Letters

RESEARCH LETTER

Four-Year Follow-up of Children Born to Women in a Randomized Trial of Prenatal DHA Supplementation

Despite the paucity of evidence, recommendations exist internationally for pregnant women to increase their docosahexaenoic acid (DHA) intake to optimize fetal brain development. Our randomized controlled trial (RCT), in which pregnant women were allocated to 800 mg/d of DHA or matched placebo, showed that children's mean cognitive, language, and motor scores did not differ between groups at 18 months, although fewer children in the DHA group had delayed development compared with controls.[1] Surprisingly, girls in the DHA group had poorer language scores than girls in the control group.[1] Herein we report neurodevelopmental outcomes at 4 years, which is when any subtle to moderate effects on development should have emerged and can be more reliably assessed.

Methods | The trial methods were previously published.[1] All study procedures were conducted with written informed consent as approved by institutional review boards at each center. Children selected for assessment at 18 months of age, who had not died or withdrawn, were invited to attend an appointment when aged 4 years with a psychologist who was blinded to group allocation (June 18, 2010, to September 25, 2012). The primary outcome was the General Conceptual Ability (GCA) score of the Differential Ability Scales, second edition (DAS II; score range, 30-170; delayed, <85). Secondary outcomes included psychologist-assessed executive functioning and language, and parent-reported executive functioning and behavior (**Table**).

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Information about children's home environment, DHA intake, and medical conditions were collected. Statistical analyses were preplanned and conducted using SAS version 9.3 (SAS Institute Inc) and Stata release 12 (StataCorp). Analyses were conducted on an intention-to-treat basis for families who consented to follow-up, with missing outcomes imputed using chained equations; 100 imputed data sets were used to account for the sampling design and weights.[2] Statistical significance was assessed at the 2-sided $P < .05$ level. Adjustments were made for center, parity, sex, and mother's education and smoking status using linear or log binomial regression models. Sensitivity analyses conducted with available data only and with data imputed for the 726 children in the original sample produced similar results. A total of 536 children would provide 80% power ($\alpha = .05$) to detect a 4-point difference in mean GCA between groups.

Results | Of 726 children selected for the 18-month evaluation, 703 were eligible for the 4-year follow-up and 646 (91.9%; n = 313 in DHA group and n = 333 in control group) were included in the analysis (eFigure in Supplement). Mean GCA scores neither differed between groups (adjusted mean difference, 0.29 [95% CI, −1.35 to 1.93], $P = .73$; Table), nor did the percentage of children with delayed or advanced GCA scores. Other objective assessments of cognition, language, and executive functioning also did not differ between groups. However, the DHA group had poorer scores on some parentally reported scales of executive functioning and behavior. There was no evidence of effect modification by sex. Diagnoses of autism (2 DHA and 4 control) and hyperactivity disorders (0 cases) did not differ between groups.

Discussion | Our data indicate that prenatal DHA supplementation does not influence objective assessments of cognition, language, and executive function at preschool age despite fewer preterm children in the DHA group, which was expected with the DHA intervention.[1]

Differences in secondary outcomes seen at 18 months (including cognitive delay and mean language scores) could no longer be detected and may have been diluted by other environmental factors or may have been chance findings. The majority of RCTs of DHA interventions during pregnancy have also reported null findings.[3] However, few RCTs have attempted assessment beyond 2 years and those that have reported attrition rates of greater than 40%.[3] Our trial has the advantages of good compliance with the intervention,[1] a large sample, and high retention.

The subjective, parentally reported assessments indicated that children in the DHA group had poorer executive function and more behavioral difficulties than children in the control group, although the differences were small and unlikely to be of any clinical significance because all measures were within the normal range. These observations may be chance effects because of the high number of comparisons, or it is possible that women in the DHA group, who were more likely to correctly guess their group allocation at birth,[4] had higher expectations of their children compared with controls.

Our data do not support prenatal DHA supplementation to enhance early childhood development.

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Table. Outcomes From the Developmental Assessments and Parent Questionnaires Assessing Children at Age 4 Years

	Weighted Mean (95% CI)					
	DHA Supplement (n = 313)	Control Supplement (n = 333)	Unadjusted Effect (95% CI)[a]	*P* Value	Adjusted Effect (95% CI)[a,b]	*P* Value
General cognitive function						
Differential Ability Scales, second edition (DAS II) score[c]						
General Conceptual Ability Scale[d]	99.57 (98.38 to 100.76)	99.44 (98.28 to 100.60)	0.13 (−1.54 to 1.80)	.88	0.29 (−1.35 to 1.93)	.73
Non-verbal Reasoning Scale[e]	98.09 (96.87 to 99.31)	98.44 (97.26 to 99.62)	−0.35 (−2.05 to 1.35)	.68	−0.24 (−1.94 to 1.46)	.78
Verbal Scale	97.85 (96.89 to 98.80)	98.20 (97.19 to 99.21)	−0.36 (−1.74 to 1.03)	.62	−0.08 (−1.42 to 1.27)	.91
Spatial Scale	103.04 (101.77 to 104.31)	102.08 (100.89 to 103.27)	0.96 (−0.79 to 2.71)	.28	0.97 (−0.77 to 2.71)	.27
Executive function						
Day-night stroop (measure of efficiency)	0.20 (0.18 to 0.21)	0.20 (0.19 to 0.22)	−0.01 (−0.03 to 0.02)	.48	−0.01 (−0.03 to 0.02)	.51
DAS II score[f]						
Recall of Digits Forwards	49.94 (48.90 to 50.98)	50.99 (50.01 to 51.98)	−1.05 (−2.49 to 0.39)	.15	−0.99 (−2.40 to 0.43)	.17
Recognition of Pictures	48.88 (47.73 to 50.02)	49.44 (48.33 to 50.55)	−0.57 (−2.19 to 1.06)	.50	−0.59 (−2.17 to 0.99)	.46
Behavior Rating Inventory of Executive Function-Preschool[g]						
Global Executive Composite score[h]	52.78 (51.77 to 53.80)	51.75 (50.75 to 52.75)	1.03 (−0.40 to 2.46)	.16	1.26 (−0.14 to 2.65)	.08
Inhibitory Self-Control Index	52.26 (51.31 to 53.22)	51.47 (50.52 to 52.42)	0.79 (−0.56 to 2.15)	.25	1.06 (−0.27 to 2.38)	.12
Flexibility Index	50.55 (49.57 to 51.53)	49.86 (48.95 to 50.77)	0.69 (−0.66 to 2.04)	.32	0.84 (−0.48 to 2.16)	.21
Emergent Meta-Cognition Index	53.89 (52.87 to 54.90)	52.55 (51.56 to 53.55)	1.33 (−0.09 to 2.76)	.07	1.52 (0.11 to 2.92)	.03
Inhibition Scale	52.22 (51.34 to 53.10)	51.47 (50.61 to 52.32)	0.76 (−0.47 to 1.98)	.23	1.01 (−0.19 to 2.22)	.10
Shift Scale	49.57 (48.71 to 50.44)	48.80 (47.99 to 49.60)	0.78 (−0.41 to 1.96)	.20	0.85 (−0.32 to 2.03)	.15
Emotional Control Scale	51.73 (50.72 to 52.74)	51.42 (50.40 to 52.43)	0.31 (−1.13 to 1.76)	.67	0.52 (−0.88 to 1.93)	.46
Working Memory Scale	54.30 (53.29 to 55.31)	53.10 (52.10 to 54.10)	1.20 (−0.22 to 2.63)	.10	1.37 (−0.03 to 2.78)	.06
Plan/Organize Scale	52.62 (51.65 to 53.59)	51.23 (50.31 to 52.15)	1.39 (0.03 to 2.74)	.04	1.54 (0.21 to 2.87)	.02
Language						
CELF-P2 Core Language score[i]	93.51 (92.11 to 94.91)	94.44 (93.02 to 95.85)	−0.93 (−2.92 to 1.06)	.36	−0.91 (−2.84 to 1.03)	.36
Behavior						
Strengths and Difficulties Questionnaire score[j]						
Total Difficulties[k]	8.75 (8.30 to 9.21)	8.13 (7.70 to 8.55)	0.63 (0.01 to 1.25)	.05	0.63 (0.03 to 1.23)	.04
Emotional Symptoms	1.63 (1.48 to 1.79)	1.50 (1.35 to 1.65)	0.13 (−0.09 to 0.35)	.24	0.11 (−0.10 to 0.33)	.31
Conduct Problems	1.76 (1.62 to 1.90)	1.62 (1.49 to 1.75)	0.14 (−0.05 to 0.33)	.15	0.12 (−0.06 to 0.31)	.20
Hyperactivity	3.88 (3.66 to 4.09)	3.59 (3.39 to 3.79)	0.28 (−0.01 to 0.58)	.06	0.30 (0.01 to 0.59)	.04
Peer Problems	1.49 (1.35 to 1.62)	1.41 (1.27 to 1.55)	0.07 (−0.12 to 0.27)	.45	0.09 (−0.10 to 0.28)	.33
Prosocial Behavior	7.80 (7.65 to 7.96)	8.00 (7.85 to 8.16)	−0.20 (−0.42 to 0.02)	.08	−0.20 (−0.42 to 0.01)	.07
Impact	0.36 (0.26 to 0.46)	0.33 (0.22 to 0.44)	0.03 (−0.13 to 0.18)	.74	0.03 (−0.13 to 0.18)	.75

Abbreviations: CELF-P2, Clinical Evaluation of Language Fundamentals Preschool, second edition; DHA, docosahexaenoic acid.

[a] Effect indicates difference in means.

[b] Adjusted for center, parity, infant sex, mother's secondary education, mother's further education, and mother's smoking status.

[c] The mean (SD) score is 100 (15); range, 30 to 170.

[d] A score of less than 85 indicates delayed development.

[e] This is also an assessment of executive function.

[f] The mean (SD) score is 50 (10); range, 10 to 90; a below average score is less than 43.

[g] This is a parent questionnaire; the mean (SD) score is 50 (10).

[h] A score of greater than 65 is clinically indicative of dysfunction.

[i] The mean (SD) score is 100 (15); range, 45 to 155. Delayed language is indicated by a score of less than 86.

[j] This is a parent questionnaire. A higher score indicates negative outcome for all scores except for Prosocial Behavior.

[k] A score between 0 and 13 indicates normal; a score of greater than 13 indicates dysfunction.

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Cholesterol Testing Among Children and Adolescents During Health Visits

Abnormal lipid values occur in 1 in 5 US children and adolescents,[1] and are associated with cardiovascular disease in adulthood.[2] Universal pediatric lipid screening is advised by the National Heart, Lung, and Blood Institute (NHLBI)[2] for those aged 9 to 11 years and 17 to 21 years, in addition to the selective screening advised by the American Academy of Pediatrics (AAP) and the American Heart Association. In contrast, the US Preventive Services Task Force (USPSTF) did not find sufficient evidence to recommend any pediatric lipid screening.[3]

Despite substantial controversy,[4] little is known about the frequency of cholesterol testing during pediatric health maintenance visits in the United States.[5] We used the National Ambulatory Medical Care Survey (NAMCS)[6] to examine (1) rates and correlates of testing and (2) trends in testing, including before and after the 2007 USPSTF and 2008 AAP cholesterol statements.

Methods | We performed a repeated cross-sectional analysis of cholesterol testing among patients aged 2 to 21 years seen by pediatric, internal medicine, or general or family medicine clinicians from 1995 through 2010 at health maintenance visits. The NAMCS generates nationally representative estimates via a multistage probability sample design using 112 geographic sampling units, clinicians within these units, and patient visits. Patient visits are assigned a weight equal to the inverse probability of that sampled visit. Data[6] include patient demographics, type of visit (health maintenance, acute problem), physician specialty, practice setting, diagnoses, and medications (**Table**). Height and weight were recorded from 2005 through 2010 and were missing approximately 18% of the time. To ensure complete data on race, we used the NAMCS imputed race variable for 36% of the visits.

Using logistic regression models within a time series analysis, we examined trends in cholesterol testing before and after 2007-2008, the years the USPSTF and AAP released their statements. We modeled the trend in testing rate by including year (1995-2010, skipping 2007 and 2008) as a continuous variable, with 2 levels for 2009-2010. Using the model output, we compared (1) the trend in testing rates through 2009-2010 if the statements had no effect and (2) the actual testing rates. We also ran logistic regression models to examine associations of patient, clinician, and geographic characteristics with cholesterol testing, amalgamated across years. We used SAS version 9.3 (SAS Institute Inc). The Harvard Pilgrim Health Care institutional review board deemed this analysis exempt from review.

Results | During the 16-year period, clinicians ordered cholesterol testing at 3.4% (95% CI, 3.1%-3.8%) of 10 159 health maintenance visits. Testing rates increased only slightly from 2.5% (95% CI, 0.4%-4.7%) in 1995 to 3.2% (95% CI, 2.0%-4.5%) in 2010 (P = .03 for unadjusted trend). The odds of testing did not increase following release of USPTSF and AAP statements (adjusted OR, 0.77 [95% CI, 0.36-1.65] for 2009-2010 vs 1995-2006) (**Figure**). Clinicians were more likely to order cholesterol testing for children who were older, taller, obese, black, or lived in the South or Northeast (Table). A sensitivity analysis for missing data on height and body mass index revealed consistent results.