The role of omega-3 fatty acids in child development*

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Abstract: *Omega-3 long chain polyunsaturated fatty acids (n-3 LCPUFA) are important constituents of the maturing brain and therefore considered crucial for brain development* in utero *and in early infancy. However, it is uncertain whether n-3 LCPUFA supplementation during pregnancy and lactation can have beneficial, sustainable effects on visual or cognitive development. Beneficial effects on child cognitive function after supplementation with EPA and DHA during pregnancy and lactation were observed at 4 years of age, but not at 3, 6 months or 7 years. In term infants LCPUFA when given in relative high dosages, seems to improve visual acuity, but not cognitive function. Evidence for an effect of LCPUFA supplementation of preterm infants remains inconclusive. In children older than 2 years of age, epidemiological evidence suggests an association between psychiatric or neurodevelopmental disorders and omega-3 fatty acid deficiencies. However, the evidence from randomized controlled trials exploring the impact of omega-3 fatty acids on cognitive performance or brain function in school-aged children is not conclusive. In conclusion, n-3 LCPUFA are highly present in the maturing brain and are important for normal brain functioning and development. When provided in relative high dosages, n-3 LCPUFA may improve visual acuity in term infants. However, it remains unclear whether supplementation with n-3 LCPUFA during pregnancy, early infancy, and childhood can improve cognitive function.*

Key words: *child development, omega-3 fatty acids, neurodevelopmental disorders psychiatric disorders*

There is considerable interest in the role of certain long chain polyunsaturated fatty acids (LCPUFA), in visual and cognitive development throughout childhood. The n-3 fatty acid docosahexaenoic acid (DHA) and the n-6 fatty acid arachidonic acid (AA) are the major LCPUFA in the brain (Martinez, 1992). DHA and AA are rapidly incorporated in the nervous tissue of retina and brain during the brain's growth spurt, which mainly takes place from the last trimester of pregnancy up to 2 years of age (Dobbing and Sands, 1973; Clandinin *et al.*, 1980; Martinez, 1992). Beyond development of the central nervous system, n-3 and n-6 fatty acids may influence brain function throughout life by modifications of neuronal membrane fluidity, membrane activity-bound enzymes, number and affinity of receptors, function of neuronal membrane ionic channels, and production of neurotransmitters and brain peptides (Yehuda, 2003). Although DHA and AA are the major structural components of the central nervous system, there is currently no consensus whether dietary supplementation of LCPUFA has benefits for visual and cognitive development of infants.

Evidence from pregnant and lactating mothers

There is suggestive evidence for a beneficial effect of early exposure to n-3 fatty acids on children's cognitive development. Repeatedly, positive findings on a beneficial effect of n-3 fatty acid supplementation or fish intake during pregnancy and/or lactation on developmental outcomes of the offspring (> 2 years) were reported from both observational studies and randomized controlled trials (RCTs) *(figure 1)*.

Three RCTs from high-income countries supplemented with n-3 fatty acids during pregnancy. Two of these trials reported improvements in problem solving at 9 months of age (Judge *et al.*, 2007) or hand-eye coordination at 30 months of age (Dunstan *et al.*, 2008). However, as a lot of outcome measures were tested in these RCTs without adjusting p-values accordingly, positive findings may have been due to chance. In contrast, one recent large study with high-DHA fishoil in Australia did not observe benefits in cognitive and language scores at 18 months of age after maternal supplementation during pregnancy (Makrides *et al.*, 2010).

Two intervention trials on prenatal supplementation with n-3 LCPUFA have

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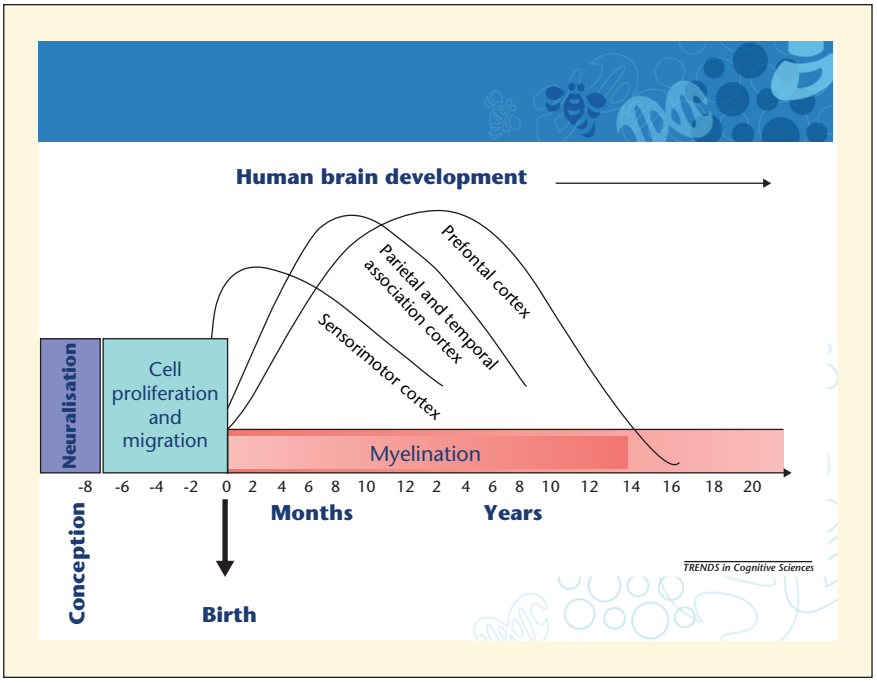

Figure 1. *Brain development in childhood. Adapted from Thompson, RA, Nelson CA. Development.* Am Psychol *2001; 56: 5-15. Animation: Gogtay* et al.*, 2007*

been conducted in low-income countries: in Bangladesh and Mexico. Both studies did not observe differences between infants from treated and control mothers in development scores at 10 or 18 months of age were observed (Tofail *et al.*, 2006; Ramakrishan *et al.*, 2010).

One study reported on the effects of maternal supplementation with 803 mg EPA and 1183 mg DHA from 18 weeks gestation until 3 months postpartum. Beneficial effects were observed on mental processing index at 4 years (Helland *et al.*, 2003; Helland *et al.*, 2008) but not any more at 7 years of age. Infant, maternal or cord blood DHA status was repeatedly found to be positively correlated to cognitive outcomes (Helland 2003 *et al.*;, Helland *et al.*, 2008; Dunstan *et al.*, 2008).

Overall, there is no consistency with regard to the areas of mental development that might benefit from maternal n-3 fatty acid supplementation; improvements were reported for general IQ, memory, verbal, motor performance, attention, hyperactivity and social behaviour.

A recent Cochrane review (Delgado-Noguera *et al.*, 2010) on the effects of supplementation with LCPUFA to breast-feeding mothers for improving child growth and development conducted a pooled analysis of outcomes on five clustered areas of neurodevelopment, i.e. language development, intelligence/problem solving ability, psychomotor development, motor development and child attention. Overall, no significant effects were found, except for attention at 5 years which was due to one single study (Jensen *et al.*, 2010). It was concluded that based on the limited evidence, LCPUFA supplementation during the lactation period did not appear to improve children's neurodevelopment.

Six (Lederman *et al.*, 2008; Oken *et al.*, 2008; Mendez *et al.*, 2008; Gale *et al.*, 2008; Budtz-Jorgensen *et al.*, 2007; Hibbeln *et al.*, 2007) out of seven (Strain *et al.*, 2008) observational studies report a significant beneficial association of maternal fish intake during pregnancy and children's development up to 14 years of age on one or more sub-scales (PDI/motor abilities; hyperactivity & social behaviour; verbal und full IQ) in combination with non-significant trends for other outcome measures suggesting beneficial effects of fish intake.

In summary, repeatedly, positive findings on a beneficial effect of n-3 or fish intake during pregnancy and/or lactation on developmental outcomes of the offspring up to 14 years were reported from observational studies. The small number of RCTs, however, reported only few positive findings on single outcome measures, which may have been due to chance. Overall, there is no consistency in the benefits observed, with improvements being reported for general IQ, memory, verbal, motor performance, attention, hyperactivity and social behaviour.

Evidence from term and pre-term infants

Evidence on the effects of LCPUFA during infancy have been well-documented and summarised in recent meta-analysis. Overall, there is no good evidence for a beneficial effect of LCPUFA supplementation on mental development in infants (< 2 yr). A recent meta-analysis on the effects of LCPUFA supplementation of *pre-term* infants on neurodevelopment up to 18 months of age reported that four out of seven studies did not show a benefit; the three trials which showed improvements on cognitive development scores all used the newer version of the Bayles Scales of Infant Development, suggesting that the effects may have been too subtle to be detected with other methods (Schulzke *et al.*, 2011). No beneficial effects of LCPUFA supplementation on visual development were seen either (Schulzke *et al.*, 2011). A meta-analysis on the effects of LCPUFA supplementation in *term* infants did not show an effect on either mental or psychomotor development (Simmer *et al.*, 2008). Outcomes on visual acuity were inconsistent, with six out of nine studies not showing a beneficial effect. Beneficial effects on visual acuity in term infants were seen with higher doses of DHA (0.35% or 0.36% in formula) and when measured by electrophysiological tests.

Evidence from healthy children

Studies in healthy children (> 2 yr) do not show consistent beneficial effects of a DHA or EPA supplementation. In total, seven out of ten randomised controlled intervention studies in 4-14 year old children did not find a beneficial effect

LCPUFA on cognitive outcomes (Kirby *et al.*, 2010; Kennedy *et al.*, 2009; Muthayya *et al.*, 2009; Ryan *et al.*, 2008; Osendarp *et al.*, 2007; de Jong *et al.*, 2010). The dosages used in this trial varied significantly and ranged from 100-1,200 mg DHA/EPA per day. In addition, all of these RCTs had some quality limitations, like a low intervention dose, a too short intervention period, use of non-validated tests, tests in non-native language, ceiling effect, multiple assessors, inappropriate control product, a small sample size, which might explain the lack of positive findings.

Three RCTs did find some beneficial effects (Dalton *et al.*, 2009; McNamara *et al.*, 2010; Portwood, 2011). One RCT in South African children of low SES with a habitual low fish intake found significant effects of a spread fortified with fish flour on verbal recognition, discrimination and spelling (Dalton *et al.*, 2009). The positive effects found cannot for sure be contributed to EPA & DHA as the fish flour also contains vitamins and minerals which might have had an effect. An fMRI study in 33 UK boys found significantly increased cortical activation during a sustained attention task upon eight weeks of supplementation with 400 or 1200 mg/d DHA (McNamara *et al.*, 2010), but no differences between groups in behavioural test outcomes. Another study in UK children found significant effects of a three month intervention with EPA (558 mg/d), DHA (174 mg/d) and GLA (60 mg/d) on reading age and working memory but not on behaviour. However, this study had some quality limitations and is still not published in a peer-reviewed paper (Portwood, 2011).

Observational (cross-sectional and longitudinal) studies in healthy children suggest that there might be a positive relationship between n-3 FA or fish intake and cognitive outcomes.

Five cross-sectional studies assessing 4-16 yr old children found a significant positive association between fish, n-3, or total PUFA intake and at least some cognitive outcomes (Kirby *et al.*, 2010, Theodore *et al.*, 2009; Kim *et al.*, 2009; Zhang *et al.*, 2005, Freire *et al.*, 2010). Two other studies did not find any significant associations (Mendez *et al.*, 2008, Eilander *et al.*, 2010).

Five longitudinal studies, followed children form birth to childhood (Bakker *et al.*, 2003, 2009; Ghys *et al.*, 2002; Gale *et al.*, 2010) or throughout childhood (Rask-Nissila *et al.*, 2002; Aberg *et al.*, 2009); two studies showed significant beneficial effects of DHA fortified formula during the first 6 months (Gale *et al.*, 2010) and fish intake during adolescence (Aberg *et al.*, 2009) on children's overall

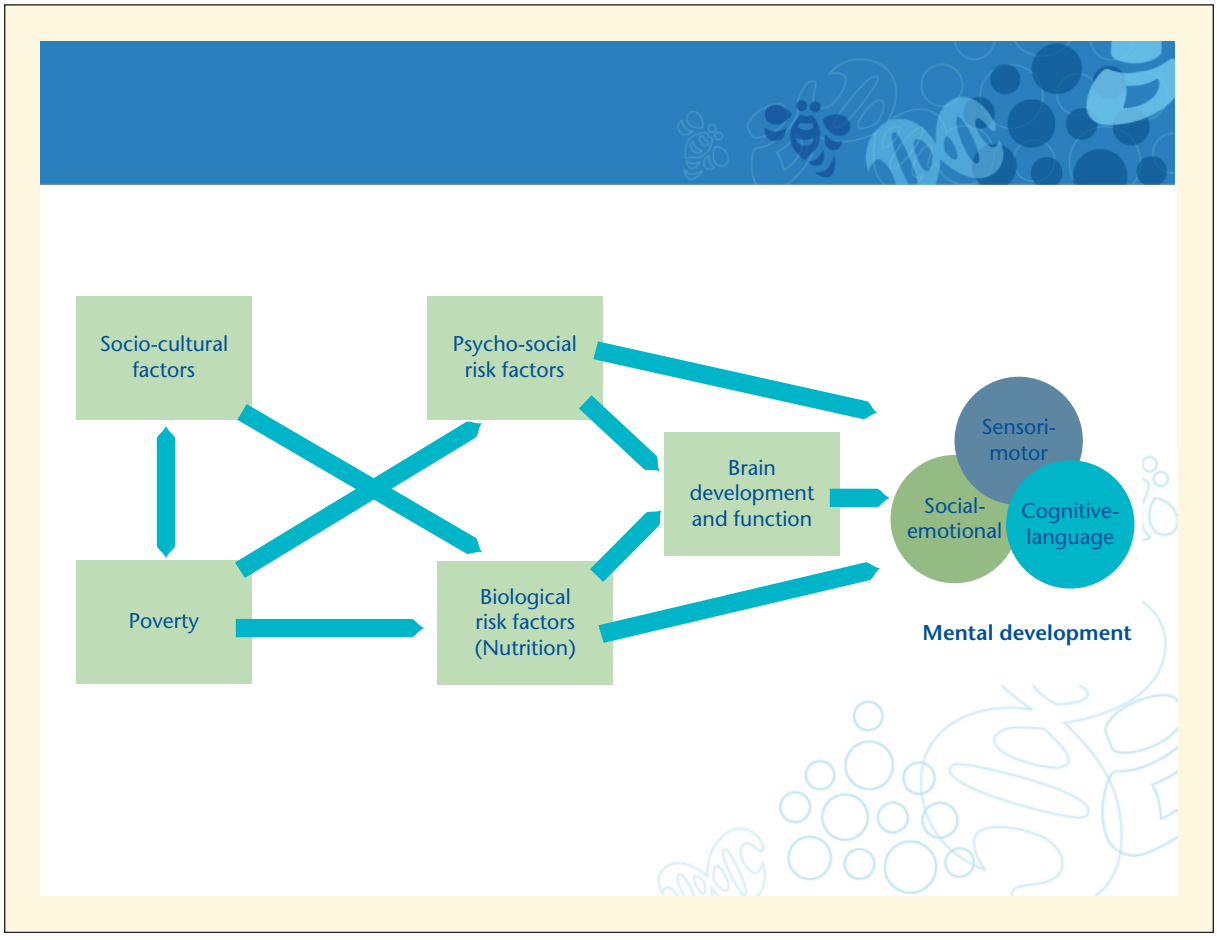

Figure 2. *Conceptual framework on role of nutrition in mental development. Adapted from Walker* et al., *Lancet 2007*

cognitive outcome measures. Other studies did not show an association between DHA status at birth or intake during the first six months with cognitive performance at 4 or 7 yr of age (Bakker *et al.*, 2003; Ghys *et al.*, 2002), but a positive relationship with improved motor performance at 5 (Rask-Nissila *et al.*, 2002) and 7 years of age (Bakker *et al.*, 2009) *(figure 2)*.

In summary, there is suggestive evidence – from *observational* studies – of a positive relationship between n-3 FA status at birth or fish intake during childhood and developmental outcomes in healthy children up to the age of 18 years. Yet the results might be confounded by other influencing factors and don't prove a cause-effect relationship. The potential beneficial effects are not confirmed in intervention trials. The majority (i.e. 7 out of 10) of randomized controlled intervention trials in healthy children does *not* show an effect of n-3 fatty acid supplementation on cognitive outcomes.

Evidence from diseased populations

There is some evidence from studies in children with phenylkenonuria (PKU) on the role of n-3 fatty acids in neurotransmission and behavioural outcomes. Children with PKU have very low natural intakes of EPA and DHA due to dietary restrictions (but a good supply of ALA). Two studies (one of them an open label study) in treated PKU children showed that these children had prolonged visual evoked potentials compared to healthy controls. After supplementation with DHA, EPA (+ALA and AA) wave latency of visual evoked potentials decreased in both studies, indicating more rapid central nervous system information processing (Beblo *et al.*, 2001). The open-label study also showed significant improvements of EPA+DHA supplementation on a test of motor function and coordination (Beblo *et al.*, 2007). When the subjects of the controlled trial were assessed again three years later after the end of the treatment to see whether improvements had lasted in the longer term, initial improvements had returned to baseline (Agostini *et al.*, 2003).

In addition, there is some evidence from EPA/DHA intervention studies on cognitive functioning in children with developmental disorders. Evidence from studies in children with ADHD show some positive findings on self-reported behaviour. Four (Richardson and Puri, 2002; Stevens *et al.*, 2003; Sinn, 2007; Johnson *et al.*, 2009) out of five (Raz *et al.*, 2009) randomized controlled trials supplementing a mix of n-3 fatty acids (120-730 mg/d) and n-6 fatty acids (60 to 135 mg/d) showed improvements on self-reported ADHD symptoms. Six more studies of varying quality, two of them were open-label studies, supplemented n-3 fatty acids alone (Voigt *et al.*, 2001; Hiramaya *et al.*, 2004; Joshi *et al.*, 2006; Sorgi *et al.*, 2007; Vaisman *et al.*, 2008; Gustafsson *et al.*, 2010). Only the open-label studies showed a significant effect of ALA (400 mg/d) or very high doses of EPA/DHA (16 g/d) on behavioural outcomes (Joshi *et al.*, 2006; Sorgi *et al.*, 2007). Three of the four randomized controlled trials supplementing DHA (+EPA) point into the same direction (Voigt *et al.*, 2001; Vaisman *et al.*, 2008; Gustafsson *et al.*, 2010) *(figure 2)*.

Discussion and conclusion

LCPUFA and DHA in particular are abundantly present in the human developing brain. However, the evidence base for a beneficial effect of dietary LCPUFA on child's development is thin and has inconsistent findings. Supportive evidence for a beneficial role of n-3 fatty acids in cognitive functioning is mainly coming from studies in specific patient groups (PKU) or children with developmental disorders (ADHD, neurophysiologic diseases, n-3 deficiency). It is questionable however, how far this evidence can be extrapolated to the general population.

It is unfortunate that most of the intervention studies reported to date suffer from methodological limitations. Failure to find positive effects of LCPUFA on child development might have been due to intervention dosages which were too low, too short interventions, limitations related to the use of psychological tests, inappropriate control products and small sample sizes. On the other hand, trials which did demonstrate positive effects, may in fact have reported false-positive findings particularly due to a high number of test outcomes included and the possibility of chance findings. The question whether additional *dietary supply* of DHA, is required for cognitive functioning after the age of 2 years, remains therefore unanswered.

Rapoport *et al.* (2007) studied the turnover of DHA in the human brain by measuring the daily incorporation of radio-labelled DHA into the brain. He stated that the incorporation rate of DHA equal the rate of loss because DHA cannot be synthesized de novo in the brain, neither does its precursor (ALA) contribute significantly (<1%) to brain DHA. He found that the adult brain uses and replaces 4.6 mg of DHA per day. This suggests that DHA in the brain might need to be replenished to maintain certain levels. However, in a rat study Rapoport et al. also showed that the rate of liver synthesis of DHA from ALA was more than sufficient to maintain brain DHA (Rapoport *et al.*, 2007).

As several studies in specific patient groups (ADHD, PKU) showed that EPA/DHA supplementation had a beneficial effect on functional cognitive outcomes (primarily behaviour related) one can hypothesise that *dietary* fatty acids do arrive at the target organ and that they are indeed used in their role in cognitive functioning. However, this would still need to be confirmed.

Because the conversion of ALA to DHA is very limited, many health authorities currently advice to ensure a minimum intake of DHA and EPA from the diet, despite the fact that in principle the body should be able to make these fatty acids. EPA and DHA are for that reason considered ''conditionally essential'' (Uauy and Dangour, 2009).

Recommendations for the intake of EPA and DHA for adults are mainly based on primary and secondary prevention of cardiovascular disease (CVD; 250-500 mg/d EPA+DHA or 1-2 portions of fatty fish per week). For children from 2-10 years the FAO recently set recommendations for an adequate EPA and DHA intake, i.e. 100 to 250 mg (depending on the age) (FAO, 2010) in line with adults aiming at the early prevention of chronic disease (Koletzko *et al.*, 2010). In children and adults, PUFA intakes are generally below the recommendations. Also EPA and DHA intakes are lower than recommended; however, data are very limited (Harika *et al.*, 2011). Despite the on-going debate on the exact role of LCPUFA in cognitive, efforts to increase

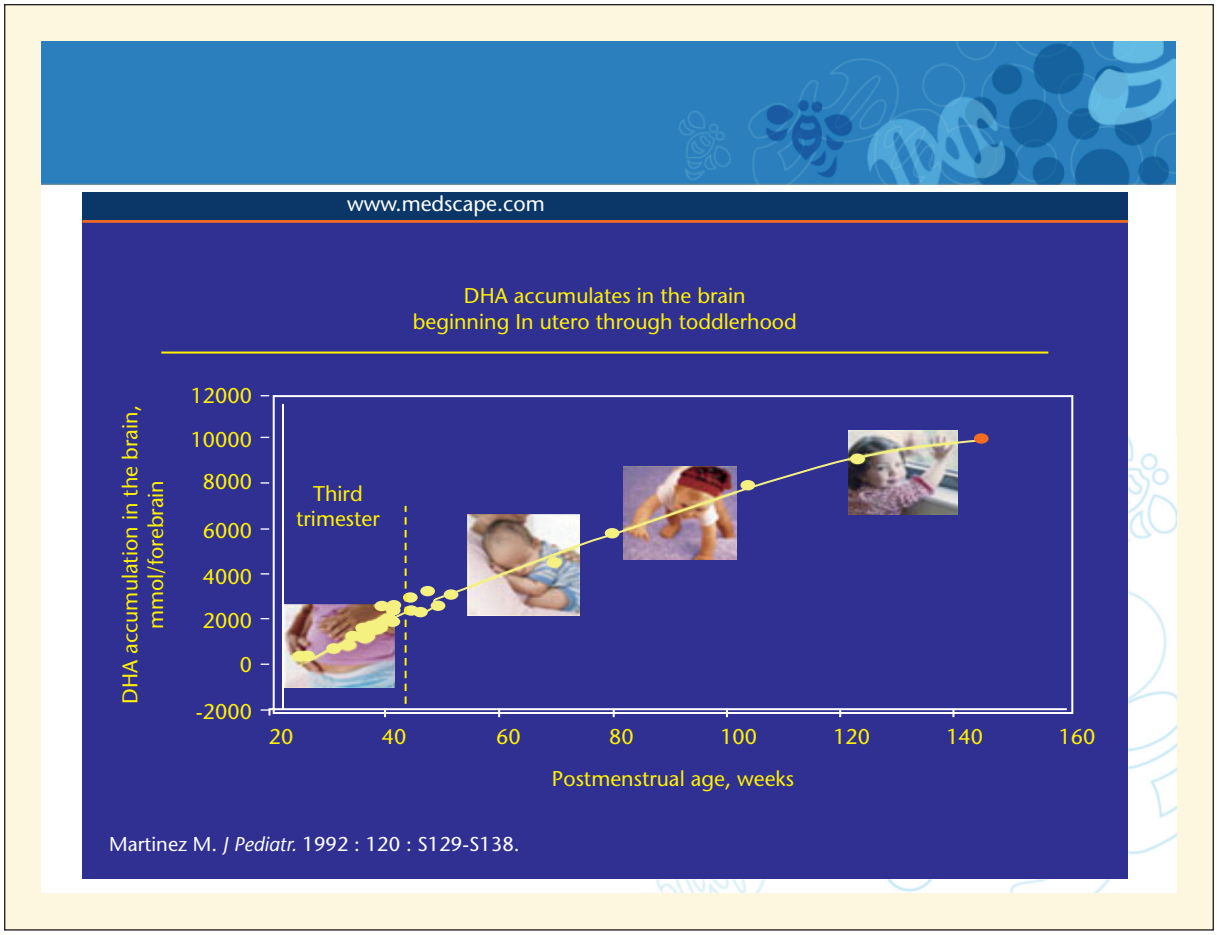

Figure 3. *Brain DHA during gestation and early childhood. Adapted from Martinez M.* J Pediatr *1992, 120: S129-s138*

consumption of these fatty acids in children should therefore be supported *(figure 3)*.

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