

Editorial

Are human milk polyunsaturated fatty acids (PUFA) related to atopy in the mother and her child?

K. Duchén

Division of Pediatrics, Department of Health and Environment, Linköping University Hospital, Linköping, Sweden

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Karel Duchén
Department of Health and Environment
Division of Pediatrics
Faculty of Health Sciences
S-581 65 Linköping
Sweden

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Polyunsaturated fatty acids (PUFA) and atopy

In this issue of *Allergy*, the composition of polyunsaturated fatty acids (PUFA) in milk from atopic and nonatopic mothers is reported (Kankaanpää et al., pp. 633–638, this issue). The significance of the n-6 and n-3 PUFA in maternal milk for the development of atopic disease in the children is also discussed. Polyunsaturated fatty acids are carbohydrate chains with different numbers of carbon moieties and different numbers of double bonds. The most important are oleic acid, an 18-carbon chain with a double bond in the ninth carbon from the end (18:1 n-9); linoleic acid (LA, 18:2 n-6); and α -linolenic acid (LNA, 18:3 n-3). These fatty acids are metabolized to 20–22 carbon chains with increasing numbers of double bonds, long-chain polyunsaturated fatty acids (LCPUFA), through a complicated metabolic pathway. Linoleic acid and LNA are the precursors of γ -linoleic acid (GLA, 18:3 n-6), arachidonic acid (AA 20:4 n-6), eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3). These LCPUFA are important factors in the synthesis of prostaglandins and leukotrienes, and they also are major components in cellular membranes with influence on membrane fluidity, receptor activity, and other membrane functions (1). Man can synthesize oleic acid (18:1 n-9), but not LA (18:2 n-6) or LNA (18:3 n-3). Thus, LA and LNA are also called the essential polyunsaturated fatty acids (EFA) and have to be ingested in the diet.

The relationship between PUFA and atopic disease has been controversial for several decades since Hansen (2) proposed an abnormal metabolism of essential fatty acids and LCPUFA in atopic disease, as higher levels of LA (C18:2 n-6) and lower levels of γ -linoleic acid (GLA, C18:3 n-6), DHGLA (C20:3 n-6), and AA (20:4 n-6) have been found in the plasma of atopic adults and children, but not in healthy controls. This has been corroborated for the n-6 and the n-3 series by several studies in serum phospholipids (3–8) (Table 1), but not by all studies (9). Disturbances in the PUFA composition of cellular membranes from atopic individuals have been reported more consistently (4, 6, 10–13) (Table 1), even in studies where similar PUFA composition in atopic and nonatopic individuals have been reported in plasma phospholipids (10). The results differ according to the type of cell membrane studied but largely agree with particularly higher LA and lower n-6 LCP and n-3 LCP also in the cell-membrane phospholipids of atopic as compared to nonatopic children and adults (Table 1).

Development of allergy in early infancy

During the last decade, the picture of a dual immune response to foreign antigens has emerged, based on different patterns of cytokine production by activated T-helper cells (14). The Th1-like cells produce preferentially IFN- γ and IL-2, while Th2-like cells secrete IL-4,

Table 1. Levels of LA, LNA, n-6 LCPUFA, and n-3 LCPUFA in different lipid fractions of atopic as compared to healthy individuals

Study	(year)	n-6 PUFA	n-3 PUFA
Manku et al. (3)	1984	High LA/low LCPUFA	Low LCPUFA
Rocklin et al. (4)	1986§	—	Low LCPUFA
Stranegård et al. (5)	1987§	High LA/low LCPUFA	Low LCPUFA
Oliwiecki et al. (6)	1990§	High LA	—
Leichsenring et al. (7)	1995§	High LA	—
Yu & Björkstén (8)	1998§	—	Low LCPUFA
Rocklin et al. (4)	1986*	High LCPUFA	High LNA
Oliwiecki et al. (6)	1990*	Low LA/low LCPUFA	Low LCPUFA
Biagi et al. (11)	1993*	High GLA/low LCPUFA	Low LCPUFA
Griese et al. (12)	1990**	—	High EPA
Lindskov & Hølmer (10)	1992**	High LA/low LCPUFA	—
Rocklin et al. (13)	1986#	High LA/low AA	—
Rocklin et al. (13)	1986##	Low LA/high AA	—

LA: linoleic acid (18:2 n-6); GLA: γ -linoleic acid (18:3 n-6); AA: arachidonic acid (20:4 n-6); LNA: α -linolenic acid (18:2 n-3); EPA: eicosapentenoic acid (20:4 n-3); LCPUFA: one or more long-chain polyunsaturated metabolites to LA or LNA.

§ Serum phospholipids.

* Erythrocyte membranes.

** Mononuclear cell membranes.

Monocytes.

Lymphocytes.

IL-5, IL-6, IL-10, and IL-13, thus modulating the functional properties of the Th1-like and Th2-like T-cell subsets (14). Th1-like cells promote the production of opsonizing antibodies, macrophage activation, and antibody-dependent cytotoxicity (14). Th2-like cells produce cytokines related to the recruitment and maturation of eosinophils and basophils, important effector cells in the allergic inflammation (15), and IL-4, the cytokine responsible for the Ig switch to IgE in allergic responses (16).

The balance between Th1 and Th2 responses is regulated in a complicated network of stimulatory and inhibitory cytokine signals (14, 17). However, a basic Th2 immunologic response to foreign antigens has been suggested, and *in vitro* studies of human Th-cell subsets has shown an initial IL-4 response upon activation of naive Th cells. IL-4 also stimulates its own production by the activated T cell and promotes maturation toward a Th2-like lymphocyte (17). Ligand–receptor interaction between the antigen-presenting cell (APC) and the naive Th cell stimulates the production of IL-12 by the APC. IL-12 deviates the Th cell toward a Th1-like lymphocyte, but the endogenous IL-4 production is dominant, suppressing the production and effect of IL-12 (17). In contrast to IL-12, APC production of PGE₂ enhances the production of IL-4, and inhibits the production of IFN- γ by activated Th cells, promoting a Th2-like cytokine response (18). This is probably achieved by the inhibitory effect of PGE₂ on the production of IL-12 (19). Thus, the microenvironment influencing the balance between PGE₂ and IL-12 production by the APC during antigen presentation, as macrophages activated by infectious micro-organisms, would influence the polarization of the naive Th cell toward either a Th1 or Th2 immune response.

The Th2-like immune responses related to atopic

disease (14) are also related to a successful pregnancy (20), and Th2-skewed cellular immune responses to common environmental antigens are present already *in utero* (21), suggesting that the Th2-like response is the primary response early in life (17). Prospective studies have shown that human infants synthesize IgE antibodies to both food and inhalant allergens early in life, but only atopic children present sustained IgE responses and develop allergic diseases (22). This further suggests that such primary immune responses later are skewed toward a Th1 response in nonatopic individuals early in life. Factors influencing early immune responses, in combination with genetic factors, could then delay or prevent the Th1-skewing, promoting transient or sustained IgE synthesis with or without symptoms of atopic disease. Breast-feeding influences the PUFA composition of membrane phospholipids in childhood (23), and disturbances in milk PUFA composition may

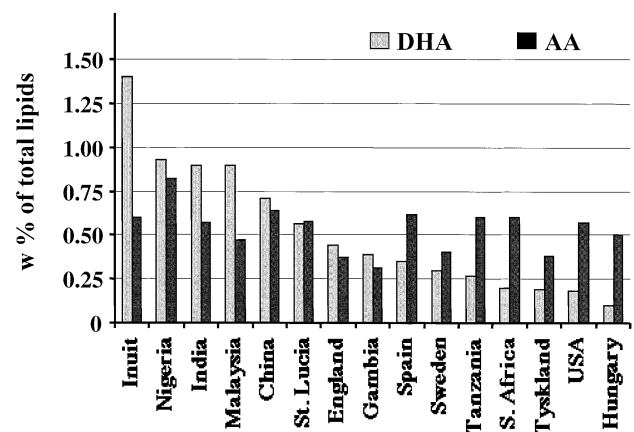


Figure 1. The composition of docosahexaenoic acid (22:6 n-3, DHA) and arachidonic acid (20:4 n-6, AA) in human milk from different countries. Adapted from Ref. 29.

Table 2. Levels of LA, LNA, n-6 LCPUFA, and n-3 LCPUFA in human milk in relation to maternal and infant atopic disease

Study	(year)	n-6 PUFA	n-3 PUFA
<i>In relation to maternal atopy</i>			
Schroten et al. (31)	1992 [#]	—	—
Yu et al. (28)	1998 ^{##}	Low LCPUFA	Low LCPUFA
Duchén et al. (34)	2000 [§]	Low LA/low LCPUFA	Low LNA/low LCPUFA
Thijs et al. (30)	2000 ^{§§}	Low AA	—
<i>In relation to atopic development in children</i>			
Wright & Bolton (32)	1989 [*]	High LA/low LCPUFA	High LNA
Businco et al. (33)	1993 [*]	—	Low LCPUFA
Duchén et al. (34)	2000 ^{**}	—	Low LCPUFA

— no difference; LA: linoleic acid (18:2 n-6); AA: arachidonic acid (20:4 n-6); LNA: α -linolenic acid (18:2 n-3); LCPUFA: one or more long-chain polyunsaturated metabolite to LA or LNA.

[#] Milk samples 13–16 days of lactation.

^{##} Milk samples at 1 month of lactation.

[§] Milk samples at 1 month of lactation.

^{§§} Milk sampling 2–12 weeks of lactation.

^{*} Milk samples 2–8 months of lactation.

^{**} Milk samples at 1 and 3 months of lactation.

influence the PUFA metabolism in infancy toward a dysregulation of arachidonic acid and prostaglandin metabolism in atopic infants.

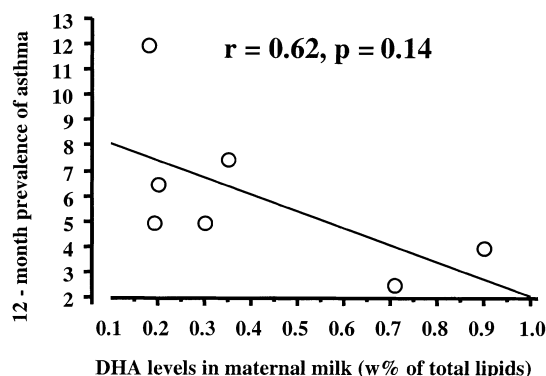
Milk PUFA and atopic disease

The fatty acid composition in human milk differs between mothers of term and preterm babies (24) and is influenced by the maternal food habits, especially in mothers on a fish or vegetarian diet (25). Milk lipid composition varies over a single day (26) and over the lactation period (27, 28). Differences in dietary habits in different countries, however, seem to influence particularly the n-3 LCPUFA, while the n-6 LCPUFA seem to be more stable, probably due to dietary intake of fish, as this is highest in the diet of the Inuit population in Greenland (29) (Fig. 1). The milk levels of LA and LNA are lower in colostrum and increase during lactation, while the LCPUFA are high in colostrum and decrease later in the lactation period, suggesting changes in milk PUFA levels independently of dietary habits (27, 28). This probably explains why some cross-sectional studies, where the milk samples were pooled, report a relation between the PUFA composition in human milk and maternal atopy (30), while others do not (31) (Table 2). Some disturbances in the n-6 milk LCPUFA composition, however, have been previously related to the development of atopic disease in the children (32, 33) (Table 2). Longitudinal studies in recent years have reported lower n-6 and n-3 LCPUFA levels in milk from atopic than nonatopic mothers at 1 month, but not later during lactation (28, 34). Furthermore, lower levels of the n-3 LCPUFA EPA, DPA, and DHA in mature milk have been related to development of atopic diseases in childhood (34, 35) (Table 2). Relatively lower n-3 LCPUFA levels, particularly EPA, in relation to the n-6 LCPUFA and AA were found in milk from mothers of atopic babies even at 1 month of lactation (34).

In this issue of *Allergy*, Kankaanpää et al. (pp.

633–638) report the composition of mature milk in atopic and nonatopic mothers and the relation of milk

A.



B.

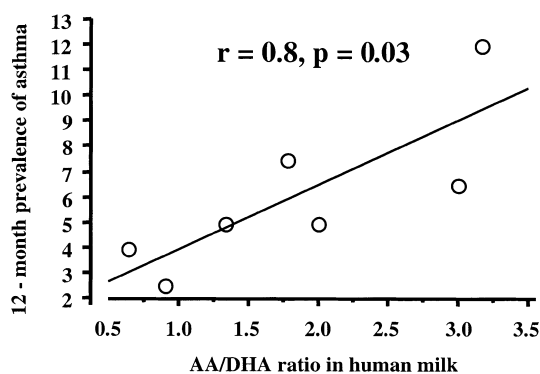


Figure 2. The relationship between milk LCPUFA composition (29) and the 12-month prevalence of asthma bronchiale in China, India, Germany, Sweden, Malaysia, South Africa and USA (from lowest to highest prevalence) according to the video questionnaire in the ISAAC study (48). A) Relationship between milk DHA levels and asthma bronchiale prevalence. B) Relationship between the ratio of AA/DHA in milk and asthma bronchiale prevalence.

PUFA and the development of atopic disease in the children. Milk sampling has been standardized (26–28) at month 3 of lactation. The levels of GLA are lower while DHA levels are higher in the mature milk of atopic than nonatopic mothers. The levels of DHA, although not significantly so, seem, however, to be particularly low in milk from healthy mothers with atopic children. This probably explains the lower DHA levels and the higher n-6/n-3 ratio in milk from all healthy mothers. Thus, the findings in mature milk are largely similar to those previously reported (34). No differences in the milk composition of individual LCPUFA levels were found in relation to the development of allergy in the children. However, this was probably due to the small size of the study groups, as the n-6/n-3 ratio was higher in milk from mothers of atopic babies. This may suggest a relationship between relatively low n-3 levels and atopic disease in the children, once again corroborating previous results (34).

The n-6 or the n-3 PUFA – that is the question

It seems, then, reasonable to conclude that atopic individuals present an abnormal PUFA metabolism in both the n-6 and the n-3 pathways. The findings are not surprising, as both the n-6 and the n-3 PUFA share the same metabolic enzyme chain. The question is whether the n-6 or the n-3 LCPUFA disturbances offer a satisfactory explanatory model. Both the n-6 and the n-3 LCPUFA dietary treatment improve clinical symptoms in inflammatory diseases (36–39). γ -linoleic acid (GLA, 18:3 n-6) and DHGLA have been considered to modulate inflammation, either through inhibition of eicosanoid synthesis or directly through intrinsic action on T-cell functions such as decreased IL-2 production (40) while n-3 PUFA, particularly EPA and DHA (Fig. 1), decreases the synthesis of proinflammatory mediators, such as PGE₂, LTB₄, and IL-1 (38, 41).

The clinical significance of n-6 and n-3 LCPUFA in atopic disease is controversial, however, as clinical improvement after treatment with Epogam®, a n-6 LCPUFA-rich oil from evening primrose, has been reported in patients with atopic eczema (42), while others have not shown such an effect (43). Furthermore, the administration of a GLA (18:3 n-6)-enriched diet only partially corrects the differences between patients with atopic eczema and healthy individuals (3). The explanatory model suggested by Melnik et al. (44), i.e., n-6 LCPUFA metabolism dysfunction, particularly lower AA and DHGLA levels leading to lower PGE₁ and PGE₂ production, has not been corroborated. Later research has, at the contrary, assigned APC production of PGE₂ an important role in the allergic inflammation, as PGE₂ enhances the synthesis of Th2-like cytokines and IgE antibodies, and inhibits the differentiation of Th1-like lymphocytes (17, 18). Enhanced production of

PGE₂ has also consistently been reported by atopic monocytes after *in vitro* stimulation (45), corroborating a dysregulation in the synthesis of PGE₂ and also probably LTB₄ in atopic individuals. Thus, there seems to be a relationship between dysregulation in AA metabolism and eicosanoid metabolism in atopic disease. As the clinical trials with n-6 LCPUFA substitution in allergic patients did not show important clinical efficacy (42, 43), it seems reasonable to conclude that other components of the FA metabolism are important.

Dietary supplementation with n-3 fatty acids has, on the other hand, improved bronchial hyperreactivity in adult asthmatics (46) and clinical symptoms in asthmatic children (47). Furthermore, although methodological differences must be taken into consideration, there seems to be a relationship between geographic variations in maternal milk n-3 LCPUFA levels, particularly DHA (29), and worldwide variations in the prevalence of bronchial asthma in 13–14-year-old children (48). The levels of DHA in milk correlates well, but not significantly so, with the 12-month prevalence of bronchial asthma according to a video questionnaire ($r=0.62$, $P=0.14$). There was no correlation at all between milk AA levels and asthma symptoms ($r=0.13$, $P=0.8$), while the AA/DHA ratio in milk correlated strongly with the prevalence of asthma in adolescents ($r=0.8$, $P<0.05$) (Fig. 2). This suggests that low levels of LCPUFA in milk are related not only to the atopic development, but also to an imbalance in the n-6/n-3 LCPUFA metabolism. Animal studies support this hypothesis, as a diet containing 1.3–3.3% of EPA and DHA given to mice suppressed the production of PGE₂ (49). This is probably explained by increased production of the less biologically active eicosanoids PGE₃ and LTB₅ from EPA, as this n-3 LCPUFA competes with AA for the same enzyme system (38, 41). Relatively lower EPA levels in milk from atopic mothers and serum phospholipids from atopic children than in healthy individuals have been previously reported (34), corroborating this hypothesis.

In conclusion, disturbed PUFA composition in serum phospholipids and membranes from erythrocytes and mononuclear cells are related to atopic disease. Eicosanoids, i.e., AA products, direct immune activity already in pregnancy and infancy toward a Th2-like response. Disturbances in the composition of the n-6 and n-3 fatty acids in milk seem to be related to atopic disease in the mother, while an imbalance in the PUFA metabolism, particularly relatively low n-3 LCPUFA levels, seems to be related to atopic disease in infancy and childhood. Further research is needed to elucidate the nature of this relationship, the relation between milk PUFA and eicosanoid synthesis, and the relation between dietary or milk n-3 LCPUFA and immune responses in pregnancy and early infancy and the development of atopic diseases later in life.

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