Letters

RESEARCH LETTER

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

The sale of prenatal supplements with docosahexaenoic acid (DHA) continues to increase, despite little evidence of benefit to offspring neurodevelopment.[1] We randomized pregnant women to receive 800 mg of DHA daily or a placebo during the last half of pregnancy and found no group differences in cognitive, language, and motor development at 18 months of age, although secondary analyses revealed less cognitive delay but lower language scores in the DHA group.[2] At 4 years of age there was no benefit of DHA supplementation in general intelligence, language, and executive functioning, and a possible negative effect on parent-rated behavior and executive functioning.[3] This follow-up was designed to evaluate the effect of prenatal DHA on intelligence quotient (IQ) at 7 years, the earliest age at which adult performance can be indicated.

Supplemental content

Methods | Methodology for the trial[2] and the 7-year follow-up[4] have been published. Written informed consent was obtained and approval granted by the local institutional ethics review boards. Children selected for neurodevelopmental assessment who were alive or withdrawn were invited to attend an appointment at age 7 years (corrected age for children born preterm). Assessments were administered by trained psychologists blinded to group allocation (June 26, 2013, to September 12, 2015; for a description of the assessments, see the eAppendix in the Supplement). The primary outcome was

Table. Developmental Outcomes From the Developmental Assessments and Parent Questionnaires Assessing Children at Age 7 Years[a]

	Weighted Mean (95% CI)					
	DHA Supplement (n = 259)	Control Supplement (n = 284)	Unadjusted Difference (95% CI)[b]	*P* Value	Adjusted Difference (95% CI)[b,c]	*P* Value
General Cognitive Function						
WASI-II full-scale IQ	98.31 (97.00 to 99.62)	97.32 (96.08 to 98.55)	0.99 (−0.80 to 2.79)	.28	1.30 (−0.47 to 3.08)	.15
Verbal comprehension	98.90 (97.50 to 100.29)	98.69 (97.34 to 100.03)	0.21 (−1.71 to 2.13)	.83	0.46 (−1.45 to 2.37)	.64
Perceptual reasoning	98.08 (96.77 to 99.40)	96.37 (95.15 to 97.59)	1.71 (−0.09 to 3.51)	.06	2.01 (0.23 to 3.79)	.03
Full-scale IQ <85[d]	12.78 (9.30 to 16.25)	13.64 (10.23 to 17.054)	0.94 (0.65 to 1.36)	.73	0.87 (0.60 to 1.26)	.46
Executive Function						
TEACh Sky Search	9.11 (8.73 to 9.50)	9.13 (8.77 to 9.48)	−0.01 (−0.55 to 0.52)	.96	0.04 (−0.50 to 0.57)	.89
Score!	7.32 (6.96 to 7.68)	7.57 (7.18 to 7.95)	−0.25 (−0.77 to 0.28)	.36	−0.20 (−0.73 to 0.34)	.47
Creature Counting	7.60 (7.19 to 8.01)	7.54 (7.16 to 7.93)	0.06 (−0.51 to 0.32)	.84	0.08 (−0.49 to 0.65)	.79
Sky Search Dual Task	5.21 (4.89 to 5.53)	5.17 (4.88 to 5.46)	0.04 (−0.39 to 0.48)	.85	0.08 (−0.36 to 0.51)	.73
RAVLT Trial 1 correct words	4.32 (4.13 to 4.51)	4.44 (4.25 to 4.63)	−0.12 (−0.39 to 0.15)	.39	−0.11 (−0.38 to 0.16)	.43
Total (trials 1-5) correct words	34.94 (33.85 to 36.02)	34.29 (33.10 to 35.48)	0.64 (−0.95 to 2.24)	.43	0.74 (−0.86 to 2.33)	.37
Delayed recall correct words	7.11 (6.77 to 7.46)	7.28 (6.94 to 7.61)	−0.16 (−0.64 to 0.32)	.51	−0.17 (−0.65 to 0.31)	.49
ReyCF Copy Raw score	16.87 (16.12 to 17.62)	16.24 (15.55 to 16.93)	0.63 (−0.39 to 1.65)	.23	0.73 (−0.31 to 1.78)	.17
Organizational Raw score	4.30 (4.03 to 4.58)	4.29 (4.01 to 4.57)	0.01 (−0.38 to 0.39)	.97	0.01 (−0.37 to 0.40)	.96
Fruit Stroop Test Interference score	1.21 (0.52 to 1.89)	0.72 (0.08 to 1.35)	0.49 (−0.44 to 1.43)	.30	0.57 (−0.36 to 1.51)	.23
CELF-4 Recall of digits total	9.05 (8.74 to 9.35)	8.90 (8.62 to 9.19)	0.15 (−0.27 to 0.56)	.49	0.21 (−0.20 to 0.61)	.31
BRIEF Global executive composite	54.89 (53.71 to 56.07)	52.54 (51.32 to 53.76)	2.35 (0.66 to 4.04)	.01	2.38 (0.67 to 4.08)	.01
Behavioral regulation index	53.66 (52.49 to 54.83)	51.54 (50.31 to 52.76)	2.12 (0.43 to 3.81)	.01	2.09 (0.40 to 3.79)	.02
Metacognition index	54.68 (53.51 to 55.84)	52.49 (51.29 to 53.69)	2.19 (0.52 to 3.86)	.01	2.25 (0.57 to 3.92)	.01

(continued)

Table. Developmental Outcomes From the Developmental Assessments and Parent Questionnaires Assessing Children at Age 7 Years[a] (continued)

	Weighted Mean (95% CI)					
	DHA Supplement (n = 259)	Control Supplement (n = 284)	Unadjusted Difference (95% CI)[b]	*P* Value	Adjusted Difference (95% CI)[b,c]	*P* Value
Language						
CELF-4 Core Language Score	92.77 (91.15 to 94.39)	92.98 (91.33 to 94.63)	−0.21 (−2.51 to 2.10)	.86	0.11 (−2.16 to 2.38)	.92
Academic Abilities						
WRAT-4 Word reading	106.85 (105.15 to 108.56)	106.57 (104.95 to 108.19)	0.28 (−2.07 to 2.63)	.81	0.75 (−1.57 to 3.08)	.52
Spelling	103.24 (101.28 to 105.21)	102.23 (100.28 to 104.18)	1.01 (−1.76 to 3.79)	.47	1.21 (−1.55 to 3.98)	.39
Math computation	91.84 (90.35 to 93.32)	90.66 (89.24 to 92.07)	1.18 (−0.86 to 3.22)	.26	1.34 (−0.72 to 3.41)	.20
Parent-Reported Behavior						
Conners 3 AI-parent ADHD score	60.94 (59.10 to 62.78)	58.37 (56.74 to 60.00)	2.56 (0.13 to 5.00)	.04	2.84 (0.38 to 5.30)	.02
SDQ total difficulties score	9.71 (9.07 to 10.35)	8.63 (7.99 to 9.28)	1.08 (0.17 to 1.98)	.02	1.09 (0.18 to 2.00)	.02

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DHA, docosahexaenoic acid; IQ, intelligence quotient.

[a] For a description of the developmental assessments, see the eAppendix in the Supplement.

[b] Effect indicates difference in means (DHA − control) estimated from a linear regression model, unless otherwise indicated. Analyses are based on 100 imputed data sets and account for both the sampling design and probability weights, calculated as the inverse of the probability of selection.

[c] Adjusted for center, parity, child's sex, mother's secondary education, mother's further education, and mother's smoking status at baseline.

[d] Data are presented as weighted percentage (95% CI) with effect being relative risk (DHA/control) estimated from a log binomial regression model.

full-scale IQ from the Wechsler Abbreviated Scale of Intelligence, Second Edition (mean, 100 [SD, 15]; delayed performance, full-scale IQ score <85). Language, academic abilities, and core components of executive functioning (memory, inhibition, and mental flexibility) were assessed as secondary outcomes (see **Table** for details).[4] Parents completed standardized questionnaires about their child's behavior and executive functioning and provided information on children's DHA intake and neurodevelopmental diagnoses.

Analyses were performed using SAS (SAS Institute), version 9.3, and Stata: Release 13 (StataCorp) on an intention-to-treat basis. All families consenting to the follow-up were included in analyses using multiple imputation to handle missing data. Continuous data were analyzed using linear regressions and binary data using log binomial regression. A 2-sided *P* value less than .05 was considered significant. No adjustment for multiple comparisons was done. Therefore, secondary outcomes should be interpreted with caution. Analyses were adjusted for center, parity, child's sex, mother's secondary and further education, and smoking status at baseline.

Results | Of those eligible, 543 children (85.1%) participated in the 7-year follow-up (DHA group: 73.8%, 259 of 351 invited; control group: 75.7%, 284 of 375 invited) compared with 96% at 18 months and 89% at 4 years (eFigure in the Supplement). Baseline data did not significantly differ between participants and nonparticipants at 7 years. Mean IQ of the DHA and control groups did not differ (98.31 for the DHA group vs 97.32 for the control group; adjusted mean difference [AMD], 1.30 [95% CI, −0.47 to 3.08], *P* = .15) (Table). Performance on direct measures of language, academic functioning, and executive functioning did not significantly differ between groups, with the exception of slightly higher perceptual reasoning scores in the DHA group. Parents in the DHA group reported more behavior problems (total difficulties score, 9.71 for the DHA group vs 8.63 for the control group; AMD, 1.09 [95% CI, 0.18 to 2.00], *P* = .02) and executive dysfunction (Global Executive composite, 54.89 for the DHA group vs 52.54 for the control group; AMD, 2.38 [95% CI, 0.67 to 4.08], *P* = .01) in their children. Diagnosis of neurodevelopmental disorders and child DHA intake did not significantly differ between groups.

Discussion | This randomized clinical trial provides strong evidence for the lack of benefit of prenatal DHA supplementation on IQ at 7 years and cognition at 18 months[2] and 4 years,[3] despite higher numbers of preterm children in the control group. Direct assessments consistently demonstrated no significant differences in language,[2,3] academic abilities, or executive functioning.[3] Although perceptual reasoning was slightly higher in the DHA group, parent-reported behavioral problems and executive dysfunction were worse with prenatal DHA supplementation. Differences found in secondary outcomes may be chance findings due to the high number of comparisons made. The small but consistent negative effects of prenatal DHA on behavior and executive functioning at 7 and 4 years[3] may reflect true effects, although effect sizes were small and neurodevelopmental diagnoses did not differ between groups. Differences are unlikely due to methodological issues as follow-up rates and variables after randomization were balanced between the groups.

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2. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P; DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children. *JAMA*. 2010;304(15):1675-1683.

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COMMENT & RESPONSE

Time to Endovascular Thrombectomy for Acute Stroke

To the Editor In an individual-patient meta-analysis using data from 5 randomized clinical trials, Dr Saver and colleagues reported improved outcomes following mechanical thrombectomy initiated up to 7.3 hours after the onset of acute ischemic stroke due to large vessel occlusion.[1] This result represents a meaningful extension of the current 6-hour treatment guideline[2] and would expand access to life-altering treatments. However, the challenges of interpreting these data must be acknowledged. Only 3 of the 5 trials allowed intervention beyond 6 hours, and these 3 trials used more stringent imaging selection criteria that varied between and even within trials. These differences in patient selection are difficult to capture in a random-effects analysis and can confound the time dependence of treatment benefit by enriching the population treated within extended time windows compared with those treated within 6 hours.

Furthermore, just 147 of 1275 patients (11.5%) with available outcome data were treated beyond 6 hours. The scarcity of extended-time data is problematic if the linear outcome model is fit primarily to more densely populated data in earlier time windows, and isolated review of the small number of patients treated in an extended time window is unlikely to attain significance. A larger number of patients may help to establish treatment benefit in extended time windows with the level of evidence now demanded of endovascular stroke interventions.

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1. Saver JL, Goyal M, van der Lugt A, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316(12):1279-1288.

2. Powers WJ, Derdeyn CP, Biller J, et al; American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(10):3020-3035.

In Reply We concur with Dr Kansagra that it is important to take into account that special penumbral and collateral imaging selection criteria were used in a minority of the participating trials, but we note that special imaging selection was used less often than Kansagra suggests. Of the 3 trials enrolling patients for intervention beyond 6 hours, 2 (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN][1] and Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset [REVASCAT][2]) did not use special imaging selection at all. (The third, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on