Review

Omega-3 Long Chain Polyunsaturated Fatty Acids to Prevent Preterm Birth

A Systematic Review and Meta-analysis

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OBJECTIVE: To evaluate the efficacy of omega-3 in reducing the incidence of preterm birth.

DATA SOURCES: Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords related to "fish oil," "pregnancy," and "omega-3."

METHODS OF STUDY SELECTION: We included all randomized controlled trials of asymptomatic women with singleton gestations who were randomized to prophylactic treatment with either omega-3 supplementation or control (either placebo or no treatment). Exclusion criteria included trials in women with multiple gestations, intrauterine growth restriction, gestational hypertension or preeclampsia at randomization, prior preterm birth, and trials with polyunsaturated fatty acids as control.

TABULATION, INTEGRATION, AND RESULTS: Nine randomized trials including 3,854 eligible women were identified. Women who received omega-3 had a similar rate of preterm birth before 37 weeks of gestation compared with women in the control group (7.7% compared with 9.1%, respectively; relative risk 0.90, 95% confidence interval [CI] 0.72–1.11). There were no significant differences in birth weight, neonatal intensive care unit admission, necrotizing enterocolitis, sepsis, or perinatal death in the omega-3 compared with control groups, respectively. There were no significant differences in the subgroup analyses, except for the rate of perinatal death, which was lower (0.3% compared with 1.2%; relative risk 0.27, 95% CI 0.09–0.80) in the women who received omega-3 before 21 weeks of gestation and in trials with low risk of bias (0.3% compared with 1.0%; relative risk 0.28, 95% CI 0.09–0.89) compared with women in the control group. However, in no randomized controlled trial was perinatal death the primary outcome.

CONCLUSION: Omega-3 supplementation during pregnancy does not reduce the incidence of preterm birth or improve neonatal outcome.

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In 1986, an epidemiologic study from the Faeroe Islands first suggested that a high intake of foods rich in omega-3 may increase birth weights by prolonging gestation.[1] Preterm birth remains the number one cause of perinatal mortality in many countries, including the United States.[2] Prior preterm birth is one of the most important risk factors for preterm birth.[3] However, most preterm births occur in women without a prior preterm birth. Randomized controlled trials have been performed to assess if omega-3 supplementation may prevent preterm birth with contradicting results.[4–12] So far, the efficacy of omega-3 in reducing the incidence of preterm birth is still unclear.

The aim of this meta-analysis was to evaluate the efficacy of omega-3 in reducing the incidence of preterm birth in asymptomatic singleton gestations without prior preterm birth.

SOURCES

The research protocol was designed a priori, defining methods for searching the literature, including and examining articles, and extracting and analyzing data.

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Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to "fish oil," "long chain polyunsaturated fatty acids," "pregnancy," and "omega-3" from inception of each database to August 2014. No restrictions for language or geographic location were applied.

STUDY SELECTION

We included all randomized controlled trials (RCTs) of asymptomatic singleton gestations who were randomized to prophylactic treatment with either omega-3 supplementation or control (either placebo or no treatment). All published randomized studies on omega-3 supplementation during pregnancy were carefully reviewed.

Only trials that enrolled women carrying singleton gestations without prior preterm birth were included. Exclusion criteria included quasirandomized trials (ie, trials in which allocation was done on the basis of a pseudorandom sequence, eg, odd and even hospital number or date of birth, alternation), trials in women with multiple gestations, intrauterine growth restriction or gestational hypertension or preeclampsia at randomization, prior preterm birth, trials with either only biochemical outcomes or no informative outcomes, trials with polyunsaturated fatty acids (PUFAs) as control, and trials with PUFAs treatment other than omega-3.

Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD42014013752). The meta-analysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses statement.[13]

Data abstraction was completed by two independent investigators (G.S., V.B.). Each investigator independently abstracted data from each study and analyzed data separately. Differences were reviewed and further resolved by common review of the entire data. Data abstracted included number of study patients, number of patients in intervention and control groups, type, route and dosage of intervention and control, gestational age at randomization, gestational age at delivery, interval from randomization to delivery (ie, latency), obstetric complications, and neonatal outcome including birth weight, admission to neonatal intensive care unit, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, and perinatal death. For studies that did not stratify data, composite data were extracted. When possible, authors were contacted for missing data.

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[14] Seven domains related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.[14]

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome included preterm birth before 37 weeks of gestation. Secondary outcomes included preterm birth before 34 weeks of gestation, spontaneous preterm birth before 37 weeks of gestation, spontaneous preterm birth before 34 weeks of gestation, gestational age at delivery, latency, preterm premature rupture of membranes, and neonatal outcome including birth weight, neonatal intensive care unit, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, and perinatal death (defined as the sum of stillbirth and neonatal death).

We planned subgroup analyses in women who received daily both eicosapentaenoic acid and dehydroacetic acid, by randomization before or after 21 weeks of gestation and by low compared with other than low risk of bias in all items according to Cochrane Collaboration's tool.[14]

The data analysis was completed independently by the authors using Review Manager 5.3. The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Cochrane Q statistic and Higgins I^2 statistics. In case of statistical significant heterogeneity (P value of the Cochrane Q statistic $<.1$), the random effects model of DerSimonian and Laird was used to obtain the pooled relative risk estimate; otherwise, a fixed effect model was planned. The summary measures were reported as risk ratio (RR) with 95% confidence interval (CI). P value $<.05$ was considered statistically significant.

RESULTS

We initially identified 29 trials on omega-3 supplementation during pregnancy.[4–12,15–34] No similar systematic reviews were found during the search process. Twenty RCTs were excluded for various reasons.[15–34] (Box 1).

Nine trials that met inclusion criteria for this meta-analysis were analyzed.[4–12] Figure 1 shows the flow diagram (Preferred Reporting Item for Systematic Reviews and Meta-analyses template) of information through the different phases of the review (Fig. 1).

The quality of RCTs included in our meta-analysis was assessed by the Cochrane Collaboration's tool[14] (Fig. 2). Most studies had a low risk of bias in allocation concealment, blinding, and selective reporting. Figure 3 shows the funnel plot for assessing publication bias for preterm birth before 37 weeks of gestation.

The characteristics of the nine included trials are summarized in Table 1. Eight studies used placebo as a control. Of the 3,854 included women, 1,868 (48.5%) were randomized to the omega-3 group and 1,986 (51.5%) to the control group. Six studies used eicosapentaenoic acid and docosahexaenoic acid together as treatment, whereas the other three used only docosahexaenoic acid (Table 1). None of the studies had preterm birth as primary outcome.

Table 2 shows extracted data and selective outcomes of included trials. Women randomized to the intervention group had the same mean age as the control group. The mean of gestational age at randomization was approximately 23 weeks in both groups. Furthermore, we found no differences in gestational age at delivery (mean difference 0.57 days, 95% CI −0.62 to 1.76) or in latency (mean difference 0.83 days, 95% CI −0.86 to 2.52) between the two groups (Table 2).

Box 1. List of Excluded Studies (n=20)

Twin gestations[31]: 1
Women with preeclampsia[29]: 1
Women with prior preterm birth[23]: 1
Only biochemical outcomes available[15–17,19,20,24,27,33]: 8
Linoleic or linolenic acids were used as treatment[25,26]: 2
Polyunsaturated fatty acids as control[21,22,30,34]: 4
Duplicate[18]: 1
Only on term-born neonates[32]: 1
No maternal characteristics available[28]: 1
Total randomized controlled trials excluded: 20

Data are n.

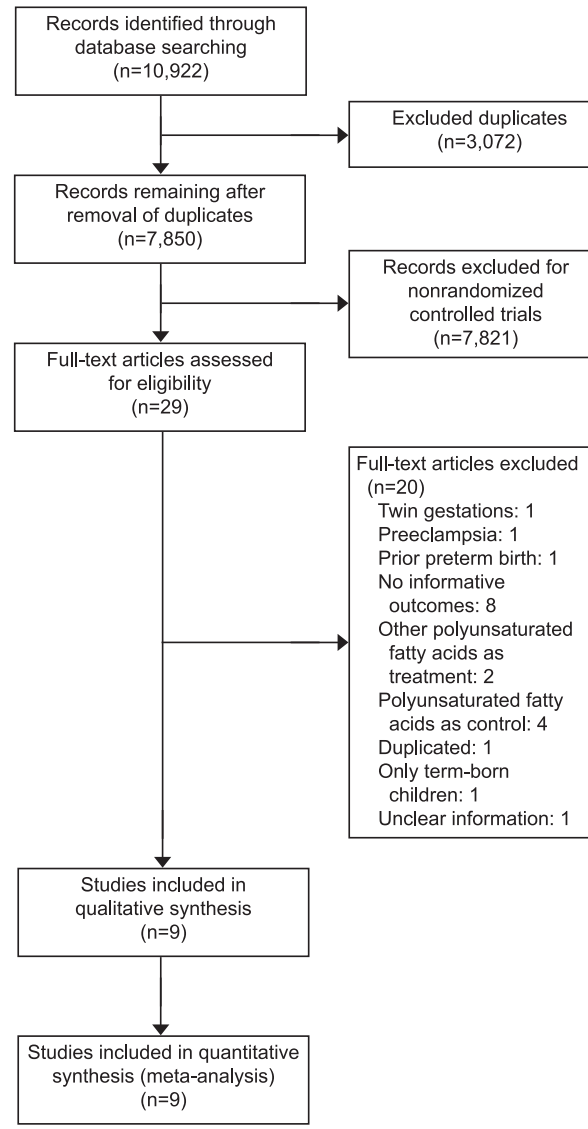

Fig. 1. Flow diagram of studies identified in the systematic review (Preferred Reporting Item for Systematic Reviews and Meta-Analyses [PRISMA] template).

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Women who received omega-3 supplementation had a similar rate of preterm birth before 37 weeks of gestation compared with women in the control group (7.7% compared with 9.1%, respectively; RR 0.90, 95% CI 0.72–1.11) (Table 3; Fig. 4). We found no significant differences in neonatal birth weight (mean difference 27.76 g, 95% CI −27.49 to 83.02), neonatal intensive care unit (0% compared with 6.9%; RR 0.19, 95% CI 0.01–3.75), necrotizing enterocolitis (0.8% compared with 0%; RR 2.98, 95% CI 0.12–73.13), sepsis (0.25% compared with 0.17%; RR 6.96, 95% CI 0.36–134.57), or perinatal death (1.0% compared

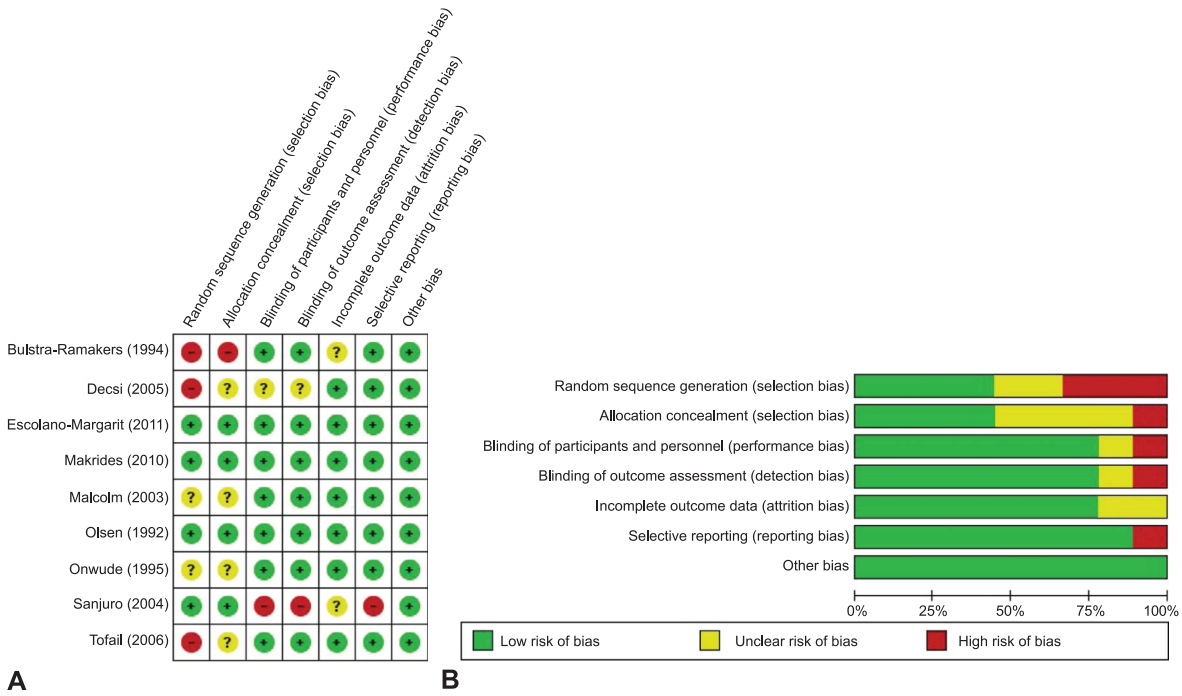

Fig. 2. Assessment of risk of bias. **A**. Summary of risk of bias for each trial. +, low risk of bias; −, high risk of bias; ?, unclear risk of bias. **B**. Risk of bias graph about each risk of bias item presented as percentages across all included studies.

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with 1.8%; RR 0.61, 95% CI 0.30–1.24) (Fig. 5) in the omega-3 compared with control groups, respectively (Table 3). No data were available about preterm birth before 34 weeks of gestation, spontaneous preterm birth before 37 weeks of gestation, spontaneous preterm birth at less than 34 weeks of gestation, preterm premature rupture of membranes, respiratory distress syndrome, bronchopulmonary dysplasia, or intraventricular hemorrhage.

We found in general no significant differences in the subgroup analyses in the outcomes with data available (Tables 4, 5, and 6), except for few significant results favoring omega-3 supplementation. In women who received both eicosapentaenoic acid and docosahexaenoic acid, birth weight was higher (mean difference 51.18 g, 95% CI 12.33–90.03) compared with neonates in the control group. In the women who received omega-3 before 21 weeks of gestation, the rate of perinatal death was lower in the omega-3 group compared with those in the control group (0.3% compared with 1.2%; RR 0.27, 95% CI 0.09–0.80) (Table 5). In the studies with low risk of bias, birth weight was higher (mean difference 60.66 g, 95% CI 19.78–101.54) and the rate of perinatal death lower (0.3% compared with 1.0%; RR 0.28, 95% CI 0.09–0.89) in women who received omega-3 compared with women in the control group (Table 6).

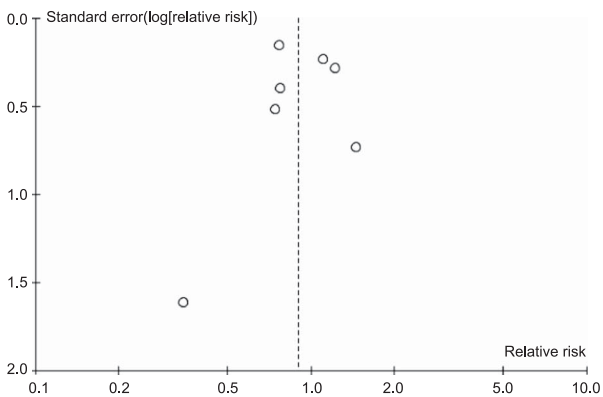

Fig. 3. Funnel plot for assessing publication bias.

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DISCUSSION

This meta-analysis of the nine RCTs evaluating the efficacy of omega-3 supplementation in 3,854 asymptomatic singleton gestations without prior preterm birth shows that omega-3 supplementation is not associated either with significant prevention of preterm birth nor with improved neonatal outcomes. A significant decrease in perinatal death, which was consistently defined in the pertinent trials as the sum of stillbirth and neonatal death, was found in the planned subgroup

Table 1. Descriptive Data of Included Trials

First Author	Study Location	No. of Patients at Randomization	Intervention*	Control*	Primary Outcome
Olsen[4]	Denmark	397 (266/131)	Eicosapentaenoic acid 1,280 mg +docosahexaenoic acid 920 mg	No treatment	Duration of gestation, birth weight
Bulstra-Ramakers[5]	The Netherlands	63 (32/31)	Eicosapentaenoic acid 3,000 mg +docosahexaenoic acid not defined	Placebo	Gestational hypertension
Onwude[6]	United Kingdom	232 (113/119)	Eicosapentaenoic acid 1,620 mg +docosahexaenoic acid 1,080 mg	Placebo	Gestational hypertension; SGA
Malcolm[7]	United Kingdom	100 (50/50)	Docosahexaenoic acid 200 mg	Placebo	Neonate retinal function
Sanjuro[8]	Spain	16 (8/8)	Docosahexaenoic acid 200 mg	Placebo	Biochemical outcomes
Decsi[9]	Multicenter	157 (77/80)	Docosahexaenoic acid 500 mg	Placebo	Biochemical outcomes
Tofail[10]	Bangladesh	400 (200/200)	Eicosapentaenoic acid 1,800 mg +docosahexaenoic acid 1,200 mg	Placebo	Infant's development
Makrides[11]	Australian	2,399 (1,197/1,202)	Eicosapentaenoic acid 100 mg +docosahexaenoic acid 800 mg	Placebo	High level of depressive symptoms
Escolano-Margarit[12]	Multicenter	90 (43/47)	Eicosapentaenoic acid 150 mg +docosahexaenoic acid 500 mg	Placebo	Neurologic assessment
Total	—	3,854 (1,986/1,868)	—	—	—

IUGR, intrauterine growth restriction; SGA, small for gestational age.
Data are total n (intervention/control).
* Intervention and control all were administered daily, except in the no-treatment arm of one study.

analyses of omega-3 supplementation started before 21 weeks of gestation and in the studies with low risk of bias. The first subgroup analysis was based on five trials, of which one was responsible for 85% of analyzed patients. The second subgroup analysis was based on three RCTs, of which one was responsible for

Table 2. Selected Characteristics and Selected Outcomes of Included Trials

First Author	Age Mean (y)	Smoking, n	Mean Gestational Age at Randomization (wk)	Mean Gestational Age at Delivery (d)	Mean Latency (d)
Olsen[4]	29 vs 29	88/266 (33.1) vs 43/131 (32.8)	30 vs 30	283 vs 281	73 vs 71
Bulstra-Ramakers[5]	NA	NA	13 vs 13	NA	NA
Onwude[6]	NA	42/113 (37.2) vs 32/119 (26.9)	24 vs 24	266 vs 266	98 vs 98
Malcolm[7]	NA	NA	15 vs 15	280 vs 280	175 vs 175
Sanjuro[8]	35 vs 31	1/8 (12.5) vs 2/8 (25.0)	26 vs 26	272 vs 275	90 vs 90
Decsi[9]	NA	NA	20 vs 20	NA	NA
Tofail[10]	22 vs 23	NA	25 vs 25	271 vs 274	96 vs 99
Makrides[11]	29 vs 29	358/1,197 (29.9) vs 407/1,202 (33.9)	19 vs 19	282 vs 281	149 vs 148
Escolano-Margarit[12]	30 vs 31	7/43 (16.3) vs 2/47 (4.3)	20 vs 20	272 vs 273	132 vs 133
Total	27 vs 27	550/1,944 (28.3) vs 540/1,822 (29.7)	23 vs 23	275 vs 274	90 vs 89
Mean difference (95% CI)	—	—	0 wk (−0.60 to 0.60)	0.57 d (−0.62 to 1.76)	0.83 d (−0.86 to 2.52)

NA, not available; CI, confidence interval.
Data are n/N for intervention (%) compared with n/N for control (%) unless otherwise specified.

Table 3. Primary and Secondary Outcomes

First Author	Preterm Birth at Less Than 37 Wk of Gestation	Mean Birth Weight (g)	NICU	NEC	Sepsis	Perinatal Death
Olsen[4]	9/266 (3.4) vs 6/131 (4.6)	3,571 vs 3,504	NA	NA	NA	1/266 (0.4) vs 1/131 (0.8)
Bulstra-Ramakers[5]	8/32 (25.0) vs 10/31 (32.3)	NA	NA	NA	NA	1/32 (3.1) vs 3/31 (9.7)
Onwude[6]	22/113 (19.5) vs 19/119 (16.0)	3,033 vs 2,983*	NA	NA	NA	1/113 (0.9) vs 2/119 (1.7)
Malcolm[7]	0/31 (0) vs 1/32 (3.1)	3,508 vs 3,645	0/31 (0) vs 2/29 (6.9)	NA	NA	NA
Sanjuro[8]	NA	3,183 vs 3,385	NA	NA	NA	NA
Decsi[9]	NA	NA	NA	NA	NA	NA
Tofail[10]	30/125 (24.0) vs 27/124 (21.8)	2,700 vs 2,700	NA	NA	NA	12/159 (7.5) vs 11/165 (6.7)
Makrides[11]	67/1,197 (5.6) vs 88/1,202 (7.3)	3,475 vs 3,407	NA	1/1,184 (0.1) vs 0/1,177 (0)	3/1,184 (0.3) vs 2/1,177 (0.2)	3/1,197 (0.3) vs 12/1,202 (1.0)
Escolano-Margarit[12]	4/43 (9.3) vs 3/47 (6.4)	3,340 vs 3,390	NA	NA	NA	NA
Total	140/1,807 (7.7) vs 154/1,686 (9.1)	3,259 vs 3,288	0/31 (0) vs 2/29 (6.9)	1/1,184 (0.1) vs 0/1,177 (0)	3/1,184 (0.3) vs 2/1,177 (0.2)	18/1,767 (1.0) vs 29/1,648 (1.8)
RR (95% CI)	0.90 (0.72 to 1.11)	Mean difference 27.76 g (95% CI −27.49 to 83.02)*	0.19 (0.01–3.75)	2.98 (0.12–73.13)	6.96 (0.36–134.57)	0.61 (0.30–1.24)

NICU, neonatal intensive care unit admission; NEC, necrotizing enterocolitis; NA, not available; RR, relative risk; CI, confidence interval. Data are n/N for intervention (%) compared with n/N for control (%) unless otherwise specified.
* Birth weight for Onwude 1995 was not included in the analysis because standard deviation was not reported.

83% of analyzed patients. However, in no RCT was perinatal death the primary outcome.

Four other meta-analyses[35] have evaluated the efficacy of omega-3 in prevention of preterm birth. The first did not include all available RCTs and did not exclude RCTs with PUFAs as a control. It showed that omega-3 supplementation may enhance pregnancy duration and head circumference, but the mean effect size was small.[35] The second meta-analysis included women with prior preterm birth. It showed no effect of omega-3 supplementation on preterm birth outcomes.[36] Another meta-analysis included women with prior preterm birth and also RCTs with PUFAs as controls. It showed that omega-3 during pregnancy reduced the rate of preterm birth and increased birth weight.[37] The Cochrane Review on omega-3 supplementation in pregnancy included also RCTs with PUFAs as a control and RCTs with prostaglandin precursor as treatment. It showed a small but consistent increase in the mean length of gestation.[38]

One of the strengths of our study is inclusion of RCT data on omega-3 supplementation during pregnancy in a specific population, that is, women carrying singleton gestations without prior preterm

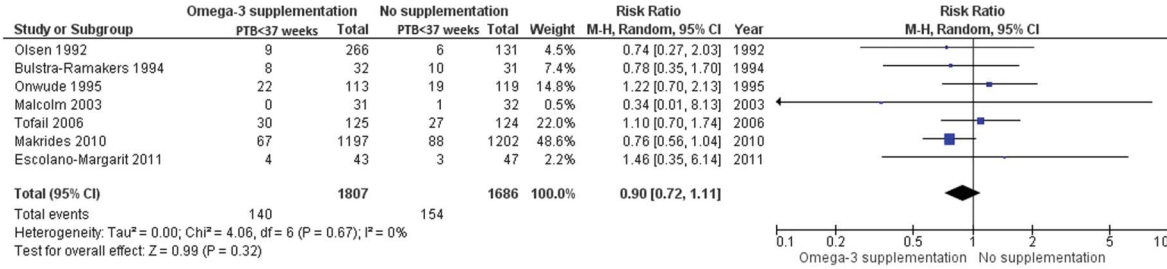

Fig. 4. Forest plot for preterm birth at less than 37 weeks of gestation. PTB, preterm birth; M-H, Mantel-Haenszel test; CI, confidence interval.

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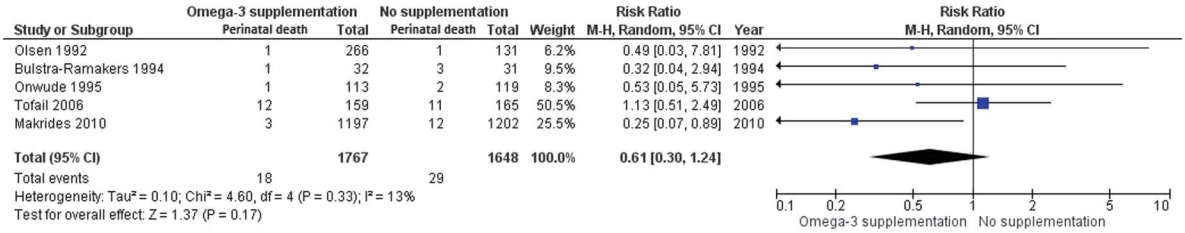

Fig. 5. Forest plot for perinatal death. M-H, Mantel-Haenszel test; CI, confidence interval.
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birth. This population represents, in all countries, usually approximately 90% or more of the pregnant population. We chose to limit inclusion of studies to this population because other interventions to prevent preterm birth have been shown to have different results in different populations of pregnant women. For example, progesterone supplementation as well as cerclage have differing effects depending on prior preterm birth history or plurality.[39,40]

Limitations of our study are inherent to the limitations of the included RCTs. Other limitations of our meta-analysis are that none of the RCTs included had preterm birth as the primary outcome and that the dosage of omega-3 differed somewhat among studies. The study reports provided no information on the use of obstetric interventions to limit preterm birth, and thus we could not control for any such interventions. The included studies came from various regions of the world, so dietary intake of omega-3 fatty acids may have differed across trials. Unknown or unmeasured factors not reported in publications could have modified the observed associations. Although no included study mentioned that women enrolled had a prior preterm birth, this characteristic was not always reported. Approximately 62% of the patients in our meta-analysis are from one trial, which was of high quality.[11]

According to the Food and Agriculture Organization of the United Nations[41] and the World Health Organization,[42] daily intake of omega-3 supplementation is recommended during pregnancy. These recommendations are based on evidence that omega-3

Table 4. Subgroup Analysis Including Trials With Omega-3 Supplementation of Both Eicosapentaenoic Acid and Docosahexaenoic Acid Daily

First Author	Smoking	Mean Gestational Age at Randomization (wk)	Preterm Birth at Less Than 37 Wk of Gestation	Mean Birth Weight (g)	Perinatal Death
Olsen[4]	88/266 (33.1) vs 43/131 (32.8)	30 vs 30	9/266 (3.4) vs 6/131 (4.6)	3,571 vs 3,504	1/266 (0.4) vs 1/131 (0.8)
Bulstra-Ramakers[5]	NA	13 vs 13	8/32 (25.0) vs 10/31 (32.3)	NA	1/32 (3.1) vs 3/31 (9.7)
Onwude[6]	42/113 (37.2) vs 32/119 (26.9)	24 vs 24	22/113 (19.5) vs 19/119 (16.0)	3,033 vs 2,983*	1/113 (0.9) vs 2/119 (1.7)
Tofail[10]	NA	25 vs 25	30/125 (24.0) vs 27/124 (21.8)	2,700 vs 2,700	12/159 (7.5) vs 11/165 (6.7)
Makrides[11]	358/1,197 (29.9) vs 407/1,202 (33.9)	19 vs 19	67/1,197 (5.6) vs 88/1,202 (7.3)	3,475 vs 3,407	3/1,197 (0.3) vs 12/1,202 (1.0)
Escolano-Margarit[12]	7/43 (12.3) vs 2/47 (4.3)	20 vs 20	4/43 (9.3) vs 3/47 (6.4)	3,340 vs 3,390	NA
Total	495/1,619 (30.6) vs 484/1,499 (32.3)	22 vs 22	140/1,776 (7.9) vs 153/1,654 (9.2)	3,271 vs 3,250	18/1,767 (1.0) vs 29/1,648 (1.8)
RR (95% CI)	*P*=.25	Mean difference 0.12 wk (95% CI −0.48 to 1.23)	0.90 (0.73–1.12)	**Mean difference 51.18 g (95% CI 12.33–90.03)***	0.61 (0.30–1.24)

NA, not available; RR, relative risk; CI, confidence interval.
Data are n/N for intervention (%) compared with n/N for control (%) unless otherwise specified.
Bold indicates statistical significance.
* Birth weight for Onwude 1995 was not included in the analysis because standard deviation was not reported.

Table 5. Subgroup Analysis of Women Randomized Before 21 Weeks of Gestation

First Author	Smoking	Mean Gestational Age at Randomization (wk)	Preterm Birth at Less Than 37 Wk of Gestation	Mean Birth Weight (g)	NICU	Perinatal Death
Bulstra-Ramakers[5]	NA	13 vs 13	8/32 (25.0) vs 10/31 (32.3)	NA	NA	1/32 (3.1) vs 3/31 (9.7)
Malcolm[7]	NA	15 vs 15	0/31 (0) vs 1/32 (3.1)	3,508 vs 3,645	0/31 (0) vs 2/29 (6.9)	NA
Decsi[9]	NA	20 vs 20	NA	NA	NA	NA
Makrides[11]	358/1,197 (29.9) vs 407/1,202 (33.9)	19 vs 19	67/1,197 (5.6) vs 88/1,202 (7.3)	3,475 vs 3,407	NA	3/1,197 (0.3) vs 12/1,202 (1.0)
Escolano-Margarit[12]	7/43 (12.3) vs 2/47 (4.3)	20 vs 20	4/43 (9.3) vs 3/47 (6.4)	3,340 vs 3,390	NA	NA
Total	365/1,240 (29.4) vs 409/1,249 (32.7)	18 vs 18	79/1,303 (6.1) vs 102/1,312 (7.8)	3,441 vs 3,480	0/31 (0) vs 2/29 (6.9)	4/1,229 (0.3) vs 15/1,233 (1.2)
RR (95% CI)	*P*=.07	Mean difference 0.05 wk (95% CI −0.58 to 0.63)	0.78 (0.59–1.03)	Mean difference 3.23 g (95% CI −112.74 to 119.20)	0.19 (0.01–3.75)	**0.27 (0.09–0.80)**

NICU, neonatal intensive care unit admission; NA, not available; RR, relative risk; CI, confidence interval.
Data are n/N for intervention (%) compared with n/N for control (%) unless otherwise specified.
Bold indicates statistical significance.

Table 6. Subgroup Analysis of Studies With Low Risk of Bias in All Items According to the Cochrane Collaboration's Tool[38]

First Author	Smoking	Mean Gestational Age at Randomization (wk)	Mean Gestational Age at Delivery (d)	Mean Latency (d)	Preterm Birth at Less Than 37 Wk of Gestation	Mean Birth Weight (g)	Perinatal Death
Olsen[4]	88/266 (33.1) vs 43/131 (32.8)	30 vs 30	283 vs 281	73 vs 71	9/266 (3.4) vs 6/131 (4.6)	3,571 vs 3,504	1/266 (0.4) vs 1/131 (0.8)
Makrides[11]	358/1,197 (29.9) vs 407/1,202 (33.9)	19 vs 19	282 vs 281	149 vs 148	67/1,197 (5.6) vs 88/1,202 (7.3)	3,475 vs 3,407	3/1,197 (0.3) vs 12/1,202 (1.0)
Escolano-Margarit[12]	7/43 (12.3) vs 2/47 (4.3)	20 vs 20	272 vs 273	132 vs 133	4/43 (9.3) vs 3/47 (6.4)	3,340 vs 3,390	NA
Total	453/1,506 (30.1) vs 452/1,380 (32.8)	23 vs 23	279 vs 278	118 vs 117	80/1,506 (5.3) vs 94/1,333 (7.1)	3,462 vs 3,433	4/1,463 (0.3) vs (1.0)
RR (95% CI)	*P*=.09	Mean difference 0.05 wk (95% CI −0.78 to 0.95)	Mean difference 0.89 d (95% CI −0.48 to 1.53)	Mean difference 0.12 d (95% CI −0.43 to 0.51)	0.78 (0.59–1.04)	**Mean difference 60.66 g (95% CI 19.78–101.54)**	**0.28 (0.09–0.89)**

NA, not available; RR, relative risk; CI, confidence interval.
Data are n/N for intervention (%) compared with n/N for control (%) unless otherwise specified.
Bold indicates statistical significance.

supplementation during pregnancy is associated with possible prolongation of pregnancy and other possible benefits, including prevention of preterm birth.[35,37,38] Our meta-analysis shows that omega-3 supplementation is not associated with prevention of preterm birth or of neonatal complications. More research is needed to evaluate whether early omega-3 supplementation started before 21 weeks of gestation is beneficial.

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