Maternal supplementation with docosahexaenoic acid during pregnancy does not affect early visual development in the infant: a randomized controlled trial¹⁻³

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ABSTRACT
Background: The docosahexaenoic acid (DHA) intake of pregnant women is lower than estimates of the DHA accretion by the fetus, and recommendations were made to increase the DHA intake of pregnant women.

Objective: The objective of this study was to determine whether the supplementation of pregnant women with DHA improved the visual acuity of infants at 4 mo.

Design: We conducted a blinded assessment of a subset of healthy, full-term infants born to women enrolled in a double-blind, randomized controlled trial called the DHA for Maternal and Infant Outcomes (DOMInO) trial. Women were randomly assigned to consume DHA-rich fish-oil capsules (~800 mg DHA/d in the treatment group) or vegetable oil capsules (control group) from midpregnancy to delivery. The primary outcome was the sweep visual evoked potential (VEP) acuity at 4 mo. The VEP latency at 4 mo was a secondary outcome.

Results: Mean (±SD) VEP acuity did not differ between treatment and control groups [treatment group: 8.37 ± 2.11 cycles per degree (cpd), n = 89; control group: 8.55 ± 1.86 cpd, n = 93; P = 0.55]. VEP latencies also did not differ between groups. Irrespective of the group, maternal smoking in pregnancy was independently associated with poorer VEP acuity in the infant.

Conclusions: DHA supplementation in women with singleton pregnancies does not enhance infant visual acuity in infants at 4 mo of age. Visual acuity in infancy is adversely associated with maternal smoking in pregnancy. This trial was registered at www.anzctr.org.au as ACTRN12605000569606. The DOMInO trial was registered at www.anzctr.org.au as ACTRN12605000569606. Am J Clin Nutr 2011;93:1293–9.

INTRODUCTION

The n−3 (omega-3) long-chain polysaturated fatty acid (LC-PUFA) docosahexaenoic acid (DHA) is concentrated in retinal photoreceptors and neuronal cell membranes where DHA has putative roles that relate to visual function, including signal transduction and neurotransmission (1, 2). During pregnancy, DHA accumulates in retinal and neural tissues (3) with fetal accretion of n−3 LC-PUFAs at its most rapid velocity during the last trimester and is estimated to be ≈50 mg DHA · kg⁻¹ · d⁻¹ (4). We previously showed that the visual acuity of preterm infants can be improved by increasing the dietary supply of DHA in the postnatal period to match the gestational supply (5). Research that suggested that a low maternal intake of DHA may result in suboptimal fetal accretion rates raised interest in studies that involved DHA supplementation during pregnancy. Fish is a rich source of DHA, and fish intake during pregnancy and a higher n−3 LC-PUFA status at birth were associated with a better visual development in infants born at term (6–8). Many women from Western countries consume diets that are low in DHA. Data from Australia show that one-half of adult women consume ≤15 mg DHA/d (9). In addition, government advice has warned pregnant women against the consumption of certain species of deep-sea predatory fish that may contain methyl mercury (10, 11), resulting in women further reducing their intake of fish while pregnant (12). Although some groups have recommended that pregnant women aim to consume DHA intakes of ≈200 mg DHA/d (13), there is limited evidence to suggest that taking DHA supplements while pregnant improves the visual development of term infants. Three previous randomized trials reported mixed results and had methodologic limitations (14–16), including sample sizes that were too small to detect differences in acuity within the range expected of infants born at term (14, 16). The aim of the current study was to evaluate whether supplementing pregnant women with DHA can enhance the visual development of singleton full-term infants.

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SUBJECTS AND METHODS

Subjects

This nested study involved a subset of infants born to mothers enrolled in a registered, multi-center, double-blind, randomized controlled trial called the DHA for Maternal and Infant Outcomes (DOMInO) trial (17). DOMInO families were approached to enroll into the visual acuity follow-up study at the time of birth at Flinders Medical Centre between June 2007 and August 2008. In addition to the DOMInO eligibility criteria of singleton pregnancies between 18–21 wk gestation with no fetal abnormalities, infants born preterm (<37 wk gestation), low birth weight (<2500 g), or with clinician-diagnosed eye pathologies were excluded. Infants whose mothers withdrew consent to participate in the parent DOMInO trial were not invited to participate in the visual follow-up study. Written informed consent was obtained from parents of all participating infants. All procedures were conducted in accordance with the trial protocol, which was approved by the Flinders Medical Centre Human Research Ethics Committee (Bedford Park, Australia).

Allocation and treatment

The procedure for allocating participants to treatment was previously described (17). Briefly, upon enrollment, women were randomly assigned to their intervention group by a telephone randomization service. The computer-generated randomization schedule was stratified by site and parity (primiparous compared with multiparous), which was prepared and kept concealed by an independent statistician. The hospital pharmacy department issued capsules to participants. Women assigned to the treatment group were asked to consume three 0.5-g capsules of DHA-rich fish oil/d ( Increomega 500TG; Croda Chemicals, East Yorkshire, United Kingdom) until delivery, which provided a total dose of 800 mg DHA/d and 100 mg eicosapentaenoic acid (EPA)/d. Women assigned to the control group were asked to consume three 0.5-g capsules of a blended vegetable oil (Efa mol Ltd) that reflected the saturated, monounsaturated and P UFA profile of the Australian diet (9). Treatment and control capsules were identical in appearance. Trial investigators, staff, and participants were unaware of the treatment allocation. At the end of the intervention period, the efficacy of the intervention was shown in the main study by increased cord blood plasma phospholipid DHA concentrations (percentage of total fatty acids) in treatment compared with control groups (17).

Outcome assessments at 4 mo

Infants were scheduled for visual assessments within ±1 wk of turning 4 mo of age. The visual evoked potential (VEP) acuity was the primary outcome, with the VEP latency and breast-milk fatty acids considered secondary outcomes. All follow-up assessments were conducted blinded to the treatment group.

VEP assessments

The VEP acuity and latency procedures were conducted according to established procedures (5). For sweep VEP-acuity measurements, infants were presented with a high-contrast sinusoidal grating pattern that swept in roughly equal increments from 0.5 to 14 cycles per degree (cpd) over a 10-s period. Responses to gratings were collected by using five 5-mm gold cup electrodes placed at the central vertex (ground) 1 cm above the inion (reference) and two 5-mm gold cup electrodes at 30% left and right of the centrally located inion electrode (active). Acuity was estimated from a regression line passing through the linearly descending section of the amplitude compared with the spatial frequency function at 0 V. The limit of acuity was considered to be the infant’s best performance in either a single sweep or vector average of ≥3 sweeps. As previously described (5), VEP latency responses were recorded as the mean of duplicate responses to the first positive peak (P100) to transient checkerboard patterns reversing at 2 Hz and subtending visual angles of 69, 48, and 20 min of arc.

Cord blood and breast-milk fatty acid analysis

Cord blood plasma phospholipids and human milk fatty acids were analyzed according to previously established methods (18). Briefly, cord blood was collected into heparinized tubes, and the plasma fraction was collected after centrifugation and stored at −20°C until analysis. Before the 4-mo appointment, lactating mothers were mailed a sterile specimen pot for the collection of a milk sample to bring to her infant’s assessment. Mothers were instructed to collect the sample in the week leading to the appointment and to immediately freeze the sample. Lactating mothers who did not supply a frozen sample of milk were asked to provide a specimen at the appointment. Milk samples were stored at −20°C until analysis of fatty acids. Plasma phospholipid and human milk fatty acids were extracted in chloroform: methanol, with the phospholipids fraction of plasma separated by thin-layer chromatography. Fatty acids were methylated in 1% sulfuric acid for 2 h at 70°C, and methyl esters were separated by using capillary column gas chromatography. Fatty acids were identified and quantified based on the retention time to authentic lipid standards (Nucheck Prep Inc, Elysian, MN). Fatty acid data were retained by the laboratory until completion of statistical analyses of VEP outcomes to prevent unblinding.

Sample size

Infants enrolled in this study were term infants with the absence of known visual pathologies and were expected to have normal visual development. To detect a shift in the visual acuity within the normal range, we calculated that a sample size of 180 infants would be required to detect a 1.5-cpd difference between the treatment and control infants with 90% power and 95% significance. This difference was approximately one-half an SD in size and was smaller than one line on a Snellen eye chart (from 20/75 to 20/60), which is considered a clinically relevant difference because the importance of an early sensory experience on visual development. We also wanted to investigate the effect of DHA supplementation on the VEP acuity by sex because our previous work showed group × sex interactions (19). Our sample was of sufficient size to detect a difference of 2 cpd in sex subgroups with an 80% power and 95% significance.

Statistical analyses

Statistical analyses were conducted with SPSS (version 15.0; SPSS, Chicago, IL). P ≤ 0.05 was considered significant, and no adjustment was made for multiple comparisons. All analyses...
were conducted on an intention-to-treat basis. The primary outcome of VEP acuity was tested in a one-factor analysis of variance to compare the main effects of visual acuity between the treatment and control groups, with maternal smoking at enrollment included as a covariate. Maternal smoking and alcohol consumption at baseline were evaluated as potential covariates by using Pearson’s correlation, and interactions between group × sex and group × maternal smoking were tested. We conducted exploratory analyses to examine the effect of the postnatal DHA supply on visual acuity. First, analyses were limited only to infants who were breastfed at 4 mo of age. Second, analyses were stratified according to whether the infant was predominately fed a source of DHA throughout the postnatal period (which included all infants fed breast milk or infants fed infant formula supplemented with DHA) and infants fed a formula with no DHA. Secondary unadjusted analyses included independent t tests to compare VEP latency and breast-milk fatty acids between treatment and control groups. Correlations between VEP outcomes and cord blood fatty acids were examined by using Pearson’s correlations.

RESULTS

Of the 271 DOMInO-trial infants screened, 248 infants met the eligibility criteria, and a total of 185 infants were enrolled in the study (Figure 1). Baseline characteristics of mothers who participated in this nested follow-up study were similar across treatment and control groups as were characteristics of infants at birth (Table 1). Postrandomization variables that may have influenced early visual development, such as the proportion of children exposed to cigarette smoke in pregnancy, breastfeeding, maternal use of DHA supplements during lactation, or feeding of a LC-PUFA–fortified formula, were balanced across groups. At completion of the intervention, mothers were asked which capsules they believed they were assigned. The proportion of mothers who guessed they were taking the DHA capsules was higher in the treatment group than in the control group [treatment group: 61 of 91 mothers (67% of mothers); control group: 12 or 94 mothers (13% of mothers)].

Primary outcome: VEP acuity

The primary outcome of sweep VEP acuity did not differ between treatment and control groups (Table 2). The covariate adjustment for maternal smoking did not alter the findings between treatment and control groups; however maternal smoking had an independent negative effect on the VEP acuity (P = 0.04). Maternal alcohol consumption at enrollment was not correlated with acuity and was not included in the analysis of variance. No interaction was observed between acuity and smoking or sex.

FIGURE 1. Flow of participants in the DHA for Maternal and Infant Outcomes (DOMInO) trial through a visual acuity study. In the treatment group, one infant was lost to follow-up despite repeated attempts to reschedule assessments, and the visual evoked potential (VEP) tester (LGS) was unavailable for one assessment. In the control group, the VEP-acuity assessment was unsuccessful in one infant.
Acuity between the treatment and control groups did not differ in secondary (unadjusted) subgroup analyses according to sex. We conducted exploratory analyses to examine the effect of postnatal feeding or the DHA supply on acuity. The mean (±SD) VEP acuity in infants who were fed only breast milk at 4 mo of age did not differ between treatment and control groups [treatment group: 8.8 ± 2.0 cpd (n = 38); control group: 8.7 ± 2.4 cpd (n = 38); 95% CI: −0.9, 1.1 cpd; P = 0.9]. An adjustment for maternal smoking was not possible because there was only one smoker (control group) who was breastfeeding their baby at age.

### TABLE 1
Characteristics of participants and their mothers at enrollment, birth, and follow-up at 4 mo of age

<table>
<thead>
<tr>
<th>Maternal data collected at enrollment</th>
<th>Treatment group (n = 91)</th>
<th>Control group (n = 94)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at trial entry (y)</td>
<td>29.5 ± 5.52</td>
<td>28.7 ± 5.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Primiparous [n (%)]</td>
<td>35 (39)</td>
<td>37 (39)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mother completed secondary education [n (%)]</td>
<td>58 (64)</td>
<td>56 (60)</td>
<td>0.26</td>
</tr>
<tr>
<td>Nonsmoker at enrollment [n (%)]</td>
<td>81 (89)</td>
<td>82 (87)</td>
<td>0.77</td>
</tr>
<tr>
<td>Nondrinker during pregnancy [n (%)]</td>
<td>82 (90)</td>
<td>82 (87)</td>
<td>0.77</td>
</tr>
<tr>
<td>Infant data collected at birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex [n (%)]</td>
<td>47 (52)</td>
<td>42 (45)</td>
<td>0.26</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.56 ± 0.49</td>
<td>3.61 ± 0.41</td>
<td>0.43</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>50.3 ± 2.2</td>
<td>49.8 ± 3.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>35.1 ± 1.3</td>
<td>35.6 ± 3.0</td>
<td>0.19</td>
</tr>
<tr>
<td>VEP latency (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69 min of arc</td>
<td>115 ± 8</td>
<td>116 ± 9</td>
<td>0.73</td>
</tr>
<tr>
<td>48 min of arc</td>
<td>121 ± 10</td>
<td>121 ± 12</td>
<td>0.73</td>
</tr>
<tr>
<td>20 min of arc</td>
<td>133 ± 15</td>
<td>133 ± 14</td>
<td>0.84</td>
</tr>
</tbody>
</table>

1 DHA, docosahexaenoic acid; LC-PUFA, long-chain polyunsaturated fatty acid.
2 Mean ± SD (all such values).
3 At 4 mo of age, 90 infants from the treatment group and 94 infants from the control group were assessed (one infant from the treatment group was lost to follow-up). Treatment and control groups did not differ in any follow-up characteristics as determined by unadjusted t tests for normally distributed variables and chi-square test for categorical variables.
4 The intervention period for the trial was midpregnancy to delivery. Eight lactating mothers (9% of mothers) in the treatment group and 4 lactating mothers (4% of mothers) in the control group reported the use of a commercially available DHA supplement during the postnatal period.

### TABLE 2
Outcome of infants at 4 mo of age

<table>
<thead>
<tr>
<th>Outcome of infants at 4 mo of age</th>
<th>Treatment group (n = 89 of 91)</th>
<th>Control group (n = 93 of 94)</th>
<th>Values2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (cpd)</td>
<td>8.37 ± 1.972</td>
<td>8.55 ± 1.97</td>
<td>0.19 (−0.8, 1.01)</td>
<td>0.53</td>
</tr>
<tr>
<td>Unadjusted VEP acuity</td>
<td>8.37 ± 2.11</td>
<td>8.55 ± 1.86</td>
<td>−0.17 (−0.76, 0.41)</td>
<td>0.55</td>
</tr>
<tr>
<td>Girls subgroup</td>
<td>8.46 ± 2.31</td>
<td>8.59 ± 1.93</td>
<td>0.13 (−0.75, 1.01)</td>
<td>0.77</td>
</tr>
<tr>
<td>Boys subgroup</td>
<td>8.30 ± 1.93</td>
<td>8.51 ± 1.82</td>
<td>0.21 (−0.57, 0.99)</td>
<td>0.60</td>
</tr>
<tr>
<td>VEP latency (ms)</td>
<td>69 min of arc</td>
<td>115 ± 8</td>
<td>0.7 (−2, 3)</td>
<td>0.59</td>
</tr>
<tr>
<td>48 min of arc</td>
<td>121 ± 10</td>
<td>121 ± 12</td>
<td>0.6 (−3, 4)</td>
<td>0.73</td>
</tr>
<tr>
<td>20 min of arc</td>
<td>133 ± 15</td>
<td>133 ± 14</td>
<td>−0.4 (−5, 4)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

1 VEP, visual evoked potential; cpd, cycles per degree. VEP assessments were successfully conducted in 89 infants in the treatment group (n = 1 lost to follow-up; n = 1 VEP tester not available) and 93 infants from the control group (n = 1 unsuccessful acuity assessment). P < 0.05 was considered significant.
2 Values are mean differences; 95% CIs in parentheses.
3 Analyzed by one-factor ANCOVA to compare main effects of visual acuity between infants in treatment and control groups with covariate adjustment for maternal smoking (no group × maternal smoking interaction was observed).
4 mo. The acuity of infants who received a postnatal source of DHA also did not differ between groups [adjusted analysis; treatment group: 8.6 ± 2.1 cpd (n = 72); control group: 8.7 ± 2.1 cpd (n = 70); 95% CI: −0.8, 0.6 cpd; P = 0.63], nor did the acuity of infants who were fed a formula that contained no DHA from birth [adjusted analysis; treatment group: 7.7 ± 1.6 cpd (n = 17); control group: 8.1 ± 1.6 cpd (n = 23); 95% CI: −1.5, 0.6 cpd; P = 0.39]. The VEP acuity was not significantly correlated with cord blood DHA or any other key PUFAs, including linoleic acid, arachidonic acid, and EPA, within the treatment or control group.

Secondary outcomes

**VEP latency**

VEP latencies at 4 mo did not differ between treatment and control groups (Table 2) but showed the expected association of longer latencies to smaller-sized patterns. Correlations between cord blood PUFAs and VEP latencies differed by group. In the treatment group, there were no significant correlations; however, in the control group, cord blood DHA concentrations were negatively associated with latencies to checks subtending 69 and 48 min of arc (r = −0.28, P = 0.01, and r = −0.27, P = 0.02, respectively).

**Cord blood and breast-milk fatty acids**

Cord blood samples were collected from 77 of 91 subjects (85% of participants) in the treatment group and from 74 of 94 subjects (79% of participants) in the control group. For n−6 PUFAs, cord blood plasma linoleic acid was higher in the treatment group than in the control group (treatment group: 7.14 ± 1.49% of fatty acids; control group: 6.61 ± 1.4% of fatty acids; 95% CI: 0.06%, 0.99%; P = 0.03), but arachidonic acid was lower in the treatment group than in the control group (treatment group: 15.44 ± 1.61% of fatty acids; control group: 17.17 ± 1.55% of fatty acids; 95% CI: −2.23%, −1.22%; P < 0.0005). EPA and DHA were higher in the treatment group than in the control group (EPA: 0.59 ± 0.28% of fatty acids in the treatment group and 0.29 ± 0.09% of fatty acids in the control group; 95% CI: 0.23%, 0.36%; P < 0.0005; DHA: 8.25 ± 1.87% of fatty acids in the treatment group and 6.76 ± 1.48% of fatty acids in the control group; 95% CI: 0.95%, 2.03%; P < 0.0005).

Although the DHA intervention ended at delivery, we asked all women who were lactating at the time of the 4-mo appointment to provide a breast-milk sample. However, in the control group, an additional 4 women who had ceased breastfeeding in the week of the appointment also provided a sample, which resulted in total number of 55 milk samples from women in the control group (Table 1). Of these women, 8 of 91 subjects (9% of subjects) in the treatment group and 4 of 94 subjects (4% of subjects) in the control group took a supplement that contained DHA during lactation. Intention-to-treat comparisons of major breast-milk fatty acids showed that DHA (percentage of total fatty acids) was 0.06% higher in the treatment group than in the control group (Table 3). The higher DHA concentrations in the milk of treatment-group mothers were not due to supplements because the milk DHA concentrations were higher even when mothers who consumed DHA supplements during lactation were excluded from the analysis [DHA: 0.25 ± 0.12% of fatty acids in the treatment group (n = 45) and 0.20 ± 0.09% of fatty acids in the control group (n = 51); 95% CI: 0.01%, 0.10%; P = 0.014].

**DISCUSSION**

We have shown that supplementing women with DHA during the latter half of pregnancy did not influence the sweep VEP acuity of 4-mo-old infants, despite the attainment of a higher DHA status at birth and exposure to DHA via breast milk to 4 mo of age in the treatment group than in the control group. This result was despite the fact that the increased exposure of DHA to preterm infants over a comparable gestational period resulted in a significant improvement in the VEP acuity (5). The inability to detect an effect could not be explained by higher DHA concentrations than expected in the control group because umbilical plasma DHA concentrations were very similar to past studies and suggestive of insufficiency (20). Indeed the supplementation strategy of ≈800 mg DHA/d was designed to address fetal growth and maternal losses to energy, which resulted in a higher dose of DHA than previously used in pregnancy supplementation trials in which assessments of acuity in infancy were included as outcome measures (14, 15). We had no evidence to suggest that DHA supplementation during pregnancy adversely affected visual development. Our findings were consistent with

### TABLE 3

<table>
<thead>
<tr>
<th>Breast-milk fatty acids at 4 mo of age1</th>
<th>Treatment group (n = 54)</th>
<th>Control group (n = 55)</th>
<th>Values2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of total fatty acids</td>
<td>% of total fatty acids</td>
<td>% of total fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linoleic acid (18:2n−6)</td>
<td>10.42 ± 2.311</td>
<td>10.47 ± 2.74</td>
<td>−0.05 (−1.02, 0.91)</td>
<td>0.9</td>
</tr>
<tr>
<td>Arachidonic acid (20:4 n−6)</td>
<td>0.37 ± 0.08</td>
<td>0.38 ± 0.09</td>
<td>−0.004 (−0.04, 0.03)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total n−6 PUFAs</td>
<td>11.56 ± 2.41</td>
<td>11.59 ± 2.86</td>
<td>−0.03 (−1.04, 0.97)</td>
<td>0.95</td>
</tr>
<tr>
<td>α-Linolenic acid (18:3n−3)</td>
<td>1.06 ± 0.40</td>
<td>1.01 ± 0.37</td>
<td>0.05 (−0.10, 0.19)</td>
<td>0.5</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (20:5n−3)</td>
<td>0.09 ± 0.05</td>
<td>0.07 ± 0.05</td>
<td>0.01 (−0.01, 0.03)</td>
<td>0.4</td>
</tr>
<tr>
<td>Docosapentaenoic acid (22:5n−3)</td>
<td>0.16 ± 0.03</td>
<td>0.17 ± 0.05</td>
<td>−0.01 (−0.02, 0.01)</td>
<td>0.5</td>
</tr>
<tr>
<td>Docosahexaenoic acid (22:6n−3)</td>
<td>0.27 ± 0.13</td>
<td>0.21 ± 0.10</td>
<td>0.06 (0.02, 0.10)</td>
<td>0.009</td>
</tr>
<tr>
<td>Total n−3 PUFAs</td>
<td>1.71 ± 0.46</td>
<td>1.61 ± 0.43</td>
<td>0.1 (−0.06, 0.28)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

1 PUFAs, polysaturated fatty acids. Fatty acid concentrations in breast milk of treatment and control groups were compared by using independent t tests. P < 0.05 was significant.

2 Values are mean differences; 95% CIs in parentheses.

3 Mean ± SD (all such values).
those of Innis and Friesen (15) who showed that the supplementation of women \(n = 135\) with 400 mg DHA/d from 16 wk gestation through to birth raised maternal erythrocyte DHA concentrations at 36 wk gestation but did not influence the acuity at 2 mo of age. In contrast, Judge et al (14) showed that supplementation with \(\approx 200\) mg DHA from cereal bars was associated with a better acuity at 4 mo; however, the study had a high risk of bias because of unsophisticated randomization processes, the poor concealment of allocation, and a small sample size \(n = 30\). Although Judge et al (14) did not report cord blood DHA concentrations, another trial showed that cord blood plasma DHA concentrations were not altered after consumption of a supplement of 200-mg DHA/d during pregnancy (21). It was suggested that the mobilization of endogenous DHA stores or the up-regulation of DHA synthesis from fatty acid precursors may be 2 mechanisms by which the mother can help meet the DHA demands of pregnancy (22). Irrespective of the mechanisms involved, the findings from the current study showed that the consumption of high-dose DHA supplements during the second half of pregnancy had no clinically-relevant effect on the infant visual acuity, even in Australian women who consumed very low concentrations of DHA (9).

As some, but not all, other trials have shown that feeding infants an \(n-3\) LC-PUFA-supplemented formula in the postnatal period improved the visual acuity of infants at 4 mo of age (23–25), we undertook exploratory analyses to determine whether an exposure to DHA in the postnatal period was a post-randomization confounding factor on visual outcomes in the DOMInO trial. When we examined infants who were fed only breast milk, the visual acuity did not differ between treatment and control groups. Likewise, Innis and Friesen (15) reported that breastfeeding did not influence the relation between DHA supplementation in pregnancy and infant acuity. After the cessation of DHA supplementation at delivery, milk DHA concentrations declined rapidly over the first month (26). The small difference in milk DHA concentrations between groups (mean difference: 0.06% of fatty acids; 95% CI: 0.02%, 0.10%) indicated that the return to baseline concentrations had not been completed by 4 mo. These data showed that DHA supplementation in pregnancy influenced breast-milk DHA concentrations, and because of the high proportion of women who breastfed their infants, it was difficult to separate out the effects of DHA in pregnancy and lactation.

Our study confirmed earlier work that showed that in utero exposure to cigarette smoking was a significant independent factor associated with poorer visual outcomes (27). Other DHA trials that involved pregnant women that measured infant acuity did not report the maternal smoking status (14) or had too few smokers to evaluate the effect of smoking (15). Although our trial was not designed to quantify the effect of smoking during pregnancy on visual acuity, the results indicated that the detrimental effect of smoking in pregnancy was likely to have a bigger effect on visual acuity than was the DHA supply during pregnancy.

Secondary visual outcomes showed DHA supplementation in pregnancy did not influence the speed of the neural transmission from the retina to the visual cortex as measured by VEP latencies. VEP latencies are thought to reflect the degree of neuronal myelination, and slower (ie, poorer) latency responses were shown in children exposed to smoking, alcohol, and other illicit substances in utero (28). Although other authors have shown that DHA supplementation in pregnancy did not influence VEP latencies in 10- and 16-wk-old infants, the findings were difficult to interpret because of the low dose (200 mg DHA/d) of supplementation (16). Higher cord blood DHA concentration were associated with shorter latencies in analyses in which treatment and control groups were combined (16). Because of the randomized design of the current study, we examined associations between plasma DHA concentrations and latency of treatment and control groups separately and showed that cord blood DHA concentrations were only negatively associated with shorter latencies in the control group. Although this may have indicated that the cord blood DHA concentrations of infants from the treatment group were saturated, the absence of a correlation might also have indicated a chance finding or a noncausal association, and confirmatory evidence from other studies is needed.

A limitation of this study was that the study sample involved a subgroup of infants from the larger DOMInO trial who were enrolled during a defined period of time at one DOMInO site where VEP-testing facilities were housed. In addition, more treated mothers correctly guessed their allocation to the treatment group than did mothers in the control group. However, selection and response biases were likely to be small because of the process of enrollment into the acuity study, and all outcome assessments and data analyses were conducted blinded to subject groups. Furthermore, characteristics of the participants in the current study were comparable with the wider cohort, which suggested that the integrity of the broader trial was retained (17). Finally, the use of less subjective measures of acuity than measures used in previous research, and because the study was powered to detect differences in acuity in healthy infants, meant that our trial was well positioned to detect an effect of the treatment if it existed.

In conclusion, we have shown that supplementing pregnant women with a high dose of DHA from midpregnancy to delivery did not influence the development of VEP acuity or latency at 4 mo of age in infants who were born at term. Our study was designed to test the effect of DHA supplementation in pregnant women known to have poor dietary intakes of DHA. Together with the results of the DOMInO trial (17), the results of this study indicated that it is not possible to endorse routine DHA supplementation in pregnancy for the improvement of infant visual acuity at 4 mo. We are implementing follow-up studies of the DOMInO children to examine whether other areas of child development are influenced by DHA supplementation in pregnancy.

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Associated honoraria for MM and RAG were paid to their institutions to support conference travel and continuing education for postgraduate students and early career researchers. LGS had no conflicts of interest to declare.

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