Long-Chain Polyunsaturated Fatty Acids and Cognition in VLBW Infants at 8 years: an RCT

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abstract

OBJECTIVE: To test the hypothesis that supplementation with the long chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid (AA) to very low birth weight (VLBW) infants would improve long-term cognitive functions and influence neuroanatomical volumes and cerebral cortex measured by MRI.

METHODS: The current study is a follow-up of a randomized, double-blinded, placebo-controlled study of supplementation with high-dose DHA (0.86%) and AA (0.91%) to 129 VLBW infants fed human milk. Ninety-eight children participated at 8 years follow-up and completed a broad battery of cognitive tests. Eighty-one children had cerebral MRI scans of acceptable quality.

RESULTS: There were no significant differences between the intervention group and the control group on any of the cognitive measures. Equally, MRI data on segmental brain volumes and cerebral cortex volume, area, and thickness suggested no overall group effect.

CONCLUSIONS: This study is the first long-term follow-up of a randomized controlled trial with supplementation of DHA and AA to human milk fed VLBW infants investigating both cognitive functions and brain macrostructure measured by MRI. No cognitive or neuroanatomical effects of the supplementation were detected at 8 years of age.

WHAT'S KNOWN ON THIS SUBJECT: Suboptimal brain development and increased risk of cognitive deficits are well documented in very low birth weight children. Supplementation with docosahexaenoic acid and arachidonic acid has been associated with positive cognitive effects.

WHAT THIS STUDY ADDS: This follow-up study of a randomized controlled trial of supplementation with docosahexaenoic acid and arachidonic acid to very low birth weight infants is the first report on both cognition and brain macrostructure measured with MRI. No cognitive or neuroanatomical effects were detected at 8 years.

Very low birth weight (VLBW; <1500 g) infants have increased risk of perinatal brain injury and adverse neurologic outcome.[1] Brain alterations in VLBW infants are well documented with MRI. Meta-analyses reveal reductions of total brain volume, white and gray matter, cerebellum, hippocampus, caudate and corpus callosum,[2,3] and these changes seem to persist into adolescence.[4–10] Alterations in brain structures correlate with intellectual and motor abilities in preterm infants.[11–14]

The neuropathology of brain development in premature infants reflects multiple factors. Extensive growth and maturation of the brain take place during the last trimester of pregnancy, and nutrition and growth seem to influence brain and cognitive development.[14–18] Docosahexaenoic acid (DHA) and arachidonic acid (AA) are essential for development of the central nervous system. Emerging evidence suggests that DHA positively influences cortical metabolic function and cognitive development.[19,20] Major accumulation of DHA and AA in the brain occurs during the last trimester and the first postnatal months, and premature children are deprived of this accumulation prenatally.[21–24] Human milk is a good natural source of DHA/AA and may contain adequate amounts to cover the demands of a full term infant.[25] The intrauterine supply of DHA during the last trimester of pregnancy (estimated to 50 mg/day)[26] is, however, much higher than what traditionally has been given via breast milk or formula to premature infants. Supplementation of DHA/AA to premature infants has been associated with positive effects on cognition in several studies.[20,27–31] Conversely, 2 systematic reviews of supplementation with low-dose long chain polyunsaturated fatty acids (LCPUFAs) revealed no significant effects on cognition.[32,33] Recent systematic reviews request further randomized controlled trials (RCTs)

with LCPUFAs and cognitive development in premature infants.[28,34,35] In our previous randomized placebo-controlled trial including 129 VLBW infants, we tested the effect of supplementation of DHA/AA or placebo after birth, and found positive effects on cognition as measured with event-related potentials at 6 months corrected age,[29] and at 20 months in terms of attention capacity in free-play sessions.[36]

The effects of LCPUFA supplementation on cerebral cortex structure and brain volumes in childhood are not well described. RCTs with essential fatty acids and cerebral MRI are scarce and inconclusive.[19,37] Thus, follow-up studies of randomized controlled intervention trials with brain development measured by MRI are warranted.[38]

In our present follow-up study, we tested the hypothesis that DHA/AA supplementation of VLBW infants fed human milk would show persistent positive effects on cognition, in line with our earlier studies of this cohort.[29,36] We also hypothesized that supplementation would have effects on brain macrostructure measured by quantitative MRI.

METHODS

Original Trial Intervention

Our present study is a follow-up of a randomized, double-blinded, placebo-controlled trial of supplementation with DHA and AA to VLBW infants. A detailed description of this trial has been published.[29] Briefly, the intervention group received supplementation of 32 mg (0.86% of total fatty acids) DHA and 31 mg (0.91%) AA per 100 mL of human milk (on average 9 weeks after birth). The supplementation was high-dose compared with the level of 0.3% typically added to preterm formula.[35] All 129 infants who completed the intervention were fed

mothers/donor milk from day 1 or 2 (starting procedure is 0.5 mL/kg per hour). All but 5 infants received some parenteral nutrition (mean 9.45 mL/day). Full enteral feeding (defined as 150 mL/kg per day) was achieved after a median of 7 days. Infants receiving donor milk changed to term formula during the last days before discharge, at the mean age of 70 days. Exclusion criteria were major congenital abnormalities and cerebral hemorrhage (grade 3 or 4). Cognitive development was evaluated at 6 months of age by using the Ages and Stages Questionnaire and event-related potential indices of recognition memory,[29] and at 20 months in terms of attention capacity in free-play sessions.[36] Written informed consent was obtained from the parents, and both the original trial and the follow-up study were approved by the Regional Committee for Medical and Health Research Ethics. The trial was registered at http://www.clinicaltrials.gov with identifier NCT00226187.

Eight-Year Follow-up Study

Participants

All 129 infants who completed the original trial were invited to participate in the follow-up study. Ninety-eight children (76%; intervention group, n = 45; control group, n = 53) met for cognitive testing at a mean age of 8.6 years. Eighty-four completed MRI, and 81 children (83% of the 98 participants at 8-year follow-up, 63% of the original 129 participants) had MRI of sufficient quality for analysis (Fig 1). Significant pathology was discovered in 4 participants on MRI.

Cognitive Assessment

Cognitive testing was administered by 1 trained pediatrician blinded to group allocation and medical history of the child.

General Intellectual Abilities

The Wechsler Abbreviated Scale of Intelligence provides measures of

CONSORT 2010 Flow Diagram

Enrollment

Assessed for eligibility
(completed intervention)
($n = 129$)

Excluded ($n = 31$)
♦ Lost to follow-up ($n = 8$)
♦ Congenital abnormalities
($n = 1$)
♦ Death ($n = 1$)
♦ Did not wish to participate
($n = 21$)

Met for follow-up ($n = 98$)

Intervention group ($n = 45$)

Cognitive testing

Control group ($n = 53$)

Analyzed ($n = 41$)

Excluded from analysis ($n = 4$)
♦ Medical reasons ($n = 1$)
♦ Anxiety ($n = 2$)
♦ Parental denial ($n = 1$)

MRI analyzed

Analyzed ($n = 40$)

Excluded from analysis ($n = 13$)
♦ Medical reasons ($n = 4$)
♦ Anxiety ($n = 5$)
♦ Parental denial ($n = 1$)
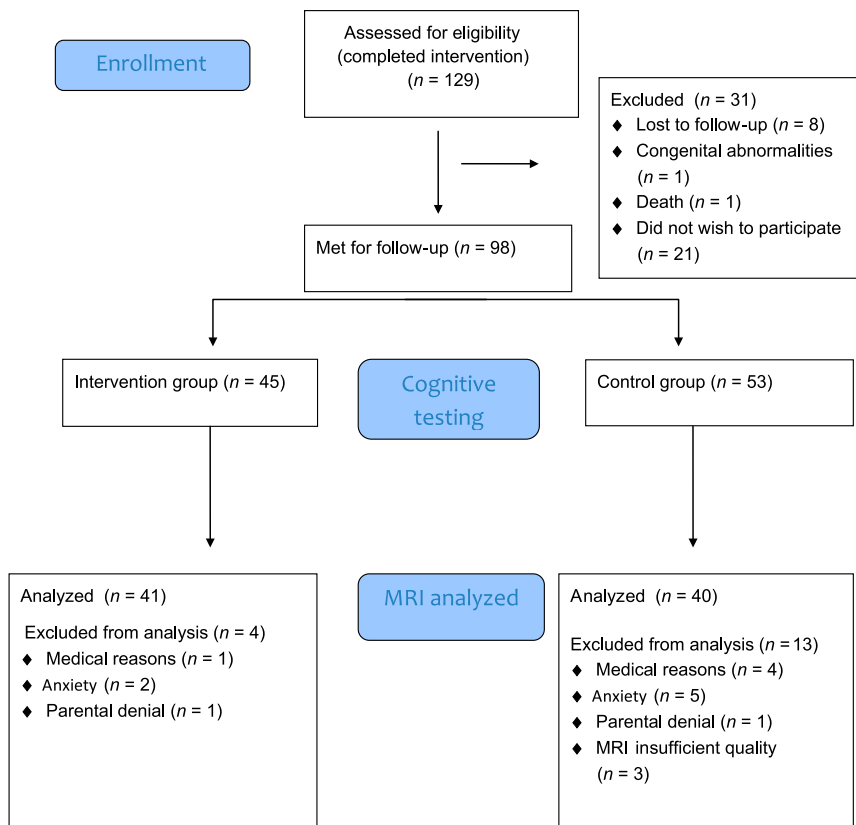♦ MRI insufficient quality
($n = 3$)

FIGURE 1
Flowchart of progress through the study.

verbal IQ (VIQ) and performance IQ (PIQ). VIQ consists of vocabulary and similarities subtests and PIQ of matrix reasoning and block design subtests. Full scale IQ (FSIQ) was estimated from all 4 subtests.[39] Each index score was age-standardized relative to the norms, with a mean of 100 and an SD of 15.

Short-Term and Working Memory

The Wechsler Intelligence Scale for Children III Digit Span Forward primarily tests verbal short-term memory, whereas Digit Span Backward tests working memory and ability to manipulate verbal information while in temporary storage.[40] Each correct response is

scored as 1 point, with a total possible score of 16 points on Digit Span Forward and 14 points on Digit Span Backward.

Learning and Memory

The California Verbal Learning Test II (CVLT-II) measures multitrial learning and long-term recall abilities for verbal information.[41] The task consists of 16 words from 4 semantic categories read 5 times; each time the child is instructed to repeat all items immediately. After a 30-minute delay during which other tasks were performed, the child was asked to recall the first list again. The total possible score was 80 on the learning measure and 16 on the recall tests.

Motor Skills

The Grooved Pegboard test was used to assess motor coordination and speed. The task exposes 25 holes with randomly positioned slots and pegs with a key along 1 side so they must be rotated to fit. Seconds used to complete the task with the dominant and the nondominant hand, respectively, are measured.[42]

MRI Acquisition

Imaging data were acquired by using a 12-channel head coil on a 1.5 Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at Oslo University Hospital, Rikshospitalet. The pulse sequence used for morphometric analyses was a 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE), repeated at minimum twice for each subject (for detailed sequence information, see Supplemental Information). The protocol also included a T2-weighted fluid-attenuated inversion recovery sequence to aid the radiologic examination.

MRI Analysis

Raw data sets were deidentified and transferred to Linux workstations for processing and analyses. Each MP-RAGE was visually inspected by 1 researcher blinded to group allocation, and for each subject the scan with the highest quality was selected for the analyses. Three subjects had no scan of acceptable quality and were excluded from further analyses. Volumetric segmentation and cortical surface reconstruction were performed with FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/)[43–46] (for details regarding the MRI analysis, see Supplemental Information). All individual segmentations and surfaces were inspected for accuracy. Intracranial volume (ICV) was estimated by using an atlas normalization procedure.[47]

Statistical Analyses

Analyses were performed with SPSS version 22.0 (IBM SPSS Statistics, IBM

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Corporation). Normally distributed data are presented as mean and SD, examined with 2-sample t test. Nonnormally distributed data are presented as median and range, and categorical data are presented as numbers (percent). Statistical significance was defined as $P < .05$. Because the number of participants in our follow-up study was already given, a posthoc power calculation was not conducted. To describe the effect in the 2 groups, we present the confidence interval (CI) of the difference between the intervention and control groups. The 95% CI for FSIQ is -5.1 to 2.5.

Cognitive data were tested for group differences with analysis of covariance, with gender, age, birth weight, and gestational age as covariates. All cognitive results were Bonferroni-corrected by a factor of 10 (reflecting the number of variables), roughly corresponding to a corrected α of $<.005$. Similar analyses were performed for birth weight ≤ 1000 g, and for boys and girls separately.

For the neuroanatomical volumes, we first applied a general linear model (GLM) on the 12 bilateral brain volumes, with hemisphere as within-subjects factors and gender, age, birth weight, gestational age, and group as the between-subject factors. There was no significant hemisphere $\times$ group interaction ($P = .15$) and for all further analyses the average value of the right and left hemisphere volumes was used. All MRI volume results were Bonferroni-corrected by a factor of 15 (reflecting the number of regions of interest), approximately corresponding to a corrected α of $<.003$.

Surface-based cortical analyses were performed on a vertex-wise (point-by-point) level by using GLMs in FreeSurfer. Main effects of group were tested while controlling for gender, age, birth weight, and gestational age. Separate analyses were performed for cortical volume,

surface area, and thickness maps. The surface maps were thresholded by a conventional criterion for correction for multiple comparisons (false discovery rate at the 5% level).[48]

All above volume and cortical analyses were repeated after removing the 4 participants with significant pathology on MRI ($n = 77$). All analyses for volume and cortex were repeated for birth weight ≤ 1000 g, and interaction analyses for gender $\times$ group were performed with 2-way analysis of covariance.

RESULTS

General Characteristics

There were no significant baseline differences between the intervention and control groups regarding age at follow-up, gender, mother's education, ethnicity, or perinatal data (Tables 1 and 2). Similar analyses were performed for the 81 children with MRI of sufficient quality, with the same results (Tables 1 and 2). There were no significant differences in baseline and perinatal data between the 98 children who met for follow-up and the 31 children lost to follow-up, except for respiratory distress syndrome (64.5% among the 98, and 38.7% among the 31 children, $P = .009$).

Cognitive Abilities

There were no significant differences between the intervention and control groups regarding general or specific cognitive outcomes (Table 3). General intellectual abilities measured with the Wechsler Abbreviated Scale of Intelligence as FSIQ, VIQ, and PIQ were not different ($P > .05$) between the 2 groups. Similarly, we did not find any significant differences between the 2 groups regarding short-term and working memory (Wechsler Intelligence Scale for Children III Digit Span), learning and memory (CVLT-II), or motor coordination (Grooved Pegboard test;

TABLE 1 Baseline Characteristics of Intervention Versus Control Group, Total Sample and MRI Sample

	Total Sample Intervention, n = 45	Total Sample Control, n = 53	P	MRI Sample Intervention, n = 41	MRI Sample Control, n = 40	P
Age at follow-up, mean (SD), y	8.6 (0.3)	8.6 (0.3)	.35	8.6 (0.2)	8.6 (0.3)	.60
Boy, No. (%)	22 (49)	27 (51)	.84	20 (49)	23 (58)	.43
Ethnicity, No. (%)			.82			.69
Norwegian/European	41 (91)	44 (83)		37 (90)	37 (93)	
Asian/African/American	4 (9)	9 (17)		4 (10)	3 (8)	
Maternal education, No. (%)			.54			.89
<9 y	3 (7)	4 (8)		3 (7)	2 (5)	
10–12 y	23 (51)	23 (43)		21 (51)	20 (50)	
>12 y	19 (42)	26 (49)		17 (42)	18 (45)	

	Total Sample Intervention, n = 45	Total Sample Control, n = 53	P	MRI Sample Intervention, n = 41	MRI Sample Control, n = 40	P
Birth weight, mean (SD), g	1028 (277)	1070 (315)	.49	1046 (265)	1113 (273)	.27
Gestational age, mean (SD), wk	28.6 (2.9)	28.6 (2.6)	.98	28.7 (2.9)	29.0 (2.6)	.68
Parenteral nutrition, median (range), d	7 (0–37)	5 (0–43)	.15	7 (0–37)	5 (0–43)	.33
Respirator, median (range), d	1 (0–36)	0 (0–64)	.17	1 (0–36)	0 (0–64)	.22
Nasal continuous positive airway pressure, median (range), d	30 (0–116)	13 (0–272)	.25	23 (0–116)	17 (0–272)	.58
Transfusion of blood, median (range), d	1 (0–14)	0 (0–18)	.07	1 (0–14)	0 (0–18)	.05
Oxygen, median (range), d	17 (0–117)	11 (0–283)	.45	14 (0–117)	10 (0–283)	.53
Small for gestational age at birth, No. (%)	13/45 (29)	16/53 (30)	.89	11/41 (27)	11/40 (28)	.95
Smoking mother at birth, No. (%)	7/37 (19)	7/47 (15)	.62	6/35 (17)	6/35 (17)	.58
Exclusively breast milk, No. (%)[a]	35/43 (81)	37/50 (74)	.40	31/39 (79)	28/38 (74)	.55
Respiratory distress syndrome, No. (%)	33/45 (74)	31/53 (59)	.12	29/41 (71)	25/40 (63)	.43
Bronchopulmonary dysplasia, No. (%)	19/45 (42)	16/53 (30)	.22	16/41 (39)	11/40 (28)	.27
Retinopathy of prematurity, No. (%)	7/45 (16)	10/53 (19)	.92	5/41 (12)	6/40 (15)	.36
Grade 1–2 intraventricular hemorrhage, No. (%)	6/45 (13)	12/53 (23)	.60	6/41 (15)	8/40 (20)	.81
Periventricular leukomalacia, No. (%)	4/45 (9)	2/53 (4)	.20	3/41 (7)	1/40 (3)	.14
Necrotizing enterocolitis, No. (%)	4/45 (9)	2/53 (4)	.29	4/41 (10)	1/40 (3)	.18

a Mother's milk or donor.

Table 3). FSIQ among the children who completed MRI was not significantly different from the total sample. Follow-up analyses of children with birth weight ≤1000 g and girls and boys separately did not reveal any effects of supplementation with DHA/AA to these subgroups. However, both study groups scored mean FSIQ values below reference norms for their age, and the lower FSIQ values were associated with lower birth weight (Pearson's correlation coefficient 0.49; $P = .01$). These results are in concordance with previous studies documenting lower IQ in premature children and imply that our study cohort is representative of the VLBW population.[49–52]

Neuroanatomical Volumes

Table 4 presents neuroanatomical volumes in the intervention and the control groups of the MRI sample ($n = 81$). There were no significant differences between the 2 groups for any of the studied brain volumes. The control group had an uncorrected trend toward larger lateral inferior ventricles; however, these results were not significant after Bonferroni correction. The same statistical analyses were repeated for the 77 participants without pathology on MRI; no corrected or uncorrected significant differences between the intervention and control groups were detected (Supplemental Table 5).

Cortical Volume, Surface Area, and Thickness

There were no significant differences between the intervention and control groups regarding cortical volume, surface area, and thickness in the total MRI sample ($n = 81$; Fig 2). The cerebral cortex is responsible for higher-order processes of thought, perception, and memory. Cortical volume is determined by both surface area and thickness. These distinct components are influenced by different evolutionary, genetic, and

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TABLE 3 Cognitive Outcome Measures at 8 Years, Intervention Versus Control Group

	Intervention, $n = 45$	Control, $n = 53$	P, uncorrected
FSIQ	92.7 (8.8)	93.9 (10.0)[a]	.73
VIQ	88.8 (10.3)	90.3 (12.5)	.73
PIQ	95.0 (12.6)	95.9 (14.4)[a]	.98
Pegboard dominant hand, s	96.4 (26.3)	86.0 (27.0)[b]	.68
Pegboard nondominant hand, s	112.3 (36.9)	111.3 (46.3)[b]	.83
CVLT verbal learning	32.8 (9.8)	35.1 (11.7)	.39
CVLT free recall	6.8 (3.4)	6.6 (3.1)	.57
CVLT delayed recall	6.8 (3.3)	6.4 (3.3)	.34
WISC forward	7.6 (1.8)	7.1 (1.5)	.11
WISC backward	3.3 (1.1)	3.5 (1.5)	.52

Data are presented as mean (SD) unless noted otherwise. Bonferroni-correction by a factor of 10 (reflecting the number of tests) roughly corresponds to a corrected α of <0.005. There were no corrected or uncorrected significant differences. CVLT, California Verbal Learning Test; FSIQ, full scale IQ; PIQ, performance IQ; VIQ, verbal IQ; WISC, Wechsler Intelligence Scale for Children.
[a] $n = 52$ (1 blind child could not complete PIQ/FSIQ).
[b] $n = 51$ (1 blind child and 1 with cerebral palsy were excluded).

cellular processes, and follow unique developmental and lifespan trajectories.[53] Thus, it is important to investigate whether these components are differentially affected by nutrition or other postnatal interventions. The same analyses were repeated for the 77 participants without pathology on MRI, and no significant differences were found. All the above volume and cortical analyses were repeated for participants with birth weight ≤1000 g, and interaction analyses with gender × group were conducted. No corrected or uncorrected significant differences between the intervention and control groups were observed.

DISCUSSION

This study is the first long-term follow-up of an RCT of supplementation with DHA/AA to human milk fed VLBW infants investigating both cognitive functions and brain macrostructure. In our previous studies of this cohort, we observed improved cognitive function in the intervention group at 6 months,[29] and a suggested effect on attention at 20 months of age.[36] In this present follow -up study at 8 years, we did not detect any significant effect on cognition or brain macrostructure.

Supplementation with high doses of DHA/AA to premature infants has

been reported to have positive short-term effects on cognition in several studies.[27–30] In contrast, 2 reviews revealed little or modest effect on cognitive outcome at 12 to 18 months of age.[32,33] However, most of the studies in these reviews included premature infants (up to 37 weeks' gestational age), supplemented with relatively low doses of DHA. To our knowledge, only 1 study has followed children into school age to determine cognitive effects of LCPUFA supplementation in infancy.[30] Here, Isaacs et al[30] reported no overall differences between the intervention and control groups, but better literacy skills in girls after supplementation. Furthermore, supplementary analyses of feeding group (exclusively formula versus some maternal milk) concluded that the exclusively formula fed children increased FSIQ and VIQ after LCPUFA supplementation (mean VIQ increased from 86 to ~97–98). However, breastfed children were already at the same level (mean VIQ 98), and this was unaltered by supplementation. The authors consequently hypothesize that the natural content of LCPUFA is a key factor in the cognitive benefits of human milk. This is in concordance with several studies revealing improved cognition as 1 of the many advantages of human milk.[18,54–56] In our present follow-up study, both groups received human milk with its natural content of DHA/AA, and in addition, the intervention group got extra DHA/AA supplementation. Thus, our design differs from that of most other studies.

Nutrition plays a crucial role in brain development, and nutritional effects have been documented with MRI.[14–17,38,55] Longitudinal studies on effects of LCPUFA-supplementation measured with cerebral MRI are, however, scarce. McNamara et al[19] showed that supplementation with DHA increased prefrontal cortex activation on

TABLE 4 Neuroanatomical Volumes, Intervention Versus Control Group

	Intervention, $n = 41$	Control, $n = 40$	P, uncorrected
ICV, mm^3	1 454 894 (134 778)	1 484 593 (131 387)	.68
Cortical GM, mm^3	268 326 (25 633)	276 107 (25 053)	.31
Cerebral WM, mm^3	196 759 (23 165)	199 846 (21 499)	.85
Cerebellar GM, mm^3	54 433 (7170)	56 460 (5717)	.39
Cerebellar WM, mm^3	11 288 (1889)	11 667 (1477)	.68
Thalamus, mm^3	6733 (642)	6818 (620)	.80
Amygdala, mm^3	1363 (177)	1432 (206)	.27
Hippocampus, mm^3	3855 (475)	3890 (441)	.79
Accumbens, mm^3	652 (117)	650 (103)	.47
Caudate, mm^3	3697 (601)	3887 (485)	.31
Pallidum, mm^3	1716 (255)	1741 (201)	.86
Putamen, mm^3	5686 (746)	5840 (640)	.75
Lateral ventricle, mm^3	5892 (3568)	7975 (5154)	**.03**[a]
Third and fourth ventricle, mm^3	2570 (601)	2744 (834)	.23
Corpus callosum, mm^3	2527 (436)	2505 (446)	.19

Data are presented as mean (SD) unless noted otherwise. Bonferroni-correction by a factor of 15 (reflecting the number of regions of interest) roughly corresponds to a corrected α of <0.003. Bold font indicates uncorrected sigificance ($P < .05$). GM, gray matter; WM, white matter.
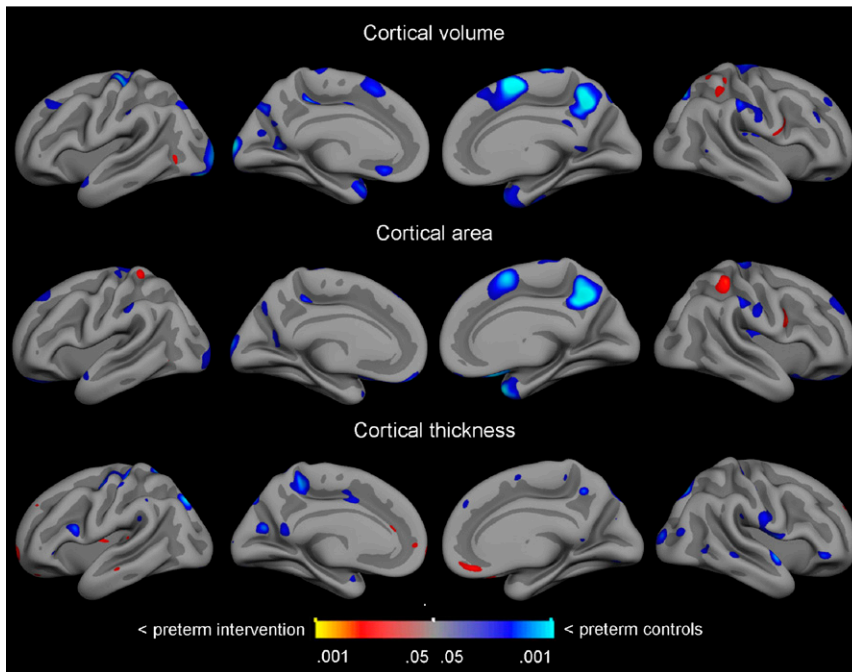[a] Uncorrected significance ($P < .05$).

FIGURE 2
Cortical volume, surface area, and thickness in the intervention group versus the control group. Colors indicate significance levels for each group. GLM was used to test the main effects of group while controlling for gender, age, birth weight, and gestational age. The results are uncorrected for multiple comparisons.

functional MRI during sustained attention in 8- to 10-year-old healthy boys. In contrast, 1 other intervention study with DHA/AA to preterm infants revealed no positive influence on structural brain maturation at 3 and 12 months.[37] However, the dosages of DHA were low (15 mg DHA per 100 mL formula, 31 mg AA per 100 mL), and the number of participants was 42.[37] To our knowledge, no other RCT with high-dose LCPUFA has MRI as end point. To further sharpen the scientific evidence of what nutrients are influencing brain growth, intervention studies with MRI are warranted.

The long follow-up time is a strength of our present study, although it allows accumulation of confounders unrelated to the intervention. Our negative findings at follow-up might be due to the limited time of supplementation after birth, and may explain why we could only report effects at 6 and

20 months age. Studies of LCPUFA supplementation to school-age children and adults have revealed improvement of literacy during the period of supplementation.[57,58] This may indicate an effect of ongoing supplementation, and such studies of VLBW infants in school age would be informative. However, nutrition is only 1 of many factors influencing the vulnerable premature brain, and the immature status of these infants may probably never be fully compensated for by nutrition or other postnatal interventions.

One limitation of our present study is that quantitative MRI might not be sensitive enough to discover subtle effects on brain structure. Fatty acids are hypothesized to improve myelinization, and further studies should examine whether this is detectable with other MRI techniques like diffusion tensor imaging.[38] Another potential weakness of our study is the exclusion criteria of

major congenital abnormalities and cerebral hemorrhage (grade 3 or 4), and in our original recruitment 59 children were excluded.[29] This neurologically vulnerable group might perform even lower on cognitive testing and have alterations on MRI, and is therefore a group who could be hypothesized to benefit from supplementation with LCPUFA.

The major strengths of our present study are the long-term follow-up and the multidisciplinary approach combining aspects of prematurity, nutrition, neuropsychology, and structural neuroimaging. We report a high follow-up rate of 98 of 129 (76%), and the children seen at 8 years did not differ significantly in baseline or prenatal characteristics from the children lost to follow-up or the MRI sample, indicating little if any bias due to the lower number of participants in the MRI sample. The 95% CI of the difference in FSIQ is −5.1 to 2.5, meaning the difference between the 2 groups is small or nonexisting (<1 SD). This gives a precise estimate, indicating that the current study should be powered to answer the question of effects of LCPUFA supplementation on IQ, even with a follow-up rate of 76%.

CONCLUSIONS

In this present follow-up study of our RCT of supplementation with high dose DHA/AA in human milk to VBLW infants, we could not detect any significant effects on cognitive abilities at 8 years of age. Equally, MRI revealed no effects of supplementation on neuroanatomical brain volumes or cortical surface volume, area, or thickness. Further RCTs with MRI-derived end points are warranted to clarify the effects of LCPUFAs on long-term brain development and hence preclude neurocognitive sequelae for next generations of premature children.

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