European Journal of Clinical Nutrition (2007), 1–6
 0954-3007/07 $30.00
www.nature.com/ejcn

ORIGINAL ARTICLE

Relationship between long-chain polyunsaturated fatty acids at birth and motor function at 7 years of age

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Background/Objectives: Long-chain polyunsaturated fatty acids (LCPUFA) rapidly accumulate in the central nervous system (CNS) during the perinatal CNS growth spurt. This particularly concerns arachidonic acid (AA: 20:4*n*−6) and docosahexaenoic acid (DHA: 22:6*n*−3), which are thought to play important roles in CNS development and function. The aim of this study was to investigate the relation between motor function at 7 years of age and the levels of AA and DHA in umbilical venous plasma phospholipids, representing the prenatal availability of these fatty acids, and in plasma phospholipids sampled at age 7 years.
Subjects/Methods: Motor function was assessed both quantitatively (the ability to perform a movement) and qualitatively (how the movement is performed) with the Maastricht Motor Test (MMT) in 306 children, born at term, at 7 years of age as part of a follow-up study.
Results: Backward stepwise multiple regression analyses revealed a significant, positive relation between umbilical plasma DHA concentrations (but not plasma DHA levels at 7 years) and the MMT total and quality score, corrected for the covariables gender, cognitive performance, gestational age and age at measurement (partial $\beta = 0.13$, $P = 0.01$ and 0.14, $P = 0.01$, respectively). The contributions of DHA and AA (both at birth and at 7 years of age) to quantitative movement scores were not significant.
Conclusions: Our results suggest that prenatal DHA availability, which can be influenced by maternal dietary DHA intake during pregnancy, can have an effect on quality of movement in later life.
European Journal of Clinical Nutrition advance online publication, 19 December 2007; doi:10.1038/sj.ejcn.1602971

Keywords: arachidonic acid; docosahexaenoic acid; motor function; movement quality; Maastricht Motor Test; LCPUFA

Introduction

The central nervous system (CNS) contains high amounts of long-chain polyunsaturated fatty acids (LCPUFA), especially arachidonic acid (AA: 20:4*n*−6) and docosahexaenoic acid (DHA: 22:6*n*−3) (Sastry, 1985). These fatty acids can either be supplied by nutrition or synthesized from their (essential) precursors linoleic acid (LA: 18:2*n*−6) or α-linolenic acid (ALA: 18:3*n*−3), respectively (Innis, 1991). During the last trimester of gestation and in the first postnatal year, the CNS undergoes a growth spurt, so an adequate supply of LCPUFA to the child during this period will be important for optimal CNS development (Innis, 1991; Reisbick, 1996).

Several studies have shown the importance of postnatal dietary LCPUFA for the development of term infants (Makrides *et al*., 1995; Birch *et al*., 1998; Willatts *et al*., 1998), although the evidence is not unequivocal (Auestad *et al*., 2001; Simmer, 2001).

It can be hypothesized that prenatal LCPUFA supply also exerts an influence on CNS development, because rapid CNS growth already starts prenatally. The absolute accretion rates of the *n*−3 fatty acids are even greater in the prenatal period compared with the postnatal period (Clandinin *et al*., 1980a, b).

Indeed, maternal LCPUFA supplementation during pregnancy seems to enhance several aspects of CNS function. Helland *et al*. (2003) found that supplementation with very long-chain *n*−3 PUFAs during pregnancy and lactation lead

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Received 30 June 2007; revised 7 November 2007; accepted 12 November 2007

to higher scores on the Mental Processing Composite of the K-ABC at 4 years of age. In the study of Dunstan *et al*. (2006), maternal fish oil supplementation during pregnancy was associated with higher scores for eye–hand coordination in children at 2.5 years of age. Recently, Bouwstra *et al*. (2006) observed that infants with an umbilical plasma DHA content within the lowest quartile had significantly lower neurologic optimality scores at 18 months of age than the other infants. We investigated the association between LCPUFA status at birth and some longer term outcomes. The present study focused on the relation between motor function at 7 years of age and DHA and AA values both in umbilical plasma, representing the prenatal availability of these fatty acids, and in venous plasma sampled at 7 years of age, reflecting the status of these fatty acids at follow-up.

Both quantitative and qualitative aspects of motor performance were studied. Quality of movement, the way in which a child performs movements, might be an even more important indicator of brain maturation and integrity than movement quantity, the ability of a child to perform certain movements (Touwen, 1979; Weisglas-Kuperus *et al*., 1994; Gabbard, 1996).

Subjects and methods

Subjects

The study described in this paper is part of a follow-up study investigating the relationship between essential fatty acid status at birth and mental development at 7–8 years of age. The eligible study population consisted of 750 Caucasian children of 7 years old, born between December 1990 and January 1994 in our earlier studies on maternal and neonatal LCPUFA status and pregnancy outcome (Al *et al*., 1995, 2000; Hornstra, 2000).

As described before (Bakker *et al*., 2003), 306 of these children eventually participated in the follow-up study. Written informed consent was obtained from the parents of each participant. The study was approved by the Ethics Committee of the University Hospital Maastricht/Universiteit Maastricht.

Measurement of motor function

At 7 years of age, all participating children were assessed at the University Hospital Maastricht for cognitive, visual and motor function. Furthermore, the neurological function of the children was examined in a standardized way by the child neurologist (JSHV). The focus of the present study is on motor performance, measured with the Maastricht Motor Test (MMT), which measures motor function not only quantitatively, but qualitatively as well (Kroes *et al*., 2004; Vles *et al*., 2004).

The MMT consists of 20 tasks, of which both quantity and quality are scored (Kroes *et al*., 2004; Vles *et al*., 2004). For example, the ability of a child to stand on one leg results in a quantitative score, based on the time the child is able to keep this position, and a qualitative score, based on the way in which the child performs the task (child stands still or wiggles). This results in 34 quantitative items and 36 qualitative items, covering the areas of static balance (14 items), dynamic balance (20 items), ball skills (8 items) and manual dexterity (28 items). All 70 items are scored on a three-point scale from 0 to 2, with low scores indicating poor performance. These scores are summed to produce a total score ranging from 0 (extremely poor) to 140 (excellent); the total quantity score ranges from 0 to 68; the total quality score from 0 to 72.

The MMT was administered in a quiet room by a single, well-trained tester (ECB), who was unaware of children's LCPUFA status.

Measurement of fatty acid status and covariables

Fatty acid profiles of umbilical venous plasma phospholipids and of venous plasma phospholipids sampled at 7 years of age were determined as described before (Bakker *et al*., 2003). All blood samples from 7-year-olds were obtained in a fasted state. Fatty acid data are presented as relative levels (% of total fatty acids, w/w).

The following covariables were included in the analyses: gender, cognitive function, gestational age and age at measurement. Cognitive function was assessed with the Kaufman-Assessment Battery for Children at 7 years of age, as a part of the follow-up study (Bakker *et al*., 2003), and included in these analyses because motor function is known to be associated with cognition (Soorani-Lunsing *et al*., 1993; Weisglas-Kuperus *et al*., 1994). Furthermore, motor function is known to be associated with gender, gestational age and age at measurement (Henderson and Hall, 1982; Johnston *et al*., 1987). Therefore, these variables are included in the analyses as well.

Statistical analyses

Outcome data were screened for normality; the quantitative motor scores showed a ceiling effect and were dichotomized in scores lower than median (<62) and median or higher scores for logistic regression analyses. The Mann–Whitney *U*-test was used to test differences between boys and girls and between formula- and breast-fed children.

The relation between motor function of the children at 7 years of age and their fatty acid status at birth was investigated with backward stepwise multiple regression analyses, thereby identifying other predictors and confounders as well. The scores on the MMT were the dependent variables and DHA or AA the (separate) independent variables. Gender, cognitive performance (K-ABC Mental Processing Composite), gestational age and age at measurement were included as covariables in the initial model. In each step of the analyses, the nonsignificant covariable with the highest *P*-value was removed from the regression model.

It was only retained if it appeared a confounder (that is, if its removal resulted in a change in the regression coefficient *B* of more than 10% or 1 s.d. unit). The fatty acid variable and the significant covariables (predictors) were always retained. This procedure resulted in a final regression model containing only the fatty acid variable and the (significant) predicting and confounding variables. The relation between motor function and fatty acid status at 7 years (as a measure of fatty acid supply in later life) was studied similarly. The MMT quantity scores could not be transformed to normality, because of a ceiling effect. Therefore, we used logistic regression on the dichotomized scores; median or higher versus lower than median scores. In the statistical analyses, a *P*-value of <0.05 was considered significant.

Results

Study population

The follow-up study population consisted of 306 children, 170 boys and 136 girls with a mean age of 7.3 years (range 6.6–8.1 years). The neurological function, as measured with a standard neurological examination, performed by the child neurologist (JSHV), was within the normal range. Only one child was excluded from the analyses, because of complete paralysis of his left arm due to a birth trauma (Erb's paralysis). Clinical characteristics (mean ± s.d.) of the participating children are given in Table 1.

There were no differences in baseline clinical characteristics between the participants and nonparticipants, except for a small difference in umbilical plasma AA percentages (16.6 versus 16.9% in participants and nonparticipants, respectively; Bakker *et al*., 2003). One hundred forty-four children had been breast-fed, 161 children only received artificial formulas without LCPUFA. The breast-feeding group included all children who received any breast milk for a period up to 40 months (mean duration of breast-feeding 4.6 ± 4.6 months). There were no significant differences between formula- and breast-fed children in total motor scores (data not shown).

We were permitted to take a venous blood sample at follow-up of 261 of the 306 children. Table 1 shows the fatty acid status at birth (in umbilical plasma phospholipids) and at 7 years of age (in venous plasma phospholipids). There was a correlation between AA plasma levels at birth with those at 7 years of age ($R=0.24$, $P=0.0001$), but not between DHA plasma levels at birth and those at age 7 ($R=0.06$, $P=0.34$). No significant differences in fatty acid percentages were observed between boys and girls.

Maastricht motor test

The MMT was performed in 290 of the 306 children, in 10 children accomplishment of this test was impossible due to organizational reasons, 4 children did not cooperate well enough, 1 child did not feel well and 1 child was excluded because of Erb's paralysis. The total score on this test, consisting of total scores for both quantitative and qualitative motor function, was normally distributed in our study population, as was the total qualitative score. The total quantitative score showed a ceiling effect, which could not be resolved by transformation of the data. Therefore, the data of this variable were dichotomized in scores lower than median (<62) and median or higher scores ($\geqslant 62$) to perform logistic regression analyses. Table 2 shows total quantity and quality scores of boys and girls separately. Differences

Table 1 Clinical characteristics of the study population ($n=306$)

Variable[a]	*Boys* (n = *170*)	*Girls* (n = *136*)
Child characteristics		
Age at measurement (years)	7.3 (3.0)	7.3 (2.9)
Gestational age at birth (weeks)	39.8 (1.7)	40.0 (1.4)
Birth order (first child/other, %)	66/34	65/35
Birth weight (g)	3377 (510)	3223 (492)[†]
Birth length (cm)	50.4 (2.4)	49.3 (2.3)[†]
Head circumference (cm)	34.6 (1.6)	33.9 (1.8)[†]
Apgar score-5	9.6 (0.7)	9.6 (0.9)
Infant feeding habits (human milk/formula, %)	49/51	45/55
Cognitive function (K-ABC MPC[b])	106.7 (11.8)	107.8 (12.2)
Fatty acid concentrations (%w/w of total FA)		
Umbilical plasma DHA	6.1 (1.4)	6.1 (1.4)
Umbilical plasma AA	16.5 (1.6)	16.8 (1.6)
Venous plasma DHA at 7 years	2.8 (0.7)	2.8 (0.7)
Venous plasma AA at 7 years	9.2 (1.3)	9.2 (1.2)

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; FA, fatty acid.
[†]Significantly different from the boys ($P<0.05$).
[a]Values are either mean (s.d.) or percentages of study population.
[b]Cognitive function measured with the Kaufman-Assessment Battery for Children; Mental Processing Composite (Bakker *et al*., 2003).

Table 2 Performance on the Maastricht motor test

Maastricht motor test	*Median (interquartile range)*		P-*value*[a]
	Boys (N = *160*)	*Girls* (N = *130*)	
Total score	111 (101–120)	119 (113–124)	<0.0001
Quantity			
Total score	62 (60–63)	62 (61–64)	0.03
Manual dexterity	24 (23–24)	24 (22–24)	
Ball skills	8 (8–8)	8 (8–8)	
Static balance	14 (13–14)	14 (13–14)	0.02
Dynamic balance	17 (16–18)	18 (17–18)	0.003
Quality			
Total score	50 (42–57)	57 (52–62)	<0.0001
Manual dexterity	20 (17–23.5)	23 (21–25)	<0.0001
Ball skills	6 (6–7)	7 (6–7)	
Static balance	6 (4–10)	10 (8–12)	<0.0001
Dynamic balance	16 (13–19)	18 (15–20)	0.0003

[a]Results of Mann–Whitney *U*-test.

between boys and girls, tested with the Mann–Whitney *U*-test, were found for total score ($P<0.0001$), total quantity score ($P=0.03$), total quality score ($P<0.0001$), static balance quantity score ($P=0.02$) and quality score ($P<0.0001$), dynamic balance quantity score ($P=0.003$) and quality score ($P=0.0003$), and manual dexterity quality score ($P<0.0001$), all in favor of the girls.

MMT total score

Table 3 shows the results of the backward stepwise multiple regression analyses predicting the total score of the MMT with umbilical plasma DHA- and AA-concentrations as independent variables, respectively. Corrected for gender, age at measurement and cognitive performance, DHA at birth showed a significant positive relation with movement outcomes (partial $\beta=0.13$, $P=0.01$). The final model explained 26% of the variance, overall $F=25$, $P<0.0001$.

The corrected (negative) contribution of umbilical plasma AA was not significant (partial $\beta=-0.10$, $P=0.069$). This model also explained 26% of the variance, overall $F=20$, $P<0.0001$.

Backward stepwise regression analyses with either DHA or AA in plasma sampled at 7 years of age (also shown in Table 3) again resulted in models with gender, cognitive performance and age at measurement as significant covariables. DHA and AA did not play a significant role in predicting the MMT total score (partial $\beta=0.07$, $P=0.19$ and 0.05, $P=0.39$, respectively).

Table 3 Regression coefficients for the relation between LCPUFA status and performance on the Maastricht motor test (total score) at 7 years of age, corrected for covariables[a]

Variables in model	*Maastricht motor test total score*		
	B (s.d.)	*β*	P-*value*
DHA (*umbilical plasma)*	1.143 (0.46)	0.13	0.01
Cognitive function	0.381 (0.05)	0.37	<0.0001
Age at measurement	0.864 (0.22)	0.20	0.0001
Gender	7.158 (1.29)	0.28	<0.0001
AA *(umbilical plasma)*	−0.747 (0.41)	−0.10	0.069
Cognitive function	0.363 (0.05)	0.35	<0.0001
Age at measurement	0.800 (0.22)	0.19	0.0004
Gender	7.146 (1.30)	0.28	<0.0001
Gestational age	0.124 (0.06)	0.11	0.037
DHA *(plasma at 7 years)*	1.295 (0.97)	0.07	0.185
Cognitive function	0.412 (0.06)	0.40	<0.0001
Age at measurement	0.914 (0.24)	0.21	0.0002
Gender	6.038 (1.37)	0.24	<0.0001
AA (*plasma at 7 years)*	0.479 (0.56)	0.05	0.389
Cognitive function	0.416 (0.06)	0.40	<0.0001
Age at measurement	0.954 (0.24)	0.22	0.0001
Gender	6.051 (1.37)	0.25	<0.0001

[a]Results of backward stepwise multiple regression analyses; B, regression coefficient, β, standardized regression coefficient. The initial models included five variables (docosahexaenoic acid status (DHA) or arachidonic acid status (AA, %, w/w), the child's gender, cognitive performance, gestational age and age at measurement).

MMT quality score

The same analyses with the MMT quality score as dependent variable resulted in similar models with cognitive performance, gender and age at measurement as significant covariables (Table 4). Umbilical plasma DHA levels showed a significant positive association with the MMT quality score (partial $\beta=0.14$, $P=0.01$). The final model explained 23% of the variance, overall $F=21$, $P<0.0001$.

The relation between umbilical plasma AA and the MMT quality score was negative and of borderline significance (partial $\beta=-0.11$, $P=0.052$). This model explained 23% of the variance, overall $F=17$, $P<0.0001$.

At 7 years of age, the associations of DHA and AA with qualitative movement scores were not significant (partial $\beta=0.08$, $P=0.19$ for DHA and partial $\beta=0.03$, $P=0.58$ for AA).

MMT quantity score

Backward stepwise logistic regression analyses with the dichotomized MMT quantity score resulted in final regression models with no significant contributions of DHA or AA, either in umbilical plasma ($P=0.30$ and 0.78, respectively) or in plasma sampled at 7 years of age ($P=0.12$ and 0.34, respectively). So children with a quantity score median or higher did not differ from children scoring below median in these LCPUFA values.

Table 4 Regression coefficients for the relation between umbilical plasma LCPUFA status and Maastricht motor test quality scores at 7 years of age, corrected for covariables[a]

Variables in model	*Maastricht motor test quality score*		
	B (s.d.)	*β*	P-*value*
DHA (*umbilical plasma*)	1.00 (0.39)	0.14	0.010
Gender	6.4 (1.1)	0.31	<0.0001
Cognitive function	0.25 (0.05)	0.30	<0.0001
Age at measurement	0.64 (0.19)	0.18	0.0006
AA (*umbilical plasma*)	−0.67 (0.34)	−0.11	0.052
Gender	6.4 (1.1)	0.31	<0.0001
Cognitive function	0.24 (0.05)	0.27	<0.0001
Age at measurement	0.58 (0.19)	0.16	0.002
Gestational age	0.12 (0.05)	0.12	0.020

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid.
[a]Results of backward stepwise regression analyses; B, regression coefficient; β, standardized regression coefficient; the initial model included five independent variables (DHA or AA, gestational age, age at measurement, gender and cognitive function).

Discussion

The influence of postnatal dietary LCPUFA on short-term infant development has been investigated in several studies with inconsistent results (Makrides *et al*., 1995; Birch *et al*., 1998; Willatts *et al*., 1998; Auestad *et al*., 2001; Simmer, 2001). Our aim was to investigate the relation between prenatal LCPUFA supply and longer term developmental outcomes. In this study, we focused on motor performance at 7 years of age in relation to DHA and AA values in umbilical plasma, representing the prenatal availability of these fatty acids.

Two aspects of motor function were measured: quantity (the ability of the child to perform a movement) and quality of movement (how the movement is performed). Consistent with results of other studies (Henderson and Hall, 1982; Johnston *et al*., 1987) gender differences were found for both aspects. In almost all categories, girls scored better.

Results of backward stepwise regression analyses consistently showed a significant contribution of cognitive performance, age at measurement and gender to the motor outcomes, as measured with the Maastricht's Motor Test (Kroes *et al*., 2004; Vles *et al*., 2004), which is also consistent with the literature (Henderson and Sugden, 1992; Soorani-Lunsing *et al*., 1993; Weisglas-Kuperus *et al*., 1994).

The resulting regression models showed a positive relation between umbilical plasma DHA concentration and movement quality outcomes, when corrected for the mentioned covariables. Although not quite significant, the umbilical plasma AA concentration showed a negative relation with the movement quality outcomes. In the models predicting movement quantity, the contributions of DHA and AA at birth were not significant. Movement quality may predict developmental problems like attention-deficit hyperactivity disorder and learning problems (Touwen, 1979; Soorani-Lunsing *et al*., 1993; Weisglas-Kuperus *et al*., 1994; Kroes *et al*., 2002). Therefore, our finding is in line with the idea that LCPUFA status might also be associated to this kind of disorders (Stevens *et al*., 1995; Burgess *et al*., 2000; Richardson and Montgomery, 2005; Sinn and Bryan, 2007), although the evidence for this idea is inconsistent (Busch, 2007).

The study recently reported by Bouwstra *et al*. (2006), described a positive relation between umbilical DHA and neurodevelopmental outcome at 18 months of age, which is in line with the results of our study. The present study indicates that the association between prenatal DHA status and neurodevelopmental outcome is not restricted to infancy and early childhood, but can still be found at 7 years of age. Hibbeln *et al*. (2007) recently studied the maternal seafood consumption during pregnancy in relation to several neurodevelopmental outcomes in childhood. One of their results was a positive association between maternal seafood consumption and fine (but not gross) motor performance, measured with a questionnaire completed by the mother at 18, 30 and 42 months. Possibly seafood nutrients like LCPUFA play an important role in this association.

The postnatal LCPUFA supply seems to have less influence on later motor function than the prenatal supply. None of the randomized trials comparing term human infants fed formula with and without LCPUFA did obtain differences in quantitative motor function (as measured with the Bayley Motor Scale PDI) at 6, 12 or 18 months between both groups (Carlson, 1996; Scott *et al*., 1998; Lucas *et al*., 1999; Birch *et al*., 2000; Makrides *et al*., 2000; Auestad *et al*., 2001). To investigate the association between LCPUFA intake in later life and motor performance, we also determined DHA and AA concentrations in venous plasma sampled at 7 years of age, reflecting the actual status of these fatty acids at follow-up. However, no significant associations were found between any of the motor scores and LCPUFA status at 7 years of age.

Our finding that the DHA status in umbilical plasma, in contrast to the LCPUFA status in plasma at 7 years, is associated with movement quality suggests that prenatal LCPUFA availability may be more important for later motor function than childhood dietary LCPUFA intake. Since neonatal LCPUFA values can be influenced by maternal diet during pregnancy (van Houwelingen *et al*., 1995; Dunstan *et al*., 2004; Helland *et al*., 2006), maternal LCPUFA intake during pregnancy can be expected to influence later movement quality of the child. Indeed, maternal seafood consumption shows a positive relation with fine motor skills (Hibbeln *et al*., 2007). Intervention studies will be necessary to find out whether increased maternal DHA intake of mothers during pregnancy has beneficial effects on this aspect of child development.

Acknowledgements

We thank all the parents and their children for participating in this study, Jeroen van den Berg (Royal Numico, Wageningen, The Netherlands) for the blinded fatty acid analyses of the blood samples at follow-up and the University Hospital Maastricht (Profileringsfonds) for the financial support.

References

Al MD, van Houwelingen AC, Hornstra G (2000). Long-chain polyunsaturated fatty acids, pregnancy, and pregnancy outcome. *Am J Clin Nutr* **71**, 285S–291S.

Al MDM, van Houwelingen AC, Kester ADM, Hasaart RHM, de Jong EAP, Hornstra G (1995). Maternal essential fatty acid pattern during normal pregnancy and their relationship to neonatal essential fatty acid status. *Br J Nutr* **74**, 55–68.

Auestad N, Halter R, Hall RT, Blatter M, Bogle ML, Burks W *et al*. (2001). Growth and development in term infants fed long-chain polyunsaturated fatty acids: a double-masked, randomized, parallel, prospective, multivariate study. *Pediatrics* **108**, 372–381.

Bakker EC, Ghys AJA, Kester ADM, Vles JSH, Dubas JS, Blanco CE *et al*. (2003). Long-chain polyunsaturated fatty acids at birth and cognitive function at 7 years of age. *Eur J Clin Nutr* **57**, 89–95.

Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG (2000). A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol* **42**, 174–181.

Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C (1998). Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. *Pediatr Res* **44**, 201–209.

Bouwstra H, Dijck-Brouwer D, Decsi T, Boehm G, Boersma E, Muskiet F *et al*. (2006). Neurologic condition of healthy term infants at 18 months: positive association with venous umbilical DHA status and negative association with umbilical *trans*-fatty acids. *Pediatr Res* **60**, 334–339.

Burgess J, Stevens L, Zhan W, Peck L (2000). Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *Am J Clin Nutr* **71**, 327S–330S.

Busch B (2007). Polyunsaturated fatty acid supplementation for ADHD? Fishy, fascinating, and far from clear. *J Dev Behav Pediatr* **28**, 139–144.

Carlson S (1996). LCPUFA and functional development of preterm and term infants. In: JG Bindels, AC Goedhart, HKA Visser (eds). *Recent Developments in Infant Nutrition*. Kluwer Academic Publishers: Dordrecht. pp 218–224.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW (1980a). Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. *Early Hum Dev* **4**, 131–138.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW (1980b). Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. *Early Hum Dev* **4**, 121–129.

Dunstan JA, Mori TA, Barden A, Beilin LJ, Holt PG, Calder PC *et al*. (2004). Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty acid composition. *Eur J Clin Nutr* **58**, 429–437.

Dunstan JA, Simmer K, Dixon G, Prescott SL (2006). Cognitive assessment at 21/2 years following fish oil supplementation in pregnancy: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed*; [e-pub ahead of print].

Gabbard CP (1996). *Livelong Motor Development* 2nd edn. McGraw-Hill Companies: Boston.

Helland IB, Saugstad OD, Saarem K, Van Houwelingen AC, Nylander G, Drevon CA (2006). Supplementation of n-3 fatty acids during pregnancy and lactation reduces maternal plasma lipid levels and provides DHA to the infants. *J Matern Fetal Neonatal Med* **19**, 397–406.

Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA (2003). Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* **111**, e39–e44.

Henderson SE, Hall D (1982). Concomitants of clumsiness in young schoolchildren. *Dev Med Child Neurol* **24**, 448–460.

Henderson SE, Sugden DA (1992). *Movement Assessment Battery for Children*. The Psychological Corporation Ltd.: London.

Hibbeln JR, Davis JM, Steer C, Emmet P, Rogers I, Williams C *et al*. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* **369**, 578–585.

Hornstra G (2000). Essential fatty acids in mothers and their neonates. *Am J Clin Nutr* **71**, 1262S–1269S.

Innis SM (1991). Essential fatty acids in growth and development. *Prog Lipid Res* **30**, 39–103.

Johnston O, Short H, Crawford J (1987). Poorly coordinated children: a survey of 95 cases. *Child Care Health Dev* **13**, 361–376.

Kroes M, Kessels AG, Kalff AC, Feron FJ, Vissers YL, Jolles J *et al*. (2002). Quality of movement as predictor of ADHD: results from a prospective population study in 5- and 6-year-old children. *Dev Med Child Neurol* **44**, 753–760.

Kroes M, Vissers Y, Sleijpen F, Feron F, Kessels A, Bakker E *et al*. (2004). Reliability and validity of a qualitative and quantitative motor test for 5-to 6 year-old children. *Eur J Paediatr Neurol* **8**, 135–143.

Lucas A, Stafford M, Morley R, Abbott R, Stephenson T, MacFadyen U *et al*. (1999). Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial. *Lancet* **354**, 1948–1954.

Makrides M, Neumann MA, Simmer K, Gibson RA (2000). A critical appraisal of the role of dietary long-chain polyunsaturated fatty acids on neural indices of term infants: a randomized, controlled trial. *Pediatrics* **105**, 32–38.

Makrides M, Neumann M, Simmer K, Pater J, Gibson R (1995). Are long-chain polyunsaturated fatty acids essential nutrients in infancy? *Lancet* **345**, 1463–1468.

Reisbick S (1996). Neural development. In: S Carlson, M Neuringer, S Reisbick (eds). *Assessment of Infant Visual and Cognitive Function in Relation to Long Chain Polyunsaturated Fatty Acids*. Editiones Roche: Basel. pp 10–18.

Richardson AJ, Montgomery P (2005). The Oxford–Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* **115**, 1360–1366.

Sastry PS (1985). Lipids of nervous tissue: composition and metabolism. *Prog Lipid Res* **24**, 69–176.

Scott DT, Janowsky JS, Carroll RE, Taylor JA, Auestad N, Montalto MB (1998). Formula supplementation with long-chain polyunsaturated fatty acids: are there developmental benefits? *Pediatrics* **102**, E59.

Simmer K (2001). Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev*, CD000376.

Sinn N, Bryan J (2007). Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. *J Dev Behav Pediatr* **28**, 82–91.

Soorani-Lunsing RJ, Hadders-Algra M, Olinga AA, Huisjes HJ, Touwen BC (1993). Is minor neurological dysfunction at 12 years related to behaviour and cognition? *Dev Med Child Neurol* **35**, 321–330.

Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR *et al*. (1995). Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *Am J Clin Nutr* **62**, 761–768.

Touwen BCL (1979). *Examination of the Child with Minor Neurological Dysfunction*. Spastics International Medical Publications: London.

van Houwelingen AC, Sorensen JD, Hornstra G, Simonis MM, Boris J, Olsen SF *et al*. (1995). Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. *Br J Nutr* **74**, 723–731.

Vles J, Kroes M, Feron F (2004). *Maastrichtse Motoriek Test (MMT)*. PITS: Leiden.

Weisglas-Kuperus N, Baerts W, Fetter WP, Hempel MS, Mulder PG, Touwen BC *et al*. (1994). Minor neurological dysfunction and quality of movement in relation to neonatal cerebral damage and subsequent development. *Dev Med Child Neurol* **36**, 727–735.

Willatts P, Forsyth JS, DiModugno MK, Varma S, Colvin M (1998). Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* **352**, 688–691.