

# n-3 long-chain polyunsaturated fatty acids for optimal function during brain development and ageing

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We and others have demonstrated that provision of n-3 long chain polyunsaturated fatty acids (n-3 LCPs) in preterm and term babies is associated with retinal electrical responses to light stimuli, and to brain cortex related visual acuity maturation, that are similar to those observed in human milk fed infants. Our follow up results in young children suggest that neurodevelopment and cognitive abilities are also enhanced by early provision of n-3 LCPs through breast milk or DHA-fortified foods. Breast fed infants also require n-3 LCPs after weaning to achieve optimal visual acuity at 12 months of age. Good quality evidence supporting a role for n-3 LCP consumption to enhance learning and/or behaviour in school-age children is currently lacking.

Evidence supporting the potential importance of n-3 LCP consumption for good cognitive health in older age is now beginning to emerge. Recent cross-sectional surveys have reported that higher fatty fish/n-3 LCP consumption and or higher n-3 LCP blood concentrations are associated with reduced risk of impaired cognitive function. Similarly, prospective cohort studies have shown that increased fish consumption and higher n-3 LCPs in blood lipid sub-fractions are associated with decreased risk of dementia in older people. We are presently conducting a large randomised controlled trial in a group of adults aged 70-79 years to assess whether an n-3 LCP supplement will preserve retinal function and prevent age related cognitive decline.

**Key Words: omega-3 fatty acids, brain, development, ageing**

## INTRODUCTION

For nearly 80 years, researchers have known that specific components of fat may be necessary for the proper growth and development of animals and humans,<sup>1</sup> and the concept of the essentiality of certain fats is now well understood. Deficiencies of n-3 fatty acids were shown to result in subtle clinical symptoms such as skin changes, abnormal visual function and peripheral neuropathy,<sup>2,3</sup> and these findings underpinned the concept that n-3 fatty acids were key to adequate development and functioning of the retina and the central nervous system.<sup>4,5</sup> The relatively high concentrations of n-3 long chain polyunsaturated fatty acids (n-3 LCPs), specifically docosahexaenoic acid (DHA), in the cerebral cortex and the retina further supported this view.<sup>6</sup> Indeed, the dry weight of the human brain is predominantly lipid, with 22% of the cerebral cortex and 24% of white matter consisting of phospholipids. Importantly, while the protein composition in the brain is fixed by the genetic code, fatty acid composition of brain phospholipids is modifiable by diet.<sup>7</sup>

Essential fatty acids play crucial structural roles in brain tissue especially in cell membranes, and much research has been conducted into functional implications associated with diet-induced compositional changes.<sup>8,9</sup> Furthermore, the oxidative products of polyunsaturated fatty acids act as key cellular mediators of inflammation, allergy and immunity, oxidative stress, bronchial constriction, vascular responses

and thrombosis.<sup>10</sup> There is also a growing body of evidence to show that LCPs can affect the expression of genes that regulate cell differentiation and growth,<sup>11,12</sup> and may thereby have a profound and long lasting impact on human health. Indeed, via this mechanism, early diet may influence the structural development of organs, as well as the formation of neurologic and sensory functions.

In this paper we review the current evidence linking n-3 LCPs with measures of brain function in infancy, childhood and later life. Given space limitations, our review is necessarily non-systematic, but reference is made, where possible, to current relevant systematic reviews.

## THE DEVELOPING BRAIN

The foetus is entirely dependent on maternal supply of essential fatty acids for its growth and development, and a total of approximately 600g of essential fatty acids are transferred from mother to foetus during a full term gestation. The progressive enrichment in the concentration

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of n-6 arachidonic acid (AA) and DHA in circulating lipids and brain tissue in the foetus that takes place during the third trimester,<sup>13,14</sup> makes preterm infants potentially vulnerable to fatty acid deficiencies.

Numerous studies have therefore investigated whether supplementation of preterm infants with LCPs effects plasma and tissue composition and/or visual and cognitive function. Results of these studies have been mixed and a Cochrane systematic review published in 2004, including 11 randomised controlled trials, concluded that there was no evidence that supplementation of formula with n-3 and n-6 LCPs had any long-term benefit for the infant.<sup>15</sup> The review noted however that the infants enrolled in the trials were relatively mature and healthy preterm infants, and also that differences between the trials made meta-analysis difficult.<sup>15</sup>

A relatively recent study, published after the Cochrane review, compared the effect among preterm infants of LCP supplementation of formula milk with AA fungal oils and DHA from either fish (n=130) or algal (n=112) sources, with control unsupplemented milk (n=199), on various measures of development.<sup>16</sup> The DHA supplemented infants had significantly greater scores than the infants fed the control formula, in the mental and psychomotor development indices of the Bayley Scales of Infant Development (second edition) at 18 months after term. All values stayed significantly below those of the reference sample of 105 term breast fed infants.<sup>16</sup> Longer term follow up of these infants or those from other studies has not been reported.

Accretion of DHA in brain tissue continues after birth, reaching a total of 4g of DHA in the brain between two and four years of age,<sup>17</sup> suggesting that n-3 LCP intake in the early years may also be important for brain development. Again, several studies have investigated the effect of LCP supplementation, although these studies are hard to design among term infants because of the influence of the mother's choice of mode of feeding. A Cochrane review of the available trial evidence conducted in 2001, included 10 trials and concluded that LCP supplementation conferred a possible beneficial effect on information processing in term infants, although larger and more long-term trials were still required.<sup>18</sup> A few recent trials have suggested a positive benefit on mental processing in term infants of supplementation of the mother during pregnancy.<sup>19,20</sup> Furthermore, more persistent benefits of LCP supplementation for both visual acuity and mental development have also been demonstrated.<sup>21-23</sup>

The lack of a consistent pattern of results in the trials conducted among both pre-term and term infants is not wholly surprising given the complexities of such studies. A good discussion of methodological problems, such as differences in the level, nature and duration of supplementation, the use of tools that are insufficiently sensitive to measure small changes in performance, and the complexities caused by the longevity and reversibility of diet induced changes in developmental outcomes has been published.<sup>24</sup>

## CHILDHOOD

Despite widespread interest in the potential use of n-3 LCP supplementation to enhance development and be-

haviour among school-age children, there has to-date been no published trial on healthy children. A recent systematic review identified five randomised controlled trials that examined the effect of n-3 LCP supplementation on learning and behaviour in childhood,<sup>25</sup> but all five trials were conducted among children with neurodevelopmental disorders (dyspraxia and attention-deficit hyperactivity disorder ADHD).<sup>26-30</sup> Study subjects were aged between 5 and 13 years, study samples were small (40-117 participants), and intervention periods ranged from 2-4 months.

Two studies assessed biochemical markers of fatty acid status.<sup>29,30</sup> Stevens<sup>29</sup> found correlations between blood concentrations of n-3 LCPs and behaviour but only small improvements in 2 out of 16 subjective behaviour and education assessments, while Voigt<sup>30</sup> showed an increase in the n-3 LCP blood concentrations in the intervention group but no differences in behavioural or education outcomes between the intervention and control group. Richardson<sup>28</sup> found small improvements in 3 out of 14 subjective parental behaviour scores in the intervention group, and Hirayama<sup>26</sup> found no difference between the intervention and control groups. The Oxford-Durham study<sup>27</sup> was the only study to report consistent improvements in objective and subjective assessments in the intervention group, although there were no measured gains in motor skills.

Quite understandably, the systematic review authors concluded that "there remain too many inconsistencies between studies to reliably inform any conclusion",<sup>25</sup> and generalisability of any findings from these trials to a mainstream population of healthy children is not possible. Given the public interest in this field, large scale properly designed trials are urgently needed.

## OLDER AGE

LCP concentrations in brain tissues appear to decrease with age,<sup>31</sup> and it has been proposed that these changes in lipid composition are associated with changes in central nervous system function.<sup>32</sup> While the underlying cause of these changes in n-3 LCP concentrations in the ageing brain is largely unknown there is clearly a role for dietary intake throughout life in determining lipid composition. For example, consumption of large amounts of n-6 fats can reduce synthesis of n-3 LCPs, while consumption of diets containing 20 or 22 carbon polyunsaturated fatty acids might increase n-3 LCP concentrations.

Information on the effects of n-3 LCP supplementation on cognitive health in older age is quite scarce and a recent systematic review identified only four cohort studies and one randomised control trial that investigated the effect of n-3 LCPs on cognitive health.<sup>33</sup> The four cohort studies<sup>34-37</sup> all suggested a positive impact of increased n-3 LCP (fish and total n-3) consumption on risk of impaired cognitive function, dementia or Alzheimer's disease. The one trial included in the review<sup>38</sup> was small, conducted among demented older people and was of poor quality.<sup>33</sup> A recent Cochrane review found no published randomised controlled trials investigating the effect of n-3 LCP supplementation on cognitive function among healthy older adults.<sup>39</sup>

Since the publication of the review, two further cohort studies,<sup>40,41</sup> and one randomised controlled trial<sup>42</sup> have

been published. A 5-year follow up of 210 surviving males in the Zutphen Elderly Study cohort who were aged 70-89 at baseline demonstrated that fish consumers had significantly less 5-year cognitive decline than non-fish consumers, and that this could be directly related to n-3 LCP intake. Older men who consumed approximately 400mg n-3 LCP a day had less cognitive decline (1.1 point less on the 30 point Mini Mental State Examination [MMSE] scale) than men who consumed only 20mg n-3 LCP a day.<sup>41</sup> While this analysis from the long-running Zutphen Elderly Study presented very detailed information on dietary intake, it did not present any information on biochemical markers of fatty acid status.

A recent report from the Framingham Heart study presented data on a 9 year follow-up of 899 men and women with a median age of 76 years at baseline.<sup>40</sup> Plasma fatty acid status was assessed at baseline and the primary outcome for the analysis was the development of all-cause dementia and Alzheimer's disease. Over the follow-up period, 99 new cases of dementia (including 77 Alzheimer's disease) were diagnosed, and study participants in the highest quartile of plasma phosphatidylcholine DHA concentration were 47% less likely to develop all-cause dementia and 39% less likely to develop Alzheimer's disease than participants in the lowest three quartiles. Highest quartile intakes were in the region of 200mg DHA per day.<sup>40</sup>

The best randomised controlled trial conducted to date, assessing the impact of n-3 LCP supplementation on cognitive function in later life, recruited 174 participants with mild to moderate Alzheimer's disease. The study participants, who had a mean age of 74 years and an MMSE score of 15 points or more (30 being the highest), were provided with 2.3g n-3 LCP per day, or placebo, for 6 months. After 6 months of intervention the decline in cognitive function as assessed by MMSE did not differ between the two trial arms. However, in a sub-group of 32 participants with mild cognitive function loss (MMSE > 27 points), the rate of cognitive decline in the n-3 LCP intervention arm was significantly slower than that in the placebo arm. While these results, suggesting that n-3 LCP supplementation can delay cognitive function loss are exciting, they must be confirmed by larger and more long term studies. We are currently conducting a large randomised controlled trial – the OPAL study<sup>43</sup> – which is investigating the effect of 0.7g n-3 LCP supplementation for 24 months on a cohort of 868 healthy adults aged 70-79 years at baseline. The results of the trial are due in late 2008.

In contrast to their proposed actions in childhood, where n-3 LCPs are required for healthy development of brain tissue, in older age n-3 LCPs are more like to act in a protective and health-maintaining manner. For example, n-3 LCPs are known to inhibit hepatic triglyceride synthesis and, by modifying eicosanoid function, cause vascular relaxation, a diminished inflammatory process and decreased platelet aggregation.<sup>44</sup> Furthermore, some new protective actions of DHA have recently been discovered that may well be directly related to its effects in maintaining cognitive health in older age.<sup>45</sup>

## CONCLUSIONS

There is now a growing body of evidence that supports the general hypothesis that n-3 LCPs are crucial for brain development and for the maintenance of good cognitive function in later life. What is clear from this review, however, is that there remain some unanswered questions, and specifically there is a lack of high-quality population-based effectiveness trials in many areas. With global population ageing continuing apace and a concomitant increase in the number of individuals suffering from poor cognitive health, we must not delay in our search for cost-effective solutions.

## ACKNOWLEDGEMENTS

The authors acknowledge funding from the UK Food Standards Agency (NO5053) which supported in part the preparation of the manuscript and research related to the topic.

## AUTHOR DISCLOSURES

Alan D Dangour and Ricardo Uauy, no conflicts of interest.

## REFERENCES

1. Burr, G. O. & Burr, M. M. Nutrition classics from The Journal of Biological Chemistry 82:345-67, 1929. A new deficiency disease produced by the rigid exclusion of fat from the diet. *Nutr Rev.* 1973;31:248-249.
2. Holman, R. T., Johnson, S. B. & Hatch, T. F. A case of human linolenic acid deficiency involving neurological abnormalities. *Am J Clin Nutr.* 1982;35:617-623.
3. Simopoulos, A. P. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr.* 1991;54:438-463.
4. Neuringer, M., Connor, W. E., Van Petten, C. & Barstad, L. Dietary omega-3 fatty acid deficiency and visual loss in infant rhesus monkeys. *J Clin Invest.* 1984;73:272-276.
5. Uauy, R. D., Birch, D. G., Birch, E. E., Tyson, J. E. & Hoffman, D. R. Effect of dietary omega-3 fatty acids on retinal function of very-low-birth-weight neonates. *Pediatr Res.* 1990;28:485-492.
6. Ballabriga, A. Essential fatty acids and human tissue composition. An overview. *Acta Paediatr.* 1994;402:S63-68.
7. Galli, C., Trzeciak, H. I. & Paoletti, R. Effects of dietary fatty acids on the fatty acid composition of brain ethanolamine phosphoglyceride: reciprocal replacement of n-6 and n-3 polyunsaturated fatty acids. *Biochim Biophys Acta.* 1971;248:449-454.
8. Mitchell, D. C., Niu, S. L. & Litman, B. J. DHA-rich phospholipids optimize G-Protein-coupled signaling. *J Pediatr.* 2003;143:S80-86.
9. Stubbs, C. D. & Smith, A. D. The modification of mammalian membrane polyunsaturated fatty acid composition in relation to membrane fluidity and function. *Biochim Biophys Acta.* 1984;779:89-137.
10. Uauy, R. & Dangour, A. D. Nutrition in brain development and aging: role of essential fatty acids. *Nutr Rev.* 2006;64:S24-33.
11. Rotstein, N. P., Politi, L. E. & Avelano, M. I. Docosahexaenoic acid promotes differentiation of developing photoreceptors in culture. *Invest Ophthalmol Vis Sci.* 1998;39:2750-2758.
12. Rojas, C. V., Martinez, J. I., Flores, I., Hoffman, D. R. & Uauy, R. Gene expression analysis in human fetal retinal explants treated with docosahexaenoic acid. *Invest Ophthalmol Vis Sci.* 2003;44:3170-3177.
13. van Houwelingen, A. C., Foreman-van Drongelen, M. M., Nicolini, U., Nicolaides, K. H., Al, M. D., Kester, A. D. & Hornstra, G. Essential fatty acid status of fetal plasma phospholipids: similar to postnatal values obtained at comparable gestational ages. *Early Hum Dev.* 1996;46:141-152.

14. Clandinin, M. T., Chappell, J. E., Leong, S., Heim, T., Swyer, P. R. & Chance, G. W. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. *Early Hum Dev.* 1980;4:121-129.
15. Simmer, K. & Patole, S. Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev.* 2004:CD000375.
16. Clandinin, M. T., Van Aerde, J. E., Merkel, K. L., Harris, C. L., Springer, M. A., Hansen, J. W. & Diersen-Schade, D. A. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. *J Pediatr.* 2005;146:461-468.
17. Martinez, M. Polyunsaturated fatty acids in the developing human brain, red cells and plasma: influence of nutrition and peroxisomal disease. *World Rev Nutr Diet.* 1994;75:70-78.
18. Simmer, K. Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev.* 2001:CD000376.
19. Helland, I. B., Smith, L., Saarem, K., Saugstad, O. D. & Drevon, C. A. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics.* 2003;111:39-44.
20. Jensen, C. L., Voigt, R. G., Prager, T. C., Zou, Y. L., Fraley, J. K., Rozelle, J. C., Turcich, M. R., Llorente, A. M., Anderson, R. E. & Heird, W. C. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. *Am J Clin Nutr.* 2005;82:125-132.
21. Birch, E. E., Hoffman, D. R., Uauy, R., Birch, D. G. & Prestidge, C. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. *Pediatr Res.* 1998;44:201-209.
22. Birch, E. E., Garfield, S., Hoffman, D. R., Uauy, R. & Birch, D. G. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol.* 2000;42:174-181.
23. Birch, E. E., Castaneda, Y. S., Wheaton, D. H., Birch, D. G., Uauy, R. D. & Hoffman, D. R. Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. *Am J Clin Nutr.* 2005;81:871-879.
24. Lauritzen, L., Hansen, H. S., Jorgensen, M. H. & Michaelsen, K. F. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. *Prog Lipid Res.* 2001;40:1-94.
25. Ells, L. J., Hillier, F. C. & Summerbell, C. D. A systematic review of the effect of nutrition, diet and dietary change on learning, education and performance of children of relevance to UK schools. (FSA project code: NO5070). University of Teeside, 2006.
26. Hirayama, S., Hamazaki, T. & Terasawa, K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study. *Eur J Clin Nutr.* 2004;58:467-473.
27. Richardson, A. J. & Montgomery, P. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics.* 2005;115:1360-1366.
28. Richardson, A. J. & Puri, B. K. A randomised double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2002;26:233-239.
29. Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstad, N., Mahon, A., Zentall, S. S., Arnold, L. E. & Burgess, J. R. EPA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids.* 2003;38:1007-1021.
30. Voigt, R. G., Llorente, A. M., Jensen, C. L., Fraley, J. K., Berretta, M. C. & Heird, W. C. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr.* 2001;139:189-196.
31. Soderberg, M., Edlund, C., Kristensson, K. & Dallner, G. Lipid compositions of different regions of the human brain during aging. *J Neurochem.* 1990;54:415-423.
32. Anonymous Fatty acid composition of brain phospholipids in aging and Alzheimer's disease. *Lipids.* 1991;26:421-425.
33. Issa, A. M., Mojica, W. A., Morton, S. C., Traina, S., Newberry, S. J., Hilton, L. G., Garland, R. H. & Maclean, C. H. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. *Dement Geriatr Cogn Disord.* 2006;21:88-96.
34. Kalmijn, S., van Boxtel, M. P., Ocke, M., Verschuren, W. M., Kromhout, D. & Launer, L. J. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology.* 2004;62:275-280.
35. Kalmijn, S., Feskens, E. J., Launer, L. J. & Kromhout, D. Polyunsaturated fatty acids, antioxidants, and cognitive function very old men. *Am J Epidemiol.* 1997;145:33-41.
36. Barberger-Gateau, P., Letenneur, L., Deschamps, V., Peres, K., Dartigues, J. F. & Renaud, S. Fish, meat, and risk of dementia: cohort study. *Bmj.* 2002;325:932-933.
37. Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Wilson, R. S., Aggarwal, N. & Schneider, J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol.* 2003;60:940-946.
38. Terano, T., Fujishiro, S., Ban, T., Yamamoto, K., Tanaka, T., Noguchi, Y., Tamura, Y., Yazawa, K. & Hirayama, T. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids.* 1999;34:S345-346.
39. Lim, W. S., Gammack, J. K., Van Niekerk, J. & Dangour, A. D. Omega 3 fatty acid for the prevention of dementia. *Cochrane Database Syst Rev.* 2006:CD005379.
40. Schaefer, E. J., Bongard, V., Beiser, A. S., Lamon-Fava, S., Robins, S. J., Au, R., Tucker, K. L., Kyle, D. J., Wilson, P. W. & Wolf, P. A. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Arch Neurol.* 2006;63:1545-1550.
41. van Gelder, B. M., Tijhuis, M., Kalmijn, S. & Kromhout, D. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *Am J Clin Nutr.* 2007;85:1142-1147.
42. Freund-Levi, Y., Eriksdotter-Jonhagen, M., Cederholm, T., Basun, H., Faxen-Irving, G., Garlind, A., Vedin, I., Vessby, B., Wahlund, L. O. & Palmblad, J. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch Neurol.* 2006;63:1402-1408.
43. Dangour, A. D., Clemens, F., Elbourne, D., Fasey, N., Fletcher, A. E., Hardy, P., Holder, G. E., Huppert, F. A., Knight, R. et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. *Nutr J.* 2006;5:20.
44. Uauy, R. & Valenzuela, A. Marine oils: the health benefits of n-3 fatty acids. *Nutrition.* 2000;16:680-684.
45. Lukiw, W. J., Cui, J. G., Marcheselli, V. L., Bodker, M., Botkjaer, A., Gotlinger, K., Serhan, C. N. & Bazan, N. G. A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J Clin Invest.* 2005;115:2774-2783.