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Effects of Eicosapentaenoic Acid Versus Docosahexaenoic Acid on Serum Lipids: A Systematic Review and Meta-Analysis

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Abstract Omega-3 fatty acid supplements containing both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to reduce triglycerides but also increase low-density lipoprotein (LDL). Whether EPA or DHA given as monotherapy has differential effects on serum lipoproteins has not been systematically evaluated. We performed a meta-analysis of randomized placebo-controlled trials of monotherapy with EPA (n=10), DHA (n=17), or EPA versus DHA (n=6). Compared with placebo, DHA raised LDL 7.23 mg/dL (95% CI, 3.98–10.5) whereas EPA non-significantly reduced LDL. In direct comparison studies, DHA raised LDL 4.63 mg/dL (95% CI, 2.15–7.10) more than EPA. Both EPA and DHA reduced triglycerides, with a greater reduction by DHA in direct comparison studies. DHA also raised high-density lipoprotein (4.49 mg/dL; 95% CI, 3.50–5.48) compared with placebo, whereas EPA did not. Although EPA and DHA both reduce triglycerides, they have divergent effects on LDL and high-density lipoprotein. Further research is needed to elucidate the mechanisms and significance of these differences.

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Abbreviations

CETP	Cholesteryl ester transfer protein
CI	Confidence interval
COMBOS	Combination of Prescription Omega-3 with Simvastatin
df	Degrees of freedom
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
HDL	High-density lipoprotein cholesterol
JELIS	Japanese EPA Lipid Intervention Study
LDL	Low-density lipoprotein cholesterol
PPAR	Peroxisome proliferator-activator receptors

Introduction

Hypertriglyceridemia is associated with increased cardiovascular disease risk in numerous prospective and randomized clinical trials [1–3]. Whether the relationship is causal or triglycerides serve as a biomarker for increased cardiovascular disease risk remains controversial. One third of US adults have triglyceride levels ≥150 mg/dL, and among these, 16.2% have high triglyceride (≥200 mg/dL) and 1.1% has very high triglyceride (≥500 mg/dL) levels [4].

Omega-3 polyunsaturated fatty acids administered as fish oil supplements or prescription omega-3 ethyl esters lower plasma triglyceride concentrations [5–7]. Omega-3

fatty acids at doses of 4 g/day have been shown to reduce serum triglyceride concentrations by 25% to 30% [5]. The 2011 American Heart Association Scientific Statement on triglycerides and cardiovascular disease recommended 2 to 4 g/day of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) for the treatment of hypertriglyceridemia [8••].

The lipid-lowering effects of fish oils have been attributed to the components EPA (20:5 [n-3]) and DHA (22:6 [n-3]). EPA and DHA have been shown to reduce hepatic synthesis of triglycerides, increase hepatic fatty acid beta-oxidation, and promote myocardial fatty acid uptake and metabolism by acting as endogenous ligands for peroxisome proliferator–activated receptor (PPAR)-α and PPAR-γ [9–11].

Although combined EPA and DHA in fish oil supplements decrease plasma triglycerides, studies have demonstrated a concomitant increase in low-density lipoprotein (LDL). Mild increases in LDL have been observed among individuals with normal to very high triglyceride concentrations [12] and in those on concurrent statin therapy, as in the Combination of Prescription Omega-3 with Simvastatin (COMBOS) trial [13]. Recent studies have shown the magnitude of increased LDL may depend on an individual's baseline triglyceride levels. In addition, a post hoc analysis of the COMBOS trial demonstrated the largest percentage increases in LDL occurred primarily among individuals with low baseline LDL levels [14•].

It has generally been assumed that EPA and DHA act through similar mechanisms and have similar effects on lipids. The isolated roles of each have received limited study due to the greater availability of combined EPA and DHA products than purified EPA and DHA. Several studies have now examined EPA and DHA administered as monotherapy; however, their distinct effects on serum lipids have not been well established. We thus performed a systemic review and meta-analysis of purified EPA and DHA administered as monotherapy on serum lipids.

Materials and Methods

Study Inclusion

Studies were identified through MEDLINE and PubMed searches from January 1996 to December 2010 using the terms EPA and DHA (full names and abbreviations) in combination with lipids, cholesterol, LDL, HDL, triglycerides, humans, adults, English language, dietary supplement or drug therapy, and randomized controlled trial study design. Other forms of search terms were searched using the National Library of Medicine Medical Subject Heading. Related articles were cross-checked to identify additional studies that may have been missed in the database search. Abstracts from national and regional meetings were also included.

Included studies met pre-specified criteria including randomized controlled trial of adults with a placebo (or control) group, minimum study duration of at least 4 weeks, inclusion of baseline and endpoint data to compute the mean difference of the treatment or placebo effect, and information on the standard deviation (SD) or standard error for the study baseline and endpoint to compute the SD of the mean difference. Individual authors were contacted for further data when study information was insufficient.

In addition, studies must have reported the purity of the omega-3 fatty acid preparations, and each individual fatty acid product could contain no more than 4% of the other omega-3 fatty acid. Participants must have been exclusively treated with EPA or DHA monotherapy for the minimum study duration. There were no minimum dose requirements for studies of EPA and DHA monotherapy versus placebo. However, studies that directly compared EPA versus DHA must have administered comparable doses to study participants: 2.2 g/day to 4.0 g/day of EPA and 2.3 to 4 g/day of DHA.

Statistical Analysis

The mean difference and SDs were extracted for each study to compute the pooled treatment effect and 95% confidence interval (CI). The appropriate weighing of each study toward the summary mean difference was determined with the provided SD or standard error.

Individual studies in this analysis were found to include different placebos that variably affected serum lipids. This could potentially obscure the effect of the exposure (EPA or DHA) on serum lipids. Thus, to reduce variability between studies based on the use of different placebos, a weighed, pooled placebo was created for the mean difference (and SD) for each lipoprotein at study baseline and endpoint. Studies contributing to the pooled placebo mean difference and SD were appropriately weighed through the factoring of study size and degrees of freedom, respectively, in the pooled computations. The pooled placebo included studies that utilized placebos of non–omega-3 fatty acid oils (eg, olive oil). The Japanese EPA Lipid Intervention Study (JELIS) trial [15] utilized a statin as its control group and was thus excluded from the pooled placebo, given an expected statin-induced reduction in LDL. For the JELIS trial, the EPA plus statin arm was compared with its statin only control arm whereas remaining studies compared EPA or DHA with the pooled placebo.

The pooled analysis used random-effects models to enable individual studies to estimate differential effects. The random-effects model assumes the effect within each study varies in a normal distribution around an overall average effect [16]. Homogeneity across studies was assessed using the methods of DerSimonian and Laird [17] to determine the appropriateness of combining mean differences from individual studies. The I^2 statistic was also assessed and represents the proportion of total variation across studies due to heterogeneity rather than chance [18]. Significance for the test of heterogeneity was established at $P<0.1$. Sensitivity analyses were conducted when heterogeneity was detected. Finally, publication bias was assessed using funnel plots.

Review Manager was used for computations and to create forest plots for the overall pooled effects (RevMan; Version 4.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003).

Results

We identified 494 citations with our electronic search and reviewed their abstracts. Most ($n=393$) did not meet inclusion criteria based on the abstract. The remaining 101 full-text articles were reviewed, and exclusions were made based on unknown or unclear omega-3 fatty acid purity ($n=51$), incomplete reporting of baseline and endpoint lipid values ($n=13$), lack of adequate control groups ($n=13$), insufficient study duration ($n=2$), and use of children as study participants ($n=1$).

Twenty-one randomized controlled trials that examined the effects of omega-3 fatty acids on serum lipid biomarkers met inclusion criteria. Ten studies compared EPA versus placebo, 17 studies compared DHA versus placebo, and six studies directly compared EPA versus DHA. Study descriptions have been presented previously [19], and a summary description of included studies can be found in Table 1.

In all EPA versus placebo studies, the dose administered was 1.8 g/day, and in the EPA versus DHA studies the EPA dose ranged from 2.2 to 4.0 g/day. DHA dosing ranged from 0.7 to 3.0 g/day in the DHA versus placebo studies and 2.3 to 4 g/day in the DHA versus EPA studies. In direct comparison studies of DHA and EPA, a comparable dose and purity was administered for both treatment arms.

LDL Cholesterol

Ten studies of EPA and LDL were identified but one [20] did not provide information to compute the SD of the mean difference. Among the nine remaining studies (baseline mean LDL 140±30.5 mg/dL), four reported EPA significantly reduced LDL [21–24], two reported EPA significantly raised LDL [25, 26] and two reported EPA non-significantly raised LDL [27, 28] compared with the pooled placebo. The overall pooled estimate of nine EPA studies was a non-significant reduction in LDL of 1.76 mg/dL (95% CI: −1.85, 5.36) compared with placebo. In the JELIS trial [15], there was no significant difference in LDL for EPA plus statin compared with its statin only control group. A sensitivity analysis that excluded the JELIS trial did not change the overall pooled results: EPA non-significantly reduced LDL by 1.85 mg/dL (95% CI: −3.01, 6.71) compared with placebo.

Among 16 studies of DHA and LDL (baseline mean LDL140±70.5 mg/dL), 12 reported DHA increased LDL compared with placebo [24, 25, 27–36], of which nine were statistically significant [24, 28, 30–36]. Four studies reported DHA non-significantly reduced LDL compared with placebo [22, 37–39]. The overall pooled estimate of DHA studies on LDL using the random-effects model was a significant 7.23 mg/dL (95% CI: 3.98, 10.5) increase in LDL compared with placebo.

Six studies directly compared EPA and DHA on LDL [22, 24–28]. When EPA and DHA were directly compared, DHA significantly raised LDL by 4.63 mg/dL (95% CI: 2.15, 7.10) more than EPA (Fig. 1). Heterogeneity was non-significant ($P=0.33$, $I^2=13.5\%$).

Triglycerides

Both EPA and DHA significantly reduced triglycerides compared with placebo in pooled analyses. At baseline, the mean triglycerides were 142 mg/dL (SD 70.5) in the EPA groups. All eight EPA studies [20, 21, 23–25, 27, 28, 32] reported significant reductions in triglycerides ranging from 7.74 to 109.5 mg/dL compared with placebo. The overall pooled effect of EPA on triglycerides was a statistically significant reduction of 45.8 mg/dL (95% CI: 9.62, 82.0) compared with placebo.

Pooled DHA studies (baseline mean triglycerides 136± 66.4 mg/dl) similarly showed a reduction in triglycerides although the magnitude was less than the pooled EPA studies. All 15 studies that examined DHA and triglycerides reported DHA reduced triglycerides compared with placebo. All but two studies [29, 34] were statistically significant. DHA reduced triglycerides by 2.43 to 56.4 mg/dL compared with placebo. The overall pooled effect was DHA significantly reduced triglycerides by 25.1 mg/dL (95% CI: 19.5, 30.7) compared with placebo.

Five studies [24–28] directly compared EPA and DHA on triglycerides and all demonstrated a greater

Table 1 Randomized placebo-controlled trials of EPA and DHA on serum LDL, HDL, and triglycerides

Study (year)	No., sex, characteristics, baseline lipids of participants	Treatment dose (g/day), No. randomized, duration	Baseline lipid (SD or 95% CI)/endpoint lipid (SD or 95% CI) in mg/dL/% change from baseline to endpoint (p-value for baseline vs endpoint) *P*-value between study groups if available		
			LDL	Triglycerides	HDL
EPA vs DHA studies					
Egert et al. [22] (2009)	*N*=28 men *N*=51 women	EPA: 2.2 *N*=25	EPA: 99.6 (25.5)/ 95.4 (23.6)/−4.3 (NS)	EPA: 82.3 (62.8–125)/ 69.9 (44.2–85.0)/−15.1 (*P*<0.001)	EPA: 63.7 (14.7)/66.0 (17.4)/+3.6 (NS)
	BMI<28				
	TC<300	DHA: 2.3 *N*=25	DHA: 91.5 (23.6)/ 90.7 (27.8)/−0.8 (NS)	DHA: 86.7 (68.1–118)/ 60.2 (48.7–83.2)/−30.6 (*P*<0.001)	DHA: 61.8 (8.9)/69.9 (12.4)/+13.1 (*P*<0.001)
	TG<200	Placebo: *N*=24	Placebo: 99.6 (30.5)/ 100 (30.5)/+0.4 (NS)	Placebo: 89.4 (67.3–111)/ 74.3 (57.5–111)/−16.8 (*P*<0.05)	Placebo: 62.9 (16.2)/ 64.5 (17.8)/+2.5 (NS)
		6 weeks		EPA and DHA vs placebo, NS	EPA vs DHA and placebo, NR
				EPA vs DHA, *P*=0.503	
Grimsgaard et al. [24] (1997)	*N*=224 men	EPA: 3.8 N=75	EPA: 157 (32.0)/154 (18.5)/–2.0 (NS)	EPA: 109 (50.4)/95.6 (35.4)/−12.2 (*P*<0.01)	EPA: 51.4 (12.0)/ 51.7/+0.8 (NS)
	TC<367	DHA: 3.6 N=72	DHA: 157 (33.2)/160 (17.8)/+1.7 (NS)	DHA: 110 (51.3)/90.3 (27.4)/−17.7 (*P*<0.001)	DHA: 52.5 (11.6)/54.8 (NR)/+4.4 (*P*<0.001)
	TG<443	Placebo: N=77	Placebo: 156 (37.8)/158 (18.5)/+1.5 (NS)	Placebo: 108 (48.7)/118 (30.1)/+9.0 (*P*<0.01)	Placebo: 54.4 (10.8)/ 54.0 (NR)/−0.7 (NS)
		7 weeks		EPA vs placebo, *P*=0.0001	EPA vs placebo, *P*=0.4
				DHA vs placebo, *P*=0.0001	DHA vs placebo, *P*=0.0005
				EPA vs DHA, *P*=0.14	EPA vs DHA, *P*=0.009
Mori et al. [32] (2000)	*N*=56 men BMI 25–30	EPA: 4 *N*=19	EPA: 165 (32.0)/172 (16.8)/+4.2 (NS)	EPA: 178 (73.3)/140 (38.6)/−21.4 (*P*<0.05)	EPA: 38.6 (6.7)/38.2 (3.4)/−1.0 (NS)
	TC>232	DHA: 4 *N*=17	DHA: 165 (27.1)/179 (15.9)/+8.7 (*p*<0.05)	DHA: 199 (146)/133 (40.1)/−33.3 (*P*<0.05)	DHA: 37.1 (6.4)/40.5 (3.18)/+9.4 (NS)
	TG>159	Placebo: *N*=20	Placebo: 170 (14.7)/ 166 (15.5)/−2.3 (NS)	Placebo: 180 (75.2)/173 (39.6)/−4.4 (NS)	Placebo: 43.2 (12.1)/ 39.4 (3.4)/−8.9 (NS)
		6 weeks	EPA vs placebo, NS	EPA vs placebo, *P*=0.012	EPA and DHA vs placebo, NS
			DHA vs placebo, *P*=0.019	DHA vs placebo, *P*=0.003	EPA: 49.0 (51.4)/51.4 (11.2)/+4.7 (NR)
Nestel et al. [27] (2002)	*N*=21 men *N*=17 post-menopausal women	EPA: 3 *N*=12	EPA: 176 (43.6)/176 (45.2)/−0.2 (NS)	EPA: 139 (70.8)/107 (59.3)/−22.9 (*P*=0.026)	DHA: 46.7 (14.7)/ 51.4 (17.0)/+9.9 (NR)
	BMI 25–29				
	TC>212	DHA: 3 *N*=12	DHA: 176 (51.0)/182 (47.5)/+3.5 (NS)	DHA: 175 (118)/120 (95.6)/−31.8 (*P*=0.026)	Placebo: 49.8 (17.0)/ 53.3 (15.8)/+7.0 (NR)
	TG>177	Placebo: *N*=14	Placebo: 175 (51.0)/ 180 (38.6)/+2.9 (NS)	Placebo: 134 (69.9)/150 (65.5)/+11.9 (*P*=0.026)	EPA vs DHA vs placebo, *P*=0.79
	HDL<39 (men)	7 weeks	EPA vs DHA vs placebo, *P*=0.83	EPA vs DHA, NS	
	HDL<46 (women)			EPA vs DHA vs placebo, *P*=0.013	
Park and Harris [25] (2003)	*N*=33 Men and women	EPA: 4 *N*=11	EPA: 103 (23.2)/108 (20.0)/+4.9 (NS)	EPA: 74.3 (16.8)/67.3 (19.5)/−9.5 (NS)	EPA: 45.0 (10.0)/45.0 (13.3)/0 (NS)
	BMI 22–30				
	TG<200	DHA: 4 *N*=11	DHA: 96.9 (26.6)/102 (29.7)/+5.2 (NS)	DHA: 90.3 (30.1)/82.3 (26.6)/−8.8 (NS)	DHA: 50.0 (13.3)/52.0 (13.3)/+4.0 (NS)
	LDL<160	Placebo: *N*=11	Placebo: 109 (19.7)/ 112 (19.7)/+2.8 (NS)	Placebo: 107 (46.0)/106 (43.4)/−0.81 (NS)	Placebo: 42.0 (10.0)/ 42.0 (10.0)/0 (NS)
	HDL>35	4 weeks		EPA and DHA vs placebo, NS	
Woodman et al. [28] (2002)	*N*=39 men	EPA: 4 *N*=17	EPA: 103 (31.8)/104 (30.2)/+0.8 (NR)	EPA: 119 (65.7)/98.2 (51.1)/−17.2 (NR)	EPA: 46.7 (14.3)/47.1 (14.3)/+0.8 (NR)

Table 1 (continued)

Study (year)	No., sex, characteristics, baseline lipids of participants	Treatment dose (g/day), No. randomized, duration	Baseline lipid (SD or 95% CI)/endpoint lipid (SD or 95% CI) in mg/dL/% change from baseline to endpoint (p-value for baseline vs endpoint) *P*-value between study groups if available		
			LDL	Triglycerides	HDL
	N=12 post-menopausal women with diabetes type II, HTN, BMI<35	DHA: 4 *N*=18	DHA: 106 (21.3)/111 (22.8)/+5.1 (NR)	DHA: 143 (52.6)/120 (48.8)/−16.7 (NR)	DHA: 38.2 (8.2)/39.8 (8.2)/+4.1 (NR)
	TC, TG<664	Placebo: *N*=16	Placebo: 105 (18.5)/ 107 (17.0)/+2.2 (NR)	Placebo: 154 (53.1)/149 (49.6)/−3.4 (NR)	Placebo: 40.9 (9.3)/41.3 (9.3)/+0.9 (NR)
		6 weeks	EPA and DHA vs placebo, NS	EPA and DHA vs placebo, $p<0.05$	EPA and DHA vs placebo, NS
EPA vs placebo studies					
Ando et al. [20] (1999)	*N*=33 men	EPA: 1.8 *N*=19	EPA: 114 (NR)/104 (NR)/−8.8 (NR)	EPA: 258 (147)/150 (104)/−42.1 ($p<0.01$)	EPA: 31.7 (6.7)/31.3 (8.4)/−1.2 (NS)
	N=5 women on dialysis	Placebo: *N*=19	Placebo: 104 (NR)/112 (NR)/+7.0 (NR)	Placebo: 272 (166)/267 (127)/−1.6 (NS)	Placebo: 30.5 (11.8)/ 30.1 (11.8)/–1.2 (NS)
		3 months		EPA vs placebo, NS	
Kurabayashi et al. [23] (2000)	*N*=141 menopausal women	EPA: 1.8 *N*=69	EPA: 165 (29.3)/151.7 (28.6)/−8.0 (*P*=0.02)	EPA: 135 (56.6)/113 (46.0)/−16.2 (*P*=0.009)	EPA: 59.1 (17.4)/57.9 (14.3)/−1.7 (NS)
	TC 220–280	Control: *N*=72	Control: 158 (28.2)/ 144 (30.9)/−8.3 (*P*=0.001)	Control: 134 (52.2)/145 (67.3)/+8.6 (NS)	Control: 61.0 (13.9)/ 61.8 (14.3)/+1.5 (NS)
	TG 150–400	48 weeks	EPA vs control, NS	EPA vs control, *P*=0.003	EPA vs control, NS
Satoh et al. [21] (2007)	*N*=44	EPA: 1.8 *N*=22	EPA: 133 (27.0)/123 (27.0)/−7.6 (*P*=0.004)	EPA: 171 (83.2)/139 (46.0)/−18.7 (*P*=0.047)	EPA: 54.8 (14.7)/53.7 (12.7)/−2.1 (NS)
	Men and women with diabetes type II, HTN, BMI>30	Placebo: *N*=22	Placebo: 123 (29.0)/ 115 (34.4)/−6.6 (NS)	Placebo: 167 (78.8)/143 (86.7)/−14.3 (NS)	Placebo: 56.4 (12.7)/ 53.3 (20.1)/−5.5 (NS)
	TG≥150	3 months	EPA vs placebo, NS	EPA vs placebo, NS	EPA vs placebo, NS
	HDL<39				
Tanaka et al. [15] (2008)	*N*=5859 men	EPA: 1.8 *N*=9326	EPA: 182 (29.7)/137 (29.7)/−23.3 (NR)	EPA: 153 (10–220)/130 (96.5–178)/−7.3 (NR)	EPA: 58.7 (17.8)/59.5 (15.1)/+3.3 (NR)
	N=12786 post-menopausal women	Control: *N*=9319	Control: 182 (29.0)/ 137 (29.0)/−23.6 (NR)	Control: 153 (109–220)/139 (104–189)/−2.6 (NR)	Control: 58.3 (17.0)/ 59.5 (15.1)/+4.5 (NR)
	TC≥251	5 years	EPA vs control, *P*=0.602	EPA vs control, *P*<0.001	EPA vs control, *P*=0.882
	LDL≥167				
DHA vs placebo studies					
Agren et al. [38] (1996)	*N*=28 men Healthy	DHA: 1.68 *N*=14	DHA: 96.1 (27.0)/93.4 (27.0)/−2.8 (NS)	DHA: 104 (33.6)/85.8 (18.6)/−17.1 (*P*<0.05)	DHA: 50.2 (NR)/53.7 (NR)/+6.9 (NR)
	TG<221	Control: *N*=14	Control: 103 (27.0)/100 (29.3)/–2.6 (NS)	Control: 116 (37.2)/126 (43.4)/+8.4 (NS)	Control: 55.6 (NR)/46.3 (NR)/–16.7 (NR)
		15 weeks	DHA vs control, NS	DHA vs control, *P*<0.05	DHA vs control, *P*<0.01
Conquer and Holub [37] (1996)	*N*=12 men	DHA: 1.62 *N*=12	DHA: 76.8 (23.9)/71.8 (22.8)/−6.5 (NS)	DHA: 85.0 (33.6)/70.8 (33.6)/−16.7 (*P*<0.05)	DHA: 46.3 (13.5)/54.0 (17.4)/+16.7 (*P*<0.05)
	N=12 women Healthy, vegetarian	Placebo: *N*=12	Placebo: 81.1 (23.9)/88.4 (23.9)/+9.0 (*P*<0.05)	Placebo: 71.7 (24.8)/81.4 (42.5)/+13.6 (*P*<0.05)	Placebo: 52.1 (12.0)/56.0 (13.5)/+7.4 (*P*<0.05)
		6 weeks	DHA vs placebo, NR	DHA vs placebo, NR	DHA vs placebo, NR
Conquer and Holub [29] (1998)	*N*=14 men	DHA: 0.75 *N*=6	DHA, low-dose: 103 (37.8)/ 93.4 (73.4)/−9.0 (NS)	DHA, low-dose: 125 (76.1)/ 114 (95.6)/−8.5 (NS)	DHA, low-dose: 42.9 (10.4)/45.2 (12.4)/+5.4 (NS)
	N=8 women Healthy, Asian Indian background	DHA: 1.5 *N*=7	DHA, high-dose: 101 (33.6)/104 (46.0)/+3.4 (NS)	DHA, high-dose: 92.0 (69.9)/86.7 (77.0)/−5.8 (NS)	DHA, high-dose: 51.0 (13.1)/48.6 (17.4)/−4.5 (NS)
		Placebo: *N*=6	Placebo: 105 (19.7)/95.4 (15.1)/−8.9 (NS)	Placebo: 90.3 (38.4)/111 (76.1)/+22.5 (NS)	Placebo: 45.2 (5.7)/46.0 (78.5)/+1.7 (NS)
		6 weeks			
Davidson et al. [13] (2007)	*N*=18 men	DHA: 1.25 *N*=9	DHA, low-dose: 157 (20.9)/ NR/+9.3 (NS)	DHA, low-dose: 250 (86.7)/ NR/−20.9 (*P*<0.01)	DHA, low-dose: 44.0 (15.1)/NR/+5.9 (*P*<0.03)
	N=8 women with non-"elevated" BMI	DHA: 2.5 *N*=9	DHA, high-dose: 158 (15.1)/NR/+13.6 (*P*<0.001)	DHA, high-dose: 296 (66.4)/ NR/−17.6 (*P*<0.01)	DHA, high-dose: 40.2 (6.2)/NR/+6.2 (*P*<0.03)

Table 1 (continued)

Study (year)	No., sex, characteristics, baseline lipids of participants	Treatment dose (g/day), No. randomized, duration	Baseline lipid (SD or 95% CI)/endpoint lipid (SD or 95% CI) in mg/dL/% change from baseline to endpoint (p-value for baseline vs endpoint) *P*-value between study groups if available		
			LDL	Triglycerides	HDL
	TG within "range"	Placebo: *N*=8	Placebo: 158 (17.0)/ NR/−2.4 (NS)	Placebo: 236 (73.4)/ NR/+3.5 (NS)	Placebo: 42.9 (5.8)/ NR/+5.6 (*P*<0.09)
		6 weeks	DHA low-dose vs high-dose vs placebo, NR	DHA low-dose vs high-dose vs placebo, NR	DHA low-dose vs high-dose vs placebo, NR
Geppert et al. [36] (2006)	*N*=27 men	DHA: 0.94 *N*=53	DHA: 94.6 (28.2)/104.6 (30.9)/+10.6 (*P*<0.001)	DHA: 95.6 (45.1)/73.4 (25.7)/−23.1 (*P*<0.001)	DHA: 63.7 (17.0)/68.3 (17.0)/+7.3 (*P*=0.002)
	N=87 women	Placebo: *N*=53	Placebo: 98.8 (30.9)/98.1 (28.2)/−0.8 (*P*=0.764)	Placebo: 94.7 (38.9)/94.7 (45.1)/0 (*P*=0.977)	Placebo: 64.5 (17.0)/64.1 (17.0)/−0.6 (*P*=0.487)
	BMI 18–25 Healthy, Vegetarian	8 weeks	DHA vs placebo, *p*=0.003	DHA vs placebo, *P*=0.034	DHA vs placebo, *P*=0.002
Kelley et al. [30] (2007)	*N*=34 men BMI 22–35	DHA: 3 *N*=17	DHA: 120 (31.7)/138 (30.1)/−18.9 (*P*<0.05)	DHA: 247 (98.2)/187 (54.9)/−13.8 (*P*<0.05)	DHA: 41.3 (9.7)/44.4 (11.2)/+7.5 (NS)
	TC<300	Placebo: *N*=17	Placebo: 120 (31.7)/120 (30.1)/+4.4 (NS)	Placebo: 257 (91.2)/236 (84.1)/−2.2 (NS)	Placebo: 36.7 (4.6)/37.8 (6.2)/+3.2 (NS)
	TG 150–400 LDL<220	90 days	DHA vs placebo, NR	DHA vs placebo, NR	DHA vs placebo, NR
Maki et al. [35] (2005)	*N*=31 men	DHA: 1.52 *N*=27	DHA: 142 (28.6)/159 (13.5)/+11.7 (NR)	DHA: 179 (72.6)/136 (42.5)/−23.8 (NR)	DHA: 42.1 (5.8)/46.0 (3.5)/+9.2 (NR)
	N=26 women BMI<40	Placebo: *N*=30	Placebo: 130 (39.0)/134 (14.3)/+2.7 (NR)	Placebo: 166 (61.1)/152 (32.7)/−8.5 (NR)	Placebo: 42.5 (6.2)/44.8 (3.9)/+5.5 (NR)
	TC<300	6 weeks	DHA vs placebo, *P* =0.001	DHA vs placebo, *P*=0.015	DHA vs placebo, *P*=0.80
	TG<350				
	HDL 35–44 (men)				
	HDL 35–54 (women)				
Sanders et al. [33] (2006)	*N*=39 men	DHA: 1.5 *N*=40	DHA: 97.3 (35.1)/104 (37.1)/+6.7 (*p*≤0.001)	DHA: 95.6 (44.2)/82.3 (36.3)/−13.9 (*P*=0.002)	DHA: 50.2 (NR)/53.7 (NR)/+6.9 (*p*≤0.001)
	N=40 women BMI 18–35 Healthy	Placebo: *N*=39	Placebo: 95.4 (30.5)/92.3 (27.8)/−3.2 (NR)	Placebo: 81.4 (38.0)/79.7 (38.9)/−2.2 (NS)	Placebo: 55.6 (NR)/46.3 (NR)/–16.7 (NR)
		4 weeks	DHA vs placebo, *P*=0.0002	DHA vs placebo, *P*=0.152	DHA vs control, *P*=0.001
Stark and Holub [31] (2004)	*N*=38 post-menopausal women, half on hormone replacement therapy	DHA: 2.8 *N*=32	DHA: 122 (41.7)/133 (43.6)/+8.5 (NS)	DHA: 142 (95.6)/114.2 (65.5)/−19.9 (*P*<0.05)	DHA: 63.7 (15.4)/68.7 (15.4)/+7.9 (NS)
		Placebo: *N*=32	Placebo: 122 (43.6)/126 (43.6)/+3.2 (NS)	Placebo: 142 (90.3)/138 (69.9)/−3.1 (NS)	Placebo: 61.2 (15.4)/64.1 (13.1)/−3.1 (NS)
		4 weeks	DHA vs placebo, NS	DHA vs placebo, *P*<0.05	DHA vs placebo, NS
Theobald et al. [34] (2004)	*N*=19 men	DHA: 0.7 *N*=38	DHA: 122 (30.9)/134 (36.3)/+10.1 (NR)	DHA: 91.2 (51.3)/89.4 (48.7)/−1.9 (NR)	DHA: 56.8 (12.4)/59.9 (15.1)/+5.4 (NR)
	N=19 women	Placebo: *N*=38	Placebo: 122 (34.8)/126 (31.3)/+2.8 (NR)	Placebo: 93.8 (57.5)/105 (55.8)/+12.3 (NR)	Placebo: 56.4 (14.7)/57.1 (13.5)/+1.4 (NR)
	BMI<35	3 months	DHA vs placebo, *P*=0.004	DHA vs placebo, NS	DHA vs placebo, *P*=0.03
	TC<301				
	TG<266				
Wu et al. [39] (2006)	*N*=27 post-menopausal women	DHA: 2.14 *N*=14	DHA: 89.6 (20.5)/86.1 (24.7)/−3.9 (NS)	DHA: 124 (54.9)/103 (40.7)/−17.1 (NS)	DHA: 42.1 (9.3)/45.2 (10.4)/+7.3 (NS)
	BMI 18–26, vegetarian	Placebo: *N*=13	Placebo: 96.1 (12.4)/100 (11.6)/+4.4 (NS)	Placebo: 134 (27.4)/137 (54.0)/+2.6 (NS)	Placebo: 40.9 (5.8)/42.5 (10.0)/+3.8 (NS)
		6 weeks	DHA vs placebo, *P*=0.181	DHA vs placebo, *P*=0.105	DHA vs placebo, *P*=0.607

BMI body mass index (kg/m^2); *CI* confidence interval; *DHA* docosahexaenoic acid; *EPA* eicosapentaenoic acid; *HDL* high-density lipoprotein cholesterol (mg/dL); *HTN* hypertension; *LDL* low-density lipoprotein cholesterol (mg/dL); *NR* not reported; *NS* non-significant (*P*>0.05); *SD* standard deviation; *TC* total cholesterol (mg/dL); *TG* triglycerides (mg/dL)

reduction in triglycerides by DHA than EPA. The overall pooled result was DHA significantly reduced triglycerides by 6.14 mg/dL (95% CI: 2.47, 9.82) more than EPA (Fig. 2). Studies of EPA versus DHA and triglycerides were consistent and not heterogeneous (*P*= 0.39, I^2=3.1%).

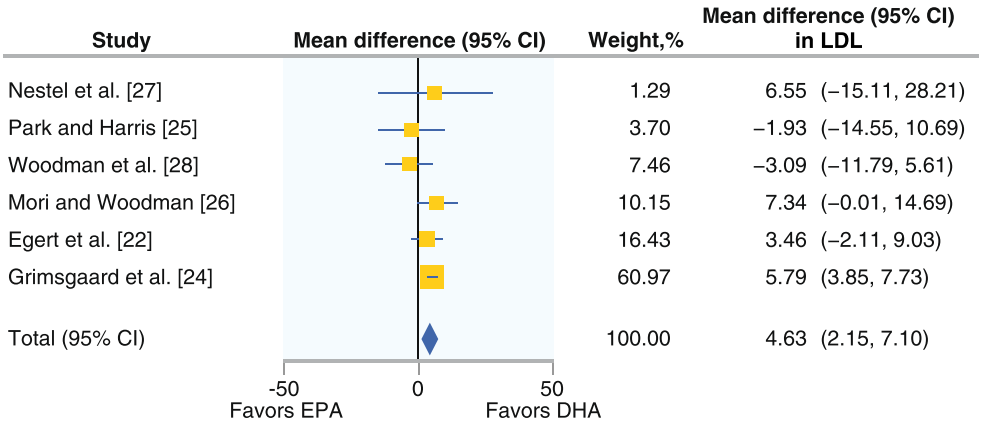

Fig. 1 Direct comparison studies of the mean difference (95% CI) of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) in increasing low-density lipoprotein cholesterol from study baseline to endpoint

HDL Cholesterol

At baseline, the mean HDL was 48±11 mg/dL in the DHA groups and 50±12.5 mg/dL in the EPA groups. Eleven [22, 26–28, 30, 31, 34–37, 39] of 13 studies of DHA and HDL reported DHA significantly raised HDL between 2.09 and 8.26 mg/dL compared with placebo. Park and Harris [25] reported a non-significant increase in HDL whereas Conquer and Holub [29] reported a non-significant decrease in HDL compared with placebo. The overall pooled effect was that DHA significantly increased HDL 4.49 mg/dL (95% CI: 3.50, 5.48) more than placebo.

Nine studies examined EPA and serum HDL. Six [22, 25–28, 32] reported EPA increased HDL between 0.15 and 2.86 mg/dL compared with placebo. Nestel et al. [27] and Egert et al. [22] reported the greatest increases in HDL that were statistically significant and of similar magnitude (2.86 and 2.85 mg/dL, respectively, compared with placebo from study baseline to endpoint). One study [15] reported a small but significant reduction in HDL for EPA compared with placebo (0.39 mg/dL; 95% CI: 0.38, 0.40). Two studies [21, 23] reported non-significant reductions in HDL. The overall pooled effect of EPA on HDL was a non-significant increase of 0.20 mg/dL (95% CI: −0.82, 0.41) compared with placebo.

Six studies [22, 24–28] directly compared EPA and DHA on HDL. All studies except Grimsgaard et al. [24] reported that DHA increased HDL more than EPA. The pooled result was a 2.15 mg/dL (95% CI: −0.92, 5.23) non-significant increase in HDL by DHA compared with EPA (Fig. 3). Because heterogeneity was detected among the studies ($P<0.00001$, $I^2=85.8\%$), a sensitivity analysis was conducted that excluded the study with the greatest weight. The overall effect of DHA compared with EPA was a stronger and statistically significant increase in HDL of 3.74 mg/dL (95% CI: 2.42, 5.05), and heterogeneity was no longer significant ($P=0.39$).

Discussion

This study examined 21 randomized controlled trials of EPA and DHA compared with placebo and/or each other on serum lipids after a minimum of 4 weeks of therapy. In pooled studies of EPA and DHA, both decreased triglycerides and increased HDL compared with placebo. However, different effects were demonstrated for LDL, whereby DHA raised LDL whereas EPA non-significantly reduced LDL compared with placebo.

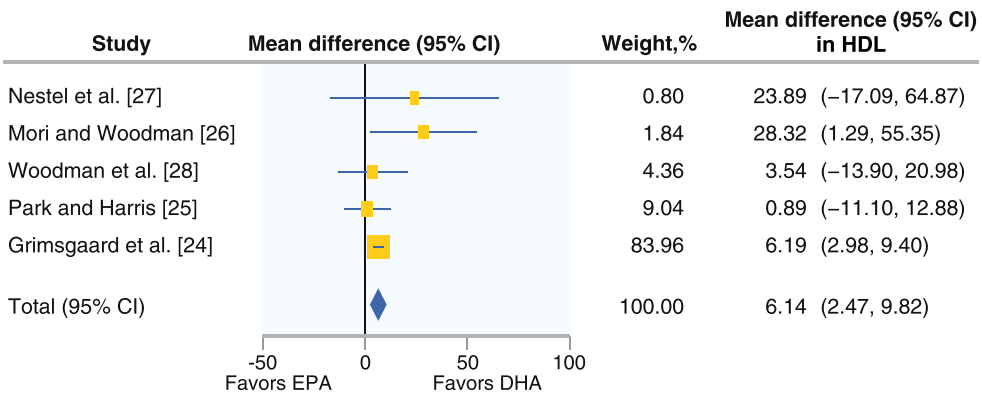

Fig. 2 Direct comparison studies of the mean difference (95% CI) of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) in reducing triglycerides from study baseline to endpoint

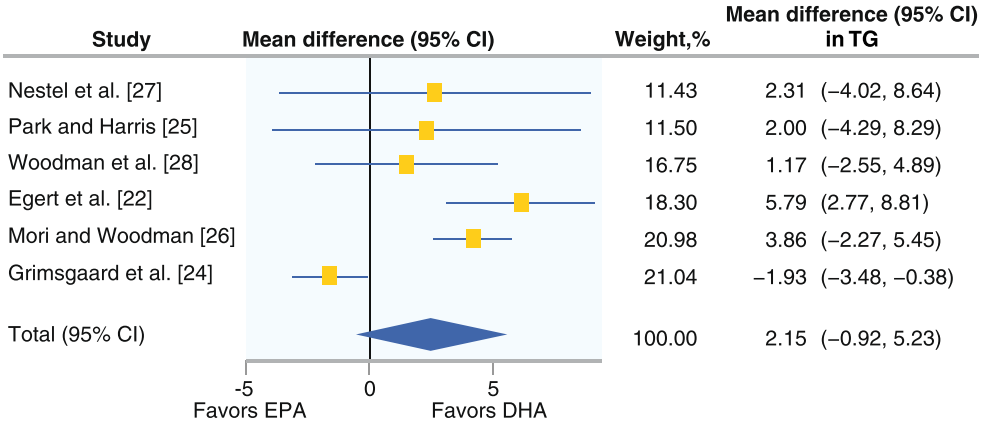

Fig. 3 Direct comparison studies of the mean difference (95% CI) of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) in increasing high-density lipoprotein cholesterol from study baseline to endpoint

Omega-3 Fatty Acids and Lipids

In pooled analyses, EPA and DHA reduced triglycerides by 45.8 and 25.1 mg/dL, respectively, compared with the pooled placebo. The greater magnitude reduction in triglycerides by EPA was driven by two studies [20, 24] that significantly reduced triglycerides compared with the pooled placebo. However, when EPA and DHA were directly compared in pooled analyses, a greater magnitude reduction in triglycerides resulted from DHA, as individual studies reported greater decreases in triglycerides by DHA than EPA. Grimsgaard et al. [24] reported DHA reduced triglycerides more than EPA, and this study had the greatest weight in the EPA versus DHA pooling due to its large sample size and tighter 95% CI compared with other studies.

DHA additionally significantly increased HDL from baseline to endpoint compared with placebo, whereas EPA had a small, non-significant increase in HDL. In pooled studies versus placebo, DHA significantly increased LDL whereas EPA had a non-significant decrease. When EPA was directly compared with DHA, EPA had a more favorable effect on LDL, with DHA significantly increasing LDL more than EPA.

Our results are consistent with recent studies that report a reduction in LDL by EPA and increase in LDL with DHA. In a recent trial of 110 participants randomized to EPA (0.6 or 1.8 g/day), DHA (0.6 g/day), or placebo, EPA reduced LDL by 2.5% and 2% with low and high doses, respectively, DHA raised LDL by 14.2%, and olive oil placebo reduced LDL by 6% [40]. Similarly, in the MARINE trial, 4 g/day of EPA (> 96% purity) for 12 weeks in participants with very high triglycerides (≥500 mg/dL) resulted in a 33.1% reduction in triglycerides ($P<0.0001$) and a non-significant 2.3% reduction in LDL [41••].

Possible Mechanistic Differences between EPA and DHA

As DHA appears to increase LDL whereas EPA does not, this suggests these individual omega-3 fatty acids have different mechanisms of action on serum lipoproteins. EPA and DHA enhance triglyceride clearance and metabolism through activation of PPARs [10] and lipoprotein lipase [25]. Activation of lipoprotein lipase promotes the clearance of triglycerides and conversion of very low density lipoprotein to LDL. The greater decrease in triglycerides (and increase in LDL) observed with DHA may result from greater lipoprotein lipase activation by DHA compared with EPA. EPA and DHA also serve as endogenous ligands for myocardial PPAR-α and PPAR-γ. Differential effects of EPA and DHA on the regulation and transcription of genes responsible for myocardial fatty acid uptake and metabolism could exist. Finally, cholesteryl ester transfer protein (CETP), which is up-regulated in hypertriglyceridemic individuals, may be variably inhibited by DHA and EPA, with a more significant reduction by DHA in in vitro studies [42]. Thus a greater reduction in CETP activity by DHA may explain the greater observed increase in HDL.

Strengths and Limitations

One strength of this study was the use of pooled data for the placebo treatment, which differed among studies and could potentially obscure the effect of the main exposure on serum lipids. This pooling procedure enabled a more accurate estimate of the effect induced by the placebo, which in principle should have no effect on the mean difference of serum lipids measured from study baseline to endpoint. Pooling of the placebos thus effectively allowed for decreased variability by reducing the standard errors associated with the test of hypothesis for population differences. Additional study strengths were the use of funnel plots to examine for publication bias and the use of sensitivity analyses when heterogeneity was suggested.

However, there are several limitations to this analysis. Studies were excluded if they did not report data in a standardized format with SD or standard errors for baseline and endpoint lipids. Another limitation is the inclusion of

small studies, which may have been inadequately powered and thus underestimate the true effect of EPA and DHA on lipids. Finally, our analysis primarily included individuals with normal triglyceride levels. Inclusion of studies with individuals with very high triglyceride levels is needed to extrapolate our findings to other populations.

Further studies are required to determine the most effective doses of EPA and DHA as monotherapy. In the MARINE trial [41••], EPA given at low (2 g/day) and high (4 g/day) doses significantly reduced triglycerides with a dose–response observed. A dose–response could not be confirmed for EPA in our analysis, as studies uniformly examined one dose of EPA. In regard to DHA, two studies [13, 29] included low and high doses of DHA but could not be pooled because sufficient data to compute the mean difference and SD were only provided in one study [29].

Additional studies are needed to examine the role of statin combination therapy with either DHA or EPA individually to assess their potential to further reduce triglycerides and non-HDL in individuals whose triglycerides remain elevated on statin therapy. In the randomized, double-blinded, placebo-controlled COMBOS trial, individuals with elevated serum triglyceride levels (200–499 mg/dL) on 40 mg/day of simvastatin were then given 4 g/day of prescription omega-3 fatty acids or placebo. This resulted in a borderline significant net increase in LDL of 3.4% in individuals randomized to omega-3 fatty acids plus simvastatin compared with simvastatin alone (P=0.052) [13]. In COMBOS, the greatest percentage increase in LDL relative to placebo occurred primarily among individuals with a low baseline LDL [14•]. Further research on EPA-statin and DHA-statin combinations is needed to assess potential synergistic effects on other important lipids, including apolipoprotein B and LDL particle number, as well as HDL and HDL function.

Conclusions

This meta-analysis examined 21 randomized controlled trials of EPA and DHA on serum lipoproteins in adults. Both decreased triglycerides compared with placebo, but in direct comparison studies a greater triglyceride reduction was demonstrated among individuals randomized to DHA compared with EPA. DHA additionally raised HDL when compared with placebo and in direct comparison studies with EPA. However, divergent outcomes for LDL were observed: DHA raised LDL whereas EPA reduced LDL, although the reduction by EPA was non-significant when compared with placebo. Further research is needed to corroborate our findings in individuals with very high triglyceride levels and to examine potential synergistic effects between individual omega-3 fatty acids and statins. The specific mechanisms for the divergent effects of EPA and DHA on lipid metabolism should be further explored.

Disclosure M.Y. Wei: none; T.A. Jacobson is a consultant for GlaxoSmithKline and Amarin.

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- • Of importance
- •• Of most importance

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