Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age

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Summary

Background Long-chain polyunsaturated fatty acids (LCPUFA) are important for normal visual and brain development. Although present in human milk, LCPUFA have until recently been absent from artificial formulas, and infants may have limited ability to synthesise LCPUFA. To determine the clinical significance of this relative deficiency of LCPUFA, we undertook a randomised trial of the relation between LCPUFA supplementation and infant cognitive behaviour.

Methods 44 term infants had been randomised to a formula supplemented with LCPUFA (21) or not supplemented with LCPUFA (23), which they had taken from birth to age 4 months. Infant cognitive behaviour was assessed at 10 months of age by a means-end problem-solving test—the intentional execution of a sequence of steps to achieve a goal. The problem required three intermediate steps to achieve the final goal, uncovering and retrieving a hidden toy.

Findings Infants who received LCPUFA-supplemented formula had significantly more intentional solutions than infants who received the no-LCPUFA formula (median 2·0 *vs* 0, p=0·021). Intention scores (median 14·0 *vs* 11·5 [maximum 18]) were also increased in this group (p=0·035).

Interpretation These findings suggest that term infants may benefit from LCPUFA supplementation, and that the effects persist beyond the period of supplementation. Since higher problem-solving scores in infancy are related to higher childhood IQ scores, supplementation with LCPUFA may be important for the development of childhood intelligence.

Lancet 1998; **352:** 688–91

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Introduction

Evidence is accumulating that long-chain polyunsaturated fatty acids (LCPUFA) have important functional effects on membrane and cellular properties of neural tissue. In rats reared on a diet deficient in α-linolenic acid, the precursor of the LCPUFA docosahexaenoic acid (DHA), learning is impaired.[1,2] In infants, LCPUFA are preferentially accumulated by the brain during the last trimester of pregnancy and the first months of life.[3,4] Breast milk contains LCPUFA but fatty acids longer than C18 used to be omitted from artificial formulas because it was assumed that infants could synthesise LCPUFA from the essential C18 fatty acids linoleic and α-linolenic acid through elongase and desaturase systems. However, evidence that concentrations of LCPUFA in plasma, red cell membrane, and cerebral cortex are lower in formula-fed infants than they are in infants receiving human milk or formula supplemented with LCPUFA suggests that these enzyme systems may be inefficient during the first months of life.[5–7]

It remains uncertain whether this relative deficiency of LCPUFA in formula-fed term infants at a critical time of early brain growth has important functional consequences. Studies have reported improved visual acuity in term infants fed a diet supplemented with DHA rather than a formula containing no DHA, and acuity scores correlated positively with erythrocyte DHA concentration.[8,9] 4-month-old term infants on a formula supplemented with DHA and arachidonic acid had higher scores on the Brunet-Lézine test of psychomotor development than did infants fed a formula containing no LCPUFA supplement[10] but this advantage was not detected at 12 months.[11] However, standard tests of infant development such as the Brunet-Lézine test and Bayley scales[12] principally measure perceptual and motor skills rather than cognitive ones, such as information processing and problem solving. Furthermore, in children less than 18 months of age the correlation with later childhood IQ is poor.[13,14] It remains to be shown whether dietary LCPUFA in term infants during the first months of life confers any later cognitive advantage.

We have done a randomised trial of formula supplemented with LCPUFA in part of which we assessed cognitive behaviour at 10 months by a technique known as "means-end problem solving". The ability to execute a sequence of planned steps to achieve a goal[15] develops rapidly after 6 months of age. By 7–8 months infants begin to solve simple one-step problems such as searching under a cover for a toy,[16,17] and at 9 months they can solve problems requiring two intermediate steps.[18] Problem-solving scores measured at 9 months correlate with IQ and vocabulary scores at 3 years.[14,18] At 10 months infants can solve problems requiring three intermediate steps.[19]

Infants and methods

Infants

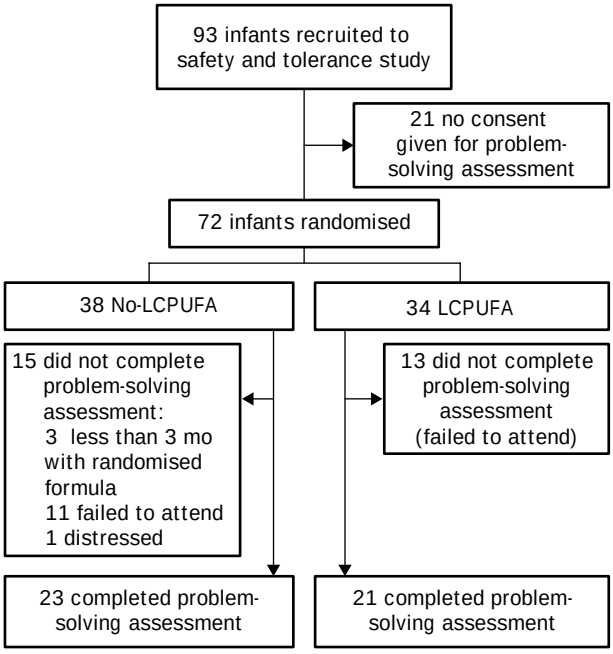
We studied term infants (birthweight 2500–4000 g; gestation 37–42 weeks) whose parents initially consented to a randomised study of the safety and tolerance of formula supplemented with LCPUFA and then consented to a problem-solving assessment at 10 months. The mothers were recruited from a single maternity hospital and were interviewed by a research nurse after they had indicated their choice of infant feeding at the antenatal clinic. Mothers were allocated to LCPUFA or no-LCPUFA formula via a computer-generated randomisation table. We used permuted blocks of six, so that after every 6th infant the two groups were numerically balanced. Randomisation was also stratified to ensure sex matching.

Immediately after the birth mothers were supplied with ready-to-feed infant formula, and subsequent supplies were delivered by a local pharmacy. Formulae were coded and the pharmacy knew the letter code which identified the formula. The LCPUFA formula was Aptamil with the fat supplement Milupan, derived from milk fat, vegetable oils, and egg lipids (table 1). The no-LCPUFA formula was Aptamil. Both were supplied by Milupa Ltd.

Problem solving

Problem solving[16–19] was assessed at age 10 months within the narrow time limit of 7 days because problem-solving ability develops rapidly at this age.[19] The infant sat on the parent's lap at the end of a table, and problems were presented on a tray (60 cm×80 cm). We used a barrier, a 20×14×5 cm block of foam covered with blue fabric; a brown cloth 22×42 cm; and a cover, a 6×6 cm blue cloth. The goal object was a small toy. To familiarise the infants with the materials and the procedure we presented the barrier, cloths, and toy on the tray individually, allowing two presentations of each object and 20 s for play.

Infants next received pretests on the component steps of the three-step problem. In the first they removed the barrier to retrieve the toy behind it; then they pulled the cloth to retrieve the toy placed on the far end; and in the third pretest infants searched for the toy after they had seen it hidden under the cover. Infants were allowed 30 s to retrieve the toy, and played with the toy for 20 s before receiving the next trial. Two trials were administered on each pretest. Finally, infants received four trials on the three-step problem. The barrier was positioned 5 cm from the front edge of the tray, and the support cloth was placed directly behind the barrier. When the infant was looking, the toy was set down on the far end of the cloth, and the cover was placed over it. The tray was immediately pushed forward, and infants were allowed 30 s to retrieve the toy. All trials were videotaped. Behaviour was scored from the videotapes for evidence of intention.[16,19]



Trial profile

Fatty acid	LCPUFA	No-LCPUFA
C12:0	4·9–5·6	4·8
C14:0	5·6–5·9	5·3
C16:0	26·1–26·8	25·0
C18:1n-9	30·2–32·2	36·0
C18:2n-6	11·5–12·8	11·4
C18:3n-3	0·60–0·65	0·70
C20:4n-6 (AA)	0·30–0·40	<0·10
C22:6n-3 (DHA)	0·15–0·25	—

Table 1: **Fatty acid composition (g/100 g fat) of LCPUFA and no-LCPUFA formulae**

An "intention score" was defined as the total of the scores for each behaviour, averaged for the four trials. For the three steps of the problem and three behaviours appropriate to the step the scores were 0, 1, or 2 so the total intention score for the entire problem could range from 0 to 18. "Intentional solutions" were trials on which each relevant behaviour was scored as intentional (1 or 2). All videotapes were scored by one independent, trained observer not involved in the assessment. A second observer scored all trials for a random sample of 33% of infants. The measures were highly reliable—for example, the percentage of agreements on identification of intentional solutions of the entire problem was 93% (kappa=0·87).*

Demographic and other data

We also obtained information on social class, housing, family size, maternal education, and maternal age at time of the assessment. Social class (I–V or unemployed) was based on occupation of the income-providing parent or on the father's occupation if both parents were earning. Housing was coded as rented or owned. Family size was recorded as the number of surviving children in the family unit. Maternal education was recorded as the age when the mother left full-time education.

Nutritional data collected by the research nurse at 1, 2, and 3 months during home visits and anthropometric measures at birth and at 3 months were also recorded but the primary outcome measures were problem-solving scores at 10 months.

Ethical approval

Throughout the study period, mothers and researchers were unaware of the type of formula given to infants. The study was approved by the Tayside Committee on Medical Research Ethics.

Statistics

Based on previous data from our laboratory,[19] a sample size of 24 in each group was calculated as being required to detect a difference of one intentional solution on the entire three-step problem with a power of 90% at p=0·05. We used the Mann-Whitney test for problem solving data, Student's *t* for demographic, anthropometric and nutritional variables, and the chi-square test for categorical variables, all statistical analyses being done with SPSS version 6·1·2 for Windows.

Results

93 infants had been recruited for the tolerance and safety study. 21 were not enrolled for the problem-solving assessment because parental consent was not given. With further exclusions (figure) 44 infants completed the assessment (LCPUFA 21; no-LCPUFA 23). There were no significant demographic, social, anthropometric, or formula intake differences between the two groups (n=21, n=23) or between the infants who completed the problem

*Further information about the problem-solving assessment may be obtained from PW.

Step	No intention (0)	Possible intention (1)	Clear intention (2)
Barrier			
Barrier behaviour	Play; barrier not removed	Hesitant removal	Remove barrier
Fixation	Fixate away from cloth	Fixate briefly away away from cloth	Fixate cloth continuously
Cloth retrieval	Ignore cloth	Attempt to grasp cloth	Pick up cloth
Cloth			
Cloth behaviour	Play; cover not within reach	Hesitant pulling	Pull cloth
Fixation	Fixate away from cover	Fixate briefly away from cover	Fixate cover continuously
Cover retrieval	Ignore cover	Attempt to grasp cover	Pick up cover
Cover			
Cover behaviour	Play; cover not removed	Hesitant removal	Remove cover
Fixation	Fixate away from toy	Fixate briefly away from toy	Fixate toy continuously
Toy retrieval	Ignore toy	Attempt to grasp toy	Pick up toy

Table 2: **Criteria for scoring intention on steps of three-step problem**

solving assessment (n=44) and infants who completed 3 months of randomised formula but who did not complete the problem-solving assessment (n=25) (data not shown).

For the entire three-step problem the LCPUFA group had significantly higher intention scores and significantly more intentional solutions (table 3). There were no significant differences between the groups on the barrier and cloth steps, but the LCPUFA group had significantly higher scores on the final cover step.

Pulling the cover and toy off the edge of the table, and thus scoring 0 for behaviours on the final step, happened less often in the LCPUFA group (median 0 trials) than in the no-LCPUFA group (1 trial) but the difference was not significant (p=0·179). If these trials that failed to get to step 3 were excluded, intention scores on the final cover step showed no significant difference between LCPUFA (median 5·0) and no-LCPUFA (3·3) (p=0·110). Nor did intention scores on the entire problem when these trials were excluded (16·0 and 13·3, respectively) (p=0·184). However, analysis of the proportion of trials that were intentional solutions on the final cover step, with exclusions of trials where cover and toy were pulled off the table, indicated that the proportion remained significantly higher for the LCPUFA group (median 0·75) than for the no-LCPUFA group (0·29) (p=0·013). The proportion of trials that were intentional solutions on the entire problem when these trials were excluded was also significantly higher in the LCPUFA group (0·75 and 0, respectively) (p=0·041).

Scores for anthropometric measures at 3 months and formula intake between 1 and 3 months revealed no significant differences between the LCPUFA and no-LCPUFA groups (data not shown).

Step	LCPUFA (n=21)	No-LCPUFA (n=23)	p
Intention score			
Entire problem	14·0 (11·8, 17·1)	11·5 (10·0, 13·3)	0·035
Barrier step	5·5 (4·3, 6·0)	4·8 (3·5, 5·8)	0·221
Cloth step	5·0 (4·5, 6·0)	4·5 (3·5, 5·8)	0·147
Cover step	4·3 (2·6, 5·3)	2·5 (1·0, 3·5)	0·032
Intentional solutions			
Entire problem	2·0 (0·5, 3·0)	0·0 (0·0, 2·0)	0·021
Barrier step	4·0 (2·0, 4·0)	3·0 (2·0, 4·0)	0·337
Cloth step	3·0 (2·0, 4·0)	3·0 (1·0, 4·0)	0·234
Cover step	3·0 (1·5, 3·5)	1·0 (0·0, 2·0)	0·005

Table 3: **Median (quartiles) problem-solving scores on entire problem and each individual step**

Discussion

We have shown that, at the age of 10 months, an infant's three-step problem-solving ability is significantly improved if the food formula has been supplemented with LCPUFA. This finding is important because higher scores on such problem solving are related to IQ in later childhood.[14,18] Only 64% of infants completing 3 months of feeding with their randomised formula in the earlier safety and tolerance study subsequently completed the problem-solving assessment at 10 months but there is no indication that this smaller sample was biased. The problem-solving scores at 10 months suggest that the benefits of LCPUFA to term babies persist beyond the period during which the infants received the supplemented formula. The lack of differences between groups in formula intake or anthropometric measures at 3 months suggests that other nutritional factors were unlikely to have contributed to problem-solving ability. We do not have precise data on the timing and nature of solid feeding during the first months of life in these babies but weaning foods have low LCPUFA content and are unlikely to have influenced LCPUFA status.[20]

Intentional solutions to the three-step problem require ability to think beyond the first step and go to the entire sequence of steps needed to achieve the final goal. Infants first show ability to think beyond the first step of a three-step problem at age 10 months.[19] The fact that problem solving scores in the LCPUFA and no-LCPUFA groups did not differ significantly on the first barrier step suggests that ability to think beyond the first step and consider the remaining steps in the solution to the problem was unrelated to infants having received formula supplemented with LCPUFA.

Additionally, three-step problems involve memory and attention control. Infants who solve the barrier and cloth steps may fail to retrieve the toy because they forget the final goal or ignore it as a result of being distracted by the other objects. The finding that the LCPUFA group had significantly higher scores on the final step suggests that memory or attention control was improved. Higher scores on the final step could also simply be explained by improved motor control, making it less likely that cover and toy would be pulled off the edge of the table. However, there was no significant difference between the groups in the frequency of this behaviour, and the fact that the LCPUFA group had significantly more intentional solutions, even when trials affected by this behaviour were excluded, indicates that this difference was not due to a motor effect.

One possible explanation for improved problem solving is that accumulation of LCPUFA in the cell membranes of the CNS speeds up information processing. In randomised trials DHA-supplemented preterm infants demonstrated shorter looking times in the Fagan test of infant intelligence,[21,22] and a similar effect of higher n-3 LCPUFA status has also been reported in infant rhesus monkeys.[23] We have reported that infants who demonstrate impaired attention control had significantly shorter fixation times if they received LCPUFA-supplemented formula.[24] Measures of looking time have been interpreted as reflecting speed of information processing,[25,26] and infants with shorter looking times have faster reaction times.[27] Although the relation between speed of processing and problem solving in infants has not been investigated, infants who process information more

quickly may be more efficient at solving a three-step problem—that is, they may be quicker to plan a solution and quicker to execute it before becoming distracted or forgetting the final goal.

Another possible mechanism is that LCPUFA affects the development of brain structures involved in releasing attention from a stimulus (disengagement). Difficulty with disengagement results in increased looking times. Disengagement improves after 3 months,[28,29] and cortical structures implicated in this ability include the parietal and prefrontal cortex and frontal eye fields.[30] LCPUFA supplementation may improve the maturation of these structures. Infants who can easily disengage from a stimulus may be able to switch rapidly from manipulating one intermediary to the next, and so solve the three-step problem. Development of prefrontal cortex in infants does seem to be related to ability to solve means-end problems,[31,32] and LCPUFA supplementation may contribute to early prefrontal maturation.

Our study demonstrates that term infants may benefit from LCPUFA supplementation, and the effects seem to persist beyond the period of supplementation. LCPUFA may influence either speed of information processing or processes of attention control, and future studies should include assessments of infant reaction times[27] and disengagement.[28]

Contributors

P Willatts and J S Forsyth designed the study, analysed the data, and were involved in writing the paper. M K DiModugno was responsible for collection and management of the problem-solving data, and contributed to the analyses and interpretation. S Varma and M Colvin were involved in recruitment, randomisation, and collection of anthropometric and formula intake data.

Acknowledgments

We acknowledge support from Milupa Ltd, UK. We thank Andrew Mirrlees for assistance with scoring the problem solving assessment.

A preliminary report on this study was presented at the American Oil Chemists Society Meeting on PUFA in Infant Nutrition (Barcelona, Nov 7–9, 1996).

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