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Effect of DHA Supplementation During Pregnancy on Maternal Depression and Neurodevelopment of Young Children

A Randomized Controlled Trial

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EPIDEMIOLOGICAL INVESTIGAtions from the United States and Europe demonstrate that higher intakes of n-3 long-chain polyunsaturated fatty acids (LCPUFA) from fish and seafood during pregnancy are associated with a reduced risk of depressive symptoms in the postnatal period,[1] as well as improved developmental outcomes in the offspring.[2,3] Of the n-3 LCPUFA, it is hypothesized that docosahexaenoic acid (DHA) may be responsible for the observed associations based on estimates of dietary requirements during pregnancy and the results of experimental animal studies.[4] However, n-3 LCPUFA intervention trials in human pregnancy have reported mixed results and have not been conclusive largely because of methodological limitations. Studies focused on perinatal mood have had open-label designs, small sample sizes, or large attrition, and most did not analyze by intention-to-treat.[5] Similarly, trials focused on the developmental outcomes of the children have made post-

See also p 1717 and Patient Page.

Context Uncertainty about the benefits of dietary docosahexaenoic acid (DHA) for pregnant women and their children exists, despite international recommendations that pregnant women increase their DHA intakes.

Objective To determine whether increasing DHA during the last half of pregnancy will result in fewer women with high levels of depressive symptoms and enhance the neurodevelopmental outcome of their children.

Design, Setting, and Participants A double-blind, multicenter, randomized controlled trial (DHA to Optimize Mother Infant Outcome [DOMInO] trial) in 5 Australian maternity hospitals of 2399 women who were less than 21 weeks' gestation with singleton pregnancies and who were recruited between October 31, 2005, and January 11, 2008. Follow-up of children (n=726) was completed December 16, 2009.

Intervention Docosahexaenoic acid–rich fish oil capsules (providing 800 mg/d of DHA) or matched vegetable oil capsules without DHA from study entry to birth.

Main Outcome Measures High levels of depressive symptoms in mothers as indicated by a score of more than 12 on the Edinburgh Postnatal Depression Scale at 6 weeks or 6 months postpartum. Cognitive and language development in children as assessed by the Bayley Scales of Infant and Toddler Development, Third Edition, at 18 months.

Results Of 2399 women enrolled, 96.7% completed the trial. The percentage of women with high levels of depressive symptoms during the first 6 months postpartum did not differ between the DHA and control groups (9.67% vs 11.19%; adjusted relative risk, 0.85; 95% confidence interval [CI], 0.70-1.02; $P=.09$). Mean cognitive composite scores (adjusted mean difference, 0.01; 95% CI, −1.36 to 1.37; $P=.99$) and mean language composite scores (adjusted mean difference, −1.42; 95% CI, −3.07 to 0.22; $P=.09$) of children in the DHA group did not differ from children in the control group.

Conclusion The use of DHA-rich fish oil capsules compared with vegetable oil capsules during pregnancy did not result in lower levels of postpartum depression in mothers or improved cognitive and language development in their offspring during early childhood.

Trial Registration anzctr.org.au Identifier: ACTRN12605000569606

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randomization exclusions,[6,7] had high attrition rates, and lacked power.[6-9] Despite the paucity of evidence, recommendations exist to increase intake of DHA in pregnancy,[4,10] and the nutritional supplement industry successfully markets prenatal supplements with DHA to optimize brain function of mother and infant. Before DHA supplementation in pregnancy becomes widespread, it is important to know not only if there are benefits, but also of any risks for either the mother or child. The DHA to Optimize Mother Infant Outcome (DOMInO) trial was designed primarily to assess whether DHA supplementation during the last half of pregnancy reduced the risk of depressed maternal mood during the postpartum period and improved early cognitive development in the offspring.

METHODS
Study Design

We conducted a double-blind, multicenter, randomized controlled trial in 5 Australian perinatal centers. Approval was granted by the local institutional review boards (human research ethics committees) of each center and written informed consent was obtained from each participant. An independent serious adverse event committee reviewed all deaths, admissions to level III care, and major congenital abnormalities.

Women with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments to participate in the trial. Women were excluded if they were already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home. Recruitment for the trial began October 31, 2005, and ended January 11, 2008.

Randomization and Trial Entry

Women were randomly assigned a unique study number and treatment group allocation through a computer-driven telephone randomization service according to an independently generated randomization schedule, with balanced variable-sized blocks. Stratification was by center and parity (first birth vs subsequent birth). Baseline characteristics, including maternal age, medical diagnosis of previous or current depression, current treatment for depression, social support using the Maternal Social Support Index,[11] weight, highest level of education, occupation, and smoking status, were recorded.

Dietary Treatments

Women allocated to the DHA group were asked to consume three 500-mg/d capsules of DHA-rich fish oil concentrate, providing 800 mg/d of DHA and 100 mg/d of eicosapentaenoic acid (EPA, 20:5n-3; Incromega 500 TG, Croda Chemicals, East Yorkshire, England); and women in the control group were asked to take three 500-mg/d vegetable oil capsules without DHA. The dose of 800 mg/d was chosen because this was above the estimated threshold associated with lower risk of depressed maternal mood and higher scores on developmental outcomes of children,[1] as well as being consistent with the estimated requirement to cover 97% of the population.[12] The vegetable oil capsules contained a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions. This blend of oils was designed to match the polyunsaturated, monounsaturated, and saturated fatty acid profile of the average Australian diet.[13] Women were asked to take their assigned capsules daily, from study entry until birth of their child. All capsules were similar in size, shape, and color and donated by Efamol, Surrey, England.

Treatment Phase Monitoring

During the intervention period, trial assistants telephoned women 2 weeks after enrollment (approximately 22 weeks' gestation) and at 28 and 36 weeks' gestation to document adverse gastrointestinal or bleeding events and to monitor and encourage adherence. The concentration of DHA in cord blood was measured using capillary gas chromatography[14] to provide an independent biomarker of adherence. Antenatal hospitalizations, antenatal hemorrhage, pregnancy and birth outcomes, and postpartum hemorrhage were recorded from a review of medical records.

Outcome Assessments

Women completed a self-administered Edinburgh Postnatal Depression Scale (EPDS) at 6 weeks and 6 months postpartum, and the primary maternal outcome was a high level of depressive symptoms documented as a score of more than 12 on the EPDS at 6 weeks or 6 months postpartum. Although a high EPDS score cannot in itself confirm a diagnosis of depression, a score of more than 12 is widely used to indicate a probable depressive disorder. Validation studies indicate high sensitivity (68%-95%) and high specificity (78%-96%) of the EPDS against a clinical psychiatric diagnosis of depression.[15-17] Women with a score of more than 12 on the EPDS were referred to their general practitioners for more formal medical assessment. Secondary analyses compared the percentage of women medically diagnosed with depression or receiving treatment for depression, as reported by women during pregnancy and at 6 weeks and 6 months postpartum, between the 2 groups.

The primary childhood outcome of neurodevelopment at 18 months was assessed by 1 of 4 study psychologists using the Cognitive and Language Composite Scales of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). The cognitive scale evaluates abilities, such as sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and simple problem solving, and the language scale

is a composite of receptive communication (verbal comprehension, vocabulary) and expressive communication (babbling, gesturing, and utterances). The motor scale, which evaluates both gross and fine motor functioning, as well as the parental report scales of social-emotional behavior and adaptive behavior were assessed as secondary outcome measures. The raw scores for each of the scales are standardized to a mean of 100 with an SD of 15 (range, 50-150). The standardized scores were also classified into the categories of accelerated performance (>115), within normal limits (85-115), and delayed performance (<85).

All 96 preterm children and 630 randomly selected term children from Adelaide, Australia, were chosen for BSID-III assessment (N=726). The families and trial staff did not know which children had been randomly selected for follow-up until the infants were 12 months old. At this time, trial assistants in each center were supplied with birthday cards for all children, and those selected for follow-up were informed and invited for a BSID-III appointment. The last BSID-III assessment was completed on December 16, 2009.

Sample Size and Statistical Analysis

Epidemiological data suggest a 7% to 8% absolute reduction (from approximately 16% to 9%) in the prevalence of high levels of depressive symptoms when n-3 LCPUFA intake is increased from the typically low-level intakes commonly observed in Westernized diets to more than 1 g/d.[1] Although these data were derived from a well-controlled cohort study, we expected that any effect size of a DHA-rich intervention would be smaller because of possible residual confounding. We therefore powered our trial to detect an absolute reduction of 4.2% (from 16.9% to 12.7%) in depressive symptoms with 80% power (α = .05), requiring a sample size of 1121 women per group. The control rate of depressive symptoms was estimated from Australian population data,[18] which was also consis-

tent with the epidemiological data from England.[1] We planned to enroll 2280 women in total, allowing for 2% loss to follow-up.

A minimum clinically meaningful difference in developmental scores is considered to be of the order of 4 points.[19] Studies showing differences between nutritional or environment interventions of 4 to 5 points or greater have been catalysts for changes in health policy.[20,21] To detect a difference of 5 points between groups (mean [SD], 100 [15]) with 80% power (α = .05) for boys and girls separately, we required a total sample size of 572 children. We therefore randomly sampled 630 term children such that half were male, allowing for 10% loss to follow-up. The selection process occurred between birth and 1 year. All children born preterm were included in the follow-up to enable modeling of the effect of DHA supplementation in pregnancy on all children; those born preterm being more nutritionally and more developmentally vulnerable than children born at term.[22]

All analyses were performed according to the intention-to-treat principle. Multiple imputation was used to deal with missing data (outcomes and covariates) and create 50 complete data sets for analysis. Sensitivity analyses were performed on the original data and on imputed data using different seeds for imputation and different imputation models. All produced similar results; therefore, we reported the results of the imputed analyses.

Continuous outcomes were analyzed by using linear regression models, following log transformations where appropriate, with treatment effects expressed as mean differences. Binary outcomes were analyzed using log binomial regression models, with treatment effects expressed as relative risks (RRs) or Fisher exact test for rare outcomes. Time-to-event outcomes were analyzed by using stratified log-rank tests. For outcomes measured at multiple time points, dependence was accounted for using generalized estimating equations. Models initially in-

cluded a treatment × time interaction. Separate estimates of treatment effect are presented at each time point if the interaction was significant or if separate estimates were prespecified. Where the interaction was not significant, this was removed from the model and an overall estimate of treatment effect is presented. Analysis of the primary maternal depression outcome was performed on all women and on the subgroup with a previous or current diagnosis of depression at trial entry. Outcomes derived from the BSID-III assessment took into account both the sampling design and probability weights, calculated as the inverse of the probability of selection. A priori secondary analyses were performed to test for effect modification by sex and results are presented both overall and by sex, because previous studies suggest that boys and girls may respond differently to DHA supplementation.

Both unadjusted and adjusted analyses were performed, with adjustment for the stratification variables, center, and parity, as well as any prespecified potential confounders. Statistical significance was assessed at the 2-sided $P < .05$ level. No adjustment was made for multiple comparisons and results for secondary outcomes should be interpreted with caution unless they are highly significant. Analyses were performed by using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) and Stata Release 11 (Statacorp LP, College Station, Texas).
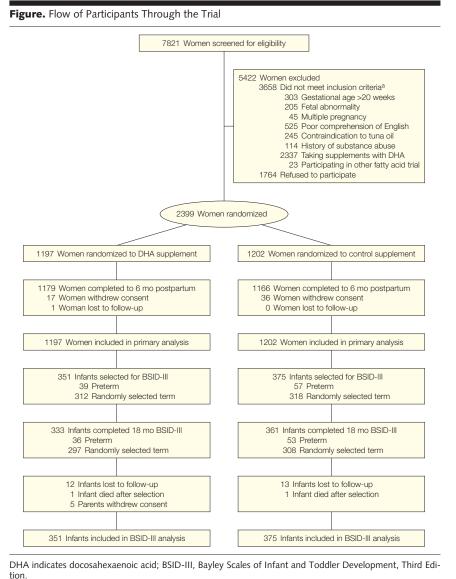
RESULTS

The number of women screened and assessed for the trial, randomly assigned to receive either DHA or control supplementation, are shown in the FIGURE. A total of 2399 women were enrolled and adequate data for the analysis of the primary outcome were available for 2320 women (97.3% in the DHA group and 96.1% in the control group). In addition, 694 children (95.6% of those selected for follow-up) were assessed at 18 months. Other outcomes and covariates were generally available

for more than 95% of participants. The demographic and clinical characteristics of the women at randomization were comparable between the 2 groups, both overall (**TABLE 1**) and for the subset assessed at 18 months (eTable 1). The families of children selected for follow-up also had similar baseline characteristics to those of all other children in the trial (eTable 2). Docosahexaenoic acid concentration in the plasma phospholipids of cord blood from women in the high-DHA group was greater than control (median, 7.22% vs 6.09% total phospholipid fatty

acids, $P < .001$ based on a comparison of mean log-transformed values). At 28 weeks' gestation, 35.6% of mothers reported that they had not missed taking any capsules and an additional 34.5% reported that they had missed 3 or less per week (from a total of 21 capsules per week). Fewer than 2% of mothers in each group chose not to take any capsules.

Efficacy

The percentage of women reporting high levels of depressive symptoms (EPDS score >12) during the first 6

months postpartum did not differ between the DHA and control groups (9.67% vs 11.19%; adjusted RR, 0.85; 95% CI, 0.70-1.02; $P = .09$) (**TABLE 2**). Depressive symptoms were more common among women with a previous or current diagnosis of depression at trial entry but did not differ between groups. The percentage of women with a new medical diagnosis for depression during the trial or a diagnosis requiring treatment also did not differ between groups.

Mean cognitive scores of children from women allocated to the DHA group did not differ from mean scores of children of women from the control group, although fewer children from the DHA group had cognitive scores indicating delayed cognitive development compared with controls (**TABLE 3**). Overall, mean language scores also did not differ between groups; however, a significant treatment × sex interaction indicated a differential response of boys and girls. Girls from the DHA group had a lower mean language score than girls from the control group, as well as an increased risk of delayed language development, and the response of boys did not differ between groups. For the secondary developmental outcomes, motor development, social-emotional behavior, and adaptive behavior did not differ between groups overall, although girls exposed to DHA in utero had poorer mean adaptive behavior scores than girls from the control group.

The secondary clinical outcomes of the infants are shown in **TABLE 4**. There were fewer very preterm births (<34 weeks' gestation) in the DHA group compared with the control group (1.09% vs 2.25%; adjusted RR, 0.49; 95% CI, 0.25-0.94; $P = .03$), but there were more postterm births requiring obstetric intervention (inductions or cesarean deliveries) in the DHA group compared with the control group (17.59% vs 13.72%; adjusted RR, 1.28; 95% CI, 1.06-1.54; $P = .01$). Mean birth weight was 68 g (95% CI, 23-114 g; $P = .003$) heavier and fewer infants were of low birth weight (3.41% vs 5.27%;

Figure. Flow of Participants Through the Trial

DHA indicates docosahexaenoic acid; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition.
[a]Women could be ineligible for more than 1 reason.

adjusted RR, 0.65; 95% CI, 0.44-0.96; $P = .03$) in the DHA group compared with the control group. However, mean birth weight z scores (corrected for gestational age and sex) did not differ between groups, indicating that group differences in birth size were largely a function of gestational age at birth.

Safety

The frequency of hemorrhage and antenatal hospitalizations did not differ between groups. Similarly, there were no differences between the groups in maternal report of nose bleeds, vaginal blood loss, constipation, nausea, or vomiting at 28 and 36 weeks' gestation. More women in the DHA group reported eructations compared with the control group (43.6% vs 25.6%; adjusted RR, 1.68; 95% CI, 1.50-1.89; $P < .001$ at 28 weeks' gestation and 41.5% vs 29.2%; adjusted RR, 1.41; 95% CI, 1.26-1.58; $P < .001$ at 36 weeks' gestation); however, fewer women from the DHA group reported diarrhea (13.4% vs 16.1%; adjusted RR, 0.83; 95% CI, 0.71-0.96; $P = .01$). There were no maternal deaths and 2 women from each group required level III (intensive care) hospital treatment (**TABLE 5**).

Thirty-six infants (3.01%) from the DHA group compared with 54 infants (4.49%) in the control group experienced at least 1 serious adverse event (RR, 0.67; 95% CI, 0.44-1.01; $P = .06$), defined as admission to level III (intensive care) hospital treatment, major congenital abnormality, or death (Table 5). There were significantly fewer infants with any admissions to neonatal intensive care in the DHA group compared with the control group (1.75% vs 3.08%; RR, 0.57; 95% CI, 0.34-0.97; $P = .04$), probably driven by

Table 1. Baseline Demographic and Clinical Characteristics[a]

Characteristics	DHA Supplement (n = 1197)	Control Supplement (n = 1202)
Recruitment hospital		
Campbelltown Hospital	123 (10.3)	123 (10.2)
Flinders Medical Center and private hospitals	312 (26.1)	313 (26.0)
Royal Brisbane and Women's Hospital	67 (5.6)	67 (5.6)
Sunshine Hospital	178 (14.9)	181 (15.1)
Women's and Children's Hospital	517 (43.2)	518 (43.1)
Mother's age at trial entry, mean (SD), y	28.9 (5.7)	28.9 (5.6)
Gestational age at trial entry, median (IQR), wk	19.0 (19.0-20.0)	19.0 (19.0-20.0)
Primiparous	471 (39.3)	474 (39.4)
Mother completed secondary education	755 (63.1)	760 (63.2)
Mother completed further education	816 (68.2)	824 (68.6)
MSSI score, median (IQR)	28.5 (25.0-31.0)	29.0 (25.0-31.0)
Mother smoked at trial entry or leading up to pregnancy	358 (29.9)	407 (33.9)
Mother has previous or current medical diagnosis of depression	298 (24.9)	287 (23.9)
Mother undergoing current treatment for depression	61 (5.1)	65 (5.4)
Infant male sex	605 (50.5)	591 (49.2)

Abbreviations: DHA, docosahexaenoic acid; IQR, interquartile range; MSSI, Maternal Social Support Index.
[a] Data are expressed as No. (%), unless otherwise indicated.

Table 2. Outcomes From the Edinburgh Postnatal Depression Scale (EPDS)[a]

Outcomes	DHA Supplement (n = 1197) No.	DHA Supplement (n = 1197) % (95% CI)	Control Supplement (n = 1202) No.	Control Supplement (n = 1202) % (95% CI)	Unadjusted RR (95% CI)	Unadjusted P Value	Adjusted[b] RR (95% CI)	Adjusted[b] P Value
EPDS score >12 for all women	116	9.67 (8.36-11.19)	134	11.19 (9.80-12.78)	0.86 (0.71-1.05)	.15	0.85 (0.70-1.02)	.09
At 6 wk postpartum	115	9.61 (8.04-11.49)	131	10.88 (9.19-12.87)	0.88 (0.69-1.13)	.33	0.87 (0.68-1.10)	.24
At 6 mo postpartum	117	9.74 (8.17-11.60)	138	11.50 (9.78-13.51)	0.85 (0.67-1.08)	.17	0.83 (0.66-1.05)	.11
EPDS score >12 for women with previous or current depression at trial entry[c]	63	20.94 (17.37-25.24)	69	24.15 (20.36-28.66)	0.87 (0.67-1.12)	.27	0.87 (0.68-1.12)	.28
At 6 wk postpartum	63	21.16 (16.91-26.48)	64	22.11 (17.70-27.62)	0.96 (0.70-1.31)	.79	0.96 (0.71-1.30)	.79
At 6 mo postpartum	62	20.83 (16.65-26.07)	75	26.15 (21.42-31.92)	0.80 (0.59-1.08)	.14	0.81 (0.60-1.08)	.15
New medical diagnosis of depression during the study period	47	3.39 (2.76-4.15)	61	4.12 (3.39-5.01)	0.82 (0.64-1.06)	.13	0.80 (0.62-1.02)	.07
New or existing diagnosis of depression requiring treatment during the study period	59	4.62 (3.81-5.62)	64	4.74 (3.89-5.77)	0.98 (0.75-1.26)	.85	0.93 (0.73-1.18)	.55

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; RR, relative risk.
[a] All data are based on analysis of 50 imputed datasets. For DHA and control groups, data are number at a particular time point or averaged across time points and % (95% CI) estimated by unadjusted model. P values for treatment × time interactions were .77 (unadjusted and adjusted) for EPDS score of more than 12 for all women; .30 (unadjusted) and .32 (adjusted) for EPDS score of more than 12 for women with previous or current depression at trial entry; .08 (unadjusted and adjusted) for new medical diagnosis of depression during the study period; and .48 (unadjusted and adjusted) for new or existing diagnosis of depression requiring treatment during the study period.
[b] Adjusted for center, parity, Maternal Social Support Index score, age, history of depression, and smoking status.
[c] Number of mothers included in this subset were 298 for DHA group and 287 for control group.

the fewer very preterm births in the DHA group. There were 4 fetal/infant deaths (0.33%) in the DHA group compared with 12 deaths (1%) in the control group at 18 months (RR, 0.33; 95% CI, 0.11-1.03; $P=.06$). All deaths occurred during the perinatal period, except for 1 infant from the DHA group who died of a malignant rhabdoid tumor of the brainstem at 15 months.

COMMENT

Recommendations to increase DHA intake during pregnancy are being implemented in the absence of well-designed, large-scale randomized controlled trials. The DOMInO trial was designed to assess the benefits and harms of DHA supplementation during pregnancy. We intervened with DHA-rich fish oil, which provided a DHA dose that was high enough to cover all the recommendations for DHA intake in pregnancy,[4] and included women with comparable demo-

Table 3. Outcomes From the Bayley Scales of Infant and Toddler Development, Third Edition[a]

	DHA Supplement (n = 351)	Control Supplement (n = 375)	Unadjusted		Adjusted[b]	
	Weighted Mean (SD)	Weighted Mean (SD)	Effect (95% CI)	P Value	Effect (95% CI)	P Value
Cognitive Standardized Score	101.81 (11.05)	101.75 (12.56)	0.05 (−1.32 to 1.43)	.94	0.01 (−1.36 to 1.37)	.99
Female	103.00 (10.24)	103.78 (11.31)	−0.78 (−2.56 to 1.00)	.39	−0.83 (−2.62 to 0.96)	.36
Male	100.62 (11.69)	99.81 (13.38)	0.81 (−1.26 to 2.88)	.44	0.83 (−1.22 to 2.88)	.43
Language Standardized Score	96.47 (13.63)	97.94 (15.33)	−1.47 (−3.16 to 0.23)	.09	−1.42 (−3.07 to 0.22)	.09
Female	98.73 (13.66)	103.24 (12.99)	−4.51 (−6.72 to −2.30)	<.001	−4.43 (−6.65 to −2.20)	<.001
Male	94.23 (13.23)	92.86 (15.70)	1.37 (−1.04 to 3.78)	.26	1.55 (−0.84 to 3.93)	.20
Motor Standardized Score	102.63 (10.17)	102.57 (11.50)	0.06 (−1.19 to 1.30)	.93	0.08 (−1.15 to 1.31)	.90
Female	104.29 (9.34)	104.94 (10.54)	−0.65 (−2.25 to 0.96)	.43	−0.69 (−2.31 to 0.93)	.40
Male	100.97 (10.68)	100.30 (11.93)	0.67 (−1.18 to 2.53)	.48	0.85 (−1.00 to 2.70)	.37
Social-Emotional Standardized Score	106.32 (17.49)	107.27 (17.66)	−0.95 (−2.99 to 1.08)	.36	−0.97 (−3.00 to 1.06)	.35
Female	108.44 (17.05)	110.77 (17.18)	−2.32 (−5.10 to 0.45)	.10	−2.07 (−4.82 to 0.69)	.14
Male	104.21 (17.69)	103.92 (17.47)	0.29 (−2.65 to 3.23)	.85	0.11 (−2.85 to 3.08)	.94
Adaptive Behavior Standardized Score	99.17 (13.95)	100.75 (14.45)	−1.58 (−3.28 to 0.11)	.07	−1.53 (−3.18 to 0.13)	.07
Female	101.27 (14.37)	104.88 (13.59)	−3.60 (−5.98 to −1.22)	.003	−3.55 (−5.89 to −1.20)	.003
Male	97.08 (13.20)	96.81 (14.15)	0.27 (−2.01 to 2.56)	.81	0.47 (−1.83 to 2.77)	.69

	No.[c]	Weighted % (95% CI)	No.[c]	Weighted % (95% CI)	Effect (95% CI)	P Value	Effect (95% CI)	P Value
Cognitive Standardized Score <85	11	2.71 (1.59 to 4.62)	24	6.64 (4.82 to 9.13)	0.41 (0.22 to 0.76)	.004	0.41 (0.22 to 0.78)	.007
Female	3	1.94 (0.82 to 4.59)	6	3.53 (1.90 to 6.57)	0.55 (0.19 to 1.58)	.26	0.52 (0.18 to 1.54)	.24
Male	7	3.45 (1.78 to 6.69)	17	9.60 (6.63 to 13.88)	0.36 (0.17 to 0.76)	.008	0.37 (0.17 to 0.79)	.01
Cognitive Standardized Score >115	22	5.97 (4.27 to 8.36)	28	7.35 (5.49 to 9.82)	0.81 (0.52 to 1.26)	.36	0.80 (0.52 to 1.25)	.33
Female	14	6.84 (4.42 to 10.59)	14	7.07 (4.67 to 10.72)	0.97 (0.53 to 1.77)	.91	0.92 (0.51 to 1.67)	.79
Male	8	5.09 (3.00 to 8.64)	14	7.60 (5.07 to 11.38)	0.67 (0.35 to 1.30)	.24	0.69 (0.36 to 1.34)	.27
Language Standardized Score <85	62	17.99 (15.00 to 21.57)	65	17.40 (14.60 to 20.73)	1.03 (0.80 to 1.34)	.80	0.97 (0.75 to 1.26)	.82
Female	20	12.76 (9.21 to 17.68)	14	7.00 (4.60 to 10.63)	1.82 (1.07 to 3.11)	.03	1.81 (1.06 to 3.08)	.03
Male	41	23.17 (18.60 to 28.86)	52	27.35 (22.65 to 33.04)	0.85 (0.63 to 1.14)	.27	0.80 (0.59 to 1.08)	.14
Language Standardized Score >115	30	8.79 (6.66 to 11.61)	39	10.47 (8.28 to 13.22)	0.84 (0.58 to 1.21)	.35	0.83 (0.58 to 1.19)	.30
Female	19	10.78 (7.64 to 15.21)	27	15.08 (11.47 to 19.83)	0.71 (0.46 to 1.11)	.13	0.72 (0.46 to 1.11)	.14
Male	11	6.80 (4.25 to 10.88)	12	6.03 (3.91 to 9.32)	1.13 (0.60 to 2.13)	.71	1.11 (0.59 to 2.10)	.74

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid.
[a] Data are expressed as weighted mean (weighted SD) with effect being difference in means or unweighted number and weighted % (95% CI) with effect being relative risk. All values are based on analysis of 50 imputed datasets. For treatment × sex interactions, $P=.26$ (unadjusted) and $P=.23$ (adjusted) for cognitive score; $P<.001$ (unadjusted and adjusted) for language score; $P=.29$ (unadjusted) and $P=.22$ (adjusted) for motor score; $P=.21$ (unadjusted) and $P=.29$ (adjusted) for social-emotional score; $P=.02$ (unadjusted and adjusted) for adaptive behavior; $P=.52$ (unadjusted) and $P=.59$ (adjusted) for cognitive score of less than 85; $P=.42$ (unadjusted) and $P=.53$ (adjusted) for cognitive score of more than 115; $P=.01$ (unadjusted) and $P=.009$ (adjusted) for language score of less than 85; $P=.25$ (unadjusted) and $P=.26$ (adjusted) for language score of more than 115.
[b] Adjusted for center, parity, sex, mother's secondary education, mother's further education, and smoking status.
[c] Unweighted.

Table 4. Secondary Clinical Outcomes[a]

Outcomes	DHA Supplement (n = 1197)	Control Supplement (n = 1202)	Unadjusted		Adjusted[b]	
			Effect (95% CI)	P Value	Effect (95% CI)	P Value
Duration of gestation, median (IQR), d	282 (275-288)	281 (275-287)	NA	.05[c]	NA	.05[c]
Birth <37 wk gestation	67 (5.60)	88 (7.34)	0.76 (0.56 to 1.04)	.09	0.77 (0.56 to 1.05)	.09
Birth <34 wk gestation	13 (1.09)	27 (2.25)	0.49 (0.25 to 0.94)	.03	0.49 (0.25 to 0.94)	.03
Postterm induction or postterm prelabor cesarean delivery	211 (17.59)	165 (13.72)	1.28 (1.06 to 1.55)	.01	1.28 (1.06 to 1.54)	.01
Birth by cesarean delivery	326 (27.25)	350 (29.14)	0.94 (0.82 to 1.06)	.31	0.94 (0.83 to 1.07)	.34
Log blood loss at birth, mean (SD)	5.64 (0.59)	5.65 (0.60)	−0.01 (−0.06 to 0.04)	.79	−0.01 (−0.05 to 0.04)	.79
Postpartum hemorrhage	57 (4.72)	64 (5.28)	0.89 (0.62 to 1.28)	.54	0.90 (0.63 to 1.28)	.55
Birth weight, mean (SD), g	3475 (564)	3407 (576)	69 (23 to 115)	.003	68 (23 to 114)	.003
Birth weight z score, mean (SD)	0.28 (1.06)	0.22 (1.02)	0.06 (−0.02 to 0.15)	.16	0.06 (−0.02 to 0.14)	.16
Birth weight <2500 g	41 (3.41)	63 (5.27)	0.65 (0.44 to 0.95)	.03	0.65 (0.44 to 0.96)	.03

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; IQR, interquartile range; NA, not applicable.
[a] Data are expressed as No. (%) with effect being relative risk or mean (SD) with effect being difference in means, unless otherwise indicated. All values are based on analysis of 50 imputed datasets.
[b] Adjusted for center and parity (birth <34 weeks' gestation adjusted for parity only).
[c] Based on a stratified log-rank test.

graphic characteristics to Australian women giving birth in 2006-2007, although our study seemed to include more women who smoked at trial entry.[23,24] We observed nonsignificant relative reductions in the percentage of women with high levels of depressive symptoms overall and in the subgroup of women with previous medically diagnosed depression. Further work is required to establish the effectiveness of DHA intervention for women with a history of depression because of the higher prevalence of depressive symptoms and the potentially larger absolute effect size, especially at 6 months.

A limitation of the depression aspect of our study is that we did not verify high EPDS scores with a clinical diagnosis of depression as part of the trial protocol. It is possible that the lower than expected rate of women with high levels of depressive symptoms in the control group is explained by the Hawthorn effect, in which simply participating in a trial with increased contact with researchers helped to prevent depressive symptoms.[25] A study comparing regular dietary advice and blood glucose monitoring with no intervention in gestational diabetes also reported a reduction in women with high levels of depressive symptoms from 17% to 8%.[26] Nevertheless, the important issue is whether the lower than

Table 5. Serious Adverse Events at 18 Months Postpartum

Serious Adverse Events	No. (%)		Unadjusted	
	DHA Supplement (n = 1197)	Control Supplement (n = 1202)	RR (95% CI)	P Value
Any maternal	2 (0.17)	2 (0.17)	NA	>.99[a]
Any level III antenatal hospitalization	2 (0.17)	2 (0.17)	NA	>.99[a]
Death	0	0	NA	NA
Any infant	36 (3.01)	54 (4.49)	0.67 (0.44-1.01)	.06
Any admission to neonatal intensive care	21 (1.75)	37 (3.08)	0.57 (0.34-0.97)	.04
Major congenital abnormality	15 (1.25)	11 (0.92)	1.37 (0.63-2.97)	.43
Death	4 (0.33)	12 (1.00)	0.33 (0.11-1.03)	.06

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; NA, not applicable; RR, relative risk.
[a] Based on Fisher exact test.

expected rate of depressive symptoms in the control group had a major affect on the power of the study. Based on the observed control rate of 11%, a post hoc power estimate indicates that we had sufficient power to detect a clinically meaningful 4% reduction in depressive symptoms between DHA treatment and control if it existed.

We also found no effect of DHA treatment during pregnancy on early childhood cognitive and language scores, although in secondary analyses 2 contrasting effects were noted. Fewer children in the DHA-treated group had delayed cognitive development compared with the control group, and girls exposed to higher-dose DHA in utero

had lower language scores and were more likely to have delayed language development than girls from the control group. There was also a group × sex interaction in our DINO (DHA for the Improvement of Neurodevelopmental Outcome of Preterm Infants) trial[19] in which preterm infants were treated with higher-dose DHA during the equivalent period ex-utero, but the response of the girls was directly opposite. This inconsistency may be due to chance or may highlight the sensitivity of girls to DHA intervention. The change in the version of the BSID scales should be noted. Most previous studies, including the DINO trial,[19] have used BSID-II (Second Edition), in which

the Mental Development Index combines elements that are in the Cognitive and Language Composite Scores of the BSID-III. Cognitive outcome at later ages will be important to determine whether any positive or negative effects of DHA supplementation remain, especially in the domain of language development.

Previous studies of marine oil interventions designed to prevent preterm birth used doses of n-3 LCPUFA that favored EPA over DHA and were 3 times higher than the DOMInO dose. The focus on EPA over DHA was targeted to alter prostaglandin balance and delay the initiation of labor. Consistent with the relevant systematic review, we demonstrated that supplementation with predominantly DHA in pregnancy caused a small to modest increase in the duration of gestation, although a precise estimate of effect size has been difficult to determine because of obstetric interventions to deliver infants to minimize the risks associated with postterm birth.[27,28] Not surprisingly, the effect of DHA treatment on gestation length was most notable at the extremes. In the DHA group, significantly fewer infants were born less than 34 weeks' gestation but significantly more women were induced or had cesarean sections because they were postterm. The clinical significance of these findings is difficult to balance, although the reduction in preterm birth at less than 34 weeks' gestation was also associated with fewer low birth weight infants and fewer admissions to neonatal intensive care in the DHA group.

Our trial could be criticized because we did not assess dietary intake of n-3 LCPUFA and because of the choice of supplement. Women in Australia are known to have low dietary intakes of n-3 LCPUFA[13]; this was evidenced by the fact the median plasma phospholipid DHA concentration in cord blood of the DOMInO control group was virtually identical to the concentration observed in a cohort of Dutch pregnant women with biochemical DHA insufficiency.[29] It is therefore unlikely that women significantly increased their intake of fish and seafood or DHA supplemented foods because of participation in the DOMInO trial. The ratio of DHA to EPA in perinatal supplements has been controversial. Although there is general agreement that supplements containing more DHA than EPA are preferred for childhood developmental outcomes, authors are divided with regard to depression outcomes and some strongly argue in favor of EPA. However, there is little direct evidence of biological plausibility. Eicosapentaenoic acid does not accumulate in the brain and most animal studies investigating n-3 fatty acid deficient diets implicate DHA in the function of dopaminergic and serotonergic pathways.[30] Furthermore, earlier trials suggesting EPA was more effective than DHA in reducing depression were plagued by methodological limitations and do not provide results with a high level of confidence.[5] With this reasoning, the supplement used in the DOMInO trial contained 800 mg/d of DHA and 100 mg/d of EPA.

Current recommendations suggest that pregnant women increase their dietary DHA to improve their health outcomes as well as those of their children.[4,10] Such recommendations are increasingly being adopted with women taking prenatal supplements with DHA. In fact, 64% of ineligible women screened for the DOMInO trial were excluded because they were already taking a prenatal supplement that contained DHA. However, the results of the DOMInO trial do not support routine DHA supplementation for pregnant women to reduce depressive symptoms or to improve cognitive or language outcomes in early childhood. Our results are at odds with the results of some large-scale epidemiological studies.[1-3] It may be that even well-conducted epidemiological studies overestimate effect size and do not adequately deal with residual confounding, or that other nutrients in fish and seafood, beyond DHA, contribute to the observations from epidemiological studies. Further studies are required to determine whether there are specific benefits of DHA supplementation for women with a previous history of depression and for women at risk of preterm birth.

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