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. 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. 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. 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.

Methods | Methodology for the trial2 and the 7-year follow-up4 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 Children selected for neurodevelopmental assessment who were alive or withdrawn were invited to attend an appointment at age 7 years (corrected age for children born preterm).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 Appendix in the Supplement). The primary outcome was

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

<table>
<thead>
<tr>
<th></th>
<th>Weighted Mean (95% CI)</th>
<th>Control Supplement (n = 284)</th>
<th>Unadjusted Difference (95% CI)</th>
<th>P Value</th>
<th>Adjusted Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Cognitive Function</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>WASI-II full-scale IQ</td>
<td>98.31 (97.00 to 99.62)</td>
<td>97.32 (96.08 to 98.55)</td>
<td>0.99 (-0.80 to 2.79)</td>
<td>.28</td>
<td>1.30 (-0.47 to 3.08)</td>
<td>.15</td>
</tr>
<tr>
<td>Verbal comprehension</td>
<td>97.90 (97.50 to 100.29)</td>
<td>98.69 (97.34 to 100.03)</td>
<td>0.21 (-1.71 to 2.13)</td>
<td>.83</td>
<td>0.46 (-1.45 to 2.37)</td>
<td>.64</td>
</tr>
<tr>
<td>Perceptual reasoning</td>
<td>98.08 (96.77 to 99.40)</td>
<td>96.37 (95.15 to 97.59)</td>
<td>1.71 (-0.09 to 3.51)</td>
<td>.06</td>
<td>2.01 (0.23 to 3.79)</td>
<td>.03</td>
</tr>
<tr>
<td>Full-scale IQ &lt;854</td>
<td>12.78 (9.30 to 16.25)</td>
<td>13.64 (10.23 to 17.054)</td>
<td>0.94 (0.65 to 1.36)</td>
<td>.73</td>
<td>0.87 (0.60 to 1.26)</td>
<td>.46</td>
</tr>
<tr>
<td>Executive Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEACH Sky Search</td>
<td>9.11 (8.73 to 9.50)</td>
<td>9.13 (8.77 to 9.48)</td>
<td>-0.01 (-0.55 to 0.52)</td>
<td>.96</td>
<td>0.04 (-0.50 to 0.57)</td>
<td>.89</td>
</tr>
<tr>
<td>Score!</td>
<td>7.32 (6.96 to 7.68)</td>
<td>7.57 (7.18 to 7.95)</td>
<td>-0.25 (-0.77 to 0.28)</td>
<td>.36</td>
<td>0.20 (-0.73 to 0.34)</td>
<td>.47</td>
</tr>
<tr>
<td>Creature Counting</td>
<td>7.60 (7.19 to 8.01)</td>
<td>7.54 (7.16 to 7.93)</td>
<td>0.06 (-0.51 to 0.32)</td>
<td>.84</td>
<td>0.08 (-0.49 to 0.65)</td>
<td>.79</td>
</tr>
<tr>
<td>Sky Search Dual Task</td>
<td>5.21 (4.89 to 5.53)</td>
<td>5.17 (4.88 to 5.46)</td>
<td>0.04 (-0.39 to 0.48)</td>
<td>.85</td>
<td>0.08 (-0.36 to 0.51)</td>
<td>.73</td>
</tr>
<tr>
<td>RAVLT Trial 1 correct words</td>
<td>4.32 (4.13 to 4.51)</td>
<td>4.44 (4.25 to 4.63)</td>
<td>-0.12 (-0.39 to 0.15)</td>
<td>.39</td>
<td>0.11 (-0.38 to 0.16)</td>
<td>.43</td>
</tr>
<tr>
<td>Total (trials 1-5) correct words</td>
<td>34.94 (33.85 to 36.02)</td>
<td>34.29 (33.10 to 35.48)</td>
<td>0.64 (-0.95 to 2.24)</td>
<td>.43</td>
<td>0.74 (-0.86 to 2.33)</td>
<td>.37</td>
</tr>
<tr>
<td>Delayed recall correct words</td>
<td>7.11 (6.77 to 7.46)</td>
<td>7.28 (6.94 to 7.61)</td>
<td>-0.16 (-0.64 to 0.32)</td>
<td>.51</td>
<td>0.17 (-0.65 to 0.31)</td>
<td>.49</td>
</tr>
<tr>
<td>ReyCF Copy Raw score</td>
<td>16.87 (16.12 to 17.62)</td>
<td>16.24 (15.55 to 16.93)</td>
<td>0.63 (-0.39 to 1.65)</td>
<td>.23</td>
<td>0.73 (-0.31 to 1.78)</td>
<td>.17</td>
</tr>
<tr>
<td>Organizational Raw score</td>
<td>4.30 (4.03 to 4.58)</td>
<td>4.29 (4.01 to 4.57)</td>
<td>0.01 (-0.38 to 0.39)</td>
<td>.97</td>
<td>0.01 (-0.37 to 0.40)</td>
<td>.96</td>
</tr>
<tr>
<td>Fruit Stroop Test</td>
<td>1.21 (0.52 to 1.89)</td>
<td>0.72 (0.08 to 1.35)</td>
<td>0.49 (-0.44 to 1.43)</td>
<td>.30</td>
<td>0.57 (-0.36 to 1.51)</td>
<td>.23</td>
</tr>
<tr>
<td>CELF-4 Recall of digits total</td>
<td>9.05 (8.74 to 9.35)</td>
<td>8.90 (8.62 to 9.19)</td>
<td>0.15 (-0.27 to 0.56)</td>
<td>.49</td>
<td>0.21 (-0.20 to 0.61)</td>
<td>.31</td>
</tr>
<tr>
<td>BRIEF Global executive composite</td>
<td>54.89 (53.71 to 56.07)</td>
<td>52.54 (51.32 to 53.76)</td>
<td>2.35 (0.65 to 4.04)</td>
<td>.01</td>
<td>2.38 (0.67 to 4.08)</td>
<td>.01</td>
</tr>
<tr>
<td>Behavioral regulation index</td>
<td>53.66 (52.49 to 54.83)</td>
<td>51.54 (50.31 to 52.76)</td>
<td>2.12 (0.43 to 3.81)</td>
<td>.01</td>
<td>2.09 (0.40 to 3.79)</td>
<td>.02</td>
</tr>
<tr>
<td>Metacognition index</td>
<td>54.68 (53.51 to 55.84)</td>
<td>52.49 (51.29 to 53.69)</td>
<td>2.19 (0.52 to 3.86)</td>
<td>.01</td>
<td>2.25 (0.57 to 3.92)</td>
<td>.01</td>
</tr>
</tbody>
</table>

(continued)
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 education 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 months2 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.1 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 years4 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.

Table. Developmental Outcomes From the Developmental Assessments and Parent Questionnaires Assessing Children at Age 7 Yearsa (continued)

<table>
<thead>
<tr>
<th>Weighted Mean (95% CI)</th>
<th>Unadjusted Difference (95% CI)b</th>
<th>P Value</th>
<th>Adjusted Difference (95% CI)A</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CELF-4 Core Language Score</td>
<td>92.77 (91.15 to 94.39)</td>
<td>92.98 (91.33 to 94.63)</td>
<td>-0.21 (-2.51 to 2.10)</td>
<td>.86</td>
</tr>
<tr>
<td><strong>Academic Abilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRAT-4 Word reading</td>
<td>106.85 (105.15 to 108.56)</td>
<td>106.57 (104.95 to 108.19)</td>
<td>0.42 (1.50 to 2.37)</td>
<td>.81</td>
</tr>
<tr>
<td>Spelling</td>
<td>103.24 (101.28 to 105.21)</td>
<td>102.23 (100.28 to 104.18)</td>
<td>1.01 (-1.76 to 3.79)</td>
<td>.47</td>
</tr>
<tr>
<td>Math computation</td>
<td>91.84 (90.35 to 93.32)</td>
<td>90.66 (89.24 to 92.07)</td>
<td>1.18 (-0.86 to 3.22)</td>
<td>.26</td>
</tr>
<tr>
<td><strong>Parent-Reported Behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conners 3 AI-parent ADHD score</td>
<td>60.94 (59.10 to 62.78)</td>
<td>58.37 (56.74 to 60.00)</td>
<td>2.56 (0.13 to 5.00)</td>
<td>.04</td>
</tr>
<tr>
<td>SDQ total difficulties score</td>
<td>9.71 (9.07 to 10.35)</td>
<td>8.63 (7.99 to 9.28)</td>
<td>1.08 (0.17 to 1.98)</td>
<td>.02</td>
</tr>
</tbody>
</table>

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.

A Adjusted for center, parity, child’s sex, mother’s secondary education, mother’s further education, and mother’s smoking status at baseline.

Data are presented as weighted percentage (95% CI) with effect being relative risk (DHA/control) estimated from a log binomial regression model.
Conflict of Interest Disclosures:
Gould, Makrides.
Supervision:
Administrative, technical, or material support:
Funding/Support:
The original randomized trial of DHA in Pregnancy to
report improved outcomes following mechanical throm-
beectomy initiated up to 7.3 hours after the onset of acute
ischemic stroke due to large vessel occlusion. This result rep-
resents a meaningful extension of the current 6-hour treat-
ment guideline 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 con-
found the time dependence of treatment benefit by enriching
the population treated within extended time windows com-
pared with those treated within 6 hours.

Furthermore, just 147 of 1275 patients (11.5%) with avail-
able 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 ear-
tier 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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Conflict of Interest Disclosures: The author has completed and submitted the
ICMJE Form for Disclosure of Potential Conflicts of Interest and none were
reported.

treatment with endovascular thrombectomy and outcomes from ischemic

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
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