PUFA NEWSLETTER

Volume 7 Issue 2

June 2003 Contents

Editorial

Maternal Health, Infant Nutrition, and More

The June issue of the *PUFA Newsletter* highlights emerging research on long-chain polyunsaturated fatty acids (LC-PUFAs) in maternal and infant nutrition. The lead article by Stewart Forsyth and colleagues at the University of Dundee, Scotland, describes the effects of LC-PUFA supplementation in infancy on blood pressure values taken nearly six years later. Infants fed LC-PUFA-supplemented formula had significantly lower mean and diastolic blood pressures in childhood compared with children receiving standard unsupplemented formula. Values from the supplemented infants were similar to those in breast-fed infants. These findings add to the list of benefits associated with the provision of LC-PUFAs in infancy and could have considerable impact on reducing the risk of high blood pressure later in life. High blood pressure substantially increases the risk of cardiovascular disease and stroke, scourges of westernized societies.

In May 2003, Susan Carlson, University of Kansas Medical Center, and colleagues organized a workshop on maternal and infant LC-PUFAs in conjunction with the annual meeting of the American Oil Chemists' Society. The workshop brought together some 60 scientists from 12 countries. Presentations included research on growth and infant development; different aspects of neurodevelopment such as visual and cognitive function, sleep patterns, and motor behavior; and discussions on new technologies for measuring behavioral and developmental outcomes, effects of LC-PUFAs on genomics, and impacts of LC-PUFAs on various clinical conditions.

I spoke with Dr. Carlson after the workshop and include excerpts from that conversation. Carlson noted that while much has been learned about the importance of LC-PUFAs in infant development, precise requirements remain uncertain.

Other features include the effect of fish consumption in reducing the incidence of coronary heart disease and in lowering mortality in women with type 2 diabetes, an explanatory review of how long-chain omega-3 PUFAs protect against sudden cardiac death from arrhythmias, differences between the plant-derived omega-3 fatty acid alpha-linolenic acid and fish oil omega-3s, and a study on the novel omega-3 fatty acid, stearidonic acid.

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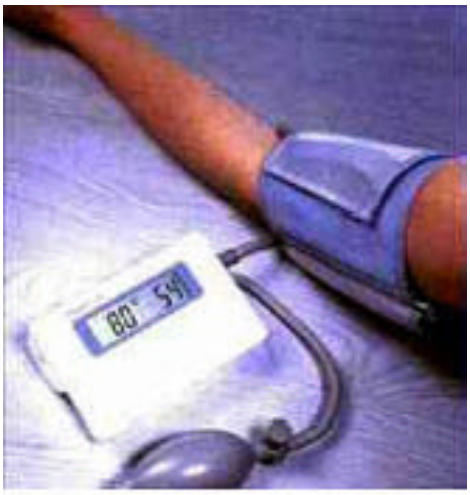
Maternal and Infant Health

LC-PUFA Supplementation of Term Infants: Lower Blood Pressure after Six Years

There is much debate about whether having insufficient long-chain polyunsaturated fatty acids (LC-PUFA) during pregnancy or infancy has detrimental effects that carry over into childhood or adulthood. Considerable attention has been given to the effects of LC-PUFA supplementation in infancy on learning ability, neurodevelopment, and visual responses. Much less is known about other potential health markers such as blood pressure.

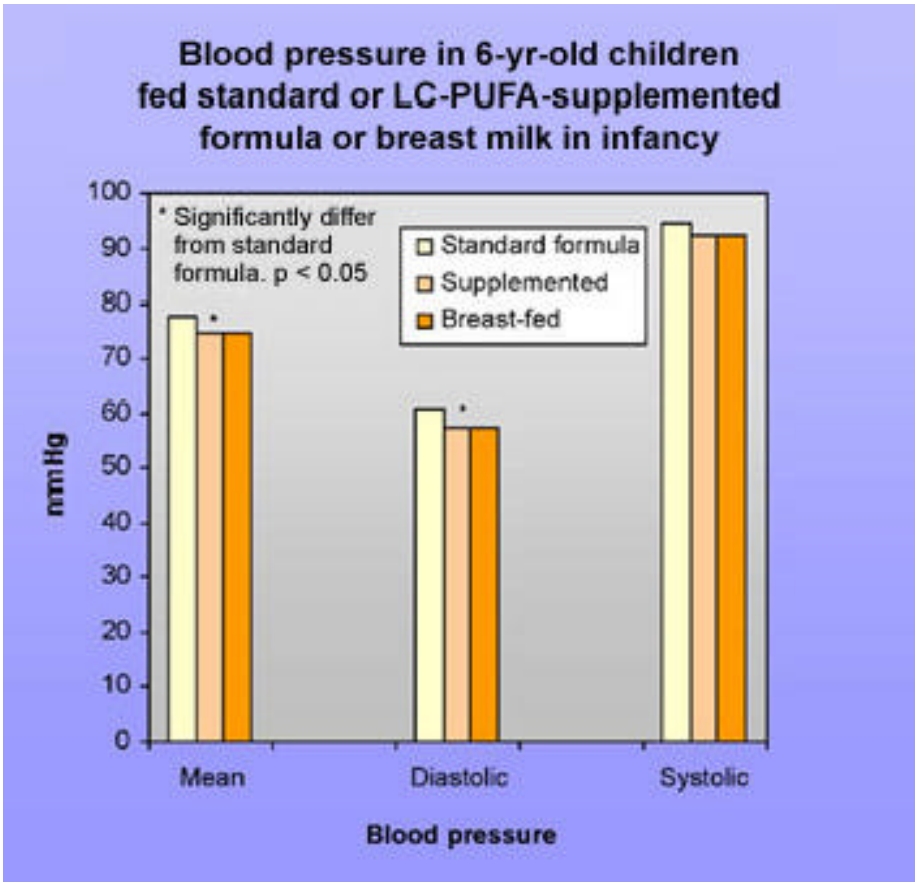
Infants obtain LC-PUFAs from breast milk or formula supplemented with these fatty acids. Those fed unsupplemented formula have no dietary source of LC-PUFA. Breast-fed infants also have lower blood pressure than those fed formula. Moreover, blood pressure in childhood carries over to adulthood. One wonders, then, whether LC-PUFA provided early in life might be associated with lower pressure at a later age. Perhaps the LC-PUFAs in breast milk are key to lower blood pressure seen in breast-fed infants.



Automated blood pressure monitor. Photo courtesy of Omron.

In adults, eating fatty fish or n-3 LC-PUFAs is associated with modest decreases in blood pressure. Stewart Forsyth and colleagues at the University of Dundee, Scotland, decided to explore this question by seeing whether the addition of LC-PUFA to formula would affect blood pressure in childhood.

The investigators studied children from four centers in the United Kingdom, Belgium, and Italy. All were term infants weighing between 2500 grams and 4000 grams at birth. Infants fed formula were assigned randomly to receive formula with or without LC-PUFAs provided as docosahexaenoic acid (omega-3) and arachidonic acid (omega-6). All formulas contained small amounts of alpha-linolenic acid (omega-3). A reference group of breast-fed infants was also included for comparison.



Two hundred and nineteen children were available for assessment. Of these, 65 consumed LC-PUFA-supplemented formula, 71 standard formula, and 83 breast milk. Infants consumed formula for the first four months of life. Children were assessed at a follow-up visit at an average age of 5.8 years. Blood pressure was measured using an automated monitor (Figure 1).

Results in Figure 2 indicate that both mean and diastolic blood pressures were significantly lower in infants fed the LC-PUFA-supplemented formula compared with those fed standard formula without LC-PUFAs. Mean blood pressure in the supplemented infants was 74.8 mm mercury compared with 77.8 mm mercury in infants fed the unsupplemented formula. Diastolic blood pressures in the supplemented and unsupplemented infants were 57.3 and 60.9 mm of mercury, respectively. Systolic blood pressure was similar in both formula-fed groups. Breast-fed infants had blood pressures similar to the supplemented infants and lower than those fed standard formula. Thus, the addition of LC-PUFAs to infant formula resulted in blood pressure values equivalent to those observed in breast-fed infants. It should be noted, however, that the analysis did not correct for differences between the groups in social conditions and anthropometrical variables.

What makes this study particularly noteworthy is that it specifically links lower blood pressure in childhood with LC-PUFAs in breast milk or added to infant formula. Even relatively small reductions in blood pressure lower the risk of cardiovascular disease. When LC-PUFAs were added to infant formula, blood pressures in six-year old children were similar to those observed in breast-fed children and significantly lower than those observed in children who were fed unsupplemented formula. Prior to this study, lower blood pressures were seen only in breast-fed infants.

Although the mechanisms underlying these observations have not been fully elucidated, it is plausible to suggest that LC-PUFAs are incorporated into cells lining the blood vessels where they have a dilatory or relaxing effect on blood vessel walls. Evidence from studies in adults and laboratory animals is consistent with such a mechanism.

Forsyth JS, Willatts P, Agostoni C, Bissenden J, Casaer P, Boehm G. Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial. *BMJ* 326:953-95.

Maternal and Infant Health LC-PUFA Workshop, USA – May 3-4, 2003

Sixty scientists from 12 countries gathered in Kansas City, Kansas, May 3-4, 2003, for an international workshop on long-chain polyunsaturated fatty acids (LC-PUFAs) in maternal and infant health. The conference was co-chaired by Susan Carlson, University of Kansas Medical Center, USA; Robert Gibson and Maria Makrides, Flinders Medical Centre, Adelaide, Australia; and Margaret Craig-Schmidt, Auburn University, USA. During the day and a half conference, 28 papers were presented on topics ranging from growth and clinical studies to neurodevelopment, methylmercury, and genomics.

Data from most workshop presentations remain confidential prior to publication in the peer-reviewed literature. General observations include:

* Infant growth, an important indicator of future healthy development, may be too crude an indicator of the effects of LC-PUFAs in infancy and childhood. Effects of LC-PUFAs in infant development are likely to be more subtle.

* Deficits in brain docosahexaenoic acid (DHA), the result of omega-3 LC-PUFA-deficient diets, can affect behavior that is linked to the brain neurotransmitter dopamine. In laboratory animals, most of the observed behavioral changes involving dopamine can be reversed by feeding DHA at weaning. These findings suggest a mechanism through which behavioral changes in humans may operate. They imply, too, that early deficits may be overcome by nutritional supplementation when provided early enough.

* The gastro-intestinal disease, necrotizing enterocolitis, is more common in infants fed formula than in

breast-fed babies. Evidence was presented from animal studies showing that the provision of arachidonic acid, an omega-6 LC-PUFA added to some infant formula, may reduce the likelihood of an infant developing this condition. If true in human infants, these findings would reinforce the importance of the addition of both DHA and arachidonic acid to infant formula.

* More sensitive quantitative methods are emerging for measuring the developmental effects of LC-PUFA consumption. Application of these methods is expected to improve the ability to measure subtle effects of dietary LC-PUFA availability in areas such as motor development, behavior, learning ability, visual and auditory responses, and other aspects of neurodevelopment.

* Long-term effects of too little LC-PUFAs in fetal and infant development were reported in children six years old. Infants receiving LC-PUFAs had significantly better scores on tests reflecting the speed and efficiency of processing information compared with infants fed unsupplemented formula. Measures of intelligence were unaffected. However, it is not known how persistent or biologically significant these observations may be.

Maternal and Infant Health LC-PUFA Workshop, Kansas City, Kansas, USA, May 3-4, 2003.

Interview: Carlson Speaks Out on LC-PUFA Research

Dr. Susan E. Carlson, Professor of Nutrition at the University of Kansas Medical Center, USA, was a co-organizer of the Maternal and Infant LC-PUFA Workshop, May 3-4, 2003 in Kansas City, Kansas. *PUFA Newsletter* editor Joyce Nettleton interviewed Carlson after the workshop.

***PUFA Newsletter:* What aspects of long-chain polyunsaturated fatty acids (PUFAs) did you hope to highlight at the Maternal and Infant Workshop?**

Carlson: We wanted to draw attention to studies on the effects of LC-PUFAs on gene expression, new measurement tools for defining brain function, and models that have been developed to account for transient and sleeper effects that occur with different interventions. Mechanistic studies on membrane function are also important.

***PUFA Newsletter:* Can you give some examples of these new measurement tools?**

Carlson: Dr. Stephen Fowler at our university has measured the time mice can walk on a rotating cylinder and their licking a sensor disk as reflections of motor coordination. By carefully controlling the experimental conditions, these highly sensitive measurement tools will detect small differences among mice treated with various interventions. These can then be linked to differences in the function of the cerebellum.

In another approach, "knockout" mice – those lacking the gene for proteins that enable brain cells to recognize the neurotransmitter, dopamine – have been used to study dietary changes that affect the dopamine communication system in the brain. LC-PUFA status appears to affect this system.

***PUFA Newsletter:* What is being learned from new measures of brain function in experimental animals?**

Carlson: Our research group found that reduced brain docosahexaenoic acid (DHA) during development altered certain behaviors linked to dopamine function. Some of these changes were modified when DHA was added at the time of weaning. Others could not be reversed when brain DHA was returned to normal after that age. Thus, the timing of the deficit or the supplementation was critical.

***PUFA Newsletter:* Are there any studies in humans?**

Carlson: We looked at the attention of toddlers at 12 and 18 months of age whose mothers had high or low levels of DHA at birth. Normally, the time that infants spend looking at a stimulus decreases during the first year, then gradually increases in the next 12 months. We found that this pattern

of attention was reversed in toddlers of mothers with low DHA at delivery compared with toddlers of the high DHA mothers. These findings may mean that infants born to mothers with higher levels of DHA have more sophisticated attention responses in the second year of life. We do not know whether these differences may be linked to learning and language development later on.

PUFA Newsletter: **What do you think is the big picture for LC-PUFAs in pregnancy?**

Carlson: There are now various findings that show a relationship between maternal LC-PUFAs during pregnancy and infant/toddler performance. In particular, infants born to mothers who have higher levels of LC-PUFAs perform better in several measures of neurodevelopment than those born to mothers whose LC-PUFA status is low. There is only one randomized clinical study of maternal DHA supplementation during pregnancy that has measured infant/child outcomes. The results were positive for maternal DHA supplementation, but it would be nice to have additional studies before we make more specific recommendations about DHA intake for pregnant women.

PUFA Newsletter: **Do you think most pregnant women in the United States have adequate LC-PUFA intake?**

Carlson: Women who eat fatty fish will have these fatty acids. Those who do not may find it difficult to meet their needs. Again, specific studies of this are needed. Many health organizations are recommending one or two servings of fatty fish a week for a variety of health benefits. It's probably just as important for pregnant women too.

PUFA Newsletter: **Dr. Carlson, thank you for your comments.**

Maternal and Infant Health LC-PUFA Workshop, Kansas City, Kansas, USA, May 3-4, 2003.

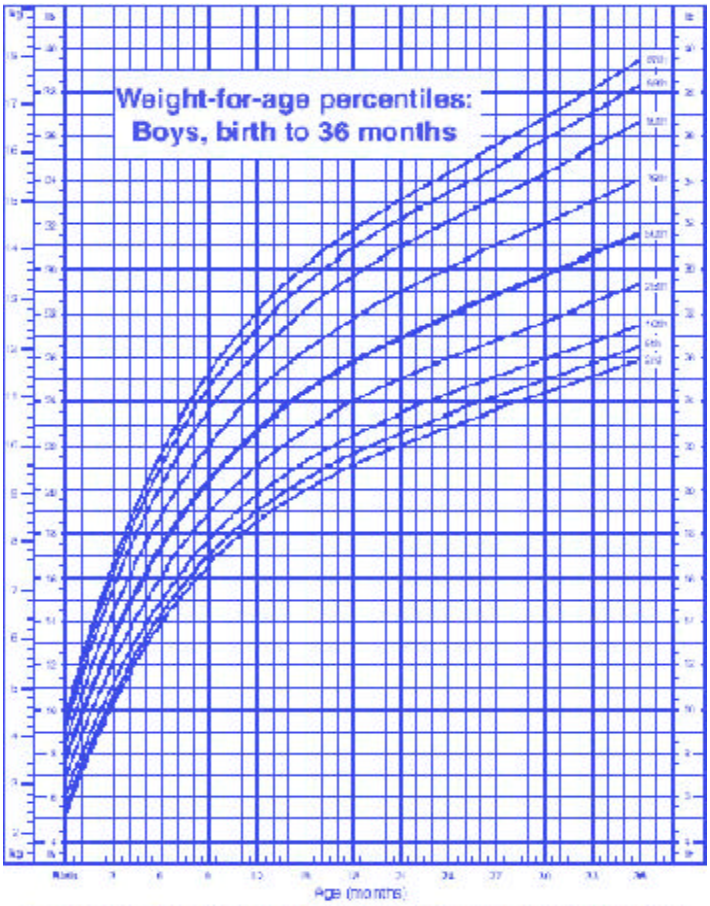
Do Docosahexaenoic and Arachidonic Acids Improve Infant Growth?

Although LC-PUFAs are present in human milk, only recently have they been added to some infant formula. The rationale behind their inclusion is to bring the essential fatty acid status of formula-fed infants closer in line with that of breast-fed infants. The addition of these fatty acids also ensures against any possible visual or neurological deficits that have been observed in infants fed formula without these fatty acids. What has been less clear are the effects of adding LC-PUFAs to infant formula on the growth of premature and term infants.

An international collaboration of researchers in LC-PUFAs, led by Robert Gibson and Maria Makrides of the Women's and Children's Hospital in Adelaide Australia, has undertaken a meta-analysis of published and unpublished randomized, controlled trials with LC-PUFAs and growth in preterm and term infants. This type of systematic rigorous statistical analysis selects eligible studies according to specified criteria, provides detailed documentation of the protocols used, and then pools and analyzes the data. Such an approach increases the statistical power of all the analysis and provides an objective basis for weighing all the evidence available.

A particular distinction of this undertaking is that the investigators obtained raw data from the original studies, including both published and unpublished studies. Fourteen studies on term infants and 13 on preterm infants, were included. The pattern of growth for weight, length, and head circumference were compared for term and preterm infants fed cow's milk formula with or without LC-PUFAs. No data are available for formulas made from soy or other sources. Only term infants fed formula for at least 12 weeks or preterm infants fed formula for at least four weeks were included. Typical growth curves for male infants are illustrated in Figure 1.

The analyses indicated that the growth parameters of preterm and term infants fed LC-PUFA-supplemented formula were no different from those fed unsupplemented formula. Comparisons in a subset of infants fed formula with n-3 LC-PUFA with and without arachidonic



Growth curves for healthy term infant boys in weight-for-age percentiles from birth to 36 mo. Source: Centers for Disease Control, U.S. Dept. Health and Human Services.

acid, indicated that the addition of arachidonic acid made no difference to any of the growth measurements.

When the investigators performed regression analyses to determine the best predictors of growth, they found that birth weight, gender, and actual age of assessment were the strongest predictors of growth. Supplementation with LC-PUFAs accounted for less than 3 percent of the variation in growth.

These findings mean that growth is determined more by genes, birth size, and other factors than by LC-PUFA supplementation. Growth is probably too crude a measure to reflect the effects of LC-PUFAs. These analyses answer the main question about the effect of LC-PUFAs on growth, but say nothing about where growth failure or enhancement begins. Clearly there are limits to the desirability of "enhanced" growth, while early indicators of potential growth failure would be useful in signaling the need for intervention.

Workshop participants discussed the effects of adding arachidonic acid to term infant formula, noting the cost of this fatty acid and the lack of an effect on growth. Participants also noted that alpha-linolenic acid, an omega-3 fatty acid from plants, is ineffective in increasing DHA levels or influencing growth.

Gibson RA, Makrides M. LC-PUFA and growth in preterm infants: meta analysis. , Kansas City, USA, May 3-4, 2003.

Cardiovascular Disease

Review Explains How Omega-3 Fatty Acids Prevent Arrhythmias

An important review of how long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) avert sudden death from uncontrolled heart rhythms was recently published by Alexander Leaf and colleagues at the Massachusetts General Hospital in Boston, Mass., USA. This review provides detailed explanations that account for the way n-3 LC-PUFAs protect against fatal heart arrhythmias. The companion editorial by Siscovick and colleagues describes how dietary fat is linked to the prevention of sudden cardiac death, not only through the reduction in atherosclerosis, but also by reduced susceptibility to uncontrolled heart rhythms, or fibrillation. In the United States alone, about 300,000 people each year die from sudden cardiac arrest. The consumption of fatty fish or n-3 LC-PUFAs has been shown to reduce these fatalities by as much as 45 to 81 percent. How do they do it?

The idea that fish oil might be anti-arrhythmic was suggested in the 1970s and confirmed with fairly simple experiments in laboratory animals in the 1980s. In the 1990s, Leaf and colleagues showed that in exercise-trained dogs, intravenous infusion of n-3 LC-PUFAs prevented the development of fatal uncontrolled heartbeats when the animals were subjected to acute cardiac stress. When purified free n-3 LC-PUFAs – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – were used,

fatal fibrillation was prevented. Soybean oil, which does not contain n-3 LC-PUFAs and free fatty acids, did not have a protective effect.

The investigators then used sophisticated technology to study the effects of n-3 LC-PUFAs in single isolated myocytes (heart cells) from rats. Beating heart cells, grown on microscope slides, were viewed individually under a microscope and filmed. The researchers showed that the addition of EPA or DHA to the heart cells slowed the rate of beating. Toxic agents, such as ouabain and high levels of calcium ions, led to rapid uncontrolled beats, similar to what happens in fatal arrhythmias in humans. When EPA was added after the toxic agent, it stopped the arrhythmias. Only the free fatty acid was effective, not its esterified derivative. Thus, n-3 LC-PUFAs were shown to affect the electrical properties of heart cells.

The investigators also demonstrated that n-3 LC-PUFAs affect the heart cell's ability to generate electrical currents, which is how these cells function and coordinate their activity. Electrical currents are developed by the flow of electrically charged particles (ions) through the heart cell membranes. Omega-3 LC-PUFAs modulate the flow of these ions making the electrical excitability of the heart much more stable. As Leaf put it, "the results of these n-3 PUFAs is that . . . myocytes are quickly made inexcitable and their potential arrhythmic mischief is aborted." And so, too, may sudden death be aborted.

In their concluding remarks, Leaf and co-authors endorsed the American Heart Association's recommendation that everyone eat at least two meals of fatty fish per week and personally recommended that those with coronary heart disease increase their intake of n-3 LC-PUFAs to one to two grams/day. Moreover, the positive effect of eating fatty fish occurs in a matter of a few weeks to about three months. No wonder clinicians and policymakers are moving n-3 LC-PUFAs to the top of the agenda. They can prolong lives.

Siscovick DS, Lemaitre RN, Mozaffarian D. The fish story. A diet-heart hypothesis with clinical implications: n-3 polyunsaturated fatty acids, myocardial vulnerability, and sudden death. (Editorial) *Circulation* 2003;107:2632-2634.

Leaf A, Kang JX, Xiao Y-F, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 2003;107:2646-2652.

Israeli Paradox: Does High Intake of Linoleic Acid Help or Hinder Heart Health?

Once high saturated fat diets became linked to increased blood cholesterol levels and hence increased risk of cardiovascular disease, dietary recommendations encouraged people to limit their consumption of saturated fatty acids and substitute polyunsaturated fatty acids instead. Health authorities also recommended polyunsaturated vegetable oils, rich in linoleic acid, to reduce blood cholesterol levels. For the past three decades, blood cholesterol levels have been the focus of cardiovascular risk assessment. As a result, the types of fats consumed changed. In the U.S., consumption of polyunsaturated vegetable oils, mainly from soy and corn, increased by about 15%, while that of animal fats, the main source of saturated fatty acids, decreased by a similar amount. Although total fat consumption declined, the proportion contributed by vegetable oils increased substantially. Polyunsaturated fatty acids comprise 6-7% of total energy intake of American adults; in Israel, the proportion is even higher at 8-10% of total energy. In Israel, where cardiovascular mortality is high, this increased intake of vegetable oils rich in linoleic acid has not been accompanied by the expected reduction in cardiovascular disease. Does the high consumption of linoleic acid affect cardiovascular risk?

In this study, Kark and colleagues studied the association between fatty acids in subcutaneous adipose tissue and the frequency of primary acute myocardial infarction in a case-control study of 180 patients aged 25 to 64 years and 492 age and gender-matched controls. All participants resided in Jerusalem and were free of preexisting ischemic heart disease. Diet was assessed by food frequency questionnaire. More than 90% of the study population consumed

more than 6% of energy from polyunsaturated fatty acids and a quarter consumed more than 12%. Saturated fat intake averaged 11% of energy.

As expected, fatty acids in adipose tissue reflected the fatty acids in the diet. Linoleic acid, the major dietary polyunsaturated fatty acid, comprised 25% of all adipose tissue fatty acids. Patients with myocardial infarction had significantly more arachidonic acid in their adipose tissue than control subjects, but linoleic acid and alpha-linolenic acid levels were similar in both groups. Arachidonic acid, but not linoleic acid was associated with significantly increased risk of myocardial infarction.

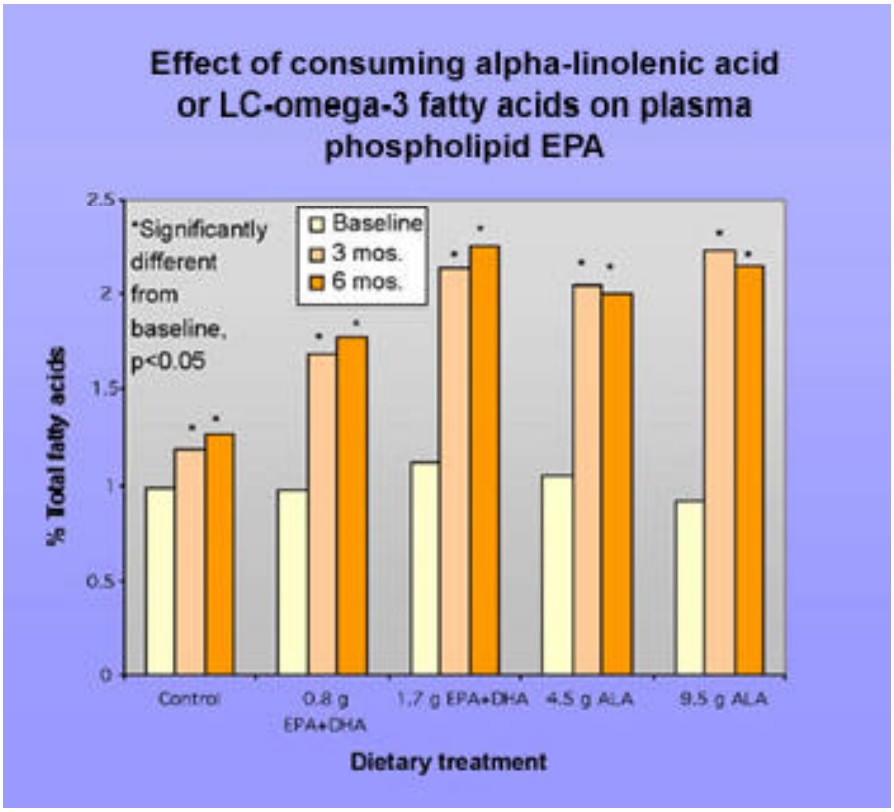
The observed association between myocardial infarction and adipose tissue arachidonic acid content needs to be confirmed. In other studies where linoleic acid consumption was lower, adipose tissue arachidonic acid content was not associated with risk of myocardial infarction. Its level in erythrocyte membranes, where it is a major component, has been linked with sudden cardiac death and has been only weakly associated with adipose tissue levels.

In this report, neither dietary PUFA intake nor adipose linoleic content were related to adipose arachidonic acid level. In spite of the high consumption of linoleic acid, adipose arachidonic acid content in cases and controls was approximately 0.6%, suggesting that if considerable linoleic acid is converted to arachidonic acid, not much of it is stored in adipose tissue. The authors cautioned that although myocardial risk was not related to adipose linoleic acid level, it cannot be assumed that such high intakes of linoleic acid are safe.

Kark JD, Kaufmann NA, Binka F, Goldberger N, Berry EM. Adipose tissue n-6 fatty acids and acute myocardial infarction in a population consuming a diet high in polyunsaturated fatty acids. *Am J Clin Nutr* 2003;77:796-802.

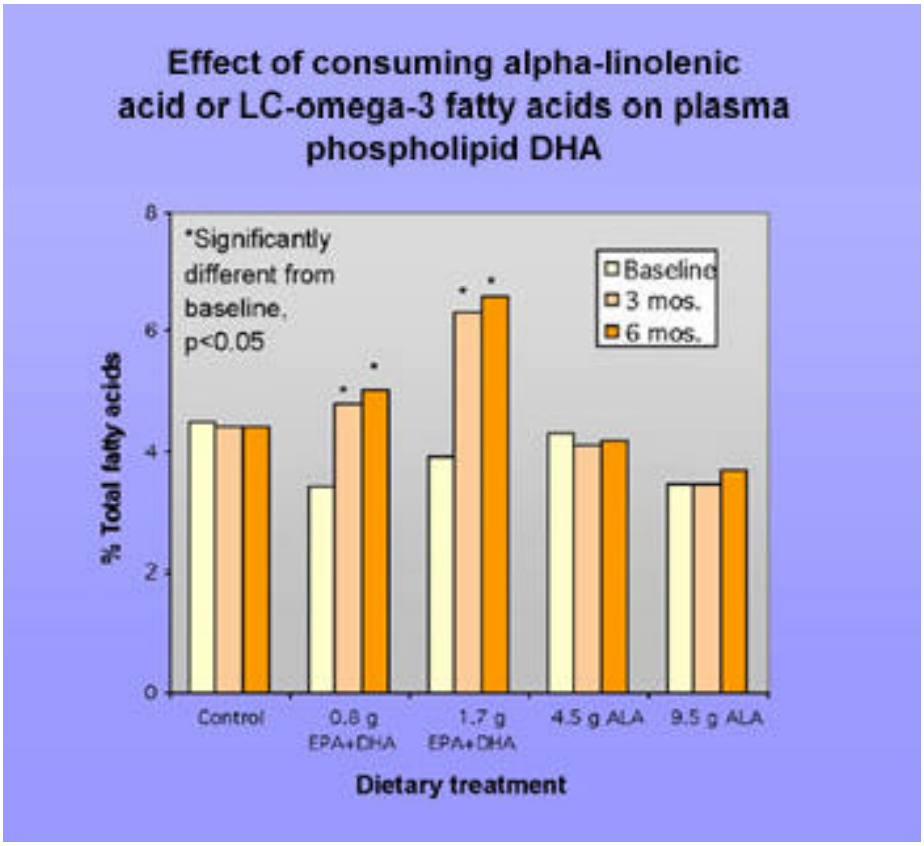
Plant and Fish Omega-3 Fatty Acids Have Different Effects

Western diets are relatively low in the omega-3 fatty acid alpha-linolenic acid (ALA) found in plants and in long-chain omega-3 fatty acids (n-3 LC-PUFAs) found mainly in seafoods. They have also become highly enriched in omega-6 polyunsaturated fatty acids whose biological effects contrast with those of omega-3 fatty acids. To redress the relative imbalance in the consumption of these two classes of fatty acids and to provide the beneficial health effects associated with the consumption of n-3 LC-PUFAs, updated dietary guidelines recommend consuming more n-3 LC-PUFAs. The ability of ALA to provide the health benefits associated with n-3 LC-PUFAs is questionable.



Omega-3 fatty acids are found in plants, mainly as the 18-carbon ALA, and in their long-chain forms in fatty fish, mainly as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although ALA can be converted to EPA and DHA, this conversion occurs to only a modest extent. Current evidence suggests that it takes about 7 grams of ALA to increase tissue EPA and DHA levels by one gram.

Whether some or all of the health effects observed with EPA and DHA can be obtained with ALA is uncertain. Cardioprotective effects of ALA consumption have been reported in some epidemiological studies and in an intervention trial using ALA-enriched margarine. Effects on a variety of disease risk factors are less certain.



Finnegan and colleagues at the University of Reading, U.K., compared the effect of consuming biologically equivalent amounts of ALA or EPA plus DHA at two different levels. Bioequivalence was based on the largely hypothetical consideration that seven grams of ALA were equivalent to one gram of EPA and DHA. One hundred and fifty moderately hyperlipidemic healthy subjects were fed either 0.8 or 1.7 grams/day of EPA and DHA, or 4.5 or 9.5 grams/day of ALA. The fatty acids were provided in specially prepared margarines with the addition of fish oil or placebo capsules. The control was a typical omega-6-rich margarine containing sunflower and safflower oils. Thirty subjects in each group consumed the margarines in lieu of their usual margarine or butter in their customary diet for six months, after a one-month run-in period with the control margarine. Investigators measured plasma lipids and phospholipids, glucose and insulin, blood pressure, and post-prandial responses to high-fat meals at baseline and after six months.

Feeding either amount of ALA significantly increased plasma EPA levels compared with baseline values, but compared with the control group, only those consuming 9.5 grams of ALA/day had significant increases in EPA (Figure 1). ALA consumption was not associated with any change in DHA. In contrast, feeding EPA and DHA increased both EPA and DHA levels significantly compared with baseline values (Figure 2). Thus, ALA consumption does not appear to boost DHA levels. None of the dietary treatments affected phospholipid arachidonic acid levels at the end of six months.

Over the six-month study period, total, LDL, and HDL cholesterol levels increased in all groups, but no significant treatment or time plus treatment effects were observed. Those consuming 1.7 grams of EPA and DHA/day had a marked increase in LDL after six months that was two to three times that observed in the control group and other treatments, but did not reach statistical significance.

Consuming the higher level of EPA and DHA significantly reduced triglyceride levels. The consumption of ALA was accompanied by an increase in triglyceride levels by about 11%, but this was not significantly different from changes in the other groups. There were no significant effects of dietary treatment or the interaction between diet and time on glucose or insulin levels and no effects of time or treatment on blood pressure.

Overall, this study showed definitively that consuming ALA, even in relatively large amounts, does not

enhance plasma phospholipid DHA levels. It raised EPA levels, but this does not appear to substitute for the consumption of preformed EPA+DHA. Consumption of ALA had no effect on arachidonic acid levels, which may cast doubt on the competition between ALA and linoleic acid. Neither fatty acid treatment affected plasma lipoproteins or lipids and the modest reduction in triglycerides usually observed with the consumption of EPA and DHA was not sustained over the six-month study period in the low EPA+DHA group. The increase in LDL with 1.7 grams of EPA and DHA /day was larger than expected. These observations lend credence to the view that n-3 LC-PUFAs protect heart health mainly through mechanisms independent of changes in plasma lipids. Here is additional evidence that the effects of ALA are different from those of EPA and DHA and are more modest.

Finnegan YE, Minihane AM, Leigh-Firbank EC, Kew S, Meijer GW, Muggli R, Calder PC, Williams, CM. Plant-and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. *Am J Clin Nutr* 2003;77:783-795.

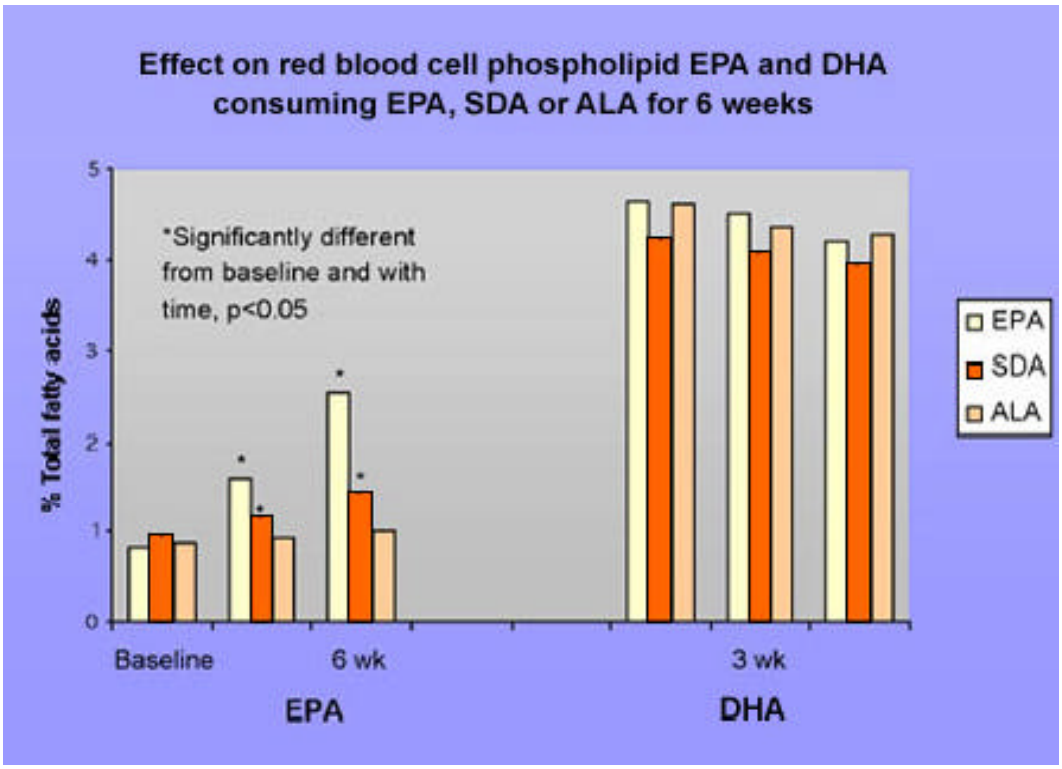
Stearidonic Acid: A Novel Omega-3 Fatty Acid

Fish oils have become synonymous with long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) because they are the most abundant food source of them. The main n-3 LC-PUFAs are docosahexaenoic acid (DHA, 22:6), eicosapentaenoic acid (EPA, 20:5) and docosapentaenoic acid (DPA, 22:5). These long-chain fatty acids are not found in terrestrial plants.

Some plants contain alpha-linolenic acid (ALA, 18:3), the omega-3 precursor that the body converts to a limited extent to the long-chain forms of omega-3 fatty acids. The low rate of conversion of plant sources of omega-3 fatty acids limits their usefulness as a source of the health benefits associated with n-3 LC-PUFAs.

A little known n-3 fatty acid, stearidonic acid (SDA, 18:4) is an intermediate product in the conversion of alpha-linolenic acid to eicosapentaenoic acid. Its production is one of the limitations in the conversion of alpha-linolenic acid to the long-chain forms. It was thought that the availability of stearidonic acid, rather than alpha-linolenic acid, might increase the availability of n-3 LC-PUFAs. To evaluate this idea, Michael James and associates at the Royal Adelaide Hospital, Australia, compared the metabolism of stearidonic acid with alpha-linolenic and eicosapentaenoic acids in healthy adults.

Forty-five healthy non-obese men and women, aged 18 to 65 years, who were not taking dietary supplements rich in n-3 or n-6 fatty acids, nor eating fish more than once a month, nor taking aspirin regularly, were randomly assigned to consume either alpha-linolenic acid, stearidonic acid, or eicosapentaenoic acid on a double-blind basis for six weeks, after



a three-week run-in period. Fatty acids were provided as capsules of fatty acid ethyl esters at a dose of 0.75 grams/day for three weeks, then 1.5 grams/day for three weeks. Blood samples were collected upon entry and every three weeks until completion of the study. Investigators measured fatty acids, eicosanoids and cytokines in appropriate fractions of blood.

The consumption of eicosapentaenoic acid and stearidonic acid led to a significant increase in red blood cell phospholipid content of eicosapentaenoic acid after three weeks and a further significant increase at the end of six weeks when compared with baseline values (Figure 1). At the end of six weeks, docosapentaenoic acid levels were significantly increased as well.

Docosahexaenoic acid levels were unaffected by any dietary treatment. No increases were observed in any of the n-3 LC-PUFAs with alpha-linolenic acid.

Similar results were observed at the end of six weeks for plasma phospholipids. Greater increases in eicosapentaenoic and docosapentaenoic acid levels were obtained with eicosapentaenoic acid compared with stearidonic acid in both red cell and plasma phospholipids. Thus, consuming stearidonic acid increased phospholipid eicosapentaenoic acid levels significantly, but not quite as extensively as eicosapentaenoic acid itself.

Analysis of the pro-inflammatory cytokine, tumor necrosis factor-alpha, showed a steadily decreasing production with each fatty acid over the six-week period. This reduced production did not reach statistical significance. None of the fatty acids affected the production of prostaglandin E2 and thromboxane A2, and the concentrations of plasma triglycerides and other lipoproteins.

This study has shown clearly that stearidonic acid is metabolized to eicosapentaenoic acid. The authors calculated the relative effectiveness of each fatty acid for increasing tissue eicosapentaenoic acid levels as:

Eicosapentaenoic acid (1.0) > Stearidonic acid (0.3) > Alpha-linolenic acid (0.07)

Thus, one gram of stearidonic acid is approximately equivalent to 300 mg of eicosapentaenoic acid. This level of effectiveness makes it a worthwhile source for increasing the availability of eicosapentaenoic acid in the food supply through its introduction into seed oils. Although eicosapentaenoic acid does not fulfill all the functions associated with docosahexaenoic acid, it has salutary effects on cardiovascular health and inflammatory responses. Its greater availability in foods would be expected to provide many of the health benefits associated with n-3 LC-PUFAs.

James MJ, Ursin VM, Cleland LG. Metabolism of stearidonic acid in human subjects: comparison with the metabolism of other n-3 fatty acids. *Am J Clin Nutr* 2003;77:1140-1145.

Clinical Conditions: Type 2 Diabetes Mellitus

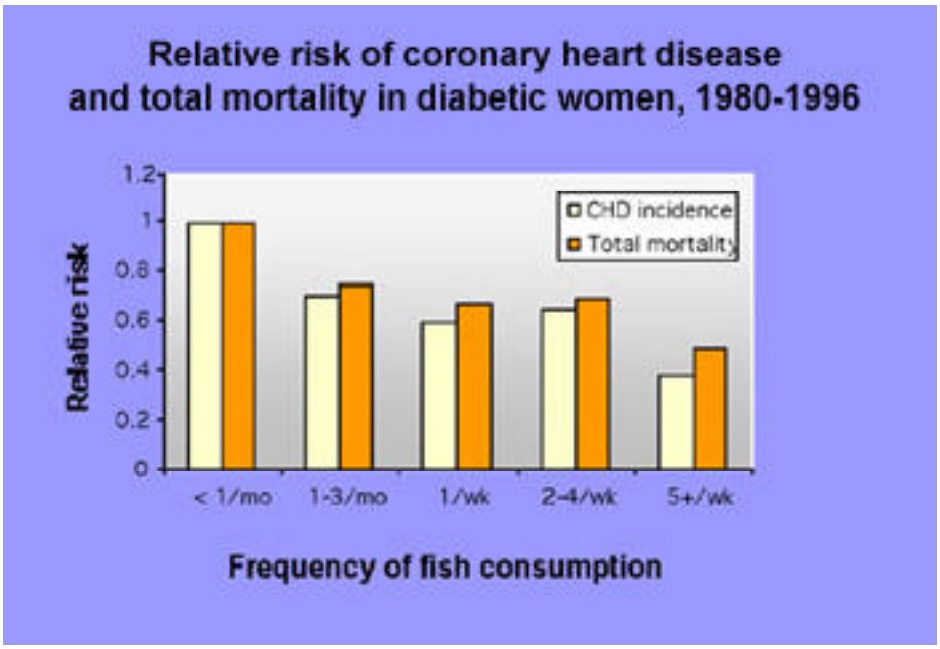
Regular Fish Consumption Lowers CHD and Mortality in Diabetic Women

A growing body of evidence indicates that long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) protect heart health in people with type 2 diabetes. Some evidence also suggests that these fatty acids may reduce the chance of developing type 2 diabetes in people at high risk for the disease. It is well known that risk of heart disease is significantly increased in diabetes.

This study reports that fish consumption is linked to lower incidence of coronary heart disease and mortality from all causes in people with type 2 diabetes. Such findings have important clinical and public health implications, because the prevalence of type 2 diabetes worldwide is increasing rapidly.

Frank Hu and associates at the Harvard School of Public Health in Boston examined the relationship between how much fish is consumed regularly and the incidence of coronary heart disease in 5103

women with type 2 diabetes. Women, aged 30 to 55 years at enrolment, were followed between 1980 and 1996. Those with heart disease or cancer at the beginning of the study were excluded.



Frequency of eating fish was divided into five groups ranging from less than once/month to five or more times per week. Those who ate higher levels of fish also consumed more fruits and vegetables, less red and processed meats, and smoked less. Findings showed that higher fish consumption was significantly associated with lower incidence of coronary heart disease (Figure 1). Those consuming fish one to three times/month were 30 percent less likely to develop heart disease compared with those eating fish less than once/month. Women who ate fish five or more times/week had a 64 percent lower incidence of heart disease in the same comparison. The analyses controlled for several established cardiovascular risk indicators and potential confounding variables.

The association between fish consumption and all causes of mortality showed a similar trend. Those with highest fish consumption were half as likely to die as those eating fish less than once a month. Even low fish consumption of one to three times/ month was associated with a 25 percent reduced risk of death.

The investigators also determined the association between the calculated intakes of eicosapentaenoic and docosahexaenoic acids estimated from the types of fish consumed. The association between n-3 LC-PUFA intake and incidence of coronary heart disease was not as strong as that based on fish consumption, and lost statistical significance when potential confounding factors were taken into consideration. These findings may be the result of greater measurement error in estimating n-3 LC-PUFA intake. The negative association with all cause mortality, however, was significant with an almost 40% reduction in mortality in the group with the highest n-3 LC-PUFA consumption. Even the group with a very low intake of n-3 LC-PUFAs had 20% lower total mortality than those whose intake was the lowest.

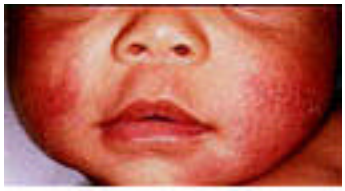
These findings present clear and convincing epidemiological evidence that women with type 2 diabetes can benefit from the cardioprotective effects of fish consumption and n-3 LC-PUFAs. There is no reason to think findings would be substantially different in men also, although this study included only women. These findings support the recommendations of the American Diabetes Association that diabetic subjects consume fatty fish twice a week. Further, it would appear that potential detrimental effects on selected risk factors for heart disease, such as elevated low density lipoprotein levels, or putative erosion of blood glucose control, that have been associated with the consumption of fish oils in type 2 diabetes, are outweighed by the overall protective effect on survival. Good news, indeed, for the millions with type 2 diabetes.

Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation* 2003;107:1852-1857.

Clinical Conditions: Skin Disorders

Gamma-Linolenic Acid Eases Severity of Atopic Dermatitis

Atopic dermatitis refers to a group of inflammatory skin conditions of which eczema is the most familiar example. These conditions tend to run in families and are more common in infancy than in adults, although about three percent of adults in the U. S. and up to eight percent in the U. K. are believed to have the condition. In infants, the condition may affect 53 percent or more of those fed formula and 35 percent or more of those who are breast-fed.



Infantile eczema. Reprinted with permission from the American Academy of Dermatology. All rights reserved.

Eczema first appears as a red, itchy rash that is characterized by inflammation. In infants the rash often appears on the face and scalp, as illustrated.

As long ago as 1937 it was known that atopic dermatitis was associated with lower blood levels of polyunsaturated fatty acids (PUFAs). Now, we know that people with atopic dermatitis have increased levels of linoleic acid in their blood. They also have lower levels of the long-chain (LC) derivatives of linoleic acid, such as gamma-linolenic acid (GLA) and arachidonic acid. In newborns with a family history of the condition, low levels of omega-6 LC-PUFAs frequently precede development of the disease. Atopic dermatitis has been treated by adding GLA to the diet, but results are mixed. The possibility that providing GLA might prevent, delay, or decrease the severity of the condition, if consumed by infants before the disease developed, has not been explored.

Van Gool and colleagues at Maastricht University in the Netherlands decided to see whether feeding GLA to infants at high risk of developing atopic dermatitis would protect them from developing the condition. Their study subjects were newborn infants of mothers who were atopic, that is had a history of allergic asthma, allergic reactions to other airborne allergens, or had a history of atopic dermatitis. Infants of atopic mothers were included if they were born at term, weighed 2500 grams or more, and were being exclusively fed formula from the age of two weeks.

Infants were randomly assigned to formula supplemented with either borage oil containing GLA or sunflower oil, a placebo in which GLA was replaced by oleic acid. The amount of GLA included in the supplement approximated the upper level of GLA reported in human milk and provided 103 mg of GLA/day. The formulas did not contain LC-PUFAs. Infants consumed the formula from the age of seven to 14 days until they reached the age of six months, and were evaluated when they were one year old. One hundred and eighteen infants completed the study, 58 and 60 in the GLA and placebo groups, respectively.

Investigators measured fatty acids in blood samples taken periodically throughout the study. Presence of atopic dermatitis was diagnosed by a trained dermatologist according to four clinical symptoms based on UK Working Party criteria. Severity of the condition was assessed and scored using clinical criteria. Full acceptance of the treatments was 85% and 88% for the GLA and placebo groups, respectively, and blood GLA levels increased in the first three months by 70% in the GLA group compared with no significant change in the placebo group. At the end of six months, GLA levels in the treatment group were elevated by about 50% with no significant change in the placebo group.

At one year of age, 23 infants fed GLA and 28 consuming the placebo oil were diagnosed with atopic dermatitis, although this difference did not reach statistical significance. Similarly, the severity of the dermatitis was lower in those receiving GLA compared with the placebo group, 6.3 vs 8.3 severity score. This difference, too, failed to achieve statistical significance. However, when the severity index was related to the GLA level in plasma phospholipids,

Starflower, source of borage oil.
Photo courtesy of Roche Vitamins Ltd.

severity was strongly and negatively associated with the GLA level. In other words, as the GLA in plasma phospholipids increased, the severity decreased. It is possible that statistical significance was not achieved because of decreasing compliance during the six-month treatment study period.

What can we make of these findings? This study showed that providing GLA to high-risk infants in the first months of life did not prevent or protect against the development of atopic dermatitis. We do not know, however, whether a higher dose might have had an effect. Although GLA treatment was associated with a favorable trend toward reduced severity of atopic dermatitis, the results were not statistically significant. Oils rich in GLA, such as borage oil, were well tolerated and easy to consume.

As the authors discussed in their paper, atopic dermatitis has both immune and inflammatory components, which entail different biological mechanisms. In this study, the immune component of atopic dermatitis was unaffected by GLA treatment. This was concluded from the absence of a significant relationship between clinical symptoms and total and specific immunoglobulin E levels. However, much more remains to be learned about the various components of this troublesome disorder.

Van Gool CJAW, Thijs C, Henquet CJM, van Houwelingen AC, Dagnelie PC, Schrander J, Menheere PPCA, and van den Brandt PA. Gamma-Linolenic acid supplementation for prophylaxis of atopic dermatitis-a randomized controlled trial in infants at high familial risk. *Am J Clin Nutr* 2003;77:943-951.

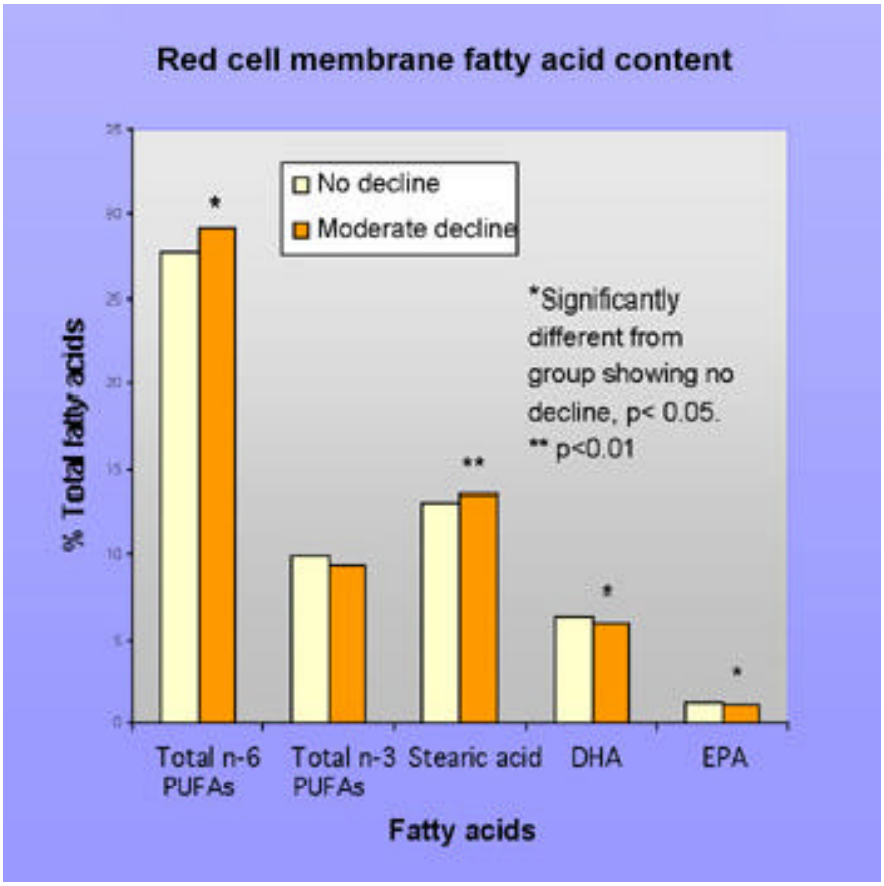
Clinical Conditions: Adult Mental Function

Long-Chain Omega-3 Fatty Acids Lower Risk of Declining Mental Function in Older People

One of the frontiers of long-chain polyunsaturated fatty acid (LC-PUFA) research is the effect of these fatty acids on mental function during aging. Various reports have suggested that LC-PUFAs, particularly those of the omega-3 family, may slow mental decline and reduce the development of Alzheimer's disease in older people. Because LC-PUFAs are structural components of neural membranes, are critical in neural development in infancy, and are linked to several aspects of nervous tissue function, it is reasonable to think they may be involved in nervous tissue function in the elderly as well.

Because one cannot study brain tissue directly, surrogate measures of fatty acid levels in brain tissue such as red cell membranes are used to assess the fatty acid status in nervous tissue. Red cell membrane fatty acid content also reflects customary dietary intake. A team of French investigators decided to find out whether the cognitive status of older French subjects was related to the relative levels of different fatty acid families, particularly LC-PUFAs, in their red cell membranes.

Heude and colleagues at the National Institute for Health and Medical Research in France examined the fatty acid content of red blood cell membranes and cognitive status in a sample of older men and women living in western France. From 1995 to 2000 cognitive assessments and blood samples were obtained from 246 subjects, aged 63-74 years. Global cognitive function was evaluated using the French version of the Mini-Mental State Examination. This test includes questions on orientation to time and place, attention, calculation, recall, language and other items. Investigators defined moderate cognitive decline as a decrease of two or more points over a four-year period.



On average, cognitive status improved over the four-year period. Of the 246 participants, 27 showed moderate cognitive decline. Those whose cognition declined had significantly lower levels of docosahexaenoic and eicosapentaenoic acids and significantly higher levels of total omega-6 PUFAs in their red cell membranes (Figure 1). The ratios of omega-3 to omega-6 PUFAs and docosahexaenoic acid to arachidonic acid were significantly lower in those whose cognition declined. Stearic acid, an 18-carbon saturated fatty acid was also significantly higher in those whose cognitive function declined. After adjustment for potential confounding factors, significance disappeared for EPA, but persisted for the other fatty acid variables.

This is the first study to report the association between cognitive decline and lower content of n-3 LC-PUFAs in red blood cell membranes in older subjects. Other studies, however, have reported an inverse relationship between fish consumption and cognitive impairment, but not all reports have reached statistical significance. A positive association for impaired cognition and linoleic acid has also been reported previously.

As these investigators noted, their subjects had, overall, a high level of education, which protects against cognitive impairment. It is plausible, however, that n-3 LC-PUFAs reduce inflammation and proinflammatory substances in the brain, which have been linked to Alzheimer's disease, a type of dementia. The findings reported in this study suggest that one never outgrows the need for n-3 LC-PUFAs.

Heude B, Ducimetière, Berr C. Cognitive decline and fatty acid composition of erythroctye membranes-The EVA Study. *Am J Clin Nutr* 2003;77:803-808.