HHS Public Access

Author manuscript

Prostaglandins Leukot Essent Fatty Acids. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Prostaglandins Leukot Essent Fatty Acids. 2016 September ; 112: 44–49. doi:10.1016/j.plefa.2016.08.007.

Predicting the effect of maternal docosahexaenoic acid (DHA) supplementation to reduce early preterm birth in Australia and the United States using results of within country randomized controlled trials

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SUMMARY

The DHA to Optimize Mother Infant Outcome (DOMInO) and Kansas DHA Outcomes Study (KUDOS) were randomized controlled trials that supplemented mothers with 800 and 600 mg DHA/day, respectively, or a placebo during pregnancy. DOMInO was conducted in Australia and KUDOS in the United States. Both trials found an unanticipated and statistically significant reduction in early preterm birth (ePTB; i.e., birth before 34 weeks gestation). However, in each trial, the number of ePTBs were small. We used a novel Bayesian approach and an arbitrary sample of 120,000 pregnancies to estimate statistically derived low, moderate or high risk for ePTB, and to test for differences between the DHA and placebo groups. In both trials, the model predicted DHA would significantly reduce the expected proportion of deliveries in the high risk group under the trial conditions of the parent studies. From these proportions we estimated the number of ePTB that could be prevented.

Keywords

docosahexaenoic acid; pregnancy; early preterm birth; randomized controlled trials

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[2]The KUDOS trial was supported by a grant from the National Institutes of Health (HD047315 and the Office of Dietary Supplements; the DOMInO trial was supported by the Australian National Health and Medical Research Council (349301). DSM, Columbia, Maryland, USA donated the investigational capsules for the KUDOS trial; Efamol, UK donated the investigational capsules for the DOMInO trial.

The other authors declare no conflicts of interest. All authors read and approved the final manuscript.

Clinical trial registries: KUDOS: ClinicalTrials.gov identifier: NCT00266825; DOMInO: anzctr.org.au Identifier: ACTRN12605000569606.

INTRODUCTION

N-3 long chain polyunsaturated fatty acid (LCPUFA) status in pregnancy was first linked to longer gestation, higher birth weight and less preterm birth (PTB) in early studies by Olsen and collaborators. They observed longer gestation among Faroe Islanders, who consume a diet higher in fish and therefore higher in two n-3 LCPUFA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), compared to Danes [1, 2]. It is now generally understood that n-3 LCPUFA supplementation during pregnancy increases gestation duration; a 2006 Cochrane review included 3 randomized controlled trials (RCT) of n-3 LCPUFA supplementation with 1621 women, revealing a significant 2.6 day increase in gestation duration favoring n-3 LCPUFA supplementation [3]. Two RCT of DHA supplementation reported since 2006 found a significant increase in gestation of 1 and 2.9 days, respectively [4, 5].

Although DHA supplementation would likely result in fewer PTBs, the overall increase in gestation of several days may have limited clinical significance. Clinical significance would be enhanced, however, if the relatively small overall increase in gestation was due to a decrease in deliveries at higher risk for PTB. In fact, our RCTs conducted in women with normal risk of PTB found a significant reduction in early PTB (ePTB), defined as births before 34 weeks.[4, 5]. The DHA to Optimize Mother Infant Outcome (DOMInO) trial, conducted in Australia, provided 800 mg DHA and 100 mg EPA daily and reduced ePTB by 51.6% [4], while a smaller trial, the Kansas DHA Outcomes Study (KUDOS), conducted in the Midwestern portion of the United States provided 600 mg DHA daily and reduced ePTB by 87.5% [5].

In the developed world, ePTB results in longer hospitalizations, increased risk of additional hospitalizations in the first year of life, and greater short and long term cost to society relative to PTBs of 34–37 weeks gestation. Although some drugs have been shown to reduce uterine contractions in an attempt to delay labor, their efficacy in preventing PTB is limited and they have undesirable side effects [6]. At present there is no effective method to prevent spontaneous ePTB. Our recent studies suggest that n-3 LCPUFA, particularly DHA, could be a promising agent for reducing ePTB [4, 5].

Our present investigation has two primary purposes: 1) to conduct an analysis of both DOMInO and KUDOS to determine if the effects of DHA on gestation and birth weight were due to a particular subset of the birth population; and 2) to use the results of DOMInO and KUDOS to model the predicted effect of DHA supplementation on ePTB within Australia and the United States. The model's utility was demonstrated in a previous report [7] in which we used the mean and variance-covariance of 3 normal distributions for birth weight and gestational age determined by Schwartz et al. [8] from more than 250,000 US births and utilized flexible commensurate priors from Hobbs et al. [9]. In that analysis we determined how many low birth weight (<2.5 kg) and preterm births (<37 wks gestation) could be prevented by providing 20,000 pregnant women 600 mg/day of DHA had they been cared for in centers demographically similar to the one where the KUDOS trial was conducted [7].

METHODS

DOMInO Trial

The DOMInO trial was a double-blind RCT conducted in five Australian perinatal centers between 2005 and 2009 (ACTRN12605000569606; anzctr.org.au). The methods and primary results for the trial are published elsewhere [4]. Briefly, English speaking women who had a singleton pregnancy between 18 and 21 weeks gestation and who were not participating in another fatty acid trial were eligible. Women who had a known fetal abnormality or a bleeding disorder in which tuna oil was contraindicated were excluded. Women who were already taking a supplement containing DHA or anticoagulant therapy, or had a documented history of drug or alcohol abuse were also excluded. Participants randomized to the DHA group were asked to consume three DHA-rich fish oil capsules, providing a total of 800mg of DHA and 100mg of EPA, daily from trial entry until delivery. Participants randomized to the placebo group received three vegetable oil capsules without LCPUFA. Demographic characteristics were collected from participants at baseline and birth details, including infant birth weight and gestational age at delivery, were obtained from medical records.

KUDOS Trial

KUDOS was a double-blind RCT conducted in the United States between 2006 and 2009 (NCT00266825; www.clinicaltrials.gov). The trial methodology and pregnancy outcomes have been reported [5]. Women were eligible if they were English-speaking, aged 16–35 years, between 8 and 20 weeks' gestation and planning to deliver at a hospital in the Kansas City metropolitan area. Women carrying more than one fetus or who had diabetes mellitus, systolic blood pressure ≥140 mm Hg, any serious health condition likely to affect the growth and development of their offspring, or a body mass index ≥40 were excluded. Participants assigned to the DHA group received three DHA-rich marine algae-oil capsules containing a total of 600 mg DHA/day from trial entry until delivery. Participants assigned to the placebo group received the same number of capsules containing vegetable oil (half soybean and half corn oil) without DHA. Demographic characteristics were obtained from participants or their medical record at baseline, along with a blood sample for measuring red blood cell phospholipid DHA as a percentage of total fatty acids by weight. Gestational age was determined from the expected date of delivery based on a late first trimester or early second trimester ultrasound and infant birth weight was collected from medical records.

Statistical Methods

Exploratory analyses were conducted to determine the effect of the DHA intervention on infant birth weight and gestational age at delivery. These outcomes were jointly modeled using a mixture of three normal distributions that represented subgroups of women at low, moderate and high risk for PTB. The mixture of these three subgroups was estimated in the DHA and placebo groups separately [7]. This novel Bayesian approach was used to estimate the percentage of pregnancies at statistically derived low, moderate or high risk for PTB, and to test for differences in these outcomes between the DHA and placebo groups. Each analysis was based on a prediction of the number of high risk PTBs that could be avoided among the next 4,000,000 births in the USA and 300,000 births in Australia assuming their

mothers received the same amount and source of DHA as in KUDOS or DOMInO, respectively. These numbers are an approximation of the total annual births in the United States and Australia. Demographic and clinical characteristics were compared descriptively between women who were classified as low, moderate or high risk for PTB using the mixture distribution. All participants who provided birth data were included in the analysis in their randomized groups. The analysis was performed separately on data from the DOMInO and KUDOS trials using SPSS 22.0 (www.ibm.com) and Matlab (www.mathworks.com).

RESULTS

Baseline characteristics were well balanced between women randomized to the DHA and placebo groups, as reported previously [4, 5]. Infant weight and gestational age at birth were available for 2363 (98.5%) of the 2399 women recruited to the DOMInO trial and 299 (85.4%) of the 350 women recruited to the KUDOS trial. Birth weight increased with gestational age in both treatment groups for each trial as expected (Figure 1).

Using the Bayesian model, DHA supplementation altered the gestational age profile at birth in both the DOMInO and KUDOS trials. Specifically, the distribution of women across the statistically derived low, moderate and high risk subgroups for PTB was altered by the DHA intervention, but this was significant only in the high risk subgroup (Table 1, and Figure 2 for DOMInO trial). In the DOMInO trial, 2.15% of women assigned to the DHA group compared with 3.76% of women assigned to the placebo group were high risk (p=0.02), while in the KUDOS trial 2.69% and 7.09% of women were high risk in the DHA and placebo groups, respectively (p=0.02).

The model from DOMInO predicted DHA would reduce ePTB by more than 40%, i.e., from 2.22% in the placebo group to 1.30% in the DHA group (p=0.02). The effect was even larger in the KUDOS trial, where the model estimated DHA supplementation would reduce the risk of ePTB by 64%, from 4.19% in the placebo group to 1.49% in the DHA group (p=0.03). At the other end of the gestational age distribution, the incidence of birth after 41 weeks was very similar between the treatment groups and across both trials, ranging from 6.28% to 6.85%.

Women at high risk of preterm birth had somewhat different characteristics compared with women in the low and moderate risk subgroups (Table 2). In the larger DOMInO trial, the high risk subgroup included more smokers, more women who did not complete secondary education, more women who did not complete further education, more female infants, and more non-Caucasian women. These women had infants with lower mean gestational age and weight at birth, as expected in a subgroup with higher risk of PTB. A similar pattern was seen in the KUDOS trial, where the high risk subgroup also included more smokers and more non-Caucasian women. Interestingly, baseline DHA concentrations in KUDOS were similar in the high risk subgroup compared with the low and moderate risk subgroups (mean concentration 4.2%, 4.3% and 4.5% of total fatty acids, respectively). Fatty acid status of women at enrollment and birth was not available for the larger DOMInO study.

Among the next 300,000 babies born in similar perinatal centers to those involved in the DOMInO trial, we estimated that 2780 ePTB (95% credible interval 128 to 5473) could be avoided by providing DHA supplements to all women. Likewise, 106,030 ePTB (95% credible interval 6400 to 175,700) could be avoided with DHA supplementation for the next 4,000,000 babies born in similar hospitals to those participating in the KUDOS trial.

DISCUSSION

DHA is a nutrient but worldwide intake of this nutrient from food is quite variable. Adult women in the United States consume on average 53 mg DHA per day [10] and the low intakes are reflected in the low DHA status observed in the KUDOS cohort (Table 2). In Australia, the average DHA intake for adult women is 80 mg per day. Intake in both countries is well below that reported in Japanese women who, for example, consume between 500 and 600 mg per day of DHA [11]. We show here that DHA supplementation in pregnancy alters the gestational age profile at birth across two large RCTs conducted in Australia and the United States. Prenatal supplementation may be helpful to reduce ePTB in some countries with low intake although the amount of DHA intake from food and supplements needed to reduce ePTB is not known. Some prenatal nutritional supplements now provide DHA, but they generally provide 200 to 300 mg per day which is much less than the amount provided in both DOMInO and KUDOS.

By using the results of DOMInO and KUDOS as commensurate priors, we were able to test the likely effect of DHA supplementation at the levels used in these trials within their respective countries. Based on this analysis, ePTB could be reduced to 1.3 or 1.5% of births in cohorts demographically similar to DOMInO and KUDOS, respectively. These percentages are remarkably similar and may reflect the lowest rate of spontaneous ePTB that can be achieved in any population. A recent meta-analysis of 4193 pregnancies that included the DOMInO and KUDOS trials and other RCTs that provided DHA or DHA precursors found a 58% reduction in ePTB[12]. A recent Cochrane Review that included over 50 studies and more than 11,000 pregnancies found a reduction of 41% in ePTB [13]. The modeled reductions for DOMInO and KUDOS were 40% and 64%, respectively, reflecting a higher percentage of ePTBs in the placebo group of KUDOS compared to DOMInO. It is obvious that country-wide rates of ePTB will affect the degree of reduction that might be anticipated.

Using a novel Bayesian approach, we found that DHA supplementation reduces the risk of women falling into the high risk subgroup for PTB. Because DHA is a nutrient and improving maternal DHA status may offer other benefits to pregnancy and the offspring, provision of DHA to all pregnant women, especially in countries where DHA intake is known to be low and ePTB rates to be high, may represent a prudent and effective strategy. Another approach would be to ensure supplementation for women identified as having the greatest needs for DHA due to documented low intake or demographic predictors associated with low intake. While some differences were seen in the characteristics of women at high risk of PTB compared to low or moderate risk, identification of this high risk subgroup is not yet definitive. Further studies collecting novel biomarkers could help identify women for whom DHA supplements or other promising interventions could reduce ePTB.

It is important to note that although gestation ages were lengthened in both DOMInO and KUDOS trials, neither observed a statistically significant increase in risk of post-term births (i.e., GA > 41 weeks) with DHA supplementation. Findings in the DOMInO and KUDOS trials were similar despite being conducted in different countries and different populations. These results may simply reflect the intervention of clinicians in pregnancies that go beyond term in both countries; in fact, a significant increase in obstetric intervention was noted in DOMInO with DHA treatment, which is also the largest trial of pregnancy DHA supplementation to date [4]. Pre-labor caesarean section after 40 weeks was increased by 28% (17.59 vs 13.72%, adjusted RR 1.28, 95% CI 1.05 to 1.54, p=0.01). Cost analyses for the infant at birth favored DHA supplementation in both of these trials [14, 15], however, KUDOS did show a small increase in cost for the maternal hospitalization at delivery [15], which may have been related to a decrease in the women who labored on their own (from 60% in the placebo group to 56.4% in the DHA-supplemented group) even though the decrease was not statistically significant [5].

It is important to weigh the risks of obstetric intervention against the possible benefits of DHA to reduce ePTB before the higher doses of DHA supplementation used in these trials can be recommended as a strategy for preventing PTB at the population level. The Omega-3 fats to Reduce the Incidence of Prematurity (ORIP) trial, which aims to recruit 5540 women (ACTRN12613001142729; anzctr.org.au), will cease DHA supplementation at 34 weeks gestation. A multi-site trial conducted in the United States with up to 1200 women (Assessment of DHA on Reducing Early Preterm Birth; ADORE) will continue DHA supplementation until delivery. These phase III RCTs will test efficacy of higher dose DHA (800 and 1000 mg, respectively) to reduce ePTB and monitor pregnancy and infant outcomes for safety. Our working hypothesis is that DHA can reduce inflammation that might lead to early birth in some pregnancies. Both will contribute to the growing body of evidence regarding the effect of DHA supplementation in pregnancy on gestation duration.

In summary, our results indicate that DHA supplementation significantly shifts the left-hand tail of the distribution for birth weight and gestational age deliveries in two large RCT that provided either 600 or 800 mg per day of DHA. There was no evidence of a corresponding shift in the right-hand tail of the distribution; supplementation had no effect on the highest birth weight and gestational age deliveries, but this may have been due to current obstetrical delivery practice. By using results from trials in Australia and the United States as commensurate priors, we were able to increase our power to estimate the expected reduction in ePTB that could be achieved in a larger population with similar demographics.

Acknowledgments

We are grateful to the women who gave their time to participate in our studies. The authors' responsibilities were as follows: SEC. JC, MM and RAG designed the parent studies; BJG and LNY did the biostatistical analyses, SEC wrote the manuscript, and all authors participated in editing of the manuscript. SEC has been a consultant for DSM, the company that donated the capsules of DHA for the parent study.

List of abbreviations

ADORE assessment of DHA on reducing early preterm birth

DHA	docosahexaenoic acid
DOMInO	DHA to Optimize Mother Infant Outcome
EPA	eicosapentaenoic acid
KUDOS	Kansas DHA outcomes study
LCPUFA	long chain polyunsaturated fatty acids
ORIP	omega-3 fats to reduce the incidence of prematurity
PTB	preterm birth
ePTB	early preterm birth
RCT	randomized controlled trials

References

1. Olsen SF, Hansen HS, Jensen B, Sorensen TI. Pregnancy duration and the ratio of long-chain n-3 fatty acids to arachidonic acid in erythrocytes from Faroese women. Journal of internal medicine Supplement. 1989; 731:185–189. [PubMed: 2706041]
2. Olsen SF, Sorensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, Grant A. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. Lancet. 1992; 339:1003–1007. [PubMed: 1349049]
3. Makrides M, Duley L, Olsen SF. Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. The Cochrane database of systematic reviews. 2006:Cd003402. [PubMed: 16856006]
4. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. Jama. 2010; 304:1675–1683. [PubMed: 20959577]
5. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, Georgieff MK, Markley LA, Kerling EH, Shaddy DJ. DHA supplementation and pregnancy outcomes. The American journal of clinical nutrition. 2013; 97:808–815. [PubMed: 23426033]
6. Smid MC, Stringer EM, Stringer JS. A Worldwide Epidemic: The Problem and Challenges of Preterm Birth in Low- and Middle-Income Countries. American journal of perinatology. 2016; 33:276–289. [PubMed: 26841086]
7. Gajewski BJ, Reese CS, Colombo J, Carlson SE. Commensurate Priors on a Finite Mixture Model for Incorporating Repository Data in Clinical Trials. Statistics in Biopharmaceutical Research. 2016; 8:1–10.
8. Schwartz SL, Gelfand AE, Miranda ML. Joint Bayesian analysis of birthweight and censored gestational age using finite mixture models. Statistics in medicine. 2010; 29:1710–1723. [PubMed: 20575047]
9. Hobbs BP, Sargent DJ, Carlin BP. Commensurate Priors for Incorporating Historical Information in Clinical Trials Using General and Generalized Linear Models. Bayesian analysis. 2012; 7:639–674. [PubMed: 24795786]
10. Papanikolaou Y, Brooks J, Reider C, Fulgoni VL 3rd. U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003–2008. Nutrition journal. 2014; 13:31. [PubMed: 24694001]
11. Kuriki K, Nagaya T, Imaeda N, Tokudome Y, Fujiwara N, Sato J, Ikeda M, Maki S, Tokudome S. Discrepancies in dietary intakes and plasma concentrations of fatty acids according to age among Japanese female dietitians. European journal of clinical nutrition. 2002; 56:524–531. [PubMed: 12032652]

12. Kar S, Wong M, Rogozinska E, Thangaratinam S. Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies. European journal of obstetrics, gynecology, and reproductive biology. 2015; 198:40–46.
13. Middleton P, Shepherd E, Gould J, Olsen S, Duley L, Makrides M. Omega-3 supplementation during pregnancy. Cochrane Database of Cochrane Reviews. 2016 under review.
14. Ahmed S, Makrides M, Sim N, McPhee A, Quinlivan J, Gibson R, Umberger W. Analysis of hospital cost outcome of DHA-rich fish-oil supplementation in pregnancy: Evidence from a randomized controlled trial. Prostaglandins, leukotrienes, and essential fatty acids. 2015; 102–103:5–11.
15. TI Shireman EK, Gajewski BJ, Colombo J, Carlson SE. Docosahexaenoic acid supplementation (DHA) and the return on investment for pregnancy outcomes. PLEFA. 2016 in press.

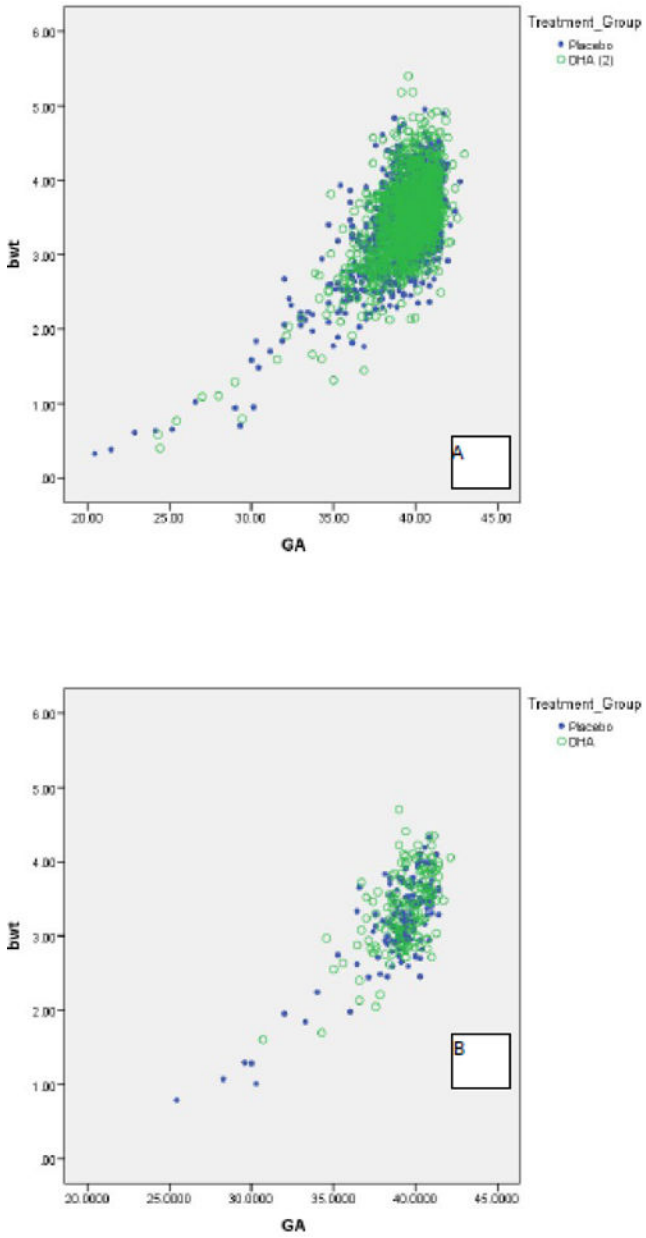

Figure 1.

Relationship between actual infant birth weight (BWT) in kg and gestational age (GA) in weeks in (A) DHA to Optimize Mother Infant Outcome (DOMInO) and (B) Kansas DHA Outcomes Study (KUDOS) trials.

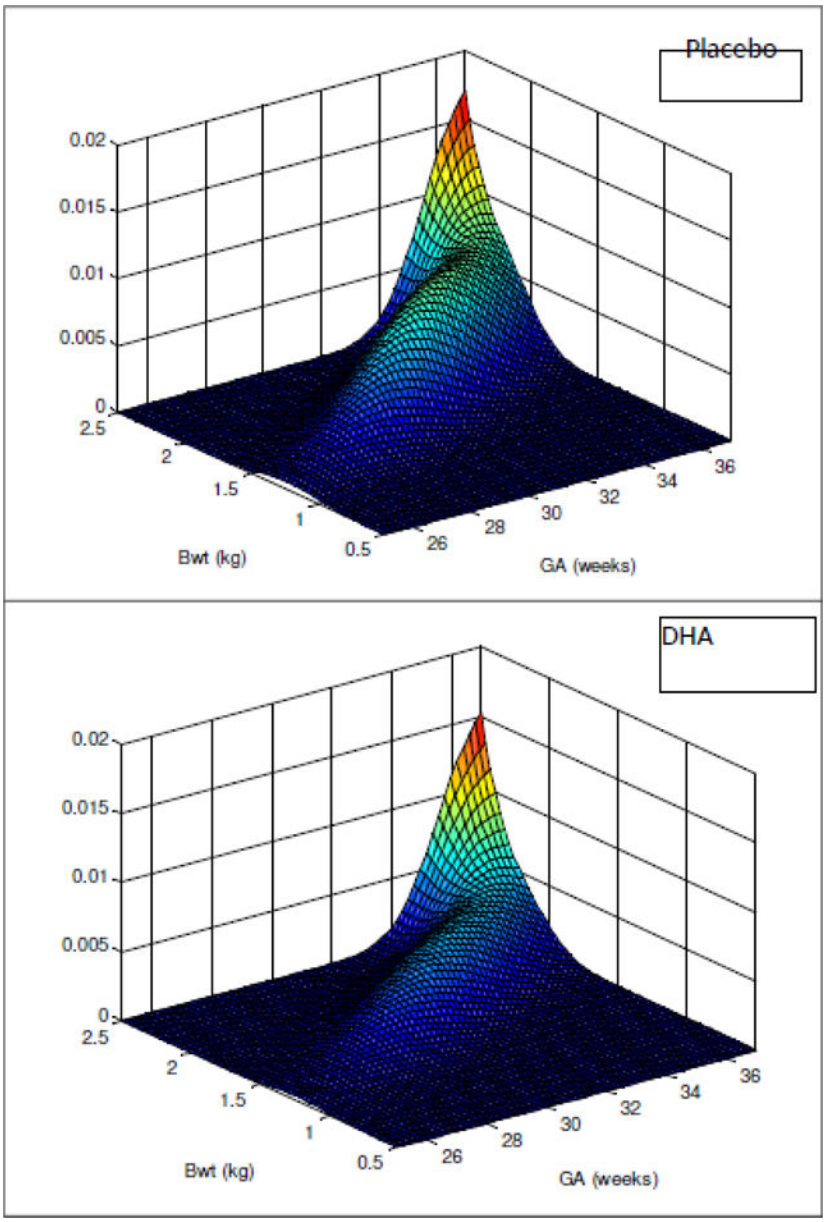

Figure 2.

Model illustration of the predictive effect of DHA on gestational age and birth weight using results from the Australian DHA to Optimize Mother Infant Outcome (DOMInO) trial. DHA supplementation significantly reduced the proportion of births anticipated in the high risk group (Placebo 3.876%, DHA 2.15% (P=0.02)) but not in the moderate risk and low risk groups: Moderate risk, placebo 17.09%; DHA 15.62%, NS; Low risk, 79.15%; DHA, 82.23%, NS.

Table 1

Modeled Outcomes for the DOMInO and KUDOS Trials by Treatment Group*

	DHA Supplement (%*)	Placebo (%*)	Bayesian posterior probability DHA differs from Placebo
DOMInO Trial	***n=1182***	***n=1181***	
Birth <34 weeks gestation	1.30	2.22	0.02
Birth >41 weeks gestation	6.85	6.70	0.06
Risk of Preterm Birth			
Low risk subgroup	82.23	79.15	0.12
Moderate risk subgroup	15.62	17.09	0.28
High risk subgroup	2.15	3.76	0.02
KUDOS Trial	***n=154***	***n=145***	
Birth <34 weeks gestation	1.49	4.19	0.03
Birth >41 weeks gestation	6.66	6.28	0.13
Risk of Preterm Birth			
Low risk subgroup	76.70	70.12	0.22
Moderate risk subgroup	20.61	22.78	0.37
High risk subgroup	2.69	7.09	0.02

* Percentages estimated from the Bayesian three component mixture model.

Table 2

Demographic and Clinical Characteristics of DOMInO and KUDOS Trial Participants by Risk of Preterm Birth

Characteristic	Low Risk Subgroup	Moderate Risk Subgroup	High Risk Subgroup	Total
DOMInO Trial (n=2363)				
Gestational age (weeks) *	40.1 (0.9)	37.9 (1.2)	34.8 (4.7)	39.3 (1.9)
Birthweight (g) *	3657 (409)	3032 (290)	2000 (604)	3445 (567)
Smoking status **				
Smoked during pregnancy	525 (69.4)	186 (24.6)	46 (6.1)	757
Did not smoke during pregnancy	1210 (75.4)	335 (20.9)	59 (3.7)	1604
Secondary education **				
Did not complete high school	627 (72.0)	197 (22.6)	47 (5.4)	871
Completed high school	1108 (74.4)	324 (21.7)	58 (3.9)	1490
Further education **				
Did not complete further study	553 (74.0)	154 (20.6)	40 (5.4)	747
Completed further study	1182 (73.2)	367 (22.7)	65 (4.0)	1614
Infant gender				
Male	907 (76.1)	247 (20.7)	38 (3.2)	1192
Female	829 (70.8)	274 (23.4)	68 (5.8)	1171
Race				
Caucasian	1542 (74.0)	453 (21.7)	89 (4.3)	2084
Non-Caucasian	194 (69.5)	68 (24.4)	17 (6.1)	279
Maternal age (years) *	28.8 (5.6)	29.3 (5.8)	28.7 (6.5)	28.9 (5.7)
KUDOS Trial (n=299)				
Gestational age (weeks) *	40.1 (0.8)	38.2 (1.1)	34.6 (4.3)	39.2 (2.1)
Birthweight (g) *	3522 (395)	3024 (243)	1936 (570)	3275 (569)
Smoking status				
Smoked during pregnancy	63 (63.6)	28 (28.3)	8 (8.1)	99
Did not smoke during pregnancy	134 (67.0)	53 (26.5)	13 (6.5)	200
Race				
Caucasian	129 (71.7)	43 (23.9)	8 (4.4)	180
Non-Caucasian	68 (57.1)	38 (31.9)	13 (10.9)	119
Maternal age (years) *	25.8 (4.9)	24.8 (4.5)	24.3 (5.0)	25.4 (4.8)
Maternal DHA (% fatty acids)	4.3 (1.2)	4.5 (1.3)	4.2 (.9)	4.3 (1.2)

Values are No. (%) unless otherwise indicated

* Values are mean (SD)

** Results missing for 2 participants