Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants[1–4]

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ABSTRACT

Background: Normal brain and visual development is thought to require exogenous docosahexaenoic acid (DHA; 22:6n−3) intake, but the amount needed is debatable. Because the supplementation of breastfeeding mothers with DHA increases the DHA content of their infants' plasma lipids, we hypothesized that it might also improve brain or visual function in the infants.

Objective: The objective was to determine the effect of DHA supplementation of breastfeeding mothers on neurodevelopmental status and visual function in the recipient infant.

Design: Breastfeeding women received capsules containing either a high-DHA algal oil (≈200 mg DHA/d) or a vegetable oil (no DHA) for 4 mo after delivery. Outcome variables included the fatty acid pattern of maternal plasma phospholipid and milk lipids 4 mo postpartum, the fatty acid pattern of plasma phospholipids and visual function in infants at 4 and 8 mo of age, and neurodevelopmental indexes of the infants at 12 and 30 mo of age.

Results: Milk lipid and infant plasma phospholipid DHA contents of the supplemented and control groups were ≈75% and ≈35% higher, respectively, at 4 mo postpartum. However, neither the neurodevelopmental indexes of the infants at 12 mo of age nor the visual function at 4 or 8 mo of age differed significantly between groups. In contrast, the Bayley Psychomotor Development Index, but not the Mental Development Index, of the supplemented group was higher ($P < 0.01$) at 30 mo of age.

Conclusion: DHA supplementation of breastfeeding mothers results in higher infant plasma phospholipid DHA contents during supplementation and a higher Bayley Psychomotor Development Index at 30 mo of age but results in no other advantages either at or before this age. *Am J Clin Nutr* 2005;82:125–32.

KEY WORDS Maternal docosahexaenoic acid supplementation, infant visual function, infant neurodevelopmental indexes, fatty acid pattern of milk lipid, infant plasma phospholipid fatty acid pattern, Bayley Scales of Infant Development

INTRODUCTION

Most studies of the effects of docosahexaenoic acid (DHA; 22:6n–3) on infant development have focused on the effect of supplementing formula-fed infants with DHA and how closely the development of supplemented infants mimics the development of breastfed infants. However, the amount of DHA in human milk is highly variable (1, 2), being low in some US women, particularly in comparison with the milk of women from regions where fish consumption is high (1–12). Thus, studies of breastfed infants receiving different DHA intakes should also be helpful in determining the role of DHA intake during early infancy on subsequent visual function and neurodevelopment.

We (13) and others (14–16) have shown that the supplementation of breastfeeding women with DHA increases the DHA content of their plasma lipids and milk as well as that of their infant's plasma lipids. Because the DHA content of plasma lipids is thought to reflect the DHA content of brain and retina, which, in turn, is important for normal brain and visual function, we hypothesized that DHA supplementation of breastfeeding mothers would increase the DHA content of the recipient infants' plasma lipids and, perhaps, improve visual and neuropsychological development in the recipient infants. The results of our attempt to test this hypothesis are reported here.

SUBJECTS AND METHODS

Subjects

Pregnant women who planned to breastfeed exclusively for ≥4 mo were recruited by newspaper ads, flyers in physicians' offices, and presentations at childbirth classes. Inclusion criteria included an age between 18 and 40 y, infant gestational age >37 wk, and infant birth weight between 2500 and 4200 g. Exclusion

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criteria included chronic maternal disorders as well as major congenital anomalies and obvious gastrointestinal or metabolic disorders of the infant. The study was approved by the Institutional Review Board for Human Subject Research of Baylor College of Medicine and Affiliated Hospitals and the Committee for the Protection of Human Subjects of the University of Texas Health Sciences Center at Houston. Written informed consent was obtained from all mothers before enrollment.

Study design

Women who qualified were assigned randomly in a double-masked manner, with the use of a computer-generated randomization scheme, to receive 1 of 2 identical capsules daily for 4 mo, starting within 5 d after delivery. One capsule contained a high-DHA algal triacylglycerol (DHASCO; Martek Biosciences Corp, Columbia, MD) that consisted of 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n−6), and 41.7% DHA (22:6n−3) by weight; it provided ≈200 mg DHA/d. The control capsule contained a 50:50 mixture of soy and corn oils consisting of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2n−6), and 3.9% α-linolenic acid (18:3n−3). Both capsules were supplied at no cost by Martek Biosciences Corp. They were dispensed at each visit before 4 mo postpartum by the Investigational Pharmacy of Texas Children's Hospital according to the previously mentioned randomization scheme. The number of capsules dispensed was always more than needed before the next appointment at 3 wk, 2 mo, or 4 mo postpartum; the subjects were instructed to ingest one capsule per day and to return all unused capsules at the next appointment. On the basis of the number of capsules returned, women in both groups took from 95% to 100% of the capsules they were instructed to take.

The primary outcome variable was performance at 30 mo of age on the Bayley Scales of Infant Development (17). Other outcome variables included the fatty acid pattern of milk lipids at 4 mo postpartum as well as that of infant plasma phospholipids at 4 and 8 mo postpartum, infant visual function at 4 and 8 mo of age, and additional indexes of neurodevelopmental status at 12 and 30 mo of age. Infant weight, length, and head circumference were monitored throughout the study.

Milk and blood collections

Mothers and infants were admitted to the Metabolic Research Unit of the Children's Nutrition Research Center at 4 mo postpartum for a 24-h milk collection. At each feeding, the infant was offered one breast, and an electrical breast pump (Egnell Inc, Cary, IL) was used to empty the contents of the other breast with each subsequent feeding. A fixed percentage of each volume collected was obtained, mixed thoroughly, added to similar collections during the 24-h collection period, and frozen at −70 °C for subsequent analysis. Blood samples from mothers and infants were obtained by venipuncture. Plasma was separated by centrifugation (2450 × *g*, 10 min, room temperature) and frozen at −70 °C until analyzed.

Plasma phospholipid and milk fatty acid measurements

Plasma and milk lipids were extracted by the method of Bligh and Dyer (18), and the phospholipid fraction of plasma was separated by one-dimensional thin-layer chromatography (Silica Gel 60; Sigma-Aldrich, St Louis, MO), as described previously (19). Methyl esters of the component fatty acids of the milk lipid and plasma phospholipid fractions were prepared with boron trifluoride methanol and quantified, as described previously (19, 20), by gas chromatography (Varian 3500; Varian Inc, Palo Alto, CA) with a DB-225 capillary column (J & W Scientific, Folsom, CA). The content of each fatty acid was expressed as the mole percentage of total fatty acids.

Assessment of visual function

Binocular visual acuity was assessed at 4 and 8 mo of age by using the Teller Acuity Card procedure as well as both sweep and transient visual evoked potentials (VEPs). The details of all methods were described previously (21). Briefly, the Teller Acuity Card procedure takes advantage of the fact that infants prefer to look at a patterned rather than an unpatterned stimulus. Cards with a grating pattern on one side and no pattern on the other side are presented to an infant by an examiner, who observes the infant through a peephole in the center of the card and determines the direction in which the infant looks without knowledge of the direction of the pattern. Cards with gratings of increasing spatial frequency (ie, smaller stripes) are presented until the infant is judged to be unable to discriminate the location of the pattern. Visual acuity is determined by the highest spatial frequency judged by the examiner to be distinguishable by the infant.

The transient and sweep VEPs were performed by using the ENFANT 4010 Electrophysiology System (NeuroScientific Corporation, Farmingdale, NY). At both ages, the infants were seated on a parent's lap, 75 cm from the monitor. During each session an investigator observed the direction of the child's gaze and either paused or resumed recording if necessary. Another investigator verified that the corneal reflection of the stimulus was aligned with the pupil and, to maximize fixation, jingled a set of metal keys in the center of the screen when the child appeared inattentive.

Transient VEPs were recorded with the use of pattern reversals of checkerboard stimuli. VEP latency (the time, in milliseconds, between the presentation of the stimulus and the peak of the occipital cortex response) and amplitude (the magnitude, in μV, of the recorded occipital cortex response) were determined. Sweep VEPs, performed by measuring the amplitude of the electrical response of the occipital cortex as visual stimuli (square wave gratings, or bars), were presented rapidly; the size of the bar gratings were "swept" from low to high spatial frequencies in 0.56 cycles/degree steps ranging from 0.56 to 6.75 cycles/degree. These stimuli have sharp edges and, hence, approximate Snellen eye chart acuity more closely than do simple sinusoidal gratings. Regression software provided by the instrument manufacturer was used to calculate the estimated threshold of resolution (ie, spatial frequency corresponding to a VEP amplitude of 0 μV).

Assessment of neurodevelopmental status

The primary outcome variable was the score on the Bayley Scales of Infant Development at 30 mo of age (17). These scales, considered the gold standard for the assessment of global abilities of children aged <3 y, assess overall mental development, including language and visual-motor problem solving [Mental Development Index (MDI)] and both fine and gross motor development [Psychomotor Development Index (PDI)]. The instrument was administered by 1 of 2 psychologists trained and

experienced in its use. It was administered at 30 mo of age because assessments at this age are more predictive of later function than are assessments at earlier ages (22).

Gross motor development of the infants was assessed at 12 and 30 mo of age by using the gross motor scale of the Gesell Developmental Inventory (23). At the same ages, language development was assessed by the Clinical Linguistic and Auditory Milestone Scale (CLAMS), and visual-motor problem-solving abilities were assessed by the Clinical Adaptive Test (CAT) (24, 25). All of these tests were administered by the same developmental pediatrician, and the results were expressed as developmental quotients (DQ). These tests were chosen because they can be administered much more quickly than can the Bayley Scales. We have shown that the overall CAT/CLAMS DQ (the mean of the CLAMS DQ and the CAT DQ) is correlated with concurrent Bayley MDI scores at both 12 ($r = 0.393$, $P = 0.008$) and 30 ($r = 0.742$, $P = 0.0001$) mo of age and that the overall CAT/CLAMS DQ at 12 mo of age is correlated modestly with the Bayley MDI at 30 mo of age ($r = 0.181$, $P = 0.036$) (26).

Anthropometric measures

Nude weights of the infants were determined with an electronic integrating scale (model LC 16000s; Sartorius, Gottingen, Germany) at 21 d as well as at 2, 4, 8, 12, 18, 24, and 30 mo of age. Length and head circumference were measured at the same times by using an infant stadiometer (Holtain Ltd, Crymych, United Kingdom) and a metal measuring tape (Executive Thinline 2 m W606 pm; Lufkin Tape, Apex, NC), respectively.

Data analysis

Data are expressed as group means ± SDs. The statistical significance of differences in continuous outcome variables between groups was tested by independent-samples *t* tests (SPSS software; SPSS, Chicago, IL).

Group differences in neurodevelopmental outcomes were further evaluated by analysis of covariance with control for sex, ethnicity, maternal age, maternal education, maternal intelligence quotient (as determined with the Slosson Intelligence Test, revised—a test that screens for the intellectual abilities of adults; 27), the composite score of the Family Environment Scale (28), birth weight, duration of breastfeeding, weight, and body length at the time each test was administered. Correlations between selected outcome variables were determined by regression analysis. The statistical significance of differences in categorical variables between groups was tested by the chi-square statistic or Fisher's exact test. A probability of ≤5% was assumed to represent statistical significance.

The number of mother-infant pairs enrolled was selected to permit detection of a difference in the Bayley MDI or PDI between groups at 30 mo of age of ≥0.5 SD (power = 80%; $P < 0.05$), assuming a completion rate through 30 mo of ≈60% (ie, an anticipated dropout rate of ≈40% through 30 mo of age). Averaging the data from twin pairs (1 in the DHA group and 2 in the control group) and treating the pair as a single subject compared with treating each twin as an individual subject did not affect any outcome variables. The data for each set of twins were reported as data for an individual subject.

RESULTS

Subjects

One hundred fourteen mothers were assigned to the DHA group and 113 to the control group. Each group included 115 infants (one group of twins in the DHA group; 2 in the control group). The number of subjects lost during the study and the number of subjects available for study at 4, 12, and 30 mo of age are summarized in **Figure 1**. Most subject losses occurred before the 4-mo assessment, primarily because breastfeeding was stopped or the intake of foods other than breast milk exceeded 20% of intake—a preset exclusion criterion; other losses occurred because the mothers decided to discontinue participation (3 in DHA group; 4 in control group) or to relocate (2 in DHA group; 0 in control group). All subject losses after 4 mo resulted because the family had relocated (2 in the DHA group between 4 and 12 mo of age and 5 in the DHA group between 12 and 30 mo; 4 in the control group between 4 and 12 mo of age and 6 in the control group between 12 and 30 mo). Thus, 90 and 87 infants in the DHA and control groups, respectively, were available for study at 12 mo and 83 and 77, respectively, were available for study at 30 mo.

The 2 groups of mothers did not differ significantly by age at delivery (31.5 ± 5 y in both groups), parity (1.8 ± 1.1 and 1.7 ± 0.9 in the DHA and control groups, respectively), or years of education (15.9 ± 2.2 and 16.3 ± 2.7 in the supplemented and control groups, respectively). The demographic characteristics of the 2 groups of infants (including 1 set of twins in the DHA group and 2 sets in the control group) also did not differ significantly at enrollment (**Table 1**) and the demographic characteristics of those remaining in the study at 4, 8, 12, and 30 mo of age did not differ significantly from those of the total group enrolled.

Milk and infant plasma fatty acids

Mean mole percentages of selected n−3 and n−6 fatty acids in milk lipid at 4 mo postpartum and in infant plasma phospholipids at 4 mo of age are shown in **Tables 2** and **3**, respectively. The DHA content of milk lipids was significantly greater in the DHA group than in the control group ($P < 0.0001$), and the contents of arachidonic acid (20:4n−6) and 22:4n−6 (docosatetraenoic acid) were lower ($P < 0.001$ and < 0.004, respectively). Infant plasma phospholipid fatty acid pattern at 4 mo of age mirrored that of milk lipid. The DHA content was significantly higher in the infants whose mothers were assigned to the DHA group than in those in the control group ($P < 0.0001$), and the contents of 20:4n−6, 22:4n−6, and 22:5n−6 (osbond acid) were significantly lower ($P < 0.001$, <0.001, and < 0.001, respectively). There were no statistically significant differences in infant plasma phospholipid fatty acid patterns between groups at 8 mo of age (data not shown).

Visual function

Visual acuity as assessed by the Teller Acuity Card procedure at 4 and 8 mo of age and by Sweep VEP at 4 mo of age, both expressed as cycles/degree ± octave, is shown in **Table 4**. There were no significant differences between groups in either measure at 4 or 8 mo of age. Acuity, as assessed by Sweep VEP at 8 mo of age, was 10.3 ± 0.24 and 10.6 ± 0.19 cycles/degree in the DHA and control groups, respectively. We have no explanation

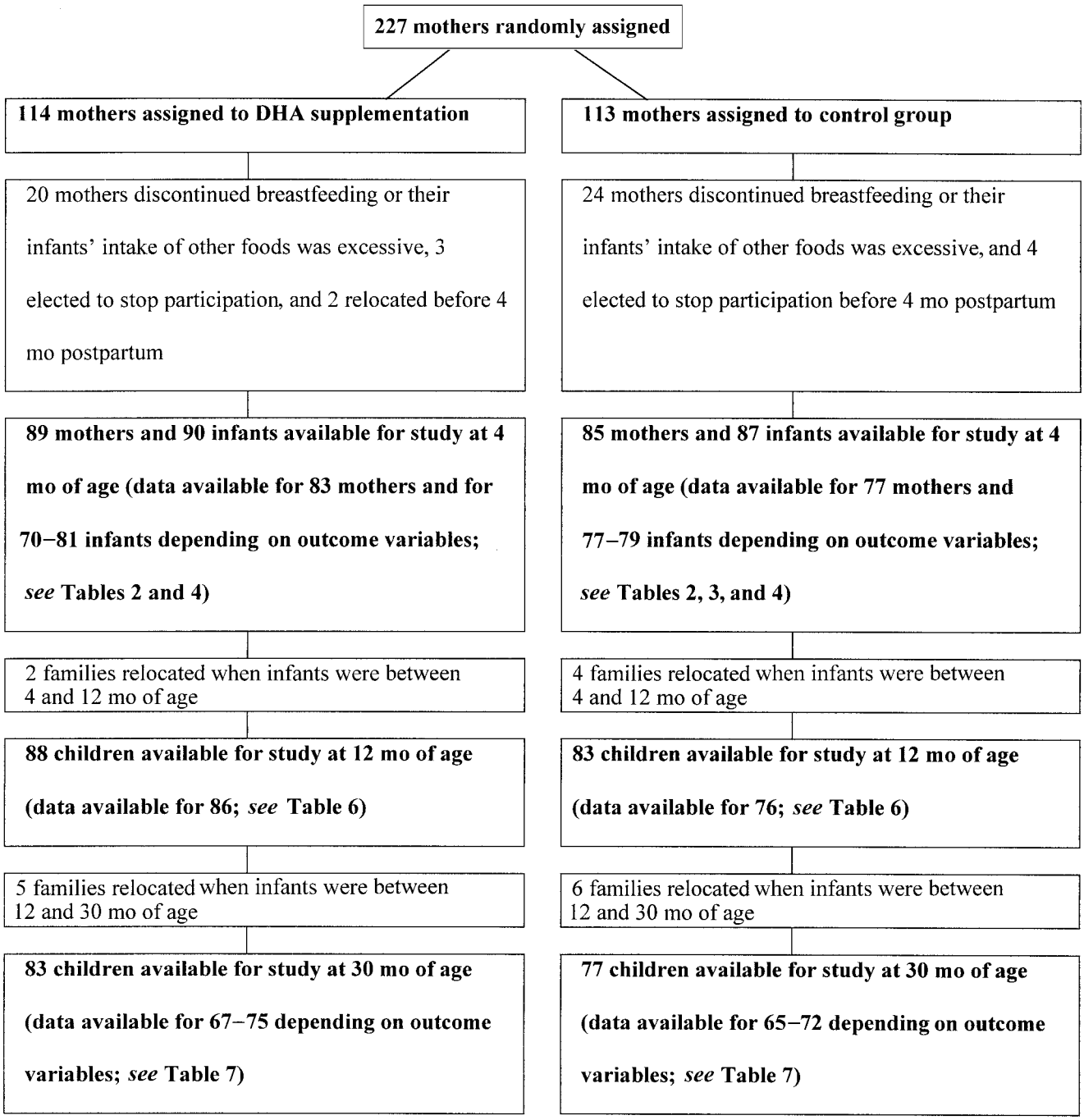

FIGURE 1. Number of subjects enrolled, lost, and tested over the 30-mo study period. The docosahexaenoic acid (DHA) group included 1 set of twins, and the control group included 2 sets of twins; thus, the number of infants in each group was identical ($n = 115$).

for why these values were lower than expected at this age, particularly because Teller acuities at this age are within the expected range (30).

Mean Transient VEP latency and amplitude at 4 and 8 mo of age at a check size of 30' are shown in **Table 5**. There was no statistically significant difference in transient VEP latency between groups at either age. However, at both 4 and 8 mo of age, the transient VEP amplitude of the group whose mothers were assigned to the DHA group was significantly lower than that of the group whose mothers were assigned to the control group.

Neurodevelopmental status

There were no statistically significant differences between groups in the Gesell Gross Motor Inventory, CAT, or CLAMS DQ at either 12 (**Table 6**) or 30 mo of age (**Table 7**). The Bayley MDI of the 2 groups at 30 mo of age, one of the primary outcome variables, also did not differ significantly, but the other primary outcome variable—the Bayley PDI at 30 mo of age—was 8.4 points higher ($P = 0.005$; independent samples t test) in the group whose mothers received DHA. This difference remained

TABLE 1
Demographic characteristics of infants whose mothers were assigned to receive algal docosahexaenoic acid (DHA) or a control treatment for 4 mo postpartum[1]

	Algal DHA group (n = 115)[1]	Control group (n = 115)[1]
Birth weight (kg)	3.46 ± 0.55[2]	3.48 ± 0.51
Gestational age at birth (wk)	39.4 ± 1.4	39.5 ± 1.3
Apgar score at 1 min	8.3 ± 1.0	8.0 ± 1.7
Apgar score at 5 min	9.0 ± 0.3	8.8 ± 1.4
Sex (% boys)	57	60
Ethnicity (%)		
White	75	79
African American	19	13
Hispanic	5	6
Other	1	2
Cesarean delivery (%)	34	29

[1] The DHA group included 1 set of twins, and the control group included 2 sets of twins; each set of twins was treated as an individual infant (*see* Data analysis).
[2] $\bar{x}$ ± SD (all such values).

statistically significant ($P = 0.008$) after infant sex, ethnicity, birth weight, duration of breastfeeding, weight and length at 30 mo of age, maternal age, maternal education, maternal IQ (27), and the composite score of the Family Environment Scale (28) were controlled for..

Three subjects whose mothers received the control capsule and one whose mother received the DHA-containing capsule had PDI scores <75. However, eliminating these subjects from the analysis, while reducing the SD of both groups, did not affect the statistical significance of the difference between groups; thus, the data presented include the scores of all subjects because we know of no reason for exclusion. Subjects whose mothers received DHA accounted for 64%, 49%, and 38% of the upper, middle, and lower tertiles of PDI scores, respectively; whereas subjects whose mothers received the control oil accounted for 36%, 51%, and 62% of the respective tertiles. There was no statistically significant correlation between infant plasma phospholipid DHA content at either 4 or 8 mo of age and any measure of visual function or neurodevelopment.

TABLE 2
Fatty acid composition of milk lipids at 4 mo postpartum[1]

Fatty acid	Algal DHA group (n = 83)	Control group (n = 77)
	% of total fatty acids	
18:3n−3	1.20 ± 0.90	1.07 ± 0.35
20:5n−3	0.07 ± 0.04	0.07 ± 0.08
22:5n−3	0.12 ± 0.04	0.14 ± 0.08
22:6n−3	0.35 ± 0.14	0.20 ± 0.24[2]
18:2n−6	16.3 ± 2.8	15.9 ± 3.6
20:4n−6	0.40 ± 0.08	0.44 ± 0.08[3]
22:4n−6	0.08 ± 0.02	0.09 ± 0.02[4]
22:5n−6	0.04 ± 0.01	0.05 ± 0.02

[1] All values are $\bar{x}$ ± SD. Data were not available for 6 participants in the docosahexaenoic acid (DHA) group and 8 in the control group.
[2–4] Significantly different from the algal DHA group (independent-samples t test): [2] $P < 0.0001$, [3] $P < 0.001$, [4] $P < 0.004$.

TABLE 3
Fatty acid composition of the phospholipid fraction of infant plasma at 4 mo postpartum[1]

Fatty acid	Algal DHA group (n = 80)	Control group (n = 79)
	% of total fatty acids	
18:3n−3	0.18 ± 0.06	0.21 ± 0.13
20:5n−3	0.29 ± 0.16	0.30 ± 0.16
22:5n−3	0.54 ± 0.12	0.76 ± 0.21
22:6n−3	4.81 ± 1.12	3.57 ± 1.08[2]
18:2n−6	21.7 ± 2.6	21.5 ± 2.9
20:4n−6	10.1 ± 2.0	11.4 ± 2.4[3]
22:4n−6	0.37 ± 0.09	0.46 ± 0.12[3]
22:5n−6	0.35 ± 0.12	0.49 ± 0.16[3]

[1] All values are $\bar{x}$ ± SD. Data were not available for 10 infants whose mothers were assigned to the docosahexaenoic acid (DHA) group and 8 whose mothers were assigned to the control group.
[2,3] Significantly different from the algal DHA group (independent-samples t test): [2] $P < 0.0001$, [3] $P < 0.001$.

Anthropometric measures

There were no statistically significant differences in weight, length, or head circumference between the 2 groups of infants at any time. At all ages, these measures were within the normal range for age in both groups.

DISCUSSION

The study reported here is one of only a few that has addressed the effects of supplementing breastfeeding mothers with DHA on visual function and subsequent neuropsychological development of the recipient infant. In this study, maternal supplementation with ≈200 mg DHA/d for 4 mo after delivery resulted in an ≈50% greater content of maternal plasma phospholipid DHA (data not shown), an ≈75% greater content of DHA in milk lipids, and an ≈35% greater content of DHA in infant plasma phospholipids. However, the higher infant plasma phospholipid DHA content was not accompanied by detectable effects on visual acuity as measured by the Teller Acuity Card procedure or

TABLE 4
Visual acuity of the 2 groups of infants at 4 and 8 mo of age as measured by the Teller Acuity Card procedure and at 4 mo of age as measured by sweep visual evoked potential (VEP)[1]

	Algal DHA group	Control group
	cycles/degree	
Teller Acuity Card procedure		
4 mo	5.6 ± 0.71 [70]	5.3 ± 0.56 [77]
8 mo	12.3 ± 0.53 [74]	13.5 ± 0.57 [73]
Sweep VEP		
4 mo	9.4 ± 0.23 [81]	9.4 ± 0.21 [79]

[1] The variance is expressed as octaves: the SD of the log-transformed values divided by 0.301 (29). Statistical analysis (independent-samples t test) was done after logarithmic transformation of raw acuity scores. Cycles/degree values are the antilog of the mean of the logarithms of individual raw cycles/degrees of each group at each time. There were no statistically significant differences in Teller acuity between groups at either age or in sweep VEP between groups at 4 mo of age (independent-samples t test).

TABLE 5
Transient visual evoked potential latency and amplitude of the 2 groups of infants at 4 and 8 mo of age[1]

	Algal DHA group	Control group
Latency (ms)		
4 mo	124.8 ± 11.7 [86]	123.9 ± 10.6 [82]
8 mo	115.1 ± 8.1 [79]	115.3 ± 10.5 [74]
Amplitude (μV)		
4 mo	28.9 ± 12.1 [86]	33.3 ± 12.4[2] [82]
8 mo	24.3 ± 8.9 [79]	27.9 ± 11.0[2] [74]

[1] All values are $\bar{x}$ ± SD; *n* values in brackets. DHA, docosahexaenoic acid.
[2] Significantly different from the algal DHA group, $P < 0.03$ (independent-samples *t* test).

Sweep VEP at either 4 or 8 mo of age. The transient VEP amplitude of the DHA-supplemented group was lower than that of the control group at both ages, but the biologic significance of this finding is not clear. Although a greater occipital cortex response to a visual stimulus suggests more optimal neural processing, transient VEP amplitude of normal infants actually declines with age, primarily because of increasing skull thickness (21).

Most other randomized controlled studies of this issue have also shown no differences in visual acuity between control infants and infants whose mothers were assigned randomly to receive even higher amounts of DHA or fish oil during pregnancy or during early lactation (15, 31, 32). However, most of these showed a statistically significant positive correlation between visual acuity and the DHA content of infant plasma or erythrocyte phospholipids at the same or earlier age. Studies that addressed the effect of the natural variation in breast-milk DHA content have also shown a statistically significant positive correlation between infant plasma or erythrocyte phospholipid content of DHA and visual acuity (33, 34). In contrast with the findings of other studies, there was no statistically significant correlation between infant plasma phospholipid DHA content and visual acuity in the present study.

Although children whose mothers were supplemented with DHA did not have a higher Gesell Gross Motor, CAT, or CLAMS DQ at either 12 or 30 mo of age, those whose mothers received DHA had an 8.4-point (>0.5 SD) higher Bayley Scales of Infant Development PDI at 30 mo of age than did those who received placebo. The meaning of this higher PDI, particularly in the absence of obvious visual advantages at 4 and 8 mo of age, developmental advantages at 12 mo of age, or other advantages at 30 mo of age, is difficult to assess. On one hand, the difference between groups was sizable and remained statistically significant after many potential covariates were controlled for. On the other hand, the PDI at 30 mo of age was not correlated with plasma phospholipid DHA at either 4 or 8 mo of age. Furthermore, although the PDI at 30 mo of age is a better predictor of development at later than at earlier ages (22), the magnitude of this advantage is not clear, particularly because the mean PDI of both groups was well above the expected mean. Considering these facts, it is tempting to attribute the higher PDI of the supplemented group at 30 mo of age to chance.

Doing so, however, may be premature. Although the delayed effect of early DHA supplementation on psychomotor development is somewhat puzzling, it could result from early supplementation or the nature of the developmental tests. For example, adequate DHA early in life may be necessary for the maturation of specific developmental domains that are not fully manifested until later. Alternatively, DHA supplementation may also confer benefits on psychomotor function early in life but these benefits cannot be detected because available tools for assessing motor function are less sensitive early in life than later in life, when these tools include more complex tasks and, hence, permit discrimination of smaller effects.

Delayed adverse neuropsychological effects secondary to nutritional as well as toxic insults early in life have been reported previously. For example, adverse effects of iron deficiency during late infancy on auditory brainstem evoked responses and visual evoked potential latency do not appear until 4 y of age (35), and adverse effects on neuropsychological function are not apparent until ≈12 y of age (36). Similarly, a deficit in the Bayley MDI of infants exposed to cocaine in utero was observed at 24 but not at 6.5 mo of age (37). These delayed effects of iron deficiency and cocaine toxicity support the possibility that beneficial effects of an early nutritional intervention, such as DHA, may not be

TABLE 6
Neurodevelopmental outcomes of the 2 groups of children at 12 mo of age[1]

	Algal DHA group (n = 86)	Control group (n = 76)
Gesell Gross Motor DQ	101.8 ± 13.8	99.5 ± 13.3
CAT DQ	109.0 ± 10.7	110.0 ± 10.8
CLAMS DQ	100.6 ± 14.6	102.5 ± 13.2

[1] All values are $\bar{x}$ ± SD. Because of scheduling difficulties, data were not available for 2 infants whose mothers were assigned to the docosahexaenoic acid (DHA)–supplemented group and for 7 infants whose mothers were assigned to the control group. DQ, developmental quotient; CAT, Clinical Adaptive Test; CLAMS, Clinical Linguistic and Auditory Milestone Scale. There were no statistically significant differences between groups for any measure.

TABLE 7
Neurodevelopmental outcomes of the 2 groups of children at 30 mo of age[1]

	Algal DHA group	Control group
Gesell Gross Motor DQ	100.8 ± 11.4 [75]	102.4 ± 10.2 [72]
CAT DQ	98.1 ± 9.0 [75]	98.3 ± 8.7 [72]
CLAMS DQ	106.8 ± 15.2 [75]	106.6 ± 14.9 [72]
Bayley MDI	107.8 ± 12.2 [67]	105.6 ± 13.8 [66]
Bayley PDI	116.8 ± 15.2 [68]	108.4 ± 18.9[2] [65]

[1] All values are $\bar{x}$ ± SD; *n* value in brackets. Eighty-three children whose mothers were assigned to the DHA-supplemented group and 77 whose mothers were assigned to the control group were available for testing, but only the numbers of children indicated could be scheduled within the designated age window (30 ± 3 mo). One child in the algal DHA group successfully completed the Bayley PDI but not the MDI, whereas one child in the control group successfully completed the Bayley MDI but not the PDI. DHA, docosahexaenoic acid; DQ, developmental quotient; CAT, Clinical Adaptive Test; CLAMS, Clinical Linguistic and Auditory Milestone Scale; MDI, Mental Development Index; PDI, Psychomotor Development Index.
[2] Significantly different from the algal DHA group, $P = 0.008$ [analysis of covariance with control for sex, ethnicity, maternal age, maternal education, maternal intelligence quotient (27), the composite score of the Family Environment Scale (28), birth weight, duration of breastfeeding, and weight and length at the time each test was administered].

apparent until later in life. A beneficial effect of maternal cod liver oil compared with corn oil supplementation (10 mL/d), from 18 wk of gestation through 3 mo postpartum, on the cognitive function of infants at 4 y of age has also been reported (38). In this study, children whose mothers received cod liver oil (≈1200 mg DHA and ≈800 mg 20:5n−3/d) scored ≈4 points higher at 4 y of age on the Mental Processing Composite of the Kaufman Assessment Battery for Children (K-ABC). However, only 84 children of the 590 pregnant women enrolled in the study completed the K-ABC at 4 y of age.

A potential relation between DHA status and neuropsychological function, even in adulthood, is supported by recent studies that suggest that low serum cholesteryl ester DHA (39) and low dietary DHA intakes (40) are associated with a higher risk of Alzheimer disease. Later effects of early DHA supplementation on cardiovascular function also have been reported (41); children who were supplemented with DHA for the first 4 mo of life had significantly lower mean and diastolic blood pressures at 6 y of age than did children who were not supplemented.

The higher 30-mo PDI in infants whose mothers received DHA rather than the control oil, for only the first 4 mo postpartum, suggests that infants of breastfeeding women whose dietary n−3 fatty acid intake is low may benefit from maternal DHA supplementation. This might also suggest that formula-fed infants may benefit from a formula with a DHA content in excess of 0.2% of total fatty acids. However, specific recommendations along these lines should await confirmation of the findings reported here in either breastfed or formula-fed infants. Although the apparent benefits of maternal DHA supplementation and, hence, a higher DHA intake by the infant on the Bayley PDI at 30 mo of age was sizeable, and possibly explicable, additional studies are required to determine whether this apparent advantage is real, whether this advantage persists, and whether other delayed effects of early DHA availability emerge.

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CLJ, JKF, and WCH had full access to all data and take responsibility for the integrity and accuracy of the data and for the data analysis. CLJ, WCH, RGV, TCP, and REA conceived and designed the study. CLJ, RGV, TCP, YLZ, JCR, MRT, and WCH acquired the data. CLJ, JKF, WCH, RGV, TCP, and AML analyzed and interpreted the data. CLJ and WCH drafted the manuscript. RGV, TCP, YLZ, JCR, MRT, AML, and REA critically revised the manuscript for important intellectual content. JKF provided statistical expertise. CLJ and WCH obtained funding. CLJ, WCH, TCP, and RGV supervised the study. The funding agencies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation (or approval) of the manuscript.

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