after adjustment for other factors)
[36]	Finland	Margarine consumption was higher in children with atopic dermatitis or with any manifestation of atopic disease compared with controls; Fish consumption was lower in children who went on to develop atopic disease over the following nine years compared with those who remained healthy (odds ratio = 0.5)
[37]	Australia	High polyunsaturated fatty acid consumption was associated with increased risk of recent asthma compared with low polyunsaturated fatty acid consumption (odds ratio = 2.03)
[38]	Germany	Margarine consumption was associated with increased the risk of allergic sensitization vs. no margarine; effect seen in boys only
[39]	Sweden	Polyunsaturated oil consumption was associated with increased risk of wheeze (odds ratio = 1.91) Fish consumption was associated with lower risk of night-time breathlessness (odds ratio = 0.36), doctor's diagnosed asthma (odds ratio = 0.54) and current asthma (odds ratio 0.31)
[40]	Australia	High dietary ratio of n-6 to n-3 PUFAs was associated with increased risk of asthma (odds ratio = 1.93; after adjustment for other factors = 2.89)
[41]	Australia	Oily fish consumption was associated with decreased risk of having asthma compared with not eating oily fish (odds ratio = 0.29; odds ratio = 0.26 after adjustment for other factors)
[42]	Six European countries	Fish consumption was associated with lower risk of cough (odds ratio = 1.31), persistent cough (odds ratio 1.30), wheeze ever (odds ratio = 1.19) and current wheeze (odds ratio = 1.24)
[43]	Norway	Fish consumption during first year of life was associated with lower risk of allergic rhinitis up to age 4 years (odds ratio = 0.45) Fish consumption during first year of life among children who were breast fed for > 6 months was associated with lower risk of asthma (odds ratio = 0.56) and allergic rhinitis up to age 4 years (adds ratio = 0.28)
[44]	Australia	Fish consumption was associated with lower risk of ryegrass-pure sensitization (odds ratio = 0.37)
[45]	Sweden	Fish consumption associated with lower risk of asthma, eczema, allergic rhinitis and sensitization up to age 4 years (all dose-dependent) Introducing fish at age 3–8 months was associated with lower risk of asthma (odds ratio = 0.73), eczema (odds ratio = 0.77), allergic rhinitis (odds ratio = 0.77) and sensitization (odds ratio = 0.78) up to age 4 years

Polyunsaturated fatty acid concentrations in breast milk from atopic women

The fatty acid composition of breast milk will be influenced by a number of factors including maternal diet during and before the lactation period and maternal metabolism, both of which may be affected by atopic disease. The fatty acid composition of breast milk provides information about the qualitative aspects of fatty acid nutrition of the breastfed infant. Thus, a difference in breast milk fatty acid composition between atopic and non-atopic women may indicate that something related to the disease has an impact on milk composition, and, furthermore, will indicate that the quality of the fat received by infants nursed by atopic women is different from that received by infants nursed by non-atopic women.

Studies reporting the PUFA concentration of breast milk from nursing women with confirmed atopic disease are summarized in Table 4 [46–54]. The data are contradictory, apart from some fairly consistent effects of atopy upon breast milk DGLA and AA concentrations. There is no consistent pattern of observations of altered concentrations of LA or GLA in breast milk of atopic mothers, although some studies report lower concentrations of these two n-6 PUFAs (Table 4). There are six reports of a lower concentration of AA in breast milk from atopic women compared with non-atopic controls, although only two of these found statistically significant differences (Table 4). The lower concentration of AA was maintained from early stages of lactation up to 3 months after delivery (Table 4). A similar trend was seen for DGLA concentration, with a lower concentration being reported in colostrum and early mature milk of atopic women as compared with non-atopic mothers (Table 4). However, this difference in DGLA was not seen at later stages, where similar concentrations were found in atopic and non-atopic mothers. There are no reports of significantly increased concentrations of n-6 PUFAs in breast milk of women with atopic disease (Table 4). There is no consistent effect reported for ALA in breast milk of atopic women. There are several reports of significantly lower concentrations of EPA in breast milk of atopic women, with some reports that this fatty acid is 35–40% lower than in breast milk from controls (Table 4). However there are also several studies reporting no effect of maternal atopy on breast milk EPA concentration (Table 4). Finally, the effect of maternal atopy on breast milk DHA appears to be inconsistent; although several studies report a lower concentration, only one of these was statistically significant, while another study reported a significantly higher concentration (Table 4).

Polyunsaturated fatty acid concentrations in cord blood of neonates at risk of atopy

The fatty acid composition of umbilical cord blood is indicative of fatty acid exposure of the fetus. It is influenced by maternal diet and metabolism, by placental transport processes and by placental and fetal metabolism. A difference in cord blood fatty acid composition in pregnancies of atopic compared with non-atopic women may indicate that something related to the disease has an impact on fatty acid supply to the fetus.

The fatty acid composition of several lipid fractions and cell types from cord blood of neonates born to atopic mothers has been investigated [55–58] (Table 5). Cord blood lipid fractions have been reported to have a lower LA concentration in several studies, but the effect is small and has been found to be significant only once (Table 5). Furthermore cord mononuclear cells and red blood cells appear to have normal LA contents. An inconsistent impact of maternal atopy on cord blood lipid DGLA has been reported, and again red cells appear normal, although there is no report for cord blood immune cells (Table 5). Likewise, inconsistent effects of maternal atopy on cord blood lipid AA concentration have been reported and both significantly higher and lower concentrations than seen in controls have been reported (Table 5). Cord red cell AA concentration appears little affected by maternal atopy, although there are only two studies reporting this, but the one study reporting cord mononuclear cells found a large and significant effect of maternal atopy on AA concentration (Table 5). Fairly large, and inconsistent, but frequently not statistically significant, effects of maternal atopy on cord blood n-3 PUFA content are reported (Table 5).

Polyunsaturated fatty acid concentrations in breast milk in relation to atopy in infancy

A number of studies report the fatty acid composition of breast milk in relation to subsequent development of atopic disease in infancy or childhood. A difference in the fatty acid composition of breast milk consumed by infants who later develop atopy compared with those who do not may indicate that there is an association between fatty acid nutrition in early infancy and later atopy; this association may or may not be causal. In other words the quality of the fatty acid composition of diet in early infancy may have a causal influence on risk of developing atopy. This may relate to the resulting fatty acid composition of the infants immune and other cells and the capacity to produce fatty-acid derived mediators that influence sensitization and allergic responses.

Twelve studies were identified that focussed on the relationship between the PUFA composition of maternal milk and development of atopy in children [46, 49, 53, 59–67] (Table 6). With regard to colostrum, one study reported significantly higher LA than seen in colostrum consumed by infants who did not develop atopy, although there are no other studies showing this difference. Several studies report lower GLA and DGLA in colostrum

Table 4. PUFA concentrations in breast milk from atopic mothers, expressed as a percentage difference from the concentration found in breast milk from matched non-atopic controls

Reference	Subjects	Atopy criteria	Controls (*n*)	Sample	LA (18 : 2n-6)	GLA (18 : 3n-6)	DGLA (20 : 3n-6)	AA (20 : 4n-6)	ALA (18 : 3n-3)	EPA (20 : 5n-3)	DHA (22 : 6n-3)
[46]	107 atopic women	Clinical history (SPT+in 84%)	55	Colostrum	3.4	8.3	−5.0	−4.8	1.5	0.0	2.2
[47]	23 women with allergic rhinoconjuntivitis or allergic asthma	Clinical history; ↑IgE	29	0.3 mo milk	1.8	0.0	0.0	0.0	0.0	0.0	0.0
[47]	20 women with atopic dermatitis	Hanifin criteria	29	0.3 mo milk	−0.9	0.0	0.0	0.0	0.0	0.0	0.0
[48]	17 atopic women	Clinical history	17	1 mo milk			−20.0*†			−25.0*†	−21.4*†
[49]	53 atopic women	Clinical history; ↑IgE; SPT+	57	1 mo milk	−17.1*	−27.3*	−10.5*	−13.3*	Lower‡		
[50]	63 women with bronchial asthma+ atopic dermatitis	Clinical history	14	1 mo milk	−6.5	8.3	−8.7	−1.7	16.4	−35.3*	−5.9
[50]	58 women with bronchial asthma+ allergic rhinitis	Clinical history	14	1 mo milk	−9.3	8.3	−10.9	−5.0	20.9	−35.3*	−7.8
[50]	23 women with bronchial asthma	Clinical history	14	1 mo milk	−7.4	0.0	−17.4	−3.3	20.0	−41.2*	−1.9
[51]	20 atopic women	Clinical history	20	1.25 mo milk	−7.7	0.0	−9.3	−15.2*	−1.9	0.0	−24.1
[52]	43 allergic women	Clinical history	51	2.3 mo milk	1.5		0.0	−8.8	4.6	11.1	
[53]	20 atopic women	Clinical history	20	3 mo milk	−7.5	−25.0*		−6.3	8.4	25.0	43.5*
[54]	168 allergic women	Clinical history	107	3 mo milk	4.5	−10.0	0.0	−5.1	2.0	−16.7	−9.1
[46]	60 atopic women	Clinical history (SPT+in 82%)	36	3 mo milk	3.9	0.0	0.0	5.3	0.0	0.0	−11.5

*Statistically significant difference ($P<0.05$) between the values found in atopic and non-atopic women.

†Calculated from a graph.

‡Data not given and so percentage difference could not be calculated.

Where there is no entry for a fatty acid, that fatty acid was not reported.

mo, month; SPT, skin prick test; PUFA, polyunsaturated fatty acid.

Table 5. PUFA concentrations in cord blood of neonates with a high risk of atopy, expressed as a percentage difference from the concentrations found in cord blood from matched controls

Reference	Subjects	Atopy criteria	Controls (*n*)	Sample	LA (18 : 2n-6)	DGLA (20 : 3n-6)	AA (20 : 4n-6)	ALA (18 : 3n-3)	EPA (20 : 5n-3)	DHA (22 : 6n-3)
[55]	33 neonates from allergic mothers	Clinical history; ↑IgE	35	Serum phospholipids	−5.8	9.6*	10.5*		25.0*	14.3*
[56]	25 neonates from allergic mothers	Clinical history; ↑IgE	22	Serum phospholipids	−11.0	7.4	13.1*	25.0*	19.5*	20.8*
[57]	50 neonates with family history of atopic disease	Clinical history	50	Plasma phospholipids	0.3	−0.2	−3.6	−16.7	5.7	−2.2
[57]	11 neonates with paternal atopic disease	Clinical history	50	Plasma phospholipids	6.4	0.7	−16.7*	41.7	68.4	−18.4*
[57]	50 neonates with family history of atopic disease	Clinical history	50	Plasma triacylglycerols	−7.5	−4.6	−8.8	0.0	−3.6	0.3
[57]	11 neonates with paternal atopic disease	Clinical history	50	Plasma triacylglycerols	−19.7*	−20.7*	−33.3*	−22.9	21.4	1.3
[57]	50 neonates with family history of atopic disease	Clinical history	50	Cholesteryl esters	−7.6	3.1	−8.0	−35.7*	17.4	0.0
[57]	11 neonates with paternal atopic disease	Clinical history	50	Plasma cholesteryl esters	−11.3	0.0	−28.4*	0.0	65.2	−2.4
[58]	32 neonates with at least one parent with atopic disease	Clinical history	30	Mononuclear cell phospholipids	6.3		−42.2*			
[57]	50 neonates with family history of atopic disease	Clinical history	50	RBC phospholipids	0.6	6.6	−1.2	0.0	0.0	0.2
[57]	11 neonates with paternal atopic disease	Clinical history	50	RBC phospholipids	1.9	1.3	−8.3	0.0	53.9*	−1.8

*Statistically significant difference ($P < 0.05$) between the values found in atopic and non-atopic children.
Where there is no entry for a fatty acid, that fatty acid was not reported.
RBC, red blood cell; PUFA, polyunsaturated fatty acid.

Table 6. PUFA concentrations in breast milk received by children who became atopic, expressed as percentage difference from concentration found in matched controls

Reference	Subjects	Atopy criteria	Controls (*n*)	Sample	LA (18 : 2n-6)	GLA (18 : 3n-6)	DGLA (20 : 3n-6)	AA (20 : 4n-6)	ALA (18 : 3n-3)	EPA (20 : 5n-3)	DHA (22 : 6n-3)
[49]	24 atopic children < 18 mo	SPT+	15	Colostrum						16.7	0.0
[59]	17 atopic children < 1 year	Sampson criteria	60	Colostrum	−3.2		−11.1	−3.6	−7.5	10.0	−9.0
[59]	31 children with allergen sensitization at 1 year†	↑IgE	32	Colostrum	−1.7		−10.5	−4.7	−7.4	−9.1	−13.9
[59]	8 children with sensitization against cows' milk at 1 year†	↑IgE	54	Colostrum	37.7*		22.9	1.2	16.7	−9.1	−3.9
[46]	29 children with food atopic dermatitis at 6 mo	SPT+	148	Colostrum	−8.1	−8.3	−3.5	8.3	2.9	40.0	25.0*
[46]	9 children with aero atopic dermatitis at 6 mo	SPT+	168	Colostrum	7.4	25.0	10.5	11.7	4.3	16.7	11.1
[46]	16 children with food atopic dermatitis at 2 years	SPT+	130	Colostrum	10.1	−15.4	6.9	10.0	7.5	0.0	18.2
[46]	30 children with aero atopic dermatitis at 2 years	SPT+	116	Colostrum	8.5	−7.7	1.7	6.7	9.1	20.0	20.9*
[49]	21 children with atopic dermatitis < 18 mo	SPT+	61	1 mo milk						−14.3*	−20.0
[60]	13 children with atopic dermatitis < 1 year	Hanifin criteria	21	1 mo milk	−8.3		−6.1	−8.3	−24.9	−33.3*	
[61]	22 atopic children < 1 year	Clinical history; SPT+	30	3 mo milk	−2.2	12.5	16.1*		−18.7*		
[49]	23 children with atopic dermatitis < 18 mo	SPT+	61	3 mo milk						−25.0	−24.0
[53]	20 atopic children < 3 mo	Clinical history; SPT+	20	3 mo milk	6.2	14.3		10.0	−4.0	0.0	−10.0
[62]	11 children with atopic dermatitis < 1 year	Clinical history; SPT+	27	3 mo milk	−11.6*						
[63]	25 children with atopic dermatitis at 2–6 mo	Clinical history	22	2–6 mo milk	25.5*	−16.7	−28.6*	−20.0	33.3*	−25.0	−16.7
[64]	23 atopic children < 6 mo	Clinical history; SPT+; ↑IgE	18	2–8.8 mo milk	8.3	−14.3	−25.0*	−16.7	28.6	0.0	−33.3*
[65]	6 children with atopic dermatitis at 1–6 mo	Clinical history; SPT+	19	5.6 mo milk	12.5	28.6	−3.9	0.0	27.1	33.3	44.0

*Statistically significant difference ($P < 0.05$) between the atopic and non-atopic values.

†Infants showed no clinical symptoms.

Where there is no entry for a fatty acid, that fatty acid was not reported.

mo, month; SPT, skin prick test; PUFA, polyunsaturated fatty acid.

consumed by infants who went on to develop atopy, although none of the differences were significant and there are a similar number of studies reporting (non-significantly) higher GLA and DGLA concentrations (Table 6). No significant differences in AA content of colostrum consumed by infants who went on to become atopic or non-atopic have been reported although several studies report a trend for higher AA (Table 6). With regard to n-3 PUFAs, the situation is similar: studies report lower or higher concentrations in colostrums consumed by infants who went on to develop atopy, but for the most part the differences are not significant (Table 6). Interestingly, the only significant differences seen were for a higher DHA concentration in the group who went on to become atopic.

With regard to mature breast milk, studies are of two types. Some studies compared the fatty acid composition of breast milk being consumed by atopic and non-atopic infants [53, 63–65]. Other studies compared the fatty acid composition of breast milk consumed by infants who went on to become atopic with that of infants who did not become atopic [49, 60–62, 66, 67].

When looking at breast milk consumed by atopic compared with non-atopic infants, the findings are fairly inconsistent with no obvious common pattern (Table 6). One study reported significantly higher LA in breast milk consumed by infants with atopic eczema; there are also other studies reporting non-significantly higher LA in breast milk consumed by such infants (Table 6). Data for GLA are inconsistent with no significant differences reported and trends to both lower and higher concentrations in breast milk consumed by atopic infants (Table 6). DGLA is reported to be significantly lower in breast milk consumed by infants with atopy in two studies (Table 6). There are several reports of lower AA concentration in breast milk consumed by atopic infants, but none of these is significant. ALA concentrations are generally reported to be higher in breast milk consumed atopic infants, with few significant differences from breast milk fed to non-atopic infants (Table 6). EPA concentration is reported to be lower or higher in breast milk consumed by atopic infants, but with no significant differences from that consumed by non-atopic infants (Table 6). DHA is reported to be significantly lower in breast milk consumed by atopic infants in one study but there are other studies reporting non-significantly higher and lower concentrations (Table 6).

With regard to breast milk consumed by infants who later became atopic, patterns tend to be more consistent, although many of the differences observed are not significant (Table 6). One study reports significantly higher DGLA and lower ALA concentrations while other studies report significantly lower EPA or trends towards lower EPA and DHA concentrations in breast milk consumed by infants who later developed atopy (Table 6). Laitinen et al. [62] reported significantly lower LA in breast milk consumed by infants who became atopic by age 1 year; they did not report values for other n-6 PUFAs or for any n-3 PUFAs, but they comment that the latter were not different between milk consumed by infants who became or who did not become atopic at 1 year of age. Wijga et al. [66] report prevalences of eczema (at age 1 year and 4 year), asthma (at age 4 year) and persistent symptoms (eczema at 1 year and asthma and or eczema at 4 year) according to breast milk fatty acid composition and according to whether the mother had allergy or not. They found that prevalences were not different according to breast milk fatty acid composition if the mother did not have allergy. However among the group whose mothers had allergy there was some impact of breast milk fatty acid composition. Prevalences of all outcomes tended to be higher if breast milk LA was high or if breast milk AA was low, although the differences in prevalences were not statistically significant. Prevalences of all outcomes tended to be higher if breast milk ALA, EPA, DHA, total n-3 PUFAs or ratio of n-3 to n-6 was low; in several cases the difference in prevalence reached statistical significance. For example, 13.5% of infants who were suckled on breast milk containing a low proportion of DHA were asthmatic at year 4, whereas only 4.8% of infants who were suckled on breast milk containing a high proportion of DHA were asthmatic at year 4. In contrast to these findings of an association with breast milk fatty acid composition, Oddy et al. [67] found that there were no differences between the fatty acid composition of breast milk at 6 weeks or 6 months consumed by infants who went on to become atopic [skin prick test (SPT) positive] or manifest atopic eczema (SPT positive plus clinical signs of eczema) at either 6 months or 5 years of age, although they do not give details of individual fatty acids. Additionally, total n-6 PUFAs and n-3 PUFAs and the ratio of n-6 to n-3 PUFAs were not different [67].

Polyunsaturated fatty acid concentrations in serum/plasma of atopic infants and children

Serum and plasma lipids represent transport pools involved in the movement of fatty acids (and other lipids like cholesterol and some fat soluble vitamins) between body compartments. This will include the delivery of fatty acids to immune cells. The fatty acid composition of serum or plasma lipids is influenced by diet and by metabolic processes, including those that control the fatty acid composition of the components. These may be influenced by atopic disease. Measurements of the fatty acid composition of whole blood will include serum lipids and cellular contents. A difference in the fatty acid composition of serum or plasma between atopic and non-atopic children would indicate a difference in exposure of body compartments to fatty acids, and may reflect diet, metabolism or the disease process.

Studies have determined the fatty acid composition of total blood, plasma or serum or of specific lipid fractions, most frequently phospholipids, in relation to childhood atopy ([36, 49, 53, 55, 65, 68–76]; Table 7). As with breast milk, studies are of two types. Some studies compared the fatty acid composition of serum or plasma from atopic and non-atopic infants and children [36, 49, 53, 65, 69, 71–76]. Other studies compared the fatty acid composition of cord blood between infants who went on to become atopic with that of infants who did not become atopic [49, 55, 68–70].

Five studies reported the fatty acid composition of cord lipids and sought to relate this to subsequent development of atopy (Table 7). Two of these studies reported higher LA and lower DGLA and AA concentrations in cord blood of infants who went ion to become atopic, with one also reporting lower DHA (Table 7). These studies did not report on EPA and one did not report DHA. Three other studies reported a trend for lower EPA (Table 7).

One study investigated the fatty acid composition of serum phospholipids over the first year of life in a group of infants who became atopic by one year of age [69]. At the earliest time-points measured (1 and 3 months) serum phospholipids had markedly lower concentrations of DGLA and AA than seen in infants who remained non-atopic at 1 year of age. However this difference diminished over time such that it was no longer significant at 6 months, although the trend was still apparent then, and there were no differences at 9 months and 1 year. This study did not find significantly different LA concentrations at any time-point and did not report concentrations of n-3 PUFAs. One other study reported the fatty acid composition of serum phospholipids at 3 months of age in children who became atopic by 18 months of age [49]. This study failed to find significant differences from controls, although there was a trend for less EPA and DHA.

A number of studies report the fatty acid composition of plasma or serum lipids in atopic infants or children (aged 3 months to 17 years) (Table 7). While the pattern of results found is not consistent, a few studies report significantly higher LA and lower AA, EPA and DHA concentrations in atopic individuals (Table 7). Several studies report markedly lower GLA concentrations in atopy (Table 7). One study reported higher EPA and a tendency to higher DHA in the atopic group (Table 7). Bolte et al. [76] related the fatty acid composition of serum cholesteryl esters from 526 children aged 8–11 years with prevalence of wheeze, asthma, bronchial hyper-responsiveness (BHR) and lung function. Children with wheeze, doctor-diagnosed asthma and/or BHR had significantly lower LA and higher AA than children not affected by these outcomes. Multivariate analysis revealed that high LA in serum cholesteryl esters was negatively associated with wheeze and current asthma and with better lung function and that high AA in serum cholesteryl esters was positively associated with wheeze, frequent asthma attacks and current asthma and with poorer lung function. These findings suggest a protective effect of LA and a harmful effect of AA. EPA in cholesteryl esters was not significantly associated with wheeze, asthma or lung function [76]. Bolte et al. [76] did not report levels of DHA or the influence of DHA.

Polyunsaturated fatty acid concentrations in cells from atopic infants and children

The fatty acid composition of cells is mainly reflective of their membrane phospholipids and will be influenced by availability of fatty acids from transport lipids in the bloodstream. As indicated above these will be influenced by diet and by metabolism; the fatty acid composition of cells and cell membranes will also be influenced by cellular metabolism. This may, in turn, be influenced by disease.

There are some studies reporting the fatty acid composition of various cell types in atopic infants and children compared with the same cells from non-atopic controls [65, 75, 77, 78] (Table 8). Cell types reported include red blood cells, cheek buccal cells, blood mononuclear cells and purified blood T cells. Studies report both higher and lower LA in cells from atopic individuals, with other studies reporting significantly lower concentrations of GLA and AA, although no significant effect on DGLA content has been reported (Table 8). With regard to n-3 PUFAs, studies report significantly higher or lower EPA, but two studies report significantly lower DHA (Table 8).

Summary of these data

In general, the findings are inconsistent with no really clear pattern of altered status of a particular fatty acid or a particular fatty acid family (Tables 4–8). With regard to breast milk from atopic women, there may be less of the n-6 PUFA DGLA and AA and less of the n-3 PUFA EPA than seen for non-atopic women. However, breast milk LA is probably little different between atopic and non-atopic women. Measurements made in umbilical cord blood of neonates at high risk of atopy (because of maternal atopy) are too inconsistent to draw any firm conclusions, although again it appears that there is little impact on LA. Some studies report that LA is higher, and EPA and DHA are lower, in breast milk consumed by infants who go on to develop atopy in infancy, although again findings are not consistent. Umbilical cord lipids from neonates who go on to develop atopy in early childhood appear to contain lower than normal amounts of DGLA, AA and perhaps also EPA and DHA, and also a higher amount of LA than normal. Likewise serum collected in early infancy contains lower amounts of DGLA and AA if

Table 7. PUFA concentrations in whole blood, serum or plasma from atopic children, expressed as percentage difference from the concentration found in matched non-atopic controls

Reference	Subjects	Atopy criteria	Controls (*n*)	Sample	LA (18 : 2n-6)	GLA (18 : 3n-6)	DGLA (20 : 3n-6)	AA (20 : 4n-6)	ALA (18 : 3n-3)	EPA (20 : 5n-3)	DHA (22 : 6n-3)
[68]	9 children with atopic dermatitis	↑IgE	107	Cord serum PC	30.0*		−17.0*	−17.0*			−15.0*
[69]	13 atopic children < 1 year	Clinical history	44	Cord blood PL	46.7		−52.0*	−28.0*			
[55]	25 children with allergy < 6 years	Clinical history	43	Cord blood PL	−1.2		7.6	2.9		−10.0	9.1
[49]	19 atopic children < 18 mo	SPT+	40	Cord serum PL	−0.2		−7.7	−5.6		−15.2	−8.4
[70]	35 atopic children < 3 years	SPT+	35	Cord plasma	−14.3	−5.5	0.5	0.1	−11.1	−17.8	−5.5
[69]	13 atopic children < 1 year	Clinical history	44	Serum PL, 1 mo	12.0		−76.5*	−45.5*			
[69]	13 atopic children < 1 year	Clinical history	44	Serum PL, 3 mo	6.3		−60.0*	−41.7*			
[69]	13 atopic children < 1 year	Clinical history	44	Serum PL, 6 mo	5.6		−11.1	−16.7			
[69]	13 atopic children < 1 year	Clinical history	44	Serum PL, 9 mo	8.6		0.0	4.0			
[69]	13 atopic children < 1 year	Clinical history	44	Serum PL, 1 year	5.3		−4.6	7.1			
[71]	17 children with atopic bronchial asthma < 9 years	Clinical history; ↑IgE	10	Serum PL	25.4*	−50.0	−1.7	−10.7			
[49]	16 atopic children < 18 mo	SPT+	35	Serum PL, 3 mo	−0.6		−5.3	−1.8		−17.9	−6.9
[53]	20 atopic children < 3 mo	SPT+with atopic eczema or food allergy	20	Serum PL, 3 mo	0.0	−25.0*	0.0	6.2	0.0	9.4	−8.3
[65]	6 children with atopic dermatitis < 6 mo	Clinical history; SPT+	19	Serum PL	4.7	−50.0*	−19.0	7.5	15.8	60.7*	23.0
[53]	20 atopic children < 3 mo	SPT+with atopic dermatitis or food allergy	20	Serum TAG, 3 mo	13.1*	16.7	−8.7	21.0	−18.5	4.6	−9.8
[71]	17 children with atopic bronchial asthma < 9 years	Clinical history; ↑IgE	10	Serum CE	17.7*	−12.1	−13.4	−19.2*			
[53]	20 atopic children < 3 mo	SPT+with atopic dermatitis or food allergy	20	Serum CE, 3 mo	2.2	17.5	0.0	5.8	−10.5	−13.7	−24.1*
[36]	126 children (3–18 years) with atopic dermatitis	Clinical history	126	Serum CE	0.5					−9.0*	−7.3*
[36]	145 children (3–18 years) with allergic rhinitis	Clinical history	145	Serum CE	−0.8					1.7	3.0
[36]	47 children (3–18 years) with asthma	Clinical history	47	Serum CE	0.5					5.1	−6.1*
[72]	51 children (3–10 years) with atopic dermatitis	Clinical history	30	Total plasma	−5.1	−12.5	−6.9	−0.8	−10.5	6.7	2.9
[73]	35 children (2–17 years) with atopic dermatitis	Clinical history; ↑IgE; sensitisation	31	Total serum	10.4	−42.6*	−30.2*	−12.9			

[73]	35 children (2–17 years) with asthma or allergic rhinitis	Clinical history; ↑IgE; sensitisation	31	Total serum	12.0	−25.8	−20.6	−4.5			
[74]	15 children with atopic dermatitis <7 years	Hanifin index; ↑IgE	6	Total serum	3.3	−55.8*	0.0	−19.0			
[74]	8 children with atopic rhinitis or asthma <7 years	Hanifin index; ↑IgE	6	Total serum	−29.9	−46.5*	−42.9	−5.7			
[75]	11 children (1–16 years) with allergic asthma	Clinical history; SPT+; ↑IgE	10	Serum PL	−5.9	18.8	6.3	9.0	6.3	50.0*	−1.1

*Statistically significant difference ($P<0.05$) between the values found in atopic and non-atopic children.
Where there is no entry for a fatty acid, that fatty acid was not reported.
CE, cholesteryl ester; Ig, immunoglobulin; mo, month; PC, phosphatidylcholine; PL, phospholipid; SPT, skin prick test; TAG, triglyceride; PUFA, polyunsaturated fatty acid.

Table 8. PUFA concentrations in cells from atopic children expressed as percentage difference from the concentration found in cells from matched non-atopic controls

Reference	Subjects	Atopy criteria	Controls (*n*)	Sample	LA (18 : 2n-6)	GLA (18 : 3n-6)	DGLA (20 : 3n-6)	AA (20 : 4n-6)	ALA (18 : 3n-3)	EPA (20 : 5n-3)	DHA (22 : 6n-3)
[77]	24 children (2–9 years) with atopic dermatitis	↑IgE; SPT+; RAST+	15	RBC phospholipids	14.8*	−51.0*	11.3	1.0	−16.7	−38.8*	0.2
[78]	26 children (6 mo–12 years) with atopic dermatitis/ dermatitis syndrome	SCORAD index†	10	RBC phospholipids	8.3*		31.3	−10.0*		285.7	−47.2*
[75]	11 children (1–16 years) with allergic asthma	Clinical history; SPT+; ↑IgE	10	MNC phospholipids	17.9	0.00	−0.6	−1.9	37.5	50.0*	25.8
[78]	26 children (6 mo–12 years) with atopic dermatitis/ dermatitis syndrome	SCORAD index	10	T cell phospholipids	−24.3*		170.6	−47.3*		−7.7	−70.3*
[65]	6 children with atopic dermatitis <6 mo	Clinical history; SPT+	19	Cheek cell phospholipids	17.5*	−33.3	−16.5	6.8	36.4	38.5	7.9

*Statistically significant difference ($P<0.05$) between the values found in atopic and non-atopic children.
†8 of 13 subjects were SPT+and RAST+.
Where there is no entry for a fatty acid, that fatty acid was not reported.
MNC, mononuclear cells; mo, month; RBC, red blood cells; SPT, skin prick test; PUFA, polyunsaturated fatty acid.

the infants go on to develop atopy than if they do not. Plasma, serum or cell lipids from children with atopic disease contain less GLA, and possibly less AA, than in non-atopic controls, but no clear pattern of difference for n-3 PUFAs is apparent, although some studies do report lower amounts of EPA and DHA than normally seen. Taken together these data clearly do not support the hypothesis that atopy is somehow associated with a high exposure to, and status of, n-6 PUFAs. There is no strong evidence of higher LA levels being associated with atopy, although there are isolated studies that do report this. If anything, there is evidence of lower levels of GLA, DGLA and AA being associated with atopy. Clearly this observation is in opposition to the ideas of Hodge et al. [4] and Black and Sharp [5]. These lower levels may represent a poor ability to convert LA to GLA, DGLA and AA in atopic individuals or they may represent increased utilization of these fatty acids in atopic disease. Clearly more needs to be understood about PUFA metabolism in atopic disease. One effect of low AA availability might be to restrict production of eicosanoid mediators, including those that play a role in resolving allergic inflammation. This may explain why low AA levels are associated with atopy.

Observations of lower amounts of EPA and DHA in breast milk from atopic women, in cord blood lipids of neonates who go on to develop atopy in infancy, in breast milk consumed by infants who go on to develop atopy and in blood lipids of children with atopic disease, accord with the idea that a low n-3 PUFA status is associated with atopic disease [4, 5]. However these observations are not consistently made. One reason may relate to dietary differences among the women and children studied, such as consumption or avoidance of seafood and use of infant formulas containing DHA. Thus, although there is some evidence that there is a low n-3 PUFA status in atopic disease, this evidence is not sufficiently strong to be certain about this relationship. This lack of certainty about the presence of fatty acid abnormalities in atopic disease means that dietary interventions that may benefit cannot be easily developed. The generally held view that atopy is associated with excess n-6 PUFAs has focused attention on the use of long chain n-3 PUFAs to bring about clinical improvement.

Intervention with long chain n-3 polyunsaturated fatty acids

If an inadequate supply of n-3 PUFAs, as seen by lower long chain n-3 PUFA status in various lipid pools, is somehow causally associated with atopy, then providing these fatty acids should bring about clinical improvements. A number of studies using fish oil supplementation as a means to increase n-3 PUFA status have been conducted in subjects with asthma, frequently reporting lung function as an outcome. Most of these studies have been conducted in adults, although there are two such studies in children [79, 80]. A meta-analysis covering 26 studies (both randomized, placebo-controlled and others) concluded that 'no definitive conclusion can yet be drawn regarding the efficacy of n-3 fatty acid supplementation as a treatment for asthma in children and adults' [81], although this conclusion was based largely upon studies in adults. Hodge et al. [79] randomized 39 Australian asthmatic children aged 8–12 years to an n-3 PUFA group or an n-3 PUFA group for 6 months; the latter group used canola oil and canola oil-based margarines (canola oil contains ALA), were encouraged to eat fish and took fish oil capsules. Daily intakes of EPA and DHA from the capsules were 0.72 and 0.48 g, respectively. Lung function (spirometry: torced vital capacity and forced expiratory volume at one second (FEV_1)), airway responsiveness (fall in FEV_1 in response to histamine) and asthma severity were not altered in the n-3 PUFA Group, although blood eosinophil numbers fell (by 19% at 3 months and by 29% at 6 months) and *ex vivo* production of TNF-α by blood mononuclear cells tended to decline (32% reduction at 6 months) [79]. A second study randomized Japanese asthmatic children aged 4–17 years (mean about 10 years) to control (olive oil) or fish oil, both provided in capsules, for 10 months [80]. The fish oil provided 500 mg EPA and 215 mg DHA per day. The outcomes reported were asthma score (reported monthly) and airway responsiveness to acetylcholine (fall in FEV_1). Asthma score did not change in the control group but was significantly improved in the fish oil group. Likewise, the concentration of acetylcholine required to cause a 20% fall in FEV_1 was not altered in the control group but was significantly increased (by almost 100%) in the fish oil group, indicating improved airway responsiveness [80]. This study is indicative that long chain n-3 PUFAs can bring about clinically relevant improvements in children suffering from asthma. Why this was not seen by Hodge et al. [79] using a higher dose of n-3 PUFAs is not clear.

Because atopy may be determined in early life or even *in utero* [82–86], long chain n-3 PUFA intervention once disease is established may be too late to be a genuine benefit. It is possible that fatty acids may have a stronger impact at the time of sensitization and when Th1 and Th2 immune responses are maturing rather than later on. Evidence that early exposure to long chain n-3 PUFAs may alter T cell cytokine profiles later on comes from the observation that $2\frac{1}{2}$-year-old children who had been breastfed for the first 4 months of life by mothers with a high intake of n-3 PUFAs had a significantly higher production of IFN-γ upon stimulation of whole blood compared with a control group with low maternal n-3 PUFA intake during lactation [87]. This observation suggests long-term immunologic effects of early exposure to long chain n-3 PUFAs.

One study that links increased consumption of long chain n-3 PUFAs in early infancy to clinical outcome is the Childhood Asthma Prevention Study. In this study, infants at risk of developing asthma received fish oil providing about 150 mg EPA+DHA/day or placebo from age 6 months. Although there was no effect of fish oil on sensitization to inhaled or ingested allergens, determined by SPT at 18 months of age, there was a significantly decreased prevalence of wheeze ever and wheeze for >1 week and a trend for decreased visits to the doctor for wheeze in the fish oil group [88]. There was no effect of fish oil on other wheeze indicators, diagnosed asthma, dermatitis or medication use. Further analysis of data at this age revealed that higher plasma levels of total n-3 PUFAs were associated with reduced wheeze, visits to the doctors because of wheeze, cough during sleep and bronchodilator use [89]. There was no effect of fish oil on total serum IgE at 18, 36 or 60 months of age [89–91]. At 36 months of age there was no effect of fish oil on prevalence of asthma, wheeze, atopic dermatitis or sensitization to ingested or inhaled allergens, although fish oil decreased the prevalence of cough and atopic cough [90]. At 60 months of age there was no effect of fish oil on prevalence of asthma, prevalence or pattern of wheeze, prevalence of atopy or atopic dermatitis, sensitization to inhaled allergens, or lung function [91, 92]. Thus, the follow-up of these infants to 5 years of age reveals that the early protective effect of n-3 fatty acids seen at 18 months of age is lost later on.

Although intervention with long chain n-3 PUFAs in the neonatal period may alter cytokine profiles [87] and possibly disease outcome in later infancy [88–90], the *in utero* period may offer an even greater opportunity to derive benefit from increased n-3 PUFA exposure. The effects of increased maternal consumption of fish oil (providing 1.1 g EPA+2.2 g DHA/day) from week 20 of pregnancy until delivery upon cord blood cytokine levels and production in response to stimulation and upon later disease outcome were reported by Dunstan et al. [93, 94] in a randomized, placebo-controlled study in women whose babies would be at increased risk of allergic disease. Cord plasma from the fish oil group was less likely to exhibit a detectable level of IL-13 and plasma IL-13 concentrations were significantly lower in the fish oil group [93]. Cord plasma IL-13 concentrations were inversely related to cord blood red cell long chain n-3 PUFA content, especially that of DHA [93]. Cord blood mononuclear cell cytokine (IFN-γ, IL-13, IL-10, IL-5) responses to stimulation by various allergens were lower in the fish oil group, although this was significant only for IL-10 production in response to house dust mite or cat hair extract [94]. However, the clinical implications of altered cord blood cytokine levels and cytokine responses are not clear because findings in the literature are not consistent. For example, purified cord blood T cells from neonates who went on to develop atopy over the first 12 months of life produced more IL-13 than those from neonates who went on to remain non-atopic [95]. These authors suggested that increased IL-13 production by cord blood T cells may be a useful marker of risk for subsequent atopic disease, perhaps because IL-13 promotes IgE production. In contrast, Prescott et al. [96] reported that purified cord mononuclear cells from neonates who went on to develop atopy produced lower amounts of several cytokines including IL-4, IL-10, IL-13 and IFN-γ than those from neonates who remained non-atopic. In the study of Dunstan et al. [93, 94] clinical outcomes in the infants were reported at one year of age [94]. Infants of mothers in the fish oil group were less likely to be sensitized to a range of allergens, determined by SPT, in particular to egg, and were significantly less likely to have severe atopic dermatitis. Thus, very early intervention with long chain n-3 PUFAs does appear to affect fetal T cell reactivity and this is associated with improved clinical outcome at 1 year of age. It is not known how long lasting the effect is. Clearly these findings require confirmation.

Conclusion

Under most conditions the main fatty acid precursor of eicosanoids is the n-6 PUFA AA. AA-derived eicosanoids play many roles in sensitization to allergens and in allergic inflammation. However, they frequently have opposing actions and some appear to be protective, perhaps through induction of inflammation resolving processes. The long chain n-3 PUFAs inhibit AA incorporation into cell membranes and inhibit AA metabolism to eicosanoids. Long chain n-3 PUFAs also give rise to less potent inflammatory eicosanoids and to anti-inflammatory resolvins. There is a hypothesis causally linking excess intake of n-6 PUFAs to atopic disease [4, 5]. This hypothesis assumes that a higher n-6 PUFA status would be associated with atopy and that there would be a low n-3 PUFA status. However, measurements of fatty acid composition do not provide a clear picture that such fatty acid abnormalities exist in atopy with no really clear pattern of altered status of a particular fatty acid or a particular fatty acid family. There are few reports of elevated LA in atopy. However some studies report lower amounts of the n-6 PUFAs GLA, DGLA and AA and of the n-3 PUFAs EPA and DHA in atopy, although observations on this are not consistent. Taken together these data clearly do not support the hypothesis that atopy is somehow associated with a high exposure to, and status of, n-6 PUFAs. Observations of lower amounts of EPA and DHA accord with the idea that a low n-3 PUFA status is associated with atopic disease. However these observations are not consistently made. The generally held view that atopy is associated with excess n-6 PUFAs has focused attention on the use of long chain n-3 PUFAs to

bring about clinical improvement. An intervention study of fish oil in children with asthma reported benefits on disease severity and lung function. An intervention study in infants demonstrated some clinical benefits of n-3 PUFAs early on but these were lost by 36 and 60 months of age, while a study in pregnant women showed effects on neonatal T cell phenotype with some benefits on atopic sensitization at one year and on severity of atopic dermatitis. The observation that there may be low AA status in atopy suggests that fish oil intervention, which targets AA status and metabolism, may not be ideal and that a combination of fish oil with some longer chain n-6 PUFAs may be more efficacious. Clearly more needs to be known about fatty acid metabolism in atopy and about the association between fatty acid availability, generation of specific eicosanoid mediators, and inflammatory responses.

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