Long-chain polyunsaturated fatty acids have a positive effect on the quality of general movements of healthy term infants[1–3]

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ABSTRACT

Background: Whether long-chain polyunsaturated fatty acids (LCPs) play a role in the development of the young nervous system in term infants is debated.

Objective: We investigated whether supplementation of formula with LCPs for 2 mo improves the quality of general movements (GMs) in healthy term infants at 3 mo of age.

Design: A prospective, double-blind, randomized controlled study was conducted with 2 groups of healthy term infants: a control-formula (CF) group (n = 131) and an LCP-supplemented-formula (LF) group (n = 119). A breastfed (BF) group (n = 147) served as a reference. Information on potential confounders was collected at enrollment. Videotapes were made of the infants' spontaneous motor behavior at 3 mo of age to assess the quality of their GMs. On the basis of quality, normal GMs were classified as normal-optimal or normal-suboptimal, and abnormal GMs were classified as mildly or definitely abnormal. Attrition at 3 mo of age was 15% and nonselective. Multivariate regression analyses with adjustment for confounders were carried out to evaluate the effect of the type of feeding.

Results: None of the infants had definitely abnormal GMs. Infants in the CF group had mildly abnormal GMs significantly more often than did infants in the LF and BF groups (31% compared with 19% and 20%, respectively). Infants in the BF group had normal-optimal GMs more frequently than did infants in the LF and CF groups (34% compared with 18% and 21%, respectively). Logistic regression analyses confirmed these findings.

Conclusion: Supplementation of healthy term infants with LCPs during the first 2 mo of life reduces the occurrence of mildly abnormal GMs. *Am J Clin Nutr* 2003;78:313–8.

KEY WORDS General movements, long-chain polyunsaturated fatty acids, infants, nutrition, nervous system, motor development, breastfeeding, term infants, n−3 fatty acids, docosahexaenoic acid

INTRODUCTION

Fatty acids and especially long-chain polyunsaturated fatty acids (LCPs) have become a major focus of attention in the field of infant nutrition. The most important LCPs are docosahexaenoic acid (DHA, 22:6n−3) and arachidonic acid (AA, 20:4n−6). During the first postnatal weeks, newborns do not seem to synthesize sufficient amounts of LCPs from their precursors to satisfy the newborns' high needs (1). Infants obtain LCPs from breast milk but generally not from formula. Because animal studies indicated that LCPs play an important role in the development of the nervous system (2), the question arose whether infant formulas should be supplemented with LCPs. Yet, no convincing evidence has been provided that LCP supplementation in full-term infants confers a benefit for visual, motor, and cognitive development that extends beyond the first year of life (3). However, studies that follow children until they reach school age have not been carried out.

When evaluating the effect of supplementation of infant formulas, it should be kept in mind that the putative positive effects are at best only subtle. It can be assumed that the composition of the optimal infant formula is such that it results in a developmental outcome that is similar to that observed in breastfed children. Studies that evaluated the differences in cognitive outcome between children who had been breastfed and those who received formula without LCPs showed that the long-term advantage of the breastfed children was ≈3–6 intelligence quotient points (4, 5). This means that at best a possible positive effect of LCP supplementation of infant formulas is on the order of a few intelligence quotient points. Until now, studies that dealt with the effect of LCP supplementation on infant motor and cognitive development frequently used the Bayley Scales of Infant Development or the Fagan Test. The Bayley Scales are a frequently used but rather gross instrument to document infants' motor and cognitive abilities. The Fagan Test is supposed to be a specific cognitive test that evaluates infants' interest in novelty. Putative positive effects of LCPs may be found when more sensitive and specific assessment techniques for infant development are used (2).

The evaluation of the quality of general movements (GMs) has been shown to be an accurate technique for evaluating the quality of brain function in young infants (6–8). GMs are complex movements that involve the head, trunk, arms, and legs. GMs arise during early fetal life and persist until 3–4 mo after full-term age. Normal GMs are characterized by fluency, variation, and complexity. These characteristics disappear when movements become abnormal. Movement fluency is the first property to disappear, which means that subtle dysfunctions of the nervous

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TABLE 1
Classification of the quality of general movements[1]

Classification	Complexity[2]	Variation[3]	Fluency[4]
Normal-optimal	+++	+++	+
Normal-suboptimal	++	++	−
Mildly abnormal	+	+	−
Definitely abnormal	−	−	−

[1] From reference 11. +++, abundantly present; ++, sufficiently present; +, present, but insufficiently; −, absent.

[2] Defined as spatial variation. The infant actively produces frequent changes in the direction of movement of the participating body parts. The changes in direction are brought about by continuously varying combinations of flexion-extension, abduction-adduction, and endorotation-exorotation of the participating joints.

[3] Defined as temporal variation. Across time, the infant produces continuously new patterns of movement, ie, the infant has an apparently infinite movement repertoire.

[4] Defined as the presence of smooth, supple, and graceful movements. Fluency in particular points to the velocity profile of the movements, which is characterized by gradual accelerations and decelerations.

system already result in movements with a jerky or stiff appearance. Movement complexity and movement variation, which in fact can be considered as 2 forms of movement variation, are the major characteristics of GM quality. Four classes of GM quality can be distinguished: 2 forms of normal GMs (normal-optimal and normal-suboptimal) and 2 forms of abnormal GMs (mildly and definitely abnormal) (**Table 1**). Various studies have shown that the quality of GMs is a strong predictor of neurologic development and that the best predictions are those that are based on the quality of movements during the last phase of GMs (9, 10). The last phase of GMs occurs at 2–4 mo after term and consists of so-called "fidgety" GMs, during which movement complexity, variation, and fluency are expressed particularly in tiny and elegant movements that occur all over the body. The occurrence of definitely abnormal GMs at the fidgety age predicts the development of cerebral palsy with a high accuracy (9, 10). The occurrence of mildly abnormal GMs at 2–4 mo of age is associated with a significant increase in the risk of development of minor neurologic dysfunction, attention problems, and aggressive behavior at school age (10). A recent study showed that in children without cerebral palsy, the quality of GMs at the fidgety age as classified according to the 4 classes shown in Table 1 was significantly correlated with neurologic development at 1.5 y of age ($\rho = 0.55$, $P < 0.001$) and at 5.5 y of age ($\rho = 0.32$, $P < 0.05$) (11).

The aim of the present study was to assess the effect of LCP supplementation of healthy term infants until the age of 2 mo on their neurologic condition at 3 mo, which was determined by evaluating the quality of their GMs. To this end, we videotaped the GMs of 119 infants who were fed formula supplemented with LCPs and of 131 infants who were fed formula without LCPs. To assess whether infants who were fed LCP-supplemented formula would perform similarly to breastfed infants, we also videotaped the GMs of 147 infants who had been breastfed.

SUBJECTS AND METHODS

From February 1997 until October 1999, 472 healthy term infants were enrolled in the study. Mother-infant pairs were recruited during pregnancy checkup visits at the various study subsites in and near Groningen, which were located at the University and Martini Hospitals in Groningen and at midwife clinics. Final enrollment in the study occurred in the neonatal period, at which time the parents provided written informed consent. All infants were born at 37–42 wk of gestation and were of native western European origin. We excluded from the study infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d. We aimed to have 3 groups of comparable size: 2 groups of formula-fed infants and 1 group of breastfed infants. After the mothers chose to either breastfeed or formula-feed their infants, the formula-fed infants were randomly allocated to either the control-formula (CF) group or the LCP-supplemented-formula (LF) group by means of a single, central computerized randomization that used a block design (blocks of 6, delivered in batches of 78). Number identification linked specific batches of formula to the infants. Accordingly, the CF group consisted of 167 newborns, the LF group consisted of 145 newborns, and the breastfed (BF) group consisted of 160 newborns. The study diets consisted of commercial formula (Nutrilon Premium; Nutricia, Zoetermeer, Netherlands) for the CF group and of a similar formula enriched with 0.45% (by wt) AA and 0.30% (by wt) DHA for the LF group. DHA was derived from egg yolk and tuna oil that was low in eicosapentaenoic acid, and the source of AA was egg yolk and a single-cell oil produced by a common soil fungus, *Mortierella alpina*. Care was taken to provide the LCPs in a ratio of phospholipids to triacylglycerol that was similar to that present in human milk. The fatty acid compositions of the study formulas and of human breast milk from a comparable Dutch reference group are provided in **Table 2**.

TABLE 2
Fatty acid composition of the study formulas and human breast milk from a comparable Dutch reference group[1]

Fatty acids	Breast milk[2]	LF	CF
		mol%	
Saturated			
6:0	0.32 ± 0.04[3]	0.21	0.38
8:0	0.66 ± 0.10	3.80	2.88
10:0	2.67 ± 0.54	2.65	1.90
12:0	8.16 ± 2.60	10.78	11.46
14:0	8.01 ± 1.98	4.53	4.50
16:0	23.04 ± 2.19	20.03	22.72
18:0	7.25 ± 0.92	3.85	3.29
20:0		0.34	0.33
22:0		0.23	0.23
Monounsaturated			
16:1n−7	—	0.21	0.20
18:1n−9	—	37.46	38.95
20:1n−9	—	0.25	0.25
Polyunsaturated			
18:2n−6	13.62 ± 4.24	11.0	11.56
18:3n−6	0.11 ± 0.03	0.18	—
20:3n−6	0.34 ± 0.06	0.03	—
20:4n−6	0.34 ± 0.06	0.39	—
18:3n−3	1.11 ± 0.35	1.30	1.27
20:5n−3	0.06 ± 0.04	0.06	—
22:6n−3	0.19 ± 0.11	0.23	—
Other fatty acids		1.53	

[1] LF, formula supplemented with long-chain polyunsaturated fatty acids; CF, control formula (Nutrilon Premium; Nutricia, Zoetermeer, Netherlands).

[2] Values from reference 12.

[3] $\bar{x}$ ± SD.

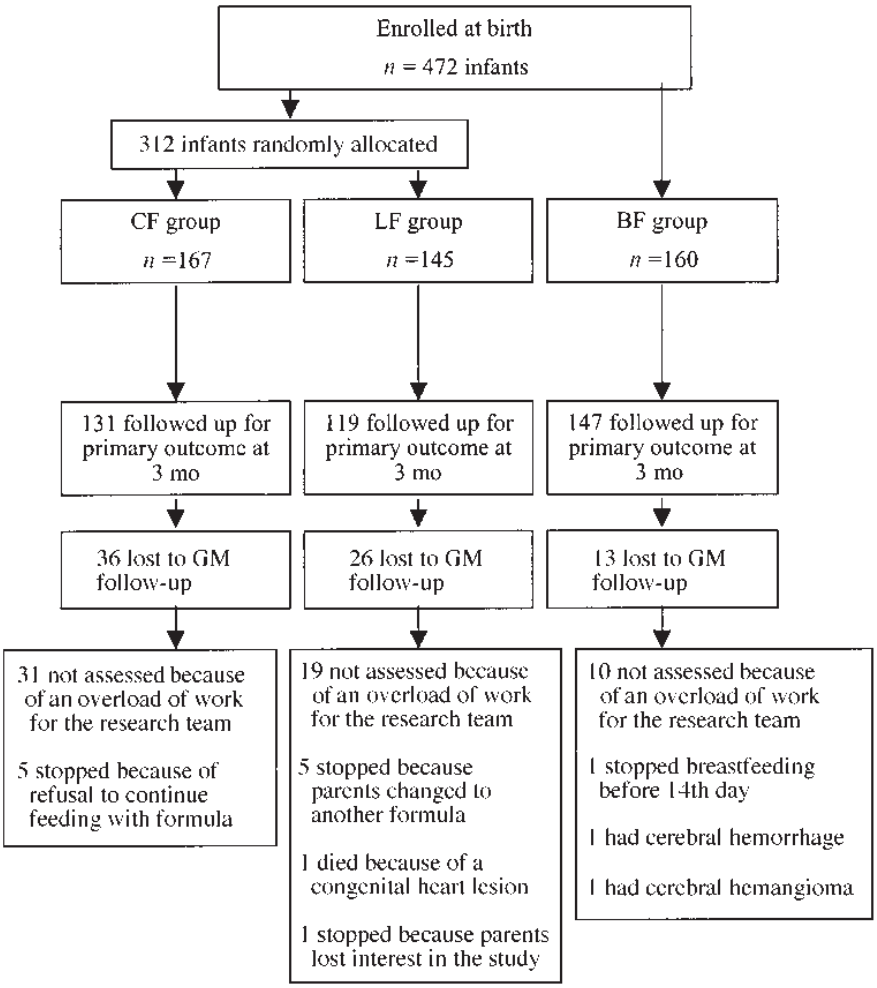

FIGURE 1. Flow diagram of infants enrolled in the study and followed up until 3 mo of age. CF, control formula; LF, formula supplemented with long-chain polyunsaturated fatty acids; BF, breastfed; GM, general movements.

The duration of supplementation was 2 mo. Seventy-three infants in the BF group stopped breastfeeding before 2 mo of age and received LCP-supplemented formula for the duration of the 2-mo period; the median duration of LCP supplementation in these infants was 3 wk. All the formula-fed infants received control formula from 2 to 6 mo of age. Compliance with the specific forms of feeding was confirmed by checking the daily diaries filled out by the mothers. The formulas were provided free of charge to the parents. The parents and the examiners were unaware of the type of formula that the infants received. The study was approved by the Ethics Committee of the Groningen University Hospital (MEC 95/08/207).

At enrollment, detailed and standardized information was collected on the infants' social and pre- and perinatal conditions. For the latter, we used the 74 variables of the Obstetrical Optimality Score (OOS), which describes the obstetric condition, ranging from the parents' socioeconomic status and health condition to the infant's condition immediately after birth. The number of items having a value within a predefined optimal range forms the optimality score for an infant (13). We used the information obtained from the OOS both as raw data and as data dichotomized into optimal and nonoptimal categories.

Follow-up at the age of 3 mo was performed for 397 infants (ie, 84% of the original population of 472 infants). The major reason that infants were not followed up was simply an overload of work for the research team (**Figure 1**). The social and pre- and perinatal background of the infants who were not included in the assessment at 3 mo of age did not differ significantly from that of the originally recruited sample. Relevant data on the obstetric, physical, and social characteristics of the 3 groups who were assessed at 3 mo of age are provided in **Table 3**.

The follow-up at 3 mo of age consisted of videotaping the infants' spontaneous motility for 15 min while they were in the supine position and in their home environment. Care was taken to ensure that the infants were awake, active, and not crying. At follow-up, the infants had a postmenstrual age of ≥49 wk; thus, all the infants were assessed in the final phase of GMs. Investigators who were blinded to the subjects' group assignments analyzed the quality of the videotaped GMs. Movements were classified as normal-optimal, normal-suboptimal, mildly abnormal, and definitely abnormal (Table 1; 11). Interscorer agreement on GM quality, which was determined in a random sample of 10 videotapes, was good ($\kappa = 0.75$; 14). At the time of follow-up, the infants' weight and length were recorded (Table 3).

TABLE 3
Obstetric, physical, and social characteristics of the 3 groups who were assessed at 3 mo of age[1]

Variable	CF group (n = 131)	LF group (n = 119)	BF group (n = 147)
Sex, male [n (%)]	72 (55)	63 (53)	75 (51)
Gestational age (wk)	39.6 ± 1.2[2]	39.6 ± 1.3	39.7 ± 1.3
Postconceptional age (wk)	54.4 ± 2.2	54.6 ± 2.8	53.4 ± 2.2[3,4]
Birth weight (g)	3514 ± 430	3534 ± 502	3592 ± 424
First born [n (%)]	51 (39)	48 (40)	71 (48)
Maternal age (y)	30 ± 4	30 ± 4	31 ± 5[3]
Maternal higher education[5] [n (%)]	8 (6)	19 (16)	61(42)[3,4]
Paternal higher education[5] [n (%)]	18 (14)	19 (16)	62 (42)[3,4]
Maternal smoking during pregnancy [n (%)]	42 (32)	38 (32)	28 (19)[3,4]
Paternal smoking during pregnancy [n (%)]	60 (46)	63 (53)	53 (36)[3,4]
Maternal alcohol consumption during pregnancy [n (%)]	13 (10)	13 (11)	38 (26)[3,4]
Obstetrical Optimality Score[6]	57, 59, 65	56, 58, 65	57, 60, 66
Weight at 3 mo of age (g)	6325 ± 714	6410 ± 714	6266 ± 746
Length at 3 mo of age (cm)	63 ± 2.2	63 ± 2.6	63 ± 2.5

[1] CF, control formula; LF, formula supplemented with long-chain polyunsaturated fatty acids; BF, breastfed.
[2] $\bar{x}$ ± SD.
[3] Significantly different from the CF group, $P < 0.05$ (Bonferroni correction).
[4] Significantly different from the LF group, $P < 0.05$ (Bonferroni correction).
[5] University education or vocational college.
[6] 25th, 50th, and 95th percentiles.

The analysis focused on the effect of type of feeding on GM quality. Besides univariate statistical analyses with chi-square, logistic regression analysis was applied because this offered the possibility of parceling out the effect of type of feeding on movement quality while taking into account the role of potential confounders (15). For calculating the effect of type of feeding, a dummy variable was created for the intake of each of the 3 diets (ie, CF, LF, and breast milk). Two runs of logistic regression analysis were carried out: one for the contribution of type of feeding to the occurrence of normal-optimal GMs and one for the effect of type of feeding on the occurrence of mildly abnormal GMs. Other factors included in the multivariate analyses were social characteristics (*see* Table 3), postconceptional age, OOS, and anthropometric variables. In addition, we used logistic regression analysis to evaluate whether the duration of LCP supplementation in the BF group played a role in the development of mildly abnormal and normal-optimal GMs. Statistical calculations were performed with SPSS version 10 (SPSS Inc, Chicago). Differences having a P value < 0.05 were considered statistically significant (two-tailed testing).

RESULTS

The distribution of the quality of GMs at 3 mo of age in the 3 groups is depicted in **Figure 2**. None of the infants had definitely

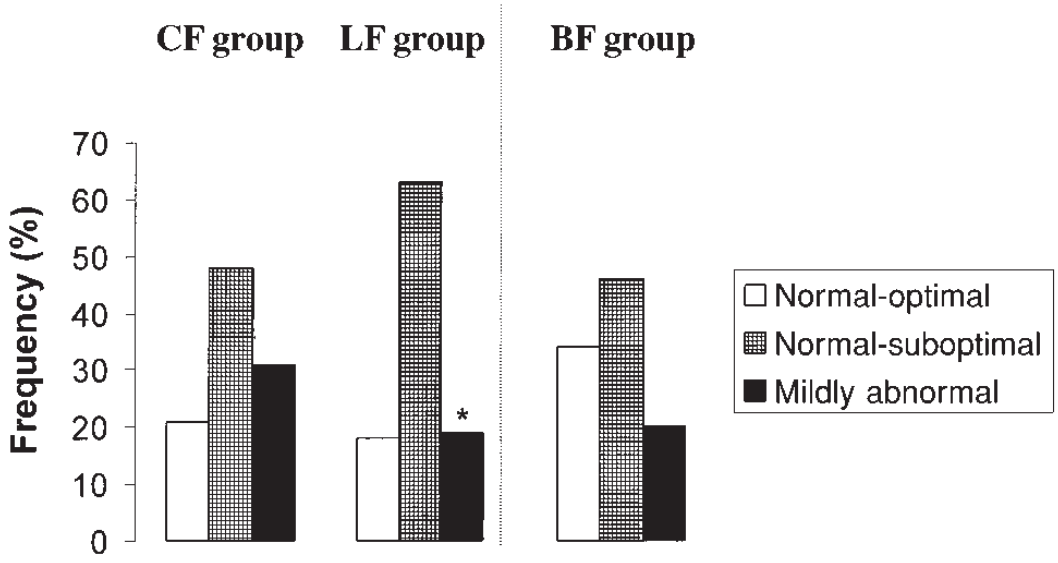

FIGURE 2. Distribution of the quality of general movements at 3 mo of age in the 3 study groups who consumed either control formula (CF group; n = 131), formula supplemented with long-chain polyunsaturated fatty acids (LF group; n = 119), or breast milk (BF group; n = 147). *Significantly different from the CF group, $P < 0.05$.

TABLE 4
Results of logistic regression analysis of factors contributing to the occurrence of mildly abnormal general movements (explained variance of 9.9%)[1]

Factors	Odds ratio (95% CI)	*P*
Type of feeding		
Breast milk	1	
CF	2.03 (1.09, 3.80)	0.039
LF	0.94 (0.48, 1.85)	0.87
LF[2]	0.49 (0.26, 0.92)	0.032
Covariates		
Marital state[3]	0.57 (0.32, 1.01)	0.039
Family history of diabetes[4]	1.86 (1.09, 3.18)	0.011
Gestational age at birth[5] (wk)	0.40 (0.21, 0.76)	0.010
Condition of perineum[6]	2.44 (1.38, 4.33)	0.002
Age at assessment (wk)	0.86 (0.76, 0.98)	0.021

[1] CF, control formula; LF, formula supplemented with long-chain polyunsaturated fatty acids.
[2] With the CF group instead of the breastfed group as the reference group.
[3] 0 = not married, 1 = married.
[4] One of the variables of the Obstetrical Optimality Score, denotes the presence (1) or absence (0) of type 1 or type 2 diabetes in ≥1 first-degree relative.
[5] 0 = <40 wk, 1 = ≥40 wk.
[6] 0 = episiotomy or grade-1–2 rupture, 1 = intact perineum or total rupture.

TABLE 5
Results of logistic regression analyis of factors contributing to the occurrence of normal-optimal general movements (explained variance of 4.6%)[1]

Factors	Odds ratio (95% CI)	*P*
Type of feeding		
Breast milk	1	
CF	0.55 (0.31, 0.97)	0.038
LF	0.42 (0.23, 0.78)	0.006
LF[2]	0.77 (0.40, 1.45)	0.41
Covariates		
Profession of mother's partner required a university or vocational-college education[3]	1.70 (0.99, 2.92)	0.055
Obstetrical Optimality Score	1.05 (0.99, 1.12)	0.11
Age at assessment (wk)	1.08 (0.97, 1.21)	0.17

[1] CF, control formula; LF, formula supplemented with long-chain polyunsaturated fatty acids.
[2] With the CF group instead of the breastfed group as the reference group.
[3] 0 = no, 1 = yes.

abnormal GMs, and ≈20–30% of the infants had mildly abnormal GMs. The frequency of mildly abnormal GMs was significantly higher in the CF group than in the LF group (31% compared with 19%; $P = 0.04$). Normal-optimal GMs tended to occur most frequently in the BF group (34% compared with 18% and 21% in the LF and CF groups, respectively), but these differences were not significant in the univariate analyses.

A summary of the results of logistic regression analysis of factors contributing to the occurrence of mildly abnormal GMs is presented in **Table 4**. The analysis confirmed that mildly abnormal GMs occurred significantly less often in the LF group than in the CF group. Similarly, the infants in the BF group had significantly fewer mildly abnormal GMs than did the infants in the CF group. Logistic regression also confirmed that the frequency of mildly abnormal GMs did not differ significantly between the LF and BF groups. Besides including the intake of CF, the model explaining the occurrence of mildly abnormal GMs also included a family history of diabetes, a gestational age at birth of <40 wk, a perineum at birth characterized as having undergone an episiotomy or a grade-1–2 rupture, a nonmarital state, and a young postnatal age at GM assessment. When gestational age and postnatal age at GM assessment were replaced in the logistic regression analysis by postconceptional age, the effect of type of feeding did not change significantly. An older postconceptional age was significantly related to a less frequent occurrence of mildly abnormal GMs (odds ratio: 0.85; 95% CI: 0.78, 0.99; cf Table 4).

A summary of the results of logistic regression analysis of factors contributing to the occurrence of normal-optimal GMs is shown in **Table 5**. The analysis indicated that breastfeeding was associated with a significantly higher prevalence of normal-optimal GMs than was CF or LF feeding. Besides including the intake of breast milk, the model explaining the occurrence of normal-optimal GMs included a profession of the mother's partner that required a university or vocational-college education, a high OOS, and an old age at GM assessment. In addition, the replacement of gestational age and postnatal age at GM assessment by postconceptional age did not significantly change the effect of type of feeding on the occurrence of normal-optimal GMs. Postconceptional age had no significant effect on normal-optimal GMs. Logistic regression analysis in the BF group showed that the duration of LCP supplementation did not significantly affect movement quality.

DISCUSSION

Our study indicated that supplementation of formula with LCPs for 2 mo after birth significantly reduces the occurrence of mildly abnormal GMs at the age of 3 mo. We showed this effect in a relatively large series of full-term, healthy infants, in whom the quality of motor behavior was assessed in a double-blind way. Fifteen percent of the original sample was lost to follow-up, but the loss was nonselective.

At an early age, the nervous system is organized basically in a nonspecific, generalized way (16). The GMs, which are the most frequently occurring movements until the age of 3–4 mo, are an expression of this organization. Various studies support the notion that the quality of GMs reflects the quality of the nervous system (7–11, 14). The finding that LCP supplementation may induce an improvement in GM quality fits with the evidence that LCP accretion in early life occurs in all cortical areas, where it might play a major role in the formation of synapses (17). It has been suggested that DHA affects synapse formation directly by means of membrane incorporation, whereas the role of AA in synapse formation is more indirect because it particularly affects signal transduction events that regulate growth cone activity and synapse formation (1).

The occurrence of mildly abnormal GMs at 3 mo of age indicates an increased vulnerability of the brain to the development of so-called minor developmental disorders, such as minor neurologic dysfunction, clumsiness, and attention problems at school age (10, 11). Thus, the finding that LCP supplementation is associated with a decrease in mildly abnormal GMs may imply that LCPs have a protective effect on the development of minor developmental disorders. Yet, the beneficial effect of LCP supplementation on neurologic condition could be a temporary one. Such a

temporary positive effect was reported by some researchers for the effect of LCPs on visual function (18, 19) and psychomotor development (20, 21), but other researchers found no significant effects (22, 23). Whether or not LCPs have a long-term beneficial effect on brain function in full-term infants is still debated. Birch et al (24) reported a positive effect on visual and mental development but not on motor development at 18 mo of age. Yet, several studies did not find an effect of LCPs on visual (22) or psychomotor (23, 25, 26) development at 1–2 y of age. Whether LCP supplementation affects the long-term developmental outcome of term infants can be determined only on the basis of follow-up studies that apply sensitive and specific tools for evaluating brain function at school age.

In the present study, the GM quality of the infants in the BF group was significantly higher than that of the infants in the CF and LF groups. The higher GM quality of the infants in the BF group was not related to the duration of LCP supplementation provided during part of the 2-mo feeding period. The breastfed infants' better performance is in agreement with the results of the literature, which indicate that the cognitive and motor development of breastfed infants is better than that of formula-fed infants (4, 5, 27). However, we cannot exclude the possibility that this result is explained by factors other than the composition of breast milk, such as maternal hormones that are not present in formula, subtle differences in caregiving practices (bonding), and genetic differences between mothers who breastfeed and those who bottle-feed (28). The logistic regression analysis indicated that the breastfed infants' better performance was not explained by their better socioeconomic background.

In conclusion, the present study indicates that LCP supplementation of healthy term infants for 2 mo improves their neurologic condition at 3 mo of age. Whether the LCP-induced advantage is transient or permanent needs to be determined.

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ERB and MH-A designed the study; HB, DAJD-B, ERB, FAJM, and MH-A analyzed and interpreted the results and wrote the report; JALW and HMT collected the video footage, participated in analyzing the videotapes, and were involved in the writing process; and JCvdH carried out the major part of analyzing the videotapes and was involved in the writing of the report. None of the authors had any conflicts of interest.

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