Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood

Peter Willatts, Stewart Forsyth, Carlo Agostoni, Paul Casaer, Enrica Riva, and Günther Boehm

ABSTRACT
Background: Evidence is accumulating that a dietary supply of long-chain polyunsaturated fatty acids (LC-PUFAs) enhances the development of attention and efficient information processing in infants. However, it is uncertain whether LC-PUFAs in infancy influence cognitive development in later childhood. Objective: The objective was to determine the effects of dietary LC-PUFAs in infancy on measures of cognitive function at age 6 y. Design: Infants were randomly assigned to receive formula containing either docosahexaenoic acid and arachidonic acid or no LC-PUFAs for a period of 4 mo. A reference breastfed group was also included. In a follow-up conducted at age 6 y, children received assessments of intelligence quotient (IQ), attention control (Day-Night Test), and speed of processing on the Matching Familiar Figures Test (MFFT).

Results: At follow-up there were 71 children in the LC-PUFA group, 76 in the control group, and 88 in the breastfed group. The formula groups did not differ on measures of Full-Scale IQ (LC-PUFA mean = 98.0; control mean = 100.9) or attention control (LC-PUFA mean = 12.7; control mean = 12.8). MFFT error scores were the same for both formula groups, but when making correct responses, the LC-PUFA group was significantly faster (mean = 6.2 s) than the control group [mean = 7.8 s; F(1, 131) = 6.09, P = 0.015].

Conclusions: IQ scores of children who were fed a formula containing either LC-PUFAs or no LC-PUFAs did not differ at age 6 y. However, children who received LC-PUFAs were faster at processing information compared with children who received unsupplemented formula. Variation in the dietary supply of LC-PUFAs in the first months of life may have long-term consequences for the development of some cognitive functions in later childhood. Am J Clin Nutr 2013;98(suppl):536S–42S.

INTRODUCTION
Long-chain PUFAs (LC-PUFAs)5, especially DHA (22:6n–3) and arachidonic acid (AA; 20:4n–6), are necessary for normal brain development and are preferentially accreted by the infant brain during the last intrauterine trimester and the first months of life (1, 2). Human milk contains LC-PUFAs, although the DHA content is highly variable, depending largely on the mother’s diet (3). Both the fetus and newborn infant are able to convert α-linolenic acid (18:3n–3) and linoleic acid (18:2n–6) to DHA and AA, respectively (4, 5), but the efficiency is related to both environmental and genetic determinants (6, 7). However, DHA concentrations are lower in the cerebral cortex of term and preterm infants fed formula containing no LC-PUFAs compared with infants fed human milk, suggesting that DHA synthesis may be inadequate to meet the infant’s needs during the first months of life (8, 9).

Structural differences in the LC-PUFA content of infants’ brain composition suggest possible associations with the development of intellectual functions. Some studies have examined the effects of LC-PUFAs on global measures of development such as the Mental Development Index (MDI) of the Bayley Scales of Infant Development (10). Although higher test scores have been reported in infants fed LC-PUFA–supplemented formula compared with infants fed unsupplemented formula (11–13), the majority of studies have found no effects of LC-PUFAs on Bayley MDI scores (14–18).

However, the use of the Bayley Scales of Infant Development to detect the effects of nutritional interventions has been criticized because the MDI provides only a general measure of development and does not assess specific cognitive abilities (19). In contrast, evidence is accumulating for the influence of LC-PUFAs on the development of specific cognitive abilities such as attention and speed of information processing. Several studies using measures of novelty preference and look duration in tests of visual recognition memory and habituation have reported faster and more efficient information processing in LC-PUFA–supplemented infants than in controls (11, 20–22), although some studies found no differences between the diet groups (16, 23).

1 From the School of Psychology (PW) and the Tayside Institute of Child Health (SF), University of Dundee, Dundee, United Kingdom; the Department of Pediatrics, Fondazione IRCCS Ca’ Granda–Ospedale Maggiore Policlinico, University of Milan, Milan, Italy (CA); the Department of Pediatric Neurology, University of Leuven, Leuven, Belgium (PC); the Department of Pediatrics, San Paolo Hospital, University of Milan, Milan, Italy (ER); Danone Research, Friedrichsdorf, Germany (GB); and Sophia Children’s Hospital, Erasmus University, Rotterdam, Netherlands (GB).
3 Partially supported by an unrestricted grant from Numico Research, Friedrichsdorf, Germany.
4 Address correspondence to P Willatts, School of Psychology, University of Dundee, Dundee, United Kingdom. E-mail: p.willatts@dundee.ac.uk.
5 Abbreviations used: AA, arachidonic acid; FSIQ, Full-Scale IQ; IQ, intelligence quotient; LC-PUFA, long-chain PUFA; MDI, Mental Development Index; MFFT, Matching Familiar Figures Test; PIQ, Performance IQ; VIQ, Verbal IQ; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence–Revised.
First published online June 19, 2013; doi: 10.3945/ajcn.112.038612.
An important question is whether the effects of LC-PUFAs on cognitive development are confined to the period of infancy or continue into later childhood. Several studies have reported no effects of feeding LC-PUFA–supplemented formula compared with standard formula on developmental tests administered to children older than 18 mo. These studies included measures of performance on the Brunet-Lézine test (24), the Bayley MDI (25), and tests of intelligence quotient (IQ) (26, 27), all of which provide global measures of cognitive function. However, as in infancy, it is possible that the effects of LC-PUFAs may be better shown by measures of specific cognitive abilities, such as attention and efficiency of information processing (28).

In a previous safety and tolerance study of LC-PUFA supplementation and its effects on cognitive development, we randomly assigned newborn infants to receive a formula with LC-PUFAs or to receive a nutritionally similar formula that contained no LC-PUFAs (12, 22, 29, 30). We therefore had the opportunity to follow up these randomly assigned groups with the aim of determining the relation of LC-PUFA supplementation in infancy to cognitive function in later childhood. The children were aged 6 y at the time of follow-up, when they were given a test of general intelligence, as well as specific tests of attention control and efficiency of information processing.

SUBJECTS AND METHODS

Study population

In 1992, 6 European centers took part in a multicenter randomized controlled trial of an infant formula that was supplemented with DHA and AA. Four of the 6 centers that participated in this original safety and tolerance investigation agreed to take part in the present follow-up study. Each center (Dundee and Birmingham in the United Kingdom, Leuven in Belgium, and Milan in Italy) had a cohort of children who had been randomly assigned to the trial formulas in the newborn period and a reference group of breastfed children. The children were healthy term singletons with a gestation between 37 and 42 wk and a birth weight between 2500 and 4000 g. Ethical approval for both studies was obtained in each center, and informed written consent was obtained from the parent or guardian of each child.

Study design

Infants whose mothers had elected to formula feed were randomly allocated during the first week of life to a formula containing LC-PUFAs or to a control formula with no LC-PUFAs (12, 22, 29, 30). Randomization to the trial formulas was achieved by means of a permuted block size of 6, so that after every sixth infant the 2 groups were balanced. The same randomization table was used in each center. The infant formulas that children had received in the original safety and tolerance study. None of the research assistants in the follow-up study had been involved in the original infant study.

Infants received their trial formula during the first 4 mo of life. Each month, the infants’ weight, length, head circumference, midarm circumference, triceps skinfold thickness, and subscapular skinfold thickness were measured. Other data relating to safety and tolerance were also recorded. In addition, measures of cognitive development were obtained in the Dundee cohort at ages 3, 9, and 10 mo (22, 29, 30) and in the Milan cohort at ages 4 and 24 mo (12, 24).

In the present follow-up study, children and their families were invited to attend a clinic or laboratory in each study center when the children were aged 6 y ± 2 mo. During these visits, which took place between April 1998 and March 2000, the parent or guardian completed a demographic and clinical questionnaire, and the child’s cognitive performance was assessed on the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R), the Day-Night Test, and the Matching Familiar Figures Test (MFFT). The child’s blood pressure was also measured. These data have previously been reported (31).

The WPPSI-R IQ test (32) was available in an appropriate language for each center (English in Dundee and Birmingham, Flemish in Leuven, and Italian in Milan). The WPPSI-R provided standardized IQ scores on 2 subscales, Performance IQ (PIQ) and Verbal IQ (VIQ), and an overall Full-Scale IQ (FSIQ) score.

The Day-Night Test measures children’s ability to inhibit interfering information while attempting to give correct answers on the basis of 2 learned rules (33). Children were first taught to say “day” when shown a black card with a picture of the moon and “night” when shown a white card with a picture of the sun. The task was demanding because the children had to inhibit a natural tendency to give the verbal response suggested by the picture. Children were first explained the rules for responding to the cards and subsequently received up to 3 pairs of practice trials with each of the cards. Only children who provided a correct response for each of the cards during practice trials were administered a total of 16 test trials in which 8 “day” cards and 8 “night” cards were presented in a pseudo-random sequence. The measure was the total number of correct responses.

The MFFT is a picture-matching task that provides measures of efficiency at processing information (34). The standard test consists of 12 problems in which the child is shown a target

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid composition of the LC-PUFA and non–LC-PUFA formulas&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fatty acid</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>12:0</td>
</tr>
<tr>
<td>14:0</td>
</tr>
<tr>
<td>16:0</td>
</tr>
<tr>
<td>18:1n–9</td>
</tr>
<tr>
<td>18:2n–6 (linoleic acid)</td>
</tr>
<tr>
<td>18:3n–3 (α-linolenic acid)</td>
</tr>
<tr>
<td>20:4n–6 (arachidonic acid)</td>
</tr>
<tr>
<td>22:6n–3 (DHA)</td>
</tr>
</tbody>
</table>

<sup>1</sup>LC-PUFA, long-chain PUFA.
picture together with 6 alternatives, of which one exactly matches the target and the remainder differ from the target in one small detail. To give children an age-appropriate MFFT that would avoid floor effects, we used a simpler version with 4 instead of 6 alternative pictures. The child was instructed to identify and point to the picture that exactly matched the target. The time taken to make the first response was recorded with a stopwatch. If the first response was incorrect, the child was told that he or she had made an error and was asked to choose another picture. The child was permitted to continue responding until the correct picture had been identified or until a maximum of 4 errors had occurred on that trial. Measures included the following: mean latency of the first response across all trials (including both correct and error responses), mean latency of the first response on trials in which the correct picture was selected, total number of errors, and total number of first-response errors. In addition, measures of impulsivity and efficiency were calculated from the z scores of mean latency of the first response across all trials and the total number of errors (35). Children who are impulsive tend to have short response latencies and high error scores, whereas children who are reflective tend to have long response latencies and low error scores. Children who are efficient at processing information tend to have short response latencies and low error scores, whereas children who are inefficient tend to have long response latencies and high error scores. Impulsivity was calculated as $z$ (errors) – $z$ (latency), with a high score indicating more impulsive behavior. Efficiency was calculated as $z$ (errors) + $z$ (latency), with a low score indicating more efficient processing.

Statistical procedures

Statistical analyses of interval measures for demographic and anthropometric variables were made with the Student’s $t$ test. Statistical analyses of categorical variables were made with the chi-square test. Analyses of WPPSI-R, MFFT, and Day-Night Test scores in the 2 formula groups were made by using ANCOVA. Analysis of the achieved power of the study based on the obtained data showed that the ANCOVA could detect the observed difference in MFFT latency with a power of 49% at the 0.05 level of significance. A $P$ value <0.05 was accepted as evidence of a significant difference. All statistical analyses were conducted with the SPSS version 21 for Windows package (IBM SPSS Statistics, IBM Corporation).

RESULTS

Almost two-thirds (235 of 376) of the children in the original safety and tolerance trial were enrolled in the present study (Table 2). The reasons for nonenrollment are shown in Figure 1. The total number of children enrolled for follow-up was 71 in the LC-PUFA group, 76 in the non–LC-PUFA group, and 88 in the reference breastfed group. There were several anthropometric differences between children in the randomized groups who were enrolled and those who were not enrolled. Children who were not enrolled had a lower birth weight [not enrolled (mean ± SD): 3108 ± 411; enrolled: 3292 ± 397; $t(229) = 3.36, P = 0.001], shorter length [not enrolled: 49.8 ± 2.0 cm; enrolled: 50.6 ± 2.4 cm; $t(229) = 2.61, P = 0.01], and smaller midarm circumference (not enrolled: 10.1 ± 0.9 cm; enrolled: 10.5 ± 1.0 cm; $t(221) = 2.70, P = 0.007) compared with children who were enrolled.

The mean (±SD) age of the children at the time of assessment was 70.1 ± 3.5 mo and ranged from 66 to 88 mo. There were no significant demographic or anthropometric differences between the 2 randomized groups (Table 3), but there were several demographic differences between the formula-fed children and the reference group of breastfed children. Children who were breastfed had older parents, fathers who had more full-time education, more siblings, and fewer smokers at home (Table 3).

Three children (1 LC-PUFA and 2 breastfed) failed to complete any cognitive assessment. Of the remaining children, 2 refused to participate in both the MFFT and Day-Night Test (1 non–LC-PUFA and 1 breastfed). Day-Night Test scores could not be obtained for an additional 6 children who failed to complete the practice trials (1 LC-PUFA, 1 non–LC-PUFA, and 4 breastfed). Three children refused to complete the WPPSI-R (1 non–LC-PUFA and 1 breastfed), although the child in the non–LC-PUFA group did complete sufficient subtests to provide a PIQ score.

WPPSI-R, Day-Night Test, and MFFT scores for the LC-PUFA, non–LC-PUFA, and breastfed groups are given in Table 4. Because incomplete follow-up may have led to imbalances in the characteristics of the formula groups, WPPSI-R scores were examined with ANCOVAs with formula group and study center as main factors and occipitofrontal circumference, birth weight, maternal age, and maternal age at completion of education as covariates. Day-Night Test and MFFT scores were also examined by using ANCOVA, which additionally included child age as a covariate because MFFT and Day-Night Test scores are correlated with age (34, 36). These statistical comparisons were undertaken only between the 2 randomized formula groups and none involved the reference breastfed group. Comparisons of WPPSI-R scores showed no significant differences between the 2 formula groups on the measures of PIQ, VIQ, and FSIQ. WPPSI-R scores tended to be higher in the breastfed group than in either of the formula groups. The number of correct Day-Night Test responses did not differ significantly between the 2 formula groups, and the formula-group means were similar to the means for the breastfed group.

The first responses on the MFFT of children in the 2 formula groups were correct on fewer than half the trials (LC-PUFA = 45%, non–LC-PUFA = 46%), but the number of correct first responses was significantly greater than the chance value of 3 (LC-PUFA (mean ± SD): 5.4 ± 2.2, $n(69) = 9.10, P < 0.00001$; non–LC-PUFA: 5.5 ± 2.5, $n(74) = 8.61, P < 0.00001$). There

---

TABLE 2

Proportions of children in the original safety and tolerance trial who took part in the follow-up study

<table>
<thead>
<tr>
<th>Center</th>
<th>LC-PUFA</th>
<th>Non–LC-PUFA</th>
<th>Breastfed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham</td>
<td>11/14(79)</td>
<td>6/15(40)</td>
<td>16/26(62)</td>
<td>33/55(60)</td>
</tr>
<tr>
<td>Dundee</td>
<td>72/40(68)</td>
<td>32/50(64)</td>
<td>30/43(70)</td>
<td>89/133(67)</td>
</tr>
<tr>
<td>Leuven</td>
<td>19/30(63)</td>
<td>20/30(67)</td>
<td>24/38(70)</td>
<td>63/98(64)</td>
</tr>
<tr>
<td>Milan</td>
<td>14/27(52)</td>
<td>18/31(58)</td>
<td>18/32(56)</td>
<td>50/90(56)</td>
</tr>
<tr>
<td>Total</td>
<td>71/111(64)</td>
<td>76/126(60)</td>
<td>88/139(63)</td>
<td>235/376(63)</td>
</tr>
</tbody>
</table>

1 All values are n/total n; percentages in parentheses. LC-PUFA, long-chain PUFA.
2 Reference group.
were no differences between the 2 formula groups in either the total number of errors or the number of first-response errors. Error scores for the breastfed group and the randomized formula groups were similar on both of these measures. In contrast, the LC-PUFA group had significantly shorter response latencies across all trials \(F(1, 132) = 4.18, P = 0.043\) and on trials in

**TABLE 3**

Demographic and anthropometric characteristics of children in the randomly assigned formula and breastfed groups who were enrolled in the follow-up study

<table>
<thead>
<tr>
<th></th>
<th>LC-PUFA</th>
<th>Non–LC-PUFA</th>
<th>Breastfed</th>
<th>LC-PUFA vs non–LC-PUFA</th>
<th>Combined formula vs breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at follow-up (y)</td>
<td>34.2 ± 5.8 (32.8, 35.5)</td>
<td>34.6 ± 5.4 (33.4, 35.9)</td>
<td>35.9 ± 4.1 (35.0, 36.8)</td>
<td>0.621</td>
<td>0.031</td>
</tr>
<tr>
<td>Maternal age at completion of education (y)</td>
<td>18.4 ± 3.4 (17.6, 19.2)</td>
<td>18.0 ± 2.8 (17.3, 18.6)</td>
<td>18.9 ± 3.6 (18.1, 19.7)</td>
<td>0.392</td>
<td>0.111</td>
</tr>
<tr>
<td>Paternal age at follow-up (y)</td>
<td>36.1 ± 5.8 (34.6, 37.5)</td>
<td>36.0 ± 4.7 (34.9, 37.1)</td>
<td>39.2 ± 5.1 (38.1, 40.3)</td>
<td>0.942</td>
<td>0.0001</td>
</tr>
<tr>
<td>Paternal age at completion of education (y)</td>
<td>17.7 ± 3.1 (16.8, 18.5)</td>
<td>17.9 ± 2.6 (17.3, 18.5)</td>
<td>19.5 ± 4.8 (18.4, 20.6)</td>
<td>0.881</td>
<td>0.003</td>
</tr>
<tr>
<td>No. of mothers married or with partner/no. of single mothers</td>
<td>61/8</td>
<td>69/6</td>
<td>78/5</td>
<td>0.467</td>
<td>0.333</td>
</tr>
<tr>
<td>No. of children in family home</td>
<td>2.1 ± 1.0 (1.9, 2.4)</td>
<td>2.0 ± 0.9 (1.8, 2.2)</td>
<td>2.5 ± 1.2 (2.2, 2.7)</td>
<td>0.589</td>
<td>0.010</td>
</tr>
<tr>
<td>No. of smokers in family home</td>
<td>0.8 ± 0.7 (0.6, 1.0)</td>
<td>0.7 ± 0.7 (0.6, 0.9)</td>
<td>0.4 ± 0.6 (0.2, 0.5)</td>
<td>0.542</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>39.4 ± 1.5 (39.0, 39.8)</td>
<td>39.5 ± 1.3 (39.2, 39.8)</td>
<td>39.6 ± 1.2 (39.3, 39.9)</td>
<td>0.611</td>
<td>0.494</td>
</tr>
<tr>
<td>Child age at follow-up (mo)</td>
<td>70.1 ± 3.8 (69.3, 71.0)</td>
<td>70.0 ± 3.1 (69.3, 70.7)</td>
<td>70.0 ± 3.4 (69.1, 70.6)</td>
<td>0.816</td>
<td>0.678</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3293 ± 438 (3188, 3399)</td>
<td>3291 ± 359 (3209, 3373)</td>
<td>3341 ± 363 (3265, 3418)</td>
<td>0.971</td>
<td>0.344</td>
</tr>
<tr>
<td>Crown-heel length (cm)</td>
<td>50.5 ± 2.8 (49.8, 51.1)</td>
<td>50.5 ± 2.5 (50.3, 51.1)</td>
<td>50.9 ± 2.4 (50.4, 51.4)</td>
<td>0.539</td>
<td>0.371</td>
</tr>
<tr>
<td>Occipitofrontal circumference (cm)</td>
<td>34.7 ± 1.4 (34.4, 34.8)</td>
<td>34.8 ± 2.4 (34.3, 34.8)</td>
<td>34.8 ± 1.2 (34.5, 35.0)</td>
<td>0.546</td>
<td>0.390</td>
</tr>
<tr>
<td>Midupper arm circumference (cm)</td>
<td>10.5 ± 1.1 (10.3, 10.8)</td>
<td>10.4 ± 0.9 (10.2, 10.6)</td>
<td>10.4 ± 1.1 (10.2, 10.6)</td>
<td>0.588</td>
<td>0.508</td>
</tr>
<tr>
<td>Subscapular skinfold thickness (mm)</td>
<td>4.7 ± 1.2 (4.5, 4.8)</td>
<td>4.6 ± 0.9 (4.4, 4.8)</td>
<td>4.6 ± 1.0 (4.4, 4.8)</td>
<td>0.410</td>
<td>0.795</td>
</tr>
<tr>
<td>Triceps skinfold thickness (mm)</td>
<td>4.8 ± 1.2 (4.5, 5.1)</td>
<td>4.8 ± 0.9 (4.6, 5.0)</td>
<td>4.8 ± 1.1 (4.6, 5.1)</td>
<td>0.621</td>
<td>0.603</td>
</tr>
</tbody>
</table>

1 Values are means ± SDs (95% CIs in parentheses), except where otherwise indicated. Statistical comparisons were made with t tests, except where otherwise indicated. LC-PUFA, long-chain PUFA.
2 Statistical comparisons made with chi-square tests.
3 Marital status of 3 mothers not known.

**FIGURE 1.** Flow chart of progress through the study. LC-PUFA, long-chain PUFA.
which their first response was correct \(F(1, 131) = 6.09, P = 0.015\). Latencies for the breastfed group were intermediate between the latencies for the 2 formula groups. MFFT impulsivity scores did not differ between the randomized formula groups, but the LC-PUFA group had significantly lower MFFT efficiency scores, with lower scores indicating more efficient processing \(F(1, 132) = 4.66, P = 0.033\).

**Discussion**

All IQ scores for both formula groups were in the normal range, but no significant differences between the 2 groups were found on any IQ measure. Other follow-up studies of the effects of LC-PUFAs in infancy on IQ scores in later childhood have also reported negative findings on measures of IQ in both term (26, 27) and preterm children (37). Although the number of such follow-up studies is small, it is notable that similar negative results have been obtained in randomized studies of the effects of LC-PUFAs on Bayley MDI scores in infancy (14–18). Both IQ and Bayley MDI scores are global measures derived from a number of subtests that assess a broad range of cognitive abilities. If LC-PUFAs influence the development of specific cognitive functions, it is possible that global tests of infant neurodevelopment and childhood IQ may be too insensitive to reveal any effects (19).

We included 2 tests in our follow-up that assessed specific cognitive functions. The Day-Night Test measures ability to control attention and ignore irrelevant and distracting information. Performance on the Day-Night Test did not differ between the 2 formula groups, and we found no evidence that LC-PUFAs in infancy influenced the development of attention control at 6 y of age. However, this assessment may have suffered from a ceiling effect that reduced its sensitivity because the mean scores in both groups approached the maximum. In future studies it would be beneficial to include a range of age-appropriate assessments of attention control and executive function.

The MFFT measures impulsivity and efficiency at processing information. Response latencies on the MFFT were shorter in 6-y-old children who in infancy were fed a formula containing LC-PUFAs compared with children who were fed a formula without LC-PUFAs. In contrast, there were no differences between the randomized formula groups in the number of MFFT errors. These results suggest that LC-PUFAs in infant formula had no effect on children’s ability to solve the MFFT problems but instead were associated with improved speed of information processing, a conclusion that is supported by the finding that efficiency scores were significantly better in the LC-PUFA-supplemented group.

It has previously been shown that hyperactive children respond faster but also make more errors than normal controls on a version of the MFFT with 6 alternative pictures (38, 39). This response pattern is thought to indicate impulsive behavior, but there was no evidence in the present study that faster MFFT responses in the LC-PUFA group were a result of greater impulsivity. Faster response time did not increase the number of errors (a characteristic of hyperactive children), and impulsivity scores did not differ between the 2 formula groups. The fact that the LC-PUFA group took less time to solve the problems with no cost to their rate of success is evidence that these children were faster and more efficient at processing information. However, we are unable to comment on the clinical significance of this finding because we used a 4-alternative version of the MFFT for which there are no published data on clinical populations such as children with attention-deficit/hyperactivity disorder.

Several studies have reported that infants fed a formula containing LC-PUFAs produce shorter look durations compared with infants fed a formula containing no LC-PUFAs (20–22). Shorter look durations are associated with faster speed of processing (40, 41), and it is possible that accumulation of LC-PUFAs in the infant brain affects the speed of processes involved in information encoding, storage, and retrieval from memory. Information processing in infants occurs during periods of sustained attention, which can be identified by a distinct pattern of change in heart rate (42, 43). Colombo et al (44) used measures of heart rate to show that infants whose mothers had high concentrations of red blood cell DHA at the time of delivery had...
significantly shorter periods of sustained attention than infants of low-DHA mothers. One interpretation of this finding is that DHA influences the duration of sustained attention and speed of processing in infants.

Our results suggest that the effects of LC-PUFAs on speed of information processing are not transient but persist beyond infancy. However, randomized studies have also shown that visual acuity development in infancy is improved by preformed dietary LC-PUFAs (45, 46). If these acuity effects persist beyond infancy, then differences in MFFT performance may reflect differences in visual acuity rather than speed of processing, given that the MFFT is a visual test. Better visual acuity has been observed in children aged 4 y who were fed DHA-enriched formula compared with control formula, although it should be noted that both groups had normal acuity, the difference was small, and was significant for only one eye (27). In contrast, 2 other studies failed to detect any differences between the randomized groups on measures of acuity at 3 y (26) or at 4–6 y (47).

It is unlikely that small differences in normal acuity could explain our results. Children with poorer acuity should have had greater difficulty identifying the key features of the figures, which ought to have produced more errors, rather than slower response times. The identical error rates in the 2 formula groups indicates that children were equally successful at detecting the relevant visual information and suggests that faster response times in the LC-PUFA–supplemented group were a result of increased speed of processing and not better acuity.

The DHA content of the supplemented formula was at the lower range of current recommendations for infants (48) and lower than the DHA content of other formulas that have shown cognitive benefits (49). Because egg yolk was used as the source of LC-PUFAs, the majority was presented in the form of phospholipids. Stable-isotope studies in baboons (50) showed that LC-PUFAs provided as phospholipids are more efficiently incorporated into neuronal membranes than LC-PUFAs provided as triglycerides. Therefore, the dosage can be seen as sufficient, even though it was at the lower border of current recommendations.

Only 62% of the children who were randomly assigned to the 2 formulas were assessed at 6 y. There were no differences in the characteristics of children in the 2 formula groups who took part in the follow-up, but some selection bias may have influenced our results. Children enrolled in the follow-up had a higher birth weight and higher scores on several other anthropometric measures compared with children who were not enrolled. The enrolled children therefore comprised a subgroup who ought to have been less vulnerable to a poorer developmental outcome. If this selection bias had any effect on the results, then it should have been to reduce the likelihood of detecting differences between the groups. The fact that we were unable to include the more vulnerable children in the follow-up suggests that our results may have underestimated the effects of LC-PUFAs.

Our findings suggest that LC-PUFAs in infancy may influence speed of processing in later childhood, but we acknowledge that other genetic and environmental factors are likely to play a greater role. One weakness of our study is that we did not obtain measures of parental cognition such as IQ or MFFT performance or the type of stimulation provided by the home environment. We were unable to control for these factors in our analyses, and it remains a possibility that, despite the random allocation of children to the formula groups, chance differences in genetic and environmental factors may have influenced the results. It is also possible that our finding of faster speed of processing in the LC-PUFA group may be a chance effect, given the number of outcome measures. Our findings should therefore be interpreted with caution.

In conclusion, this study found that children who received LC-PUFA–supplemented formula in infancy showed no differences on measures of IQ scores and attention control at 6 y of age compared with children who received unsupplemented formula. However, LC-PUFA–supplemented children were faster and more efficient at processing information. Speed of processing has been identified as an important factor in a wide range of cognitive processes such as reasoning, memory, and problem solving (51), and our findings suggest that dietary preformed LC-PUFAs in the first months of life may have long-term consequences for the development of cognitive function in later childhood.

We thank J Bissenden from the Department of Paediatrics, City Hospital, Birmingham, for his substantial contribution to the study.

The authors’ responsibilities were as follows—PW, SF, CA, PC, and ER: performed the follow-up in their hospitals; PW and SF: analyzed the data; and PW and GB: wrote the initial manuscript. The original infant study was funded by Milupa GmbH. During the performance of the study, GB was an employee of the study sponsor, Numico Research Germany. In the past, PW, SF, ER, CA and PC have conducted clinical trials funded by the formula industry. They have no financial interest in the production and sales of infant formula or nutritional supplements.

REFERENCES

12. Agostoni C, Trojan S, Bellù R, Riva E, Giovannini M. Neuro-developmental quotient of healthy term infants at 4 months and feeding


