

von Willebrand Factor. Deslypere reported no difference in effect on vWF after 1 year in monks taking 3 different doses of fish oil supplements⁸⁵. Hansen found similar effects among men taking either fish oil triglycerides or fish oil ethyl ester¹⁴⁷. Across studies, though, the study by Seljeflot et al., which tested the largest dose of omega-3 fatty acid supplementation, found the largest, significant decrease in vWF. However, the study of mackerel paste diet, with a similar omega-3 fatty acid level, found no effect. The single study of plant oils found a non-significant decrease in vWF with an ALA-rich flaxseed oil diet that was similar to most marine oil studies.

Exposure Duration

Factor VII. Five studies measured factor VII levels at different time periods, ranging from 2 to 16 weeks^{56,115,138,149,155}. No differences were seen in factor VII levels at any time point.

Factor VIII. Three studies measured factor VIII activity at different time periods. Haines et al. found no effect of fish oil supplements on factor VIII at either 3 or 6 weeks¹¹⁵. Deslypere et al. did find an occasional significant decrease of factor VIII from the second trial month on in multiple measurements done between 4 weeks and 12 months⁸⁵. However, this effect was also seen in the olive oil group and no net differences were found. Mezzano et al. found similar responses to Mediterranean diet at both 1 and 3 months¹³⁸.

von Willebrand Factor. Three studies measured vWF at different time periods. Muller et al. found no change in vWF in either study arm at both 3 and 6 weeks¹⁴⁹. Both Deslypere et al. and Leng et al. found that vWF levels fluctuated at different time points ranging from 3 weeks to 1 year, but that there were no differences among arms^{69,85}.

Sustainment of Effect

Factor VII. Only Freese et al. reported data on factor VII levels after stopping treatment¹⁴³. There was no difference 4 weeks after finishing 4 weeks of treatment compared to either pre- or post-treatment levels.

Factor VIII and von Willebrand Factor. Only Deslypere et al. reported data on factor VIII activity and vWF after stopping treatment⁸⁵. There was a large increase in factor VIII activity in all study arms, including the olive oil group, at both 1 and 2 months after stopping treatment. There were no differences between fish oil supplement and control groups. There was no difference in vWF after treatment.

Platelet Aggregation

(Table 3.20)

Platelet aggregation plays a central role in the pathogenesis of acute atherothrombosis and has been associated with cardiovascular disease in some, but not all, epidemiological studies. However, pharmacological agents that inhibit platelet aggregation, such as aspirin, clearly reduce the incidence of adverse clinical cardiovascular events. The most common method of measuring platelet aggregation involves *in vitro* tests of blood samples. Aggregating agents such as adenosine diphosphate (ADP) and collagen are added to the blood samples, or spontaneously occurring aggregation is measured. The resulting platelet aggregation is used as a measurement of the potential for platelets to aggregate in the human body. There is little agreement as to which

method is most meaningful and little standardization of dose of aggregating agent or test methodology. Omega-3 fatty acids may directly affect platelets, thus both reducing CVD but also possibly increasing bleeding risk.

We found 84 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on platelet aggregation (See Table 3.1). Of these, we analyzed the 11 randomized trials with data on at least 15 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids and that also reported platelet aggregation in tabular or text format. Studies that presented platelet aggregation data graphically only were not analyzed. This additional criterion was used because of the particular difficulty in estimating data from graphs for this outcome and because of the large number of specific outcomes reported in each study.

Overall Effect ^{54,57,108,115,116,128,140,157-160}

Within the 11 studies, heterogeneous effects of omega-3 fatty acids were generally found depending on the aggregating agent, the dose of agent, and the measurement metric used. However, in most studies either no effect on platelet aggregation was found with omega-3 fatty acids or no difference in effect was seen between treatments and controls.

Sub-populations

Seven studies were performed in generally healthy individuals. Salonen et al., Junker et al., and Wensing et al. all found no effect of omega-3 fatty acid consumption and no difference with control groups in healthy men, non-obese individuals and elderly individuals, respectively ^{56,159,160}. Freese et al. (1994) found no significant effect from rapeseed oil supplements in male students; however, they did find an apparent comparative effect since Trisun sunflower oil, which was used as the comparison, significantly increased platelet aggregation ⁵⁴. Hansen et al., Freese et al. (1997a), and Agren et al. found mixed effects in younger individuals (Agren et al. in male students), with significantly decreased platelet aggregation in some study arms with some specific tests ^{128,140,157}.

Two studies evaluated hypercholesterolemic subjects, both of which found no effect of omega-3 fatty acids on measures of platelet aggregation. An additional 2 studies included diabetic patients. Haines et al. reported no effect among insulin-dependent diabetics, while Hendra et al. reported small, but significant increases in spontaneous platelet aggregation among type 2 diabetics ^{115,116}. However, in the latter study it was also reported, without supporting evidence, that epinephrine-induced aggregation was unaffected by either treatment or control. No studies specifically included patients with known or suspected CVD.

Table 3.20 Effects of omega-3 fatty acids on platelet aggregation in randomized trials (4 to 15 weeks)

Author, Year	Omega-3 Fatty Acid Arm ^a				Control		Results ^b			Quality ^c			Applicability ^d	
	N	Source	g/d		N	Source	Method, Unit	Base	Net Δ	P	Summary	Jadad		Allocation Conceal
DHA/EPA Oils														
Hansen, 1993b	14 ^e Women	Cod liver oil	ED	5.3	14 ^e	No oil	Collagen 0.5 µg/mL, %	47.0	+1.2	NS	C	1	Un	GEN II
							Collagen 4 µg/mL, %	95.0	+1.4	NS				
							ADP 2.5 µmol/L, %	81.0	-4.3	NS				
	20 ^e Men	Cod liver oil	ED	5.3	20 ^e	No oil	Collagen 0.5 µg/mL, %	56.0	-24.7	<.01				
							Collagen 4 µg/mL, %	95.0	-2.6	NS				
							ADP 2.5 µmol/L, %	76.0	-5.9	NS				
Haines, 1986	19	Fish oil	ED	4.6	22	Olive oil	Collagen 1 µg/mL, Unit	49.3	-3.1	NS	B	2	Ad	IDDM II
							Collagen 10 µg/mL, Unit	59.1	+2.2	NS				
Sirtori, 1992	12 ^e	Fish oil	ED	4.5	12 ^e	No oil	Collagen AC ₅₀ , mg/L ^f	0.35	+0.05	NS	C	2	Un	DysLip II
							Iloprost IC ₅₀ , nmol/L ^g	0.65	+0.07	NS				
Hendra, 1990	35	Fish oil	ED	3.0	32	Olive oil	Spontaneous 10 min, ^h	77.3	+3.2	.06	B	4	Un	DM II I
							Spontaneous 20 min, ^h	70.3	+4.4	.02				
							Spontaneous 30 min, ^h	67.4	+4.7	.02				
							Spontaneous 60 min, ^h	62.9	+4.2	.02				
Salonen, 1987	20	Fish oil	ED	2.7	24	Olive oil	ADP 2.3-9.0 µmol/L Aggregation extent, mV	16.2	+3.3	NS	B	3	Un	GEN II
							ADP 2.3-9.0 µmol/L Aggregation velocity, mV/sec	0.16	+0.05	NS				
Plant Oils														
Kwon, 1991	16	Canola oil diet	T	8-9% ⁱ	14	Safflower oil diet	Collagen 1 mg/L Maximum aggregation, Ω	43.5	0	NS	C	1	Un	DysLip II
							Collagen 2 mg/L Maximum aggregation, Ω	46.3	+1.5	NS				
Junker, 2001	18	Rapeseed oil diet	T	2.5% ^j	40	Olive or Sunflower oil diet	ADP 0.5 µmol/L, %	7.8	+19.7 ^k	NS	C	1	Un	GEN I
							ADP 2 µmol/L, %	27.1	+31.4 ^k	NS				
							Adrenaline 1 µmol/L, %	82.3	+9.9 ^k	NS				
							Adrenaline 4 µmol/L, %	85.1	7.8 ^k	NS				
							Spontaneous	7.2	+1.3 ^k	NS				
Freese, 1994	20	Rapeseed oil diet	A	2.3% ^j	20	Trisun Sunflower oil diet ^L	ADP 1 µmol/L slope, %/min	19.9	-5.4 ^m	.004	C	1	Un	GEN III
							ADP 2 µmol/L slope, %/min	43.4	-9.5 ^m	.002				
							ADP 3 µmol/L slope, %/min	56.4	-6.6 ^m	.001				
							Thrombin 0.12 NIH/mL slope, %/min ⁿ	20.7	-1.0	NS				
							Thrombin 0.15 NIH/mL slope, %/min ⁿ	33.5	-3.8	.03				
							Thrombin 0.18 NIH/mL slope, %/min ⁿ	36.7	-3.0 ^m	.02				

Continued

Table 3.20 Effects of omega-3 fatty acids on platelet aggregation in randomized trials (continued)

Author, Year	Omega-3 Fatty Acid Arm ^a			Control		Results ^b			Quality ^c			Applicability ^d					
	N	Source	g/d	N	Source	Method, Unit	Base	Net Δ	P	Summary	Jadad		Allocation Conceal				
Freese, 1997a	Combinations																
	16	Fish oil	ED 5.2	--	--	ADP 1 μmol/L, %/min	34.4	+3.8 ^o	nd ^p	C	3	Un	GEN II				
						ADP 2 μmol/L, %/min	60.0	+4.6 ^o	nd ^p								
						ADP 3 μmol/L, %/min	72.3	-0.7 ^o	nd ^p								
						Collagen 0.5 μg/mL, %/min	53.3	-22.2 ^o	nd ^p								
						Collagen 1 μg/mL, %/min	81.2	-2.2 ^o	nd ^p								
						Collagen 3 μg/mL, %/min	99.6	-3.4 ^o	nd ^p								
	14	Linseed oil	A 5.9	--	--	ADP 1 μmol/L, %/min	34.8	-0.7 ^o	nd ^p								
						ADP 2 μmol/L, %/min	56.3	-1.6 ^o	nd ^p								
						ADP 3 μmol/L, %/min	68.8	-5.0 ^o	nd ^p								
						Collagen 0.5 μg/mL, %/min	44.8	-9.6 ^o	nd ^p								
						Collagen 1 μg/mL, %/min	78.6	-1.8 ^o	nd ^p								
						Collagen 3 μg/mL, %/min	94.3	+4.1 ^o	nd ^p								
	Agren, 1997	14	Fish oil	ED 2.3	14	No oil	ADP 2 μmol/L, %T ⁿ	49.9	-5.8					NS	B	3	Un
ADP 5 μmol/L, %T ⁿ							74.2	-9.3	NS								
Collagen 50 μg/mL, %T ⁿ							51.3	-31.2	<.05								
ADP 2 μmol/L, %T ⁿ		37.2	+7.5	NS													
ADP 5 μmol/L, %T ⁿ		64.5	-0.1	NS													
Collagen 50 μg/mL, %T ⁿ		39.3	+13.7	NS													
ADP 2 μmol/L, %T ⁿ		35.1	+4.6	NS													
ADP 5 μmol/L, %T ⁿ		70.0	-2.9	NS													
Collagen 50 μg/mL, %T ⁿ		66.1	-20.7	<.05													
Wensing, 1999	14	Fish oil shortening	ED 1.6	11	Sunflower oil	ADP 1.5 μmol/L V _a , % ^q	48.2	+6.7	NS	B	2	Un	GEN II				
						ADP 1.5 μmol/L I _{max} , % ^r	69.6	+2.2	NS								
						Collagen 1.0 μg/mL V _a , % ^q	46.5	-6.2	NS								
						Collagen 1.0 μg/mL I _{max} , % ^r	65.7	+2.8	NS								
	13	Linseed oil shortening	A 6.5			--	--	ADP 1.5 μmol/L V _a , % ^q	52.9					-1.9	NS		
								ADP 1.5 μmol/L I _{max} , % ^r	73.3					-15.6	NS		
								Collagen 1.0 μg/mL V _a , % ^q	40.2					-3.8	NS		
								Collagen 1.0 μg/mL I _{max} , % ^r	50.2					+10.4	NS		

nd = no data

- a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.
- b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; P = P value of difference between treatment and control arms; NS = not statistically significant.
- c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to subgroup; III = narrow applicability. See Methods.
- e Cross-over study.
- f Concentration of collagen giving a 50% decrease in optical density.
- g Concentration of Iloprost resulting in 50% inhibition of platelet aggregation.
- h Percent platelets remaining after aggregation.
- i Percent of total methyl esters in diet.
- j Kcal.
- k Difference compared to average change in 2 control groups.
- L High linoleic acid (18:2 n-6) oil.
- m No significant effect compared to baseline. Significant increase compared to Trisun oil, which increased platelet aggregation rate.
- n No definition of unit provided.
- o Pre-post difference (not compared to control).
- p Not significant between treatments.
- q Aggregation velocity.
- r Maximal velocity.

Covariates

Hansen et al., recognizing that male and female sex hormones have different effects on platelet function, made an *a priori* evaluation of the potentially different effect of cod liver oil supplementation on platelet aggregation in men and women¹⁵⁷. Healthy, young, normolipemic men and women were included in the study. A large, significant decrease in platelet aggregation with low dose collagen was seen in men on cod liver oil supplements, but not in women ($P < .01$ men vs. women). Otherwise the effect of fish oil was generally mixed and not different between the sexes. No explanation was offered for why the effect would have been seen only with low-dose collagen aggregation. In contrast, Haines et al. made the blanket statement that the baseline variables smoking, alcohol consumption, and sex were not related to the response to fish oil supplementation¹¹⁵. Four other studies included only men^{54,57,140,159}. No clear difference was seen between these studies and studies that included both men and women. No other covariate was specifically analyzed in any study.

Dose and Source Effect

No study compared different doses of the same type of oil. Among the studies of fish oil supplements or diets, there was no clear association across studies between dose and change in platelet aggregation.

No significant effect was seen in any of the studies of plant oil supplements or diets, regardless of dose. Two studies compared fish oil (EPA+DHA) to linseed oil (ALA). Freese et al (1997a) was inconclusive regarding a difference between fish oil and linseed oil supplements¹²⁸. However, Wensing et al. reported that platelet aggregation was prolonged by greater amounts in subject who consumed fish oil shortening compared to those who consumed linseed oil shortening¹⁶⁰. Agren et al. compared 3 sources of EPA and/or DHA¹⁴⁰. Collagen aggregation

was reduced in subjects on both fish oil supplementation and fish diet, but not in those consuming pure DHA oil. From this, they concluded that while omega-3 fatty acids impair platelet aggregation, DHA is less potent than fish oil or dietary fish at moderate doses.

Exposure Duration

Three studies measured platelet aggregation at different time points. Haines et al. and Junker et al. reported data at 3 and 6 weeks, and 2 and 4 weeks, respectively, but did not comment on a potential time effect^{56,115}. However, no apparent difference in effect was seen between the earlier and later times. Kwon et al. noted that with 2 mg/L collagen aggregation a significant decrease in platelet aggregation was found at 3 weeks on canola oil diet, which reverted to baseline by 8 weeks⁵⁷.

Sustainment of Effect

Freese et al. (1997a) reported that the decrease in collagen-induced aggregation in the fish oil supplement arm did not return to baseline during a 12 week follow-up period, although, the other tests did¹²⁸.

Coronary Artery Restenosis

(Table 3.21, Figure 3.3)

The benefit of treatments given after percutaneous transluminal coronary angioplasty (PTCA) is often measured, in research studies, by performing a subsequent angiography and measuring the change in the luminal diameter at the sites of dilatation performed in the original angioplasty. The most common metric is restenosis rate, although there is no single standard definition of restenosis. Most researchers use minor variations of a 50% narrowing of the dilated vessel from the immediately post-dilation diameter. In theory, this level of restenosis corresponds with recurrence of angina, although clearly some patients develop symptoms with lesser levels of stenosis and some patients stay asymptomatic with greater levels of stenosis. If omega-3 fatty acids are effective at reducing clinical coronary artery disease, including angina and myocardial infarction, then the effect should be manifested in the diagnostic testing by angiography.

We found 17 studies that met eligibility criteria and reported data on coronary arteriography in patients taking omega-3 fatty acids (See Table 3.1). Of these, we analyzed the 12 randomized trials with data on restenosis rate after PTCA. Most studies re-evaluated patients at 6 months after PTCA. Maresta et al. started patients on omega-3 fatty acids 1 month prior to the initial PTCA⁸¹. In general, other studies started omega-3 fatty acid treatment up to a week prior to PTCA.

Overall Effect^{63,64,81,161-169}

All studies compared a single dosage of fish oil supplementation to control. Definitions of restenosis, however, were not uniform as noted in the footnotes of the summary table. In particular, 3 studies included abnormal exercise tolerance tests (ETT) as a potential definition of

restenosis^{166,167,169}. The results of random effects model meta-analysis are presented in both the Table 3.21 and Figure 3.3. Overall, although there is heterogeneity among the studies, there is a trend toward a net reduction of coronary artery restenosis with fish oil supplementation. The meta-analysis estimate is a lowering of risk of 14% (95% confidence interval -29%, +3%).

Table 3.21 Effects of omega-3 fatty acids on restenosis in randomized trials (approximately 3 months to 1 year)

Author, Year	Omega-3 Fatty Acid Arm ^a			Control		Results ^b			Quality ^c			Applicability ^d
	N	Source	g/d	N	Source	CR (%)	RR ^e	(95% CI)	Summary	Jadad	Allocation Concealment	
DHA/EPA Oils												
Reis, 1989 ^f	124	Fish oil	T 6.0	63	Olive oil	22	1.60	(0.95, 2.68)	B	2	Un	CVD I
Cairns, 1996	312	Fish oil	ED 5.4	313	Corn oil	45	1.04	(0.88, 1.23)	B	3	Un	CVD II
Dehmer, 1988	43	Fish oil	ED 5.4	39	No oil	46	0.40	(0.20, 0.82)	B	3	Un	CVD II
Johansen, 1999	196	Fish oil	ED 5.0	192	Corn oil	45	1.03	(0.82, 1.28)	A	3	Ad	CVD I
Milner, 1989 ^g	84 ^h	Fish oil	ED 4.5	99	No oil	35	0.54	(0.32, 0.90)	B	3	Un	CVD I
Bairati, 1992a	59	Fish oil	ED 4.5	60	Olive oil	48	0.63	(0.40, 1.01)	B	5	Un	CVD I
Nye, 1990	35	Fish oil	ED 3.6	34	Olive oil	30	0.38 ^h	(0.17, 0.84)	C	4	Un	CVD I
Franzen, 1993	92	Fish oil	ED 3.1	83	Olive oil	35	0.93	(0.62, 1.41)	B	5	Ad	CVD II
Grigg, 1989	52	Fish oil	ED 3.0	56	Olive/corn	31	1.09 ⁱ	(0.65, 1.84)	C	3	Ad	CVD I
Bellamy, 1992	60	Fish oil	ED 3.0	53	No oil	40	0.80 ^j	(0.49, 1.32)	C	3	Un	CVD I
Kaul, 1992 ^k	58	Fish oil	ED 3.0	49	No oil	27	1.23	(0.68, 2.24)	B	2	Un	CVD II
Maresta, 2002	125	Fish oil	ED 2.6 ^L	132	Olive oil	41	0.76	(0.55, 1.06)	B	3	Un	CVD I
REM MA^m	1,240			1,173		0.86 (0.71, 1.03)						

- a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.
b CR = control rate (the rate of restenosis in the control arm); RR = relative risk; 95% CI = 95% confidence interval.
c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
d Applicability based on generalizability to patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for coronary stenosis. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
e Relative risk calculated based on reported data.
f Three patients refused angiography and underwent exercise tolerance test instead. Angiographic restenosis defined as >70% narrowing.
g In asymptomatic patients, restenosis defined by abnormal exercise tolerance test. In patients with symptoms, restenosis defined by either exercise tolerance tests, angiography, or both.
h Based on lesions, not subjects
i Numbers in various sections of text and graph are not consistent. Data here derived from graph. Apparently, these numbers are based on numbers of lesions, but this is unclear.
j Only percentage of patients with restenosis reported. Percentage does not exactly match number of patients reported to have had follow-up restenosis.
k In asymptomatic patients, lack of restenosis defined by normal exercise tolerance test. Patients with symptoms or abnormal exercise tolerance tests underwent angiography.
L 5.1 g for 1 month before and 1 month after PTCA, then reduced to 2.6 g for an additional 5 months.
m Random effects model meta-analysis. See Methods.

Sub-populations and Covariates

Most studies included all patients who were undergoing first PTCA, therefore with known or suspected coronary artery disease. No study restricted eligibility to patients with either diabetes or dyslipidemia. A number of studies performed multivariate analysis including diabetic, lipid, and cardiovascular variables, generally finding no association between these covariates and

restenosis in the randomized trials. Only Bairati et al. commented about the effect of multivariate analysis on the relative risk of restenosis from fish oil supplement treatment ¹⁶¹. The authors reported that after controlling for history of hypertension, myocardial infarction, and diabetes, and for smoking, body mass index, angina class, degree of stenosis, location and number of stenoses, and ejection fraction, the inverse association between fish oil supplementation and restenosis was stronger and of higher statistical significance (because of a higher risk profile in the fish oil group).

Reis et al. and Kaul et al. both compared relative risk of restenosis in men and women; neither found a significant difference in effect, although both found a higher (worse) relative risk in women than in men ^{166,169}. In men, the relative risks of restenosis were 1.33 and 1.29, respectively, compared to 2.20 and 1.78 in women. Notably, though, these 2 studies had the lowest control rates (the rate of restenosis in the control arm, a commonly used metric to estimate the underlying severity of disease) and were the only 2 studies with relative risks substantially greater than 1.0. Interestingly, the 1 study which was restricted to men, Dehmer et al., had about the lowest relative risk of restenosis among the studies.

Dose and Source Effect

No study compared doses of fish oils and all evaluated only fish oil. Across studies, no effect is apparent based on dose of fish oil supplement.

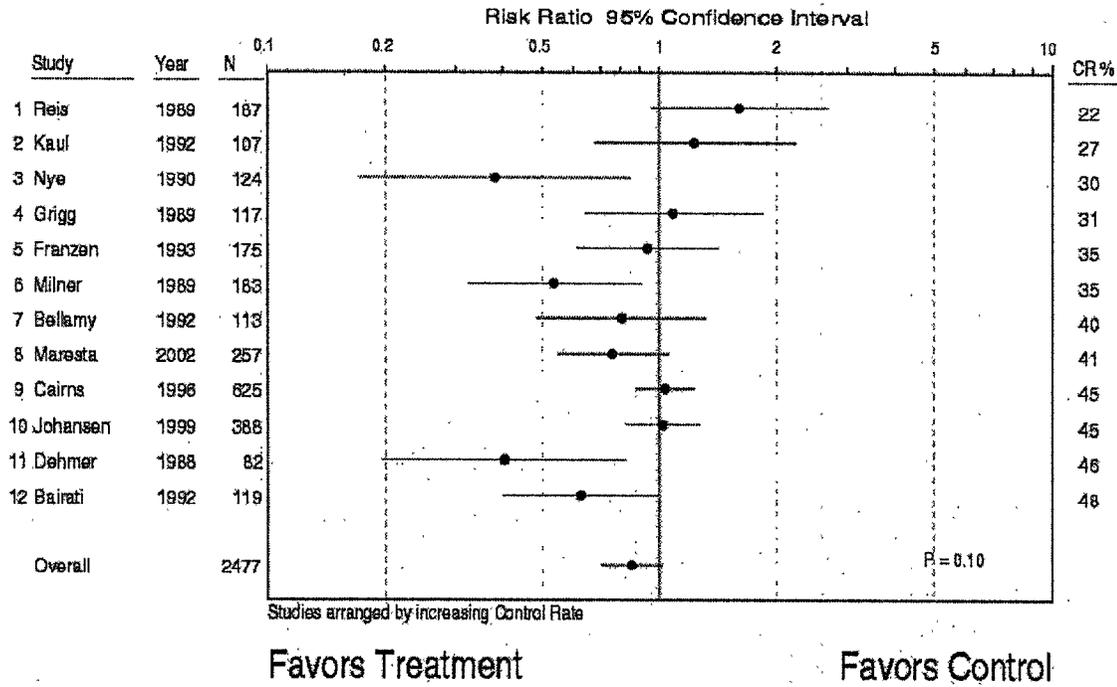
Exposure Duration

Each study evaluated restenosis at one time point only. Across studies, the duration of treatment does not appear to correlate with the relative risk of restenosis. In fact, both the longest study ¹⁶⁸ (12 months) and the shortest study ¹⁶³ (approximately 3-4 months) had similarly, low and statistically significant relative risks of restenosis.

Sustainment of Effect

No study re-evaluated for restenosis after stopping treatment.

Figure 3.3 Random effects model of effect of fish oil on coronary artery restenosis following percutaneous transluminal coronary angioplasty.



N = number of patients, except for 2 studies that reported number of lesions: Nye¹⁶⁸ had 35 patients on fish oil, 34 on control; Grigg¹⁶⁴ had 52 patients on fish oil, 56 on control. CR% = control rate, the restenosis rate in the control arm.

Carotid Intima-Media Thickness

(Table 3.22)

Ultrasound measurement of the thickness of the carotid arterial wall, termed carotid intima media thickness (IMT), has emerged as a practical technique that carries significant prognostic information in terms of future cardiovascular outcomes^{170,171}. There are numerous methods of measuring carotid IMT, including using different sites and averaging different numbers of measurements. The more commonly reported methods include measurements of the common carotid artery and an average of multiple sites in the common and internal carotid arteries and the carotid bifurcation.

Four studies met eligibility criteria and reported data on the effect of omega-3 fatty acids on carotid IMT. Only one was a randomized trial of fish oil supplements. A second study reported IMT measurements only from the intervention arm of a randomized trial of ALA margarine. Two cross-sectional studies compared residents of a Japanese fishing village to a farming village and quartiles of white Americans based on ALA intake.

Table 3.22 Effects of omega-3 fatty acids on carotid intima-media thickness (mm) in studies (2 yr or cross-sectional)

Author, Year	Omega-3 Fatty Acid Arm ^a			Results ^b				Quality ^c			Applicability ^d
	N	Source	g/d	Arteries ^e	Base	Net Δ	P	Summary	Jadad	Allocation Conceal	
RCT											
DHA/EPA Oils											
Angerer, 2002	87	Fish oil	ED 1.7	Overall; mean maximum	1.26	+0.02	NS	B	4	Ad CVD II	
				CCA; mean maximum	0.86	+0.02	NS				
	84	Fatty acid		CB; mean maximum	1.54	+0.03	NS				
				ICA; mean maximum	1.11	+0.02	NS				
Longitudinal Cohort (No Control)											
Plant Oils											
Bemelmans, 2002	95	ALA margarine	A 1.7	Overall; mean	0.83	+0.05 ^f	<.01 ^g	--	--	--	CVD I
Cross-Sectional											
Plant Oils											
Djousse, 2003 ^h	175	Mean total	A 1.2	CCA; mean ⁱ	0.64	-0.06	.01 Trend	--	--	--	GEN I
	176	linolenic acid	A 0.8		0.60	-0.10					
	174	intake ⁱ	A 0.6		0.63	-0.07					
	173		A 0.4		0.70	--					
	175	Mean total	A 1.2	CB; mean ^j	0.94	-0.05	.0008 Trend				
	176	linolenic acid	A 0.8		0.86	-0.13					
	174	intake ⁱ	A 0.6		0.91	-0.08					
	173		A 0.4		0.99	--					
	175	Mean total	A 1.2	ICA; mean ⁱ	0.71	-0.01	NS Trend				
	176	linolenic acid	A 0.8		0.70	-0.02					
	174	intake ⁱ	A 0.6		0.70	-0.02					
	173		A 0.4		0.72	--					
Fish and Mediterranean Diets											
Yamada, 1997	248	Fishing village	F 146	CCA; mean	0.70	-0.03	<.05	--	--	--	GEN II
	197	Farming village	F 84		0.73	--					

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; F = Fish; T = Total omega-3 fatty acids.

- b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Pre-Post Δ = change in omega-3 fatty acid arm (no control); Cohort Δ = difference in IMT between cohort and reference cohort (cross-sectional); $P = P$ value of difference between treatment and control arms; NS = not statistically significant.
- c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to subgroup; III = narrow applicability. See Methods.
- e CB, Carotid bifurcation; CCA, Common carotid artery; ICA, Internal carotid artery.
- f Change from baseline.
- g Compared to baseline.
- h The N's represent the number of subjects with baseline data. The numbers of subjects with each measurement of arteries' IMTs were not recorded. The range of number of arteries measured is 181-348 across arteries.
- i By staff-administered semi-quantitative food-frequency questionnaire.
- j Mean values adjusted for sex, age, energy, waist-to-hip ratio, field center, and smoking status.

Overall Effect ^{51,79,172,173}

The only placebo-controlled randomized trial found small, non-significant net thickening of carotid IMT, using 4 different measurements at 24 months, with fish oil supplementation. The uncontrolled cohort of subjects consuming ALA margarine had a significant thickening in IMT at 2 years. However, the absolute change in IMT in this cohort of subjects was similar to the absolute change in IMT in the fish oil supplementation arm in the randomized trial (an absolute increase of between 0.05 mm and 0.11 mm in the study by Angerer et al.)^{79,172}. The cross-sectional studies both found that people with greater dietary intake of omega-3 fatty acids, either as total linolenic acid or as fish, had significantly thinner IMTs than those with less intake.

Sub-populations and Covariates

Other than study design, the primary difference between the studies that found no effect and the studies that found a beneficial effect of omega-3 fatty acids is that the former were both trials in patients with cardiovascular disease and the latter were both studies of generally healthy individuals. There is insufficient data, however, to conclude that the differences were due to study populations. There is no evidence among people with diabetes or hyperlipidemia. Bemelmans et al. performed a regression analysis of predictors of change in IMT among subjects taking ALA margarine¹⁷². Age, sex, blood pressure, LDL, and weight were not predictive of change in IMT. In addition, change in intake of polyunsaturated fatty acids, cholesterol and alcohol were not predictive of change in IMT. Change in intake of saturated fatty acids (SFA) was positively associated, and change in intake of fruit was negatively associated, with change in IMT in univariate analysis but not in multivariate analysis (although it is not clear what factors were included in multivariate analysis since none was significant).

In the cross-sectional study, IMT was greater in older than younger subjects in both the fishing and farming villages. Among younger villagers, IMT was non-significantly lower in the fishing village than the farming village; however, in subjects in their seventh and eighth decades IMT was marginally greater in the fishing village.

Dose and Source Effect, Exposure Duration, Sustainment of Effect

There are insufficient data to draw conclusions regarding dose effect, oil type, duration of intervention or exposure, or sustainment of effect after stopping omega-3 fatty acids.

Exercise Tolerance Test

(Table 3.23)

The exercise tolerance test (ETT), or stress test, measures the heart's aerobic exercise capacity and is a common test to determine clinical severity of coronary artery disease. The standard method of performing ETT is with the modified Bruce protocol on a treadmill. Some studies instead used a bicycle ergometer. A wide range of different metrics are used to measure patients' performance.

All eligible studies that reported data on the effect of omega-3 fatty acids on ETT were included; 6 studies qualified. Three were randomized trials and 3 were longitudinal cohort studies without control arms of subjects with known coronary artery disease who were treated with fish oil supplements.

Table 3.23 Effects of omega-3 fatty acids on treadmill and bicycle exercise tolerance tests in studies (6 weeks-6 months)

Author, Year	Omega-3 Fatty Acid Arm ^a			Test	Results ^b			Quality ^c			Applicability ^d
	Control Arm				Base	Net Δ	P	Summary	Jadad	Allocation Conceal	
	Source	g/d	N								
DHA/EPA Oils											
RCTs											
Solomon, 1990	Fish oil	ED 4.6	5	Work load producing angina, kwatt-sec	18.87	-1.47	NS	B	4	Un	CVD II
	Olive oil		5								
Franzen, 1993	Fish oil	ED 3.1	92	Exercise capacity, kwatt-sec	29	+5.2	NS	B	5	Ad	CVD II
		Olive oil		83	Sum ST depression, mV	2.0	-0.2				
Salachas, 1994	Fish oil	ED 3.0	20	Exercise duration, min	8.2	+1.7	<.05	B	4	Un	CVD II
		Olive oil		19	Maximum double product ^e	16.5	+6.2				
Longitudinal Cohorts (No Control)											
Warren, 1988	Cod liver oil	E 3.1	7	Peak exercise RPP ^f	18,800	+300	NS	--	--	--	CVD II
			7	Ratio resting/exercise RPP ^f	0.45	-0.08	<.05				
			6	Time to ischemia, min	7.6	+0.9	NS				
Verheugt, 1986	Fish oil	ED 3.0	5	Exercise duration, min	6.8	-0.2	NS	--	--	--	CVD I
				Max ST depression, mm	2.6	+0.2	NS				
Toth, 1995	Fish oil	T 1.7	10	Peak exercise TPR ^g	730 ^h	-40 ^h	<.01	--	--	--	CVD DysLip II
				Peak exercise Cardiac Index ⁱ	6.3 ^h	+1.0 ^h	<.05				
				Relative aerobic capacity, %	70 ^h	+10 ^h	<.01				
				ST score	1.2 ^h	-0.4 ^h	<.05				

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; F = Fish; T = Total omega-3 fatty acids.

- b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Pre-Post Δ = change in omega-3 fatty acid arm (no control); $P = P$ value of difference; NS = not statistically significant.
- c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
- e Maximum heart rate x maximum systolic pressure; likely divided by 1000
- f Rate-pressure product; equivalent to work load.
- g Total peripheral resistance during exercise, measured using impedance-cardiography.
- h Estimated from graph.
- i Cardiac index during exercise, measured using impedance-cardiography.

Overall Effect ^{64,174-178}

The 3 randomized trials each found a small relative improvement in exercise capacity in subjects with coronary artery disease who took fish oil supplements compared to those who took olive oil supplements. However, with a single exception, exercise capacity measurements improved in all study arms, regardless of whether subjects consumed fish oil or olive oil supplements. The maximum double product (heart rate multiplied by blood pressure) fell by a non-significant amount in the olive oil arm in Salachas et al. ¹⁷⁴.

Warren et al. evaluated 7 patients with stable angina who took cod liver oil supplements for 6 weeks ¹⁷⁸. Exercise workload and time to ischemia improved, although the changes were not significant. The ratio of resting to exercise workload fell significantly. Verheugt et al. studied 5 men with moderate to severe exercise-induced angina ¹⁷⁷. They were given fish oil for 6 months. The patients' angina was sufficiently severe that all ETTs both before and after treatment were discontinued because of angina symptoms. Essentially no change was found in either exercise duration or maximal ST depression. Toth et al. enrolled 10 men with coronary artery disease and hyperlipidemia ¹⁷⁶. They fish oil supplements for 2 months. A variety of measures of cardiac function significantly improved.

Overall, given the small number of studies and subjects, the different metrics used across studies, and the lack of placebo control in half the studies, only limited conclusions can be drawn about the effect of omega-3 fatty acids in improving cardiac function in patients with coronary artery disease. The studies suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small.

Sub-populations, Dose Effect, Duration, Sustainment of Effect

There is no evidence regarding different doses, duration of fish oil consumption, other omega-3 fatty acids, the effect in various sub-populations, or sustainment of effect.

Heart Rate Variability

(Table 3.24)

Heart rate variability is measured on 24-hour ambulatory electrocardiography recordings. A number of different measurements can be used to estimate heart rate variability. The studies of omega-3 fatty acids primarily measured the mean standard deviation (SD) of the RR interval (the time between heart beats). Abnormal QRS complexes were excluded. The larger the SD of the RR interval (SDNN), the greater the variability of the time between heart beats. An increase in SDNN is protective against ventricular arrhythmias and, in post-myocardial infarction patients, is protective against mortality^{179,180}. Notably, both beta blockers and angiotensin converting enzyme inhibitors both increase heart rate variability¹⁷⁹.

Only one set of investigators, in Denmark, have reported data on the effect of omega-3 fatty acids on heart rate variability in studies that met eligibility criteria. They analyzed 2 sets of subjects in randomized trials and also analyzed the cross-sectional data of one of the sets of subjects.

Table 3.24 Effects of omega-3 fatty acids on heart rate variability – SD of RR (msec) – in studies (12 weeks or cross-sectional)^a

Author, Year	Omega-3 Fatty Acid Arm ^b				Control		Results ^c			Quality ^d			Applicability ^e
	N	Source	g/d		N	Source	Base	Net Δ	P	Summary	Jadad	Allocation Conceal	
RCTs													
DHA/EPA Oils													
Christensen, 1999	20	Fish oil	ED	5.9	20	Olive oil	136	+13	NS	B	4	Un	GEN II
	20	Fish oil	ED	1.7			164	+3	NS				
Christensen, 1996	26	Fish oil	ED	4.3	23	Olive oil	115	+18	<.05	B	4	Ad	CVD III
Cross-sectional													
Fish and Mediterranean Diets													
Christensen, 1997 ^f	Frequency				Cohort Δ								
	18	Fish diet	≥2x/wk		9	No fish	119	+16 ^g	NS	--	--	--	CVD III
25	Fish diet	1x/wk		122			+19 ^g	NS					

a Standard deviation of RR intervals on 24 hour ambulatory electrocardiography recordings.

b A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

c Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Cohort Δ = difference in IMT between cohort and reference cohort (cross-sectional); P = P value of difference between treatment and control arms; NS = not statistically significant.

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

f Cross-sectional evaluation of baseline data from Christensen, 1996.

g Difference between fish cohort and no-fish cohort.

Overall Effect¹⁸¹⁻¹⁸³

One randomized controlled trial was performed in 60 healthy volunteers who took either low or high dose fish oil supplements, or olive oil capsules for 12 weeks¹⁸³. No significant effect was

found either within study arms or compared to olive oil. The authors concluded that among all subjects, fish oil supplementation had no effect on heart rate variability.

In a randomized trial of 49 patients who had had a recent myocardial infarction and had a ventricular ejection fraction below 0.40 those who consumed fish oil supplements (for 12 weeks) had a significant increase in SDNN compared to controls¹⁸¹. The authors concluded that omega-3 fatty acids may increase heart rate variability in survivors of myocardial infarction which may be protective against ventricular arrhythmias and mortality.

The same patients with recent myocardial infarction were divided at baseline into 3 groups based on their regular level of fish consumption¹⁸². Both groups who consumed at least 1 fish meal per week had greater SDNN than those who did not consume fish, though the difference was not statistically significant. This finding may suggest that dietary fish consumption increases SDNN and thus is protective against ventricular arrhythmia.

Sub-populations and Covariates

Neither study directly compared healthy subjects with those with CVD. Neither examined subjects with either diabetes or dyslipidemia. While the effect of fish oil supplementation appeared greater in the study of subjects with recent myocardial infarction, there is insufficient evidence to compare the effect in subjects with or without heart disease.

In the study of healthy subjects, sub-group analyses based on sex and baseline SDNN suggested that the effect of fish oil supplementation was greatest in the 18 men with below median (<150 msec) baseline SDNN. However, data were not reported for the other 3 subgroups (women and those with above median SDNN).

Dose and Source Effect and Exposure Duration

The study among healthy subjects compared low and high dose fish oil supplementation. While it appears that there may be a trend toward increasing SDNN with higher dose fish oil, it is noteworthy that the subjects on high dose fish oil had no change in their SDNN while those on olive oil had a decrease in SDNN. Both trials lasted 12 weeks. There is no evidence regarding the effect of duration of intervention or exposure.

Sustainment of Effect

Neither study re-examined subjects after stopping fish oil supplementation.

Tissue Levels of Dietary Omega-3 Fatty Acids

(Tables 3.25-3.31, Figures 3.4-3.6 [Figures at end of Tissue Levels section])

As noted in Chapter 1, in theory, the most immediate outcome related to omega-3 fatty acid intake is a change in tissue levels of the fatty acids. In this section, we review studies that examined the correlation between omega-3 fatty acid intake and tissue levels. Among studies analyzed for other outcomes, we found 60 studies that reported data on the association between omega-3 fatty acid consumption and changes in omega-3 fatty acid composition in various tissues. Of these, we analyzed the 33 largest randomized trials that reported percent phospholipid

levels in either plasma or serum or in 1 of 4 blood cell membranes (Table 3.25). For plasma and serum phospholipid composition and for platelet phospholipid composition we analyzed randomized trials with data on at least 25 subjects and crossover trials with at least 20 subjects in omega-3 treatment arms. Because few studies reported erythrocyte, granulocyte, or monocyte membrane phospholipid compositions, we analyzed all eligible randomized trials.

Summary (Table 3.26)

Meta-regression revealed direct relationships between dose of consumed EPA+DHA and changes in measured levels of EPA and DHA, either as plasma or serum phospholipids, platelet phospholipids, or erythrocyte membranes. The correlation between dose and change in level appears to be fairly uniform, where 1 g supplementation of EPA and/or DHA is associated with, approximately, a 1% increase in EPA+DHA level. Granulocyte and monocyte membrane phospholipid levels also increased by roughly similar amounts after omega-3 fatty acid supplementation in individual studies. In these studies, ALA level did not change significantly after supplementation in any blood marker. In most studies, there was a decrease in arachidonic acid (AA, 20:4 n-6) level, which corresponded to the increase in EPA+DHA level.

Among eligible studies, only 3 included ALA supplementation arms^{53,143,160}. The dose of ALA in these 3 studies ranged from 4.5 to 9.5 g/d. The studies consistently found an increase in both ALA and EPA levels in the blood markers, at these doses of ALA. In contrast, there was no significant change in DHA level when lower dose of ALA was used (up to 6.8 g/d) but in the study arm that received 9.5 g/d ALA a significant increase in DHA level was also found.

Table 3.25. Studies reporting plasma/serum, platelet, erythrocyte, and other phospholipid changes

Study	Study Design	N ^a	Plasma or Serum PL	Platelet PL	RBC PL	Granulocyte PL	Monocyte PL
Agren, 1988	RCT	29		√	√		
Agren, 1991	RCT	49		√	√		
Agren, 1996	RCT	41	√				
Angerer, 2002	RCT	87			√		
Bonaa, 1992	RCT	72	√				
Brox, 2001	RCT	80	√				
Cobiac, 1991	RCT	25	√				
Dehmer, 1988	RCT	43		√			
Dunstan, 1997	RCT	26		√ ^b			
Dunstan, 1999	RCT	26			√ ^b		
Finnegan, 2003	RCT	116	√ ^c				
Freese, 1997b	RCT	29		√ ^c			
Green, 1990	Crossover	27	√	√	√		
Grimsgaard, 1997	RCT	147	√				
Grundt, 1995	RCT	28	√				
Haines, 1986	RCT	19			√		
Hansen, 1989	Crossover	40	√				√
Hansen, 1993b	Crossover	34	√				
Hendra, 1990	RCT	37		√			
Leigh-Firbank, 2002	Crossover	55		√			
Luo, 1998	Crossover	10			√		
Madsen, 2003	RCT	40		√		√	
McVeigh, 1993	Crossover	23		√			
Mori, 1994	RCT	85		√			
Mori, 1999	RCT	27	√ ^b				
Mori, 2000	RCT	36	√	√			

Nenseter, 2000	RCT	34	√	
Osterud, 1995	RCT	106	√	
Rivellese, 1996	RCT	8		√
Sacks, 1994	RCT	60	√	
Solomon, 1990	RCT	5		√
Wensing, 1999	RCT	27		√ ^c
Woodman, 2002	RCT	35	√	

PL = phospholipids; RBC = red blood cell (erythrocyte); RCT = randomized controlled trial.

a Subjects consuming omega-3 fatty acids.

b Study reported total omega-3 fatty acids only. Not in the meta-regression analyses.

c Study included an ALA treatment arm.

Table 3.26. Association of EPA+DHA consumption and tissue levels: Meta-Regression Results

Markers	Studies	Arms ^a	Slope	SE ^b of Slope	Intercept	r ²	P value
Plasma or serum phospholipids	15	28	0.93	0.20	1.41	0.45	<.001
Excluding studies with incomplete data ^c	12	24	1.24	0.20	0.89	0.63	<.001
Platelet phospholipids	12	20	0.74	0.16	1.16	0.52	<.001
Excluding studies with incomplete data ^d	10	18	0.80	0.12	1.25	0.72	<.001
Erythrocyte membrane	10	13	0.63	0.40	3.22	0.11	.14
Excluding studies with incomplete data ^c	9	12	1.05	0.37	2.69	0.39	.02
Granulocyte membrane	1	2	--				
Monocyte membrane	1	1	--				

a Number of separate study arms of subjects who consumed omega-3 fatty acids.

b Standard error. Use number of treatment arms to back-calculate standard deviation.

c Hansen, 1989¹⁴⁶; Hansen, 1993b¹⁵⁷; Green, 1990¹⁰¹; Sacks, 1994⁷⁵ were excluded because only change of EPA in the marker's phospholipid profile was reported.

d Green, 1990¹⁰¹; Hendra, 1990¹¹⁶ were excluded because only change of EPA in the marker's phospholipid profile was reported.

e Green, 1990¹⁰¹ was excluded because only the change of EPA in the marker's phospholipid profile was reported.

Plasma or Serum Phospholipid

Composition^{48,53,62,66,74,90,97,100,101,120,129,131,132,146,157,184} (Table 3.27, Figure 3.4)

EPA/DHA. For plasma and serum phospholipid composition, 16 randomized trials with 30 omega-3 fatty acid arms were initially included; however, we excluded 1 study that reported only total omega-3 fatty acid dose and levels¹³¹. Among the 15 trials of EPA and/or DHA supplementation (which had 28 treatment arms), the dose of EPA+DHA ranged from 0.2 to 5.8 g/day. Study populations include general healthy population, and people with diabetes, dyslipidemia or cardiovascular diseases. Meta-regression shows a significant dose-response relationship between the dietary EPA and DHA supplementations and the changes in EPA+DHA compositions in plasma or serum phospholipids across studies. Across studies, the effect was similar regardless of source of EPA or DHA. Three studies compared purified EPA to purified DHA^{66,120,132}. All found that purified EPA increased EPA and decreased DHA in plasma phospholipid and that purified DHA increased DHA by about 4 to 7 times as much as EPA in plasma phospholipid; however, combined EPA+DHA was increased by about the same amount by both fatty acids.

Meta-regression equation ($r^2 = 0.45$, $P < .001$):

$$\text{Change in Plasma/Serum EPA+DHA Level (\%)} = 0.93 \times [\text{EPA+DHA Intake (g/day)}] + 1.41$$

Because 4 studies reported only EPA levels, we re-analyzed the data with only the 12 studies with a complete EPA and DHA profile of plasma/serum phospholipids. As expected, since no study excluded DHA levels, the revised meta-regression equation indicates that the EPA+DHA level increases by a greater amount for each unit of omega-3 fatty acid supplementation and the r^2 was greater than in the meta-regression that included all studies.

Meta-regression equation ($r^2 = 0.63, P < .001$):

$$\text{Change in Plasma/Serum EPA+DHA Level (\%)} = 1.24 \times [\text{EPA+DHA Intake (g/day)}] + 0.89$$

ALA. One study also evaluated 2 linseed/rapeseed oil supplementation doses, which included primarily ALA with minimal EPA and DHA⁵³. Finnegan et al. found that with higher dose ALA (9.5 g/d), EPA, DHA and ALA levels all significantly increased. With lower dose ALA (4.5 g/d), EPA and ALA levels rose by a degree consistent with the lower dose of omega-fatty acids; although DHA levels did not change. In the remaining study arms of fish oils and sunflower oils, small amounts of ALA (≤ 1.5 g/d) did not affect ALA levels. In this study, a daily dose of 9.5 g or 4.5 g ALA (with 0.3 g EPA+DHA) had similar effects on plasma EPA levels as a daily dose of 1.7 g or 0.8 g EPA+DHA (with 1.4 g ALA), respectively. The plasma level of AA did not decrease in either ALA arm.

Table 3.27 Effect of omega-3 fatty acid supplementation on fatty acid profile of serum/plasma phospholipids in randomized trials (6 weeks to 14 months)

Study, Year	Omega-3 Fatty Acid Arms ^a				Base ED (%) ^b	Results ($\Delta\%$) ^c				Quality ^d			Applicability ^e	
	Control Arm			N		AA ^f	ALA	EPA	DHA	Summary	Jadad	Allocation Concealment		
	Source	g/d	ED											
EPA/DHA Oils														
Bonaa, 1992	72	Fish oil	ED	5.1	11.8	-1.00	0.00	+5.10	+1.70	B	4	Un	DysLip	I
	74	Corn oil	ED	0	11.5	+0.60	+0.10	-0.20	-0.20					
Green, 1990	27 ^g	Fish oil	ED	4.3	nd	0.00		+2.60		B	4	Un	DysLip	II
		Corn/Olive oil	ED	0	nd	nd		nd						
Grimsgaard, 1997	75	EPA ester	E	4.0	6.0	-0.98	-0.05	+4.65	-0.55	A	5	Un	GEN	I
	72	DHA ester	D	4.0	6.0	-0.82	-0.02	+0.47	+3.30					
	77	Corn oil	ED	0	6.2	+0.11	+0.01	-0.06	-0.10					
Mori, 2000	19	Purified EPA	E	4.0	nd	-3.00		+8.25	-0.25	B	4	Un	DysLip	II
	17	Purified DHA	D	4.0	nd	-2.25		+1.00	+7.25					
	20	Olive oil	ED	0	nd	+0.10		-0.10	+0.50					
Woodman, 2002	17	Purified EPA	E	4.0	5.9			+8.64	-1.29	B	3	Un	DM II	II
	18	Purified DHA	D	4.0	6.0			+1.09	+6.71					
	16	Olive oil	ED	0	6.8			nd	nd					
Grundt, 1995	28	Fish oil	ED	3.4	nd	-0.60		+3.80	+1.50	B	2	Un	DysLip	II
	28	Corn oil	ED	0	nd	-0.30		-0.50	-0.40					
Brox, 2001	40	Cod liver oil	ED	3.3	5.2	-0.34	-0.39	+1.27	+1.49	C	1	Un	DysLip	I
	40	Seal oil	ED	2.6	4.8	+0.14	-0.35	+2.61	+1.81					
	36	No oil	ED	0	5.1	+0.26	+0.91	+0.04	+0.81					
Osterud, 1995 ^h	26	Cod liver oil	ED	3.1	nd	-0.25	-0.09	+2.36	+1.51	C	2	Un	GEN	I
		A	0.2											
	27	Seal/Cod liver oil	ED	2.8	nd	-0.30	-0.04	+2.66	+1.85					
27	Seal oil	ED	2.4	nd	-0.20	-0.07	+2.01	+1.29						
		A	0.2											

Study, Year	Omega-3 Fatty Acid Arms ^a				Base ED (%) ^b	Results (Δ%) ^c				Quality ^d			Applicability ^e
	Control Arm			g/d		AA ^f	ALA	EPA	DHA	Summary	Jadad	Allocation Concealment	
	N	Source											
	26	Whale oil	ED 1.7 A 0.2	nd	-0.15	-0.06	+1.14	+0.74					
	28	No oil	ED 0	nd	nd	nd	nd	nd					
Hansen, 1989	40 ^g	Cod liver oil	ED 5.8	nd	-0.70		+4.10		C	1	Un	GEN	I
		No oil	ED 0	nd	+0.10		0.00						
Hansen, 1993b	34 ^g	Cod liver oil	ED 5.3	nd			+5.44		B	1	Un	GEN	II
		No oil	ED 0	nd			nd						
Sacks, 1994	60	Fish oil	ED 2.4	nd			+2.95		C	3	Un	CVD	I
	60	Olive oil	ED 0	nd			+0.10						
Nenseter, 2000	34	Fish powder	ED 0.2	5.4	+0.20	-0.10	+0.20	+0.20	B	3	Un	GEN	II
	36	Cellulose	ED 0	6.1	+0.30	+0.10	-0.30	0.00					
Fish Diets													
	13	Fish & WMD ⁱ	T 3.7	nd	Total n-3 fatty acids: +6.0								
Mori, 1999	16	WMD ⁱ	T nd	nd	Total n-3 fatty acids: -1.5				B	2	Un	GEN	II
	14	Fish & ERD ^j	T 3.7	nd	Total n-3 fatty acids: +5.0								
	16	ERD ^j	T nd	nd	Total n-3 fatty acids: -1.0								
Combinations													
Cobiac, 1991	13	Fish oil	ED 4.6	2.5	-0.10	0.00	+5.80	+3.10	B	2	Un	GEN	II
	12	Fish ^k	ED 4.5	2.5	-0.70	+0.20	+3.10	+3.50					
	6	No oil	ED 0	2.4	+0.60	+0.10	-0.20	-0.20					
Agren, 1996	14	Fish oil	ED 2.3	nd			+4.00	+2.20					
	14	Algae DHA oil	D 1.7	nd			+0.50	+3.10	B	3	Un	GEN	III
	13	Fish ^k	ED 1.1	nd			+1.50	+1.50					
	14	No oil	ED 0	nd			-0.10	0.00					
Finnegan, 2003	28	Fish oil margarine and Fish oil	ED 1.7 A 1.4	5.02	-0.56	-0.07	+1.13	+2.71					
	30	Fish oil margarine	ED 0.8 A 1.3	4.41	+0.44	-0.08	+0.80	+1.61					
	29	Rapeseed/Linseed margarine	ED 0.3 A 9.5	4.38	+0.53	+0.46	+1.22	+0.21	A	4	Un	DysLip	I
	29	Rapeseed/Linseed margarine	ED 0.3 A 4.5	5.34	+0.74	+0.15	+0.95	-0.13					
	30	Sunflower seed oil margarine	ED 0.5 A 1.5	5.47	+0.64	-0.05	+0.28	-0.08					

nd = no data; n-3 = omega-3;

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.

b Baseline EPA + DHA profile (% of total fatty acids) of plasma/serum phospholipids.

c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to subgroup; III = narrow applicability. See Methods.

f Arachidonic acid (20:4 n-6)

g Cross-over study.

h Differences are from the control after 10-week treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.

i Weight-maintaining diet.

j Energy-restricted diet.

k Chemically analyzed.

Platelet Phospholipid Composition ^{68,71,95,96,101,116,122,123,132,137,143,163} (Table 3.28, Figure 3.5)

EPA/DHA. For platelet phospholipid composition, we analyzed 12 randomized trials with 21 omega-3 fatty acid arms. All of these studies evaluated EPA and/or DHA supplementation. One treatment arm was ALA; therefore, there were 20 EPA and/or DHA treatment arms. The dose of EPA+DHA ranged from 0.8 to 5.9 g/day. Study populations include general healthy population and people with diabetes, dyslipidemia, or cardiovascular diseases. Meta-regression results show a significant dose-response relationship between the dietary EPA and DHA supplementations and the changes in EPA+DHA compositions in platelet phospholipids across studies. Studies that used fish or fish combined with fish oil supplement treatments generally had greater increases in platelet phospholipid EPA+DHA amounts than studies of fish oil supplements. This effect was seen in Mori, et al. (1994), which compared fish, fish oil supplements, and combination fish and fish oil ⁷¹. They reported that the largest increase in DHA occurred in the groups consuming fish. In contrast to the finding in plasma phospholipids, Mori et al. (2000) reported that platelet EPA+DHA levels rose more in subjects taking DHA than in subjects taking EPA, although it is not reported whether this difference is statistically significant ¹³².

Meta-regression equation ($r^2 = 0.52$, $P < .001$):

$$\text{Change in Platelet EPA+DHA Level (\%)} = 0.74 \times [\text{EPA+DHA Intake (g/day)}] + 1.16$$

As was the case for plasma/serum phospholipid levels, the re-analysis of the platelet phospholipid data that excluded the 2 studies without a complete EPA and DHA profile indicates a larger increase in EPA+DHA level and a larger r^2 than in the complete meta-regression.

Meta-regression equation ($r^2 = 0.72$, $P < .001$):

$$\text{Change in Platelet EPA+DHA Level (\%)} = 0.80 \times [\text{EPA+DHA Intake (g/day)}] + 1.25$$

ALA. One study also evaluated linseed oil supplementation, which included only ALA without EPA or DHA ¹⁴³. Freese et al. found that a 5.9 g/d ALA supplementation significantly increased EPA and ALA platelet phospholipid levels. However, the effect on EPA levels was small in comparison to the effect of a similar dose of fish oil (+0.41% vs. +3.32% for 5.2 g/d EPA+DHA). In addition, DHA levels were unaffected. The AA level decreased in the ALA arm.

Table 3.28 Effect of omega-3 fatty acid supplementation on fatty acid profile of platelet phospholipids in randomized trials (6 weeks to 4 months)

Study, Year	Omega-3 Fatty Acid Arms ^a				Base ED (%) ^b	Results (Δ%) ^c				Quality ^d			
	Control Arm			AA ^f		ALA	EPA	DHA	Summary	Jadad	Allocation Conceal	Applicability ^e	
N	Source	g/d											
EPA/DHA Oils													
Madsen, 2003	20	Fish oil	ED	5.9	3.6	-4.49	-0.03	+3.82	+0.92	B	3	Un	GEN I
	20	Fish oil	ED	1.7	3.2	-1.97	+0.01	+1.27	+0.36				
	20	Olive oil	ED	0	3.2	+0.19	+0.01	+0.01	-0.06				
Dehmer, 1988	43	Fish oil	ED	5.4	0.6	-2.50		+3.66	+2.30	B	3	Un	CVD III
	39	No oil	ED	0	nd	nd		nd	nd				
Green, 1990	27 ^g	Fish oil	ED	4.3	nd	-0.50		+1.90		B	4	Un	DysLip II
		Corn/Olive oil	ED	0	nd	nd		nd					
Mori, 2000	19	Purified EPA	E	4.0	nd	-4.80		+3.80	-0.60	B	4	Un	DysLip II
	17	Purified DHA	D	4.0	nd	-2.40		+0.60	+4.20				
	20	Olive oil	ED	0	nd	-0.60		+0.05	+0.10				
Leigh-Firbank, 2002	55 ^g	Fish oil	ED	3.0	3.3	+2.90		+2.60	+1.11	B	3	Un	DysLip I
		Olive oil	ED	0	3.3	+0.60		+0.20	+0.10				
McVeigh, 1993	23 ^g	Fish oil	ED	3.0	2.5	-3.00		+1.70	+2.70	A	4	Un	DM II II
		Olive oil	ED	0	2.5	-0.40		-0.10	+0.30				
Hendra, 1990	37	Fish oil	ED	3.0	nd			+1.75		B	4	Un	DM II I
	37	Olive oil	ED	0	nd			-0.02					
Fish Diets													
Dunstan, 1997	26	Fish and exercise	T	3.6	nd	Total n-6: -5.80		EPA+DPA+DHA: +4.80		B	2	Un	NIDDM DysLip I
	23	No fish and exercise	T	nd	nd	nd		nd					
Agren, 1988	14	Fish	ED	0.8	4.5	-2.1	+0.10	+1.20	+1.20	B	3	Un	GEN III
	15	Fish and low SFA ^h	ED	0.8	4.4	-2.6	+0.10	+0.80	+1.30				
	19	Control diet	ED	0.05	nd	nd	nd	nd	nd				
Agren, 1991	22	Fish	ED	0.8	3.8	-1.30		+0.70	+0.70	B	2	Un	GEN III
	23	Control diet	ED	0.1	3.7	-0.10		0.00	0.00				
	27	Fish and exercise	ED	0.8	3.6	-0.90		+0.70	+0.70				
	27	Control diet and exercise	ED	0.1	3.8	+0.10		0.00	0.00				
Combinations													
Freese, 1997b	14	Fish oil	ED A	5.2 0.1	5.2 ⁱ	-3.35	-0.21	+3.32 ⁱ	+0.88	C	3	Un	GEN II
	15	Linseed oil	ED A	0 5.9	4.7 ⁱ	-0.79	+0.39	+0.41 ⁱ	-0.14				
Mori, 1994	16	Fish ^j and Fish oil (40% ^k)	ED	5.2	5.2	-5.00		+3.75	+2.50	B	2	Un	GEN II
	17	Fish oil (40% ^k)	ED	4.2	5.2	-4.75		+3.25	+1.50				
	17	Fish ^j (40% ^k)	ED	3.0	5.2	-3.75		+2.50	+2.50				
	17	Fish oil (40% ^k)	ED	2.1	5.2	-1.50		+1.60	+0.50				
	18	Control ^l oils (40% ^k)	ED	nd	5.2	+0.75		-0.05	-0.40				
	18	Fish ^j (40% ^k)	ED	3.0	5.2	-4.00		+2.30	+2.50				
	17	Control ^l oils (40% ^k)	ED	nd	5.2	-0.40		-0.20	-0.50				

nd = no data; n-6 = omega-6

- a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.
- b Baseline EPA + DHA profile (% of total fatty acids) of platelet phospholipids.
- c $\Delta\%$ = Difference of the marker's profile (post-treatment minus pre-treatment).
- d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to subgroup; III = narrow applicability. See Methods.
- f Arachidonic acid (20:4 n-6)
- g Crossover study.
- h Low saturated fatty acid diet.
- i Plus some 22:0.
- j Chemically analyzed.
- k Percent of fat in diet
- L Olive/Palm/ Safflower oils

Erythrocyte Membrane Phospholipid Composition^{79,88,95,96,101,115,134,141,160,175} (Table 3.29, Figure 3.6)

EPA/DHA. For erythrocyte membrane phospholipid composition, 10 randomized trials with 15 omega-3 fatty acid arms were included. All of these studies evaluated EPA and/or DHA supplementation. One study included 2 ALA treatment arms; therefore, there were 13 EPA and/or DHA treatment arms. The dose of EPA+DHA ranged from 0.8 to 4.6 g/day. Study populations include general healthy population and people with diabetes, dyslipidemia or cardiovascular diseases. Meta-regression results show no significant dose-response relationship between the dietary EPA and DHA supplementations and the changes in EPA plus DHA compositions in platelet phospholipids. No clear difference is seen in effect based on source of omega-3 fatty acids. No study compared different sources of EPA+DHA oil.

Meta-regression equation ($r^2 = 0.11$, $P = .14$):

$$\text{Change in Erythrocyte EPA+DHA Level (\%)} = 0.63 \times [\text{EPA+DHA Intake (g/day)}] + 3.22$$

The re-analysis of the data, excluding 1 study by Green et al. who did not report the change in DHA levels, greatly affected slope and statistical significance of the meta-regression equation¹⁰¹. The large effect of this single study can be explained by outlier status of the study. The change in EPA level reported in this study is considerably lower than the change in EPA+DHA levels in studies with similar supplementation doses.

Meta-regression equation ($r^2 = 0.39$, $P < .02$):

$$\text{Change in Erythrocyte EPA+DHA Level (\%)} = 1.05 \times [\text{EPA+DHA Intake (g/day)}] + 2.69$$

ALA. One study also evaluated a diet enriched in ALA and that contained no EPA or DHA among both young (16-33 years old) and old (60-78 years old) subjects¹⁶⁰. Wensing et al. found that a 6.8 g/d ALA supplementation significantly increased both EPA and ALA levels but not DHA level. The effects on the changes in EPA and ALA compositions were larger among older subjects than among younger subjects. The higher dose ALA (6.8 g/d) had a smaller effect on EPA levels (+0.20% and +0.40%, for younger and older subjects, respectively) than a lower dose

of EPA+DHA (1.6 g/d, +1.30%). The AA level decreased among old subjects while it increased among young subjects.

Table 3.29 Effect of omega-3 fatty acid supplementation on fatty acid profile of red blood cell (erythrocyte) membrane/ghosts in randomized trials (6 weeks to 2 years)

Study, Year	Omega-3 Fatty Acid Arms ^a				Base ED (%) ^b	Results (Δ%) ^c				Quality ^d			
	Control Arm			g/d		AA ^f	ALA	EPA	DHA	Summary	Jadad	Allocation Conceal	Applicability ^e
N	Source	ED											
EPA/DHA Oils													
Haines, 1986	19	Fish oil	ED	4.6	6.1	-2.20		+3.77	+2.23	B	2	Ad	IDDM II
	22	Olive oil	ED	0	6.1	0.00		-0.05	-0.22				
Solomon, 1990	5	Fish oil	ED	4.6	6.7	-3.44		+5.92	+2.19	B	4	Un	CVD II
	5	Olive oil	ED	0	6.4	+0.23		-0.07	-0.31				
Green, 1990	27 ^g	Fish oil	ED	4.3	nd	-2.00		+2.70		B	4	Un	DysLip II
		Corn/Olive oil	ED	0	3.6	nd		nd					
Rivellese, 1996	8	Fish oil	ED	1.97	5.8	-2.30		+1.50	+1.60	A	3	Un	DysLip NIDDM II
	8	Olive oil	ED	0.0	5.7	0.10		-0.10	-0.30				
Luo, 1998	10 ^g	Fish oil	ED	1.8	6.3			+1.44 ^h	+1.33 ^h	C	3	Un	DM II II
		Sunflower oil	ED	0	6.3			nd	nd				
Angerer, 2002	87	Fish oil	ED	1.65	nd			+2.60	+4.20	B	4	Ad	CVD II
	84	Fatty acid	ED	nd	nd			+0.10	+0.10				
Fish Diets													
Dunstan, 1999	14	Fish and moderate exercise	T	3.6	nd	Total n-6: -4.50		EPA+DPA+DHA: +6.60		B	2	Un	NIDDM DysLip I
	11	No fish and moderate exercise	T	nd	nd	Total n-6: +0.60		EPA+DPA+DHA: 0.00					
	12	Fish and light exercise	T	3.6	nd	Total n-6: -6.7		EPA+DPA+DHA: +8.40					
	12	No fish and light exercise	T	nd	nd	nd		nd					
Agren, 1988	14	Fish	ED	0.8	8.8	-2.70	0.00	+1.30	+3.20	B	3	Un	GEN III
	15	Fish and low SFA ⁱ	ED	0.8	9.3	-2.40	0.00	+0.90	+2.70				
	19	Control diet	ED	0.05	nd	nd	nd	nd	nd				
Agren, 1991	22	Fish	ED	0.8	9.2	-1.30		+0.70	+1.80	B	2	Un	GEN III
	23	Control diet	ED	0.1	8.7	+0.10		0.00	-0.10				
	27	Fish and exercise	ED	0.8	8.7	-1.20		+0.80	+2.00				
	27	Control diet and exercise	ED	0.1	8.6	+0.40		0.00	-0.10				
Wensing, 1999	14	EPA+DHA	ED	1.6	4.5	-0.80	0.00	+1.30	+0.80	B	2	Un	GEN II
	13	ALA (old)	ED	0.0	4.1	-0.70	+0.40	+0.40	-0.30				
	12	ALA (young)	ED	0.0	4.0	+0.90	+0.20	+0.20	-0.10				
	11	Oleic acid	ED	0.0	3.8	-0.20	0.00	+0.00	+0.10				

nd = no data; n-6 = omega-6

- a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.
- b Baseline EPA + DHA profile (% of total fatty acids) of erythrocyte phospholipids.
- c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).
- d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
- f Arachidonic acid (20:4 n-6)
- g Crossover study.
- h Difference from the control after 2-month treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.
- i Low saturated fatty acid diet.

Granulocyte Membrane Phospholipid Composition ¹³⁷ (Table 3.30)

One randomized controlled trial examined the changes of EPA+DHA composition in granulocyte membrane phospholipids after fish oil supplementation. Madsen et al. found that EPA and DHA compositions in granulocyte phospholipids significantly increased after 12 weeks of fish oil supplement treatment, while no significant changes were found in the placebo group ¹³⁷. In addition, the change in DHA profile was significantly larger in the higher-dose fish oil supplementation group than in the lower-dose fish oil group.

Table 3.30 Effect of omega-3 fatty acid supplementation on fatty acid profile of granulocyte membrane in randomized trials (12 weeks)

Study, Year	Omega-3 Fatty Acid Arms ^a				Base ED (%) ^b	Results (Δ%) ^c				Quality ^d			Applicability ^e
	Control Arm					AA ^f	ALA	EPA	DHA	Summary	Jadad	Allocation Conceal	
	N	Source	g/d										
	EPA/DHA Oils												
Madsen, 2003	20	Fish oil	ED	5.9	2.2	-2.71	-0.03	+3.50	+0.57	B	3	Un	GEN I
	20	Fish oil	ED	1.7	2.1	-1.21	0.00	+1.25	+0.29				
	20	Olive oil	ED	0	2.0	+0.03	+0.01	+0.04	-0.02				

- a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.
- b Baseline EPA + DHA profile (% of total fatty acids) of granulocyte phospholipids.
- c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).
- d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
- f Arachidonic acid (20:4 n-6).

Monocyte Membrane Phospholipid Composition ¹⁴⁶ (Table 3.31)

One crossover study examined the changes of EPA+DHA composition in monocyte phospholipids after cod-liver oil supplementation. Hansen, et al. showed the EPA profile in monocyte phospholipids significantly increased, while the arachidonic acid profile significantly decreased after 8 weeks of cod liver oil supplement treatment compared to the no treatment controls ¹⁴⁶.

Table 3.31 Effect of omega-3 fatty acid supplementation on fatty acid profile of monocyte phospholipids in randomized trials (8 weeks)

Study, Year	Omega-3 Fatty Acid Arms ^a				Base ED (%) ^b	Results (Δ%) ^c				Quality ^d			
	Control Arm			N		AA ^f	ALA	EPA	DHA	Summary	Jadad	Allocation Concealment	Applicability ^e
	Source	g/d	ED										
EPA/DHA Oils													
Hansen, 1989	40 ^g	Cod liver oil	ED 5.8	nd	-4.00 ^h		+3.00 ^h		C	1	Un	GEN I	
		No oil	ED 0	nd	nd		nd						

nd = no data

- a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.
- b Baseline EPA + DHA profile (% of total fatty acids) of monocyte phospholipids.
- c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).
- d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
- e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
- f Arachidonic acid (20:4 n-6)
- g Cross-over study.
- h Difference from the control after 8-week treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.

Figure 3.4 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in plasma or serum phospholipids (PL)

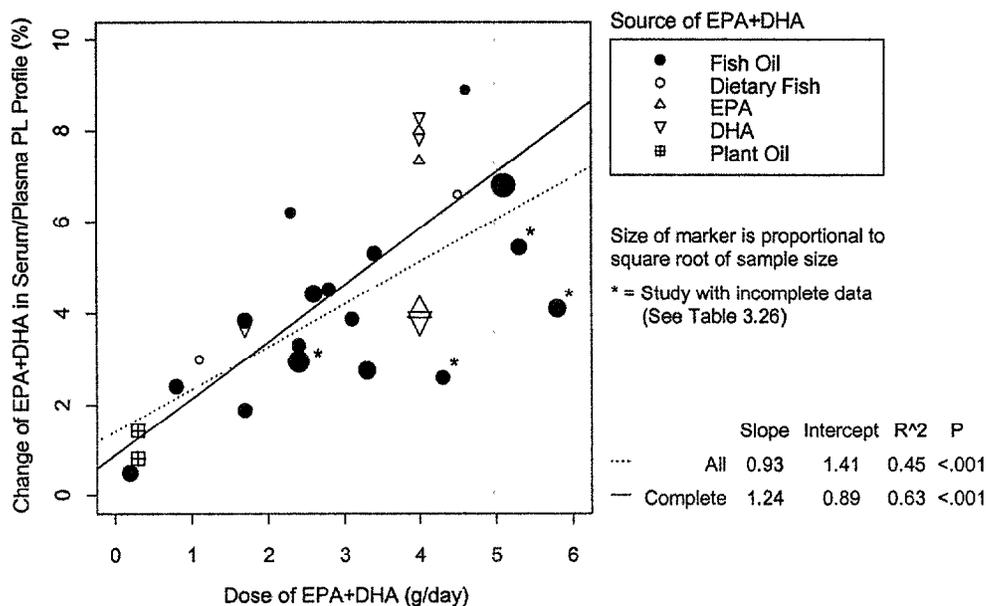


Figure 3.5 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in platelet phospholipids (PL)

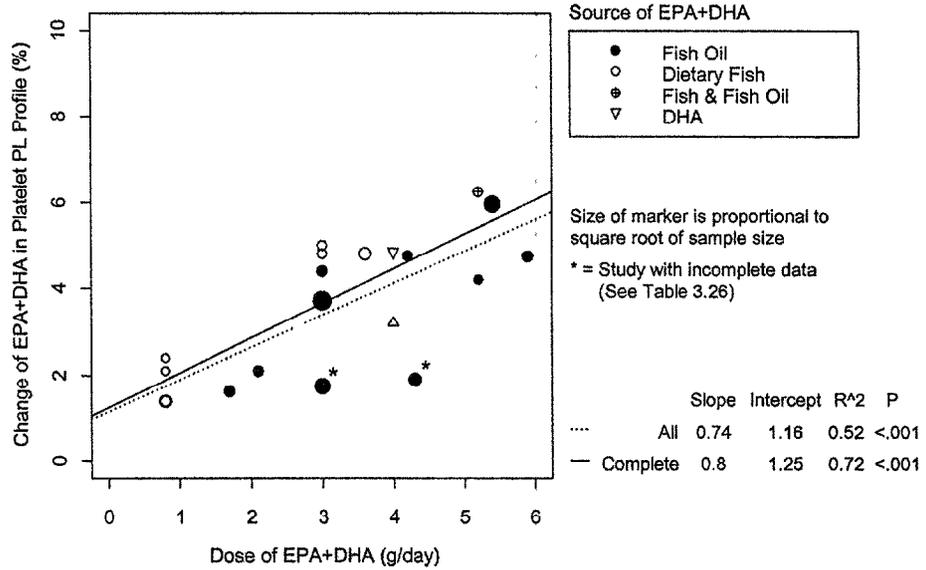
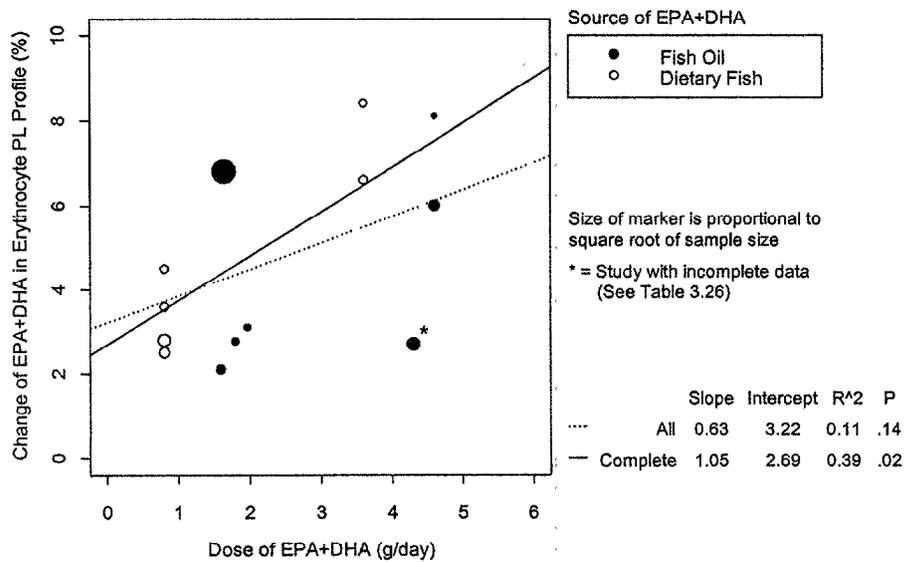


Figure 3.6 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in red blood cell (RBC, erythrocyte) membrane phospholipids (PL)



Chapter 4. Discussion

In this chapter, we summarize findings from our review of studies examining the effect of omega-3 fatty acids on cardiovascular disease (CVD) risk factors and intermediate markers of CVD, discuss limitations of our review, and offer recommendations for future research.

Overview

Through a structured literature review process, we screened over 7,464 abstracts and retrieved and screened 807 full text articles that addressed omega-3 fatty acids and CVD risk factors and intermediate markers of CVD. After narrowing the list of outcomes of interest and applying specific eligibility criteria, we analyzed 123 articles that examined the effects of eicosapentaenoic acid (EPA, 20:5 n-3), docosahexaenoic acid (DHA, 22:6 n-3), and alpha linolenic acid (ALA, 18:3 n-3) on one of the following risk factors or intermediate markers:

- Lipids (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides [Tg], lipoprotein (a), apolipoproteins [apo] A-I, B, B-100, and LDL apo B)
- Blood pressure
- Measures of glucose tolerance (hemoglobin A_{1c} [Hgb A_{1c}], fasting blood sugar [FBS], and fasting insulin)
- C-reactive protein (CRP)
- Measures of hemostasis (fibrinogen, factors VII and VIII, von Willebrand factor [vWF], and platelet aggregation),
- Non-serum diagnostic tests (coronary artery restenosis – following angioplasty, carotid intima-media thickness [IMT], exercise tolerance testing [ETT], heart rate variability)
- Tissue levels of fatty acids including plasma or serum phospholipids, platelet phospholipids, erythrocyte membrane phospholipids, granulocyte membrane phospholipids, and monocyte membrane phospholipids.

For most outcomes, we analyzed only the approximately 20 to 30 largest randomized trials. The main findings from our review and analysis are summarized in the next section. While doing the review, we found that several of the key questions and sub-questions posed at the beginning of this report were not addressed by the available studies. For example, most studies that we analyzed evaluated fish or other marine oils and only a few evaluated plant oils. Furthermore, few studies compared doses of similar omega-3 fatty acids, compared different omega-3 fatty acids, reported on potential covariates such as age and sex, analyzed effects based on duration of intake, or repeated measurements after subjects had stopped omega-3 fatty acid supplementation. No study incorporated an analysis of how varying dietary omega-6 to omega-3 ratio may alter

the effect of omega-3 fatty acid consumption on outcomes. These and other limitations are addressed in more detail in the Limitations section of this chapter.

Main Findings

Overall, we found evidence that fish oils have a strong beneficial effect on Tg that is dose-dependent and similar in various populations. There is also evidence of a very small beneficial effect of fish oils on blood pressure, and possible beneficial effects on coronary artery restenosis after angioplasty, exercise capacity in patients with coronary atherosclerosis, and, possibly, heart rate variability, particularly in patients with recent myocardial infarctions. No consistent beneficial effect is apparent for the other CVD risk factors or intermediate markers of CVD we analyzed. In addition, there is also no consistent evidence of a detrimental effect of omega-3 fatty acids on glucose tolerance. Details on these and other key findings are summarized below.

As discussed in the accompanying report, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*, consumption of omega-3 fatty acids from dietary sources or from marine oil or ALA supplements reduces all cause mortality and various CVD outcomes. The cardiovascular benefits of omega-3 fatty acid consumption, though, are not well explained by the fatty acids' effects on the cardiovascular risk factors that we examined. However, the overall cardiovascular benefit may be due to the constellation of effects on lipids, blood pressure, coronary atherosclerosis, and heart rate variability. Reviewing the studies evaluated in this and the accompanying report on cardiovascular outcomes, we found no article that analyzed potential associations between omega-3 fatty acid's effect on cardiovascular risk factors and cardiovascular outcomes.

Effect on Triglycerides and Other Serum Lipids

The strongest, most consistent effect of omega-3 fatty acids was among the 19 studies of Tg. Most of these studies reported a net decrease in Tg of about 10% to 33%. The effect was dose-dependent and generally consistent among healthy subjects and patients with CVD, dyslipidemia, or at elevated risk of CVD. The effect was also greater in studies with higher mean baseline Tg. However, 1 of 2 studies of plant oils (ALA) found a net increase in Tg. Limited data suggest that the effect is not related to sex, age, weight, background diet, or lipid treatment. The effect of duration of intervention is unclear and there were no data regarding sustainment of effect. In addition, no study of diabetic patients had sufficient number of subjects to be analyzed.

The effect of omega-3 fatty acids on other serum lipids was weaker. The 23 studies of total cholesterol and the 19 studies of HDL we analyzed were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in levels of both lipids. The 15 analyzed trials of LDL were fairly uniform in finding small net increases in LDL. The effect of plant oils (ALA) on these lipoproteins was possibly weaker but similar to the effect of marine oils. No differences in effect were seen among different populations, including the diabetic subjects who were evaluated in a sub-analysis. One study found a larger net increase in total cholesterol among subjects on a higher fat diet compared to those on a lower fat diet, but this effect was not seen for other lipids. A single study of fish oil reported a steady increase in HDL levels over time beginning at 6 weeks and ending at 12 months. No other studies found an effect of time on lipids and no other covariates were reported to interact with fish oil effects on lipids.

One study compared the effect of purified EPA to purified DHA on these 4 lipids. The results were mixed. EPA lowered total cholesterol significantly (and substantially) more than DHA, DHA increased HDL by a small but significant amount more than EPA, and the effects of the 2 oils were similar in their lack of effect on LDL and their ability to lower Tg.

Effect on Blood Pressure

A recent meta-regression of the effect of fish oils on blood pressure found a small but significant reduction in both systolic and diastolic blood pressure of about 2 mm Hg. The effect was stronger in older and hypertensive populations. Because the meta-regression excluded diabetic populations, we evaluated the 6 randomized studies of diabetics and found similar results. One study reported that neither sex nor Hgb A_{1c} levels were related to the fish oil effect on blood pressure. No study analyzed plant oils. One study reported no significant difference in blood pressure effect of purified EPA compared to purified DHA.

Effect on Restenosis after Coronary Angioplasty

We performed a meta-analysis of the 12 randomized trials that reported restenosis rates after coronary angioplasty. All evaluated fish oils. We found heterogeneity of results across studies but an overall trend toward a net reduction of relative risk of 14% with fish oil intake. Two studies reported no significant difference in effect between men and women.

Effect on Exercise Capacity and Heart Rate Variability

The 6 available studies examining exercise tolerance testing suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small. Three analyses of heart rate variability in 2 study populations concluded that fish oil supplementation among patients with recent myocardial infarction, and dietary fish consumption in healthy people, improves heart rate variability, which may, in turn, reduce the incidence of ventricular arrhythmias. However, fish oil supplementation did not improve heart rate variability in the same healthy population.

Effect on Other Cardiovascular Risk Factors and Intermediate Markers

The effects of omega-3 fatty acids on the other outcomes that we evaluated were either small or inconsistent across studies.

Apolipoproteins. No consistent effect was found across 14 studies of Lp(a), although one study reported a small but significant net decrease in subjects with elevated baseline Lp(a) levels compared to those with lower baseline levels. There were insufficient studies to compare different omega-3 fatty acids. The 27 studies of apo A-I that we analyzed generally found no effect or either a small increase or decrease in level with omega-3 fatty acid consumption. Limited evidence suggested that purified EPA may decrease apo A-I levels while DHA has no effect, and that there is no difference in effect between fish oils and ALA. There was little consistency of effect in the 25 studies of total apo B. The 4 available studies of apo B-100 found

a range of effects from a 5% decrease to a 15% increase in level. Most of the 6 studies of LDL apo B found large, significant net increases in LDL apo B with omega-3 fatty acid consumption.

C-reactive protein. The 5 available studies of CRP found no effect with fish oil supplementation or dietary fish.

Measures of hemostasis. No consistent effect was found among the 24 analyzed studies of fibrinogen, the 19 analyzed studies of factor VII, or the 5 available randomized trials of factor VIII. The 9 randomized trials of vWF mostly found a small, non-significant decrease in level with omega-3 fatty acid consumption. The results among the 11 analyzed studies of platelet aggregation were heterogeneous depending on aggregating agent, dose of agent, and measurement metric used, however, generally no effect was found with omega-3 fatty acid intake. The few studies that compared types of omega-3 fatty acids found no difference in effect on these measures of hemostasis, with the exception that 2 studies came to opposite conclusions regarding whether fish oil prolonged platelet aggregation by a greater degree than ALA, and 1 study concluded that DHA may be less potent at prolonging platelet aggregation than EPA.

Carotid intima-media thickness. The 4 available studies of carotid IMT were heterogeneous. The randomized trial found no effect of fish oil but 2 cross-sectional studies found that dietary omega-3 fatty acid was correlated with thinner IMT; the cohort study of plant oil margarine was inconclusive.

Glucose tolerance. Overall, the studies of markers of glucose tolerance found no consistent effect of omega-3 fatty acids. There was a wide range of net effects of omega-3 fatty acids on fasting blood sugar across the 17 analyzed studies. Heterogeneity was present regardless of the make-up of the study population, although the range of effect was widest among diabetic patients. Within studies there were no apparent differences in effect of different omega-3 fatty acids on fasting blood sugar. Among the 18 analyzed studies of Hgb A_{1c} there was no substantial significant effect of omega-3 fatty acid consumption, regardless of study population. A single study found no difference in effect of purified EPA and purified DHA on Hgb A_{1c}. The 15 randomized trials of fasting insulin levels were very heterogeneous. Similar heterogeneity existed among the 9 studies of generally euglycemic populations as among the studies of diabetics and obese subjects. Within studies there were no apparent differences in effect of different omega-3 fatty acids on fasting insulin levels.

Tissue Levels of Fatty Acids

Meta-regression of 30 studies revealed direct relationships between dose of omega-3 fatty acids consumed and changes in measured levels of eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), either as plasma or serum phospholipids, platelet phospholipids, or erythrocyte membranes. The correlation between dose and change in level appears to be fairly uniform, where 1 g supplementation of EPA and/or DHA corresponds to approximately a 1% increase in EPA+DHA level. Granulocyte and monocyte membrane phospholipid levels also increased after omega-3 fatty acid supplementation in individual studies.

Limitations

We identified about 60 potential CVD risk factors and intermediate markers of CVD and evaluated 23 of these in this evidence report. While some of these outcomes have been demonstrated to be important risk factors for CVD or markers of CVD, it is unclear whether this is true for all. The measurement techniques for a number of the outcomes we evaluated also have not been standardized, which complicated our interpretation of individual study findings and limited our ability to compare studies. Thus, the effects of omega-3 fatty acids on various putative risk factors and intermediate markers, and the implications for risk of CVD events, are uncertain.

While we endeavored to do a complete, systematic review of the literature on the effect of omega-3 fatty acids on CVD risk factors and intermediate markers of CVD, we were unable to critically evaluate all 350 potentially eligible studies due to time and resource limitations. Nevertheless, our findings regarding the main effects of omega-3 fatty acids on the outcomes we evaluated should be valid since we analyzed the largest randomized trials. Thus, studies not included were either non-randomized studies, which would provide more biased effect estimates, or smaller trials, which, by definition, are generally less powered than the larger studies. However, excluding non-randomized studies and small trials may have affected the availability of evidence regarding many of the secondary questions related to the effect of covariates, dosage, duration, and the like. In particular, few of the studies we analyzed evaluated plant oils. However, since few of the excluded studies evaluated plant oils, broadening our inclusion criteria may not have been helpful to this area of inquiry. In addition, for several outcomes, we analyzed a minority of the potentially available studies of diabetic patients. This was particularly the case for studies of lipid outcomes.

Although several studies performed multivariate analyses to adjust for potential confounders, few studies explicitly evaluated the effects of omega-3 fatty acids on specific subgroups as identified in the key questions. Thus, conclusions regarding these questions are all weak and based on limited data. With the exceptions of studies confined to men or to specific populations of interest (e.g., diabetics), studies generally did not base eligibility criteria on factors of particular interest here. Furthermore, only one study evaluated only women, limiting conclusions that could be made across studies based on sex.

Most conclusions that we were able to draw, particularly for different populations, were based on across-study comparisons, which cannot account for confounders.

Many studies evaluated multiple risk factors. Thus, many of the outcomes we analyzed were secondary outcomes that were often inadequately powered and reported. Many studies simply reported that the results were not significant without quantifying their results; these studies were not included in our analyses. Non-significant results would still be useful in a systematic review and meta-analysis.

Finally, the ratio of omega-6 to omega-3 fatty acids was so rarely reported that no analyses could be performed on this metric.

Future research

We offer the following recommendations for future research on omega-3 fatty acids and their effect on CVD risk factors and intermediate markers of CVD:

- Future studies on CVD risk factors and intermediate markers of CVD should address the question of possible differences in the effect of omega-3 fatty acids in different sub-populations and as related to different covariates, including dose and duration of intake.
- The potential effect of alpha linolenic acid (ALA, 18:3 n-3) is unknown. More multi-center trials are needed to assess the effect of ALA, separate from the effect of EPA+DHA, on CVD risk factors.
- Additional research is needed to clarify the effect of omega-3 fatty acids on markers of glucose tolerance. Specifically, sufficiently large trials are needed that perform appropriate sub-analyses to determine the cause of heterogeneity in effect across studies.
- The total dietary omega-6 to omega-3 fatty acid ratio should be estimated, reported, and analyzed in terms of its effect on outcomes and its association with any effect of omega-3 fatty acid treatment.
- Future research should attempt to determine the effect of higher fish intake on the consumption of other foods in the diet, specifically sources of saturated fat such as meat and cheese.
- Future prospective cohort studies and diet trials on fish consumption should place special emphasis to collecting data regarding the quantity and type of fish consumed and the method of preparation.

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Solomon SA, Cartwright I, Pockley G, et al. A placebo-controlled, double-blind study of eicosapentaenoic acid-rich fish oil in patients with stable angina pectoris. *Current Medical Research & Opinion* 1990;12(1):1-11.

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Wensing AG, Mensink RP, Hornstra G. Effects of dietary n-3 polyunsaturated fatty acids from plant and marine origin on platelet aggregation in healthy elderly subjects. *Br J Nutr* 1999 Sep;82(3):183-91.

Westerveld HT, de Graaf JC, van Breugel HH, et al. Effects of low-dose EPA-E on glyceic control, lipid profile, lipoprotein(a), platelet aggregation, viscosity, and platelet and vessel wall interaction in NIDDM. *Diabetes Care* 1993 May;16(5):683-8.

Wilt TJ, Lofgren RP, Nichol KL, Schorer AE, Crespin L, Downes D, Eckfeldt J. Fish oil supplementation does not lower plasma cholesterol in men with hypercholesterolemia. Results of a randomized, placebo-controlled crossover study. *Annals of Internal Medicine* 1989; 111(11):900-5.

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Yamada T, Malcom GT, Strong JP, et al. Difference in atherosclerosis between the populations of a fishing and a farming village in Japan. *Ann N Y Acad Sci* 1997;811:412-9.

Listing of Excluded Studies

Excluded studies were categorized by the following sets of reasons for exclusion. Only the primary reason for exclusion is listed here, along with the number of articles in each category.

- Studies not analyzed because of non-randomized design or small size (N=221)
- Articles rejected because in English (N=1)
- Articles rejected because not Human study (N=4)
- Articles rejected because not primary study (N=7)
- Articles rejected because not omega-3 fatty acid (n-3) intake study, insufficient data regarding omega-3 fatty acid trial, or no data on omega-3 fatty acid intake amount (N=95)
- Articles rejected because inappropriate human population (N=15)
- Articles rejected because pediatric population (N=5)
- Articles rejected because no outcome of interest or insufficient data to extract outcomes (N=110)
- Articles rejected because sample size too small (N=45)
- Articles rejected because omega-3 fatty acid dose > 6 g (N=46)
- Articles rejected because duration < 4 weeks (N=80)
- Articles rejected because cross-over study with < 4 week washout (N=32)
- Articles rejected because duplicate publications (N=14)
- Articles rejected for other listed reasons (N=9)

Adler AI, Boyko EJ, Schraer CD, Murphy NJ. Lower prevalence of impaired glucose tolerance and diabetes associated with daily seal oil or salmon consumption among Alaska Natives. *Diabetes Care* 1994; 17(12):1498-1501.

(Not n-3 study, Insufficient data on n-3)

Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. *American Journal of Clinical Nutrition* 1997; 65(2):445-450.

(Non -randomized or Small size)

Agren JJ, Hanninen O, Hanninen A, Seppanen K. Dose responses in platelet fatty acid composition, aggregation and prostanoid metabolism during moderate freshwater fish diet. *Thrombosis Research* 1990; 57(4):565-575.

(No outcome of interest or Insufficient data)

Ahmed AA, Holub BJ. Alteration and recovery of bleeding times, platelet aggregation and fatty acid composition of individual phospholipids in platelets of human subjects receiving a supplement of cod-liver oil. *Lipids* 1984; 19(8):617-624.

(Duration < 4 weeks)

Akoh CC, Hearnberger JO. Effect of catfish and salmon diet on platelet phospholipid and blood clotting in healthy men. *Journal of Nutritional Biochemistry* 1991; 2(6):329-

333.

(Duration < 4 weeks)

Allard JP, Kurian R, Aghdassi E, Muggli R, Royall D. Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans. *Lipids* 1997; 32(5):535-541. (No outcome of interest or Insufficient data)

Allard JP, Royall D, Kurian R, Muggli R, Jeejeebhoy KN. Effect of omega 3 fatty acids and vitamin E supplements on lipid peroxidation measured by breath ethane and pentane output: a randomized controlled trial. *World Review of Nutrition & Dietetics* 1994; 75:162-165.

(No outcome of interest or Insufficient data)

Allman MA, Pena MM, Pang D. Supplementation with flaxseed oil versus sunflowerseed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. *European Journal of Clinical Nutrition* 1995; 49(3):169-178.

(Duration < 4 weeks)

Almario RU, Vonghavaravat V, Wong R, Kasim-Karakas SE. Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. *American Journal of Clinical Nutrition* 2001; 74(1):72-79.

(Non -randomized or Small size)

Almdahl SM, Nilsen DW, Osterud B. Thromboplastin activities and monocytes in the coronary circulation of

reperfused human myocardium. No effect of preoperative treatment with n-3 fatty acids. *Scandinavian Journal of Thoracic & Cardiovascular Surgery* 1993; 27(2):81-86. (No outcome of interest or Insufficient data)

Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men. *Journal of Lipid Research* 1995; 36(6):1370-1384. (Duration < 4 weeks)

Almendingen K, Seljeflot I, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on hemostatic variables in men. *Arteriosclerosis Thrombosis & Vascular Biology* 1996; 16(3):375-380. (Duration < 4 weeks)

Anderssen SA, Hjermann I, Urdal P, Torjesen PA, Holme I. Improved carbohydrate metabolism after physical training and dietary intervention in individuals with the "atherothrombotic syndrome". *Oslo Diet and Exercise Study (ODES). A randomized trial. J Intern Med* 1996; 240(4):203-209. (Not n-3 study, Insufficient data on n-3)

Ando M, Sanaka T, Nihei H. Eicosapentanoic acid reduces plasma levels of remnant lipoproteins and prevents in vivo peroxidation of LDL in dialysis patients. *Journal of the American Society of Nephrology* 1999; 10(10):2177-2184. (Inappropriate Human population)

Anttolainen M, Valsta LM, Alfthan G, Kleemola P, Salminen I, Tamminen M. Effect of extreme fish consumption on dietary and plasma antioxidant levels and fatty acid composition. *European Journal of Clinical Nutrition* 1996; 50(11):741-746. (Non -randomized or Small size)

Archer SL, Green D, Chamberlain M, Dyer AR, Liu K. Association of dietary fish and n-3 fatty acid intake with hemostatic factors in the coronary artery risk development in young adults (CARDIA) study. *Arteriosclerosis Thrombosis & Vascular Biology* 1998; 18(7):1119-1123. (Non -randomized or Small size)

Arjmandi BH, Khan DA, Juma S, Drum ML, Venkatesh S, Sohn E et al. Whole flaxseed consumption lowers serum LDL-cholesterol and lipoprotein(a) concentrations in postmenopausal women. *Nutrition Research* 1998; 18(7):1203-1214. (n-3 dose > 6 g)

Armstrong RA, Chardigny JM, Beaufrere B, Bretillon L, Vermunt SH, Mensink RP et al. No effect of dietary trans isomers of alpha-linolenic acid on platelet aggregation and haemostatic factors in European healthy men. *The TRANSLINE study. Thrombosis Research* 2000; 100(3):133-141. (Not n-3 study, Insufficient data on n-3)

Atkinson PM, Wheeler MC, Mendelsohn D, Pienaar N, Chetty N. Effects of a 4-week freshwater fish (trout) diet on platelet aggregation, platelet fatty acids, serum lipids, and coagulation factors. *American Journal of Hematology*

1987; 24(2):143-149. (Non -randomized or Small size)

Avellone G, Garbo Vd, Cordova R, Scaffidi L, Bompiani GD, di G, V. Effects of Mediterranean diet on lipid, coagulative and fibrinolytic parameters in two randomly selected population samples in Western Sicily. *Nutrition Metabolism and Cardiovascular Diseases* 1998; 8(5):287-296. (Not n-3 study, Insufficient data on n-3)

Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D. Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double-blind, controlled study. *Diabetes Care* 1994; 17(1):37-44. (Non -randomized or Small size)

Bach R, Schmidt U, Jung F, Kiesewetter H, Hennen B, Wenzel E et al. Effects of fish oil capsules in two dosages on blood pressure, platelet functions, haemorheological and clinical chemistry parameters in apparently healthy subjects. *Annals of Nutrition & Metabolism* 1989; 33(6):359-367. (Non -randomized or Small size)

Bagdade JD, Buchanan WE, Levy RA, Subbaiah PV, Ritter MC. Effects of omega-3 fish oils on plasma lipids, lipoprotein composition, and postheparin lipoprotein lipase in women with IDDM. *Diabetes* 1990; 39(4):426-431. (Sample size too small)

Bagdade JD, Ritter M, Subbaiah PV. Marine lipids normalize cholesteryl ester transfer in IDDM. *Diabetologia* 1996; 39(4):487-491. (Non -randomized or Small size)

Baggio B, Budakovic A, Nassuato MA, Vezzoli G, Manzato E, Luisetto G et al. Plasma phospholipid arachidonic acid content and calcium metabolism in idiopathic calcium nephrolithiasis. *Kidney International* 2000; 58(3):1278-1284. (Inappropriate Human population)

Baggio B, Gambaro G, Zambon S, Marchini F, Bassi A, Bordin L et al. Anomalous phospholipid n-6 polyunsaturated fatty acid composition in idiopathic calcium nephrolithiasis. *Journal of the American Society of Nephrology* 1996; 7(4):613-620. (Inappropriate Human population)

Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension* 1998; 32(4):710-717. (Non -randomized or Small size)

Barcelli U, Glas-Greenwalt P, Pollak VE. Enhancing effect of dietary supplementation with omega-3 fatty acids on plasma fibrinolysis in normal subjects. *Thrombosis Research* 1985; 39(3):307-312. (Duration < 4 weeks)

Barstad RM, Roald HE, Petersen LB, Stokke KT, Kierulf P, Sakariassen KS. Dietary supplement of omega-3 fatty acids has no effect on acute collagen-induced thrombus

formation in flowing native blood. *Blood Coagulation & Fibrinolysis* 1995; 6(5):374-381.

(No outcome of interest or Insufficient data)

Basu A, De JK, Datta S. Studies on the lipid profile and atherogenic factors in adult males. *Indian Journal of Nutrition and Dietetics* 2001; 38(12):441-454.

(Not n-3 study, Insufficient data on n-3)

Bates C, van Dam C, Horrobin DF. Plasma essential fatty acids in pure and mixed race American Indians on and off a diet exceptionally rich in salmon. *Prostaglandins Leukotrienes and Medicine* 1985; 17(1):77-84.

(No outcome of interest or Insufficient data)

Baumann KH, Hessel F, Larass I, Muller T, Angerer P, Kiefl R et al. Dietary omega-3, omega-6, and omega-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes. A randomized volunteer study. *Arteriosclerosis Thrombosis & Vascular Biology* 1999; 19(1):59-66.

(No outcome of interest or Insufficient data)

Baumstark MW, Frey I, Berg A, Keul J. Influence of n-3 fatty acids from fish oils on concentration of high- and low-density lipoprotein subfractions and their lipid and apolipoprotein composition. *Clinical Biochemistry* 1992; 25(5):338-340.

(Non-randomized or Small size)

Beil FU, Terres W, Orgass M, Greten H. Dietary fish oil lowers lipoprotein(a) in primary hypertriglyceridemia. *Atherosclerosis* 1991; 90(1):95-97. (Letter)

Beilin LJ, Mori TA, Vandongen R, Morris J, Burke V, Ritchie J. The effects of omega-3 fatty acids on blood pressure and serum lipids in men at increased risk of cardiovascular disease. *Journal of Hypertension - Supplement*. 1993 11 Suppl 5:S318-9.

(Non-randomized or Small size)

Beitz J, Schimke E, Liebaug U, Block HU, Beitz A, Honigsmann G et al. Influence of a cod liver oil diet in healthy and insulin-dependent diabetic volunteers on fatty acid pattern, inhibition of prostacyclin formation by low density lipoprotein (LDL) and platelet thromboxane. *Klinische Wochenschrift* 1986; 64(17):793-799.

(Duration < 4 weeks)

Bemelmans WJ, Broer J, de Vries JH, Hulshof KF, May JF, Meyboom-de Jong B. Impact of Mediterranean diet education versus posted leaflet on dietary habits and serum cholesterol in a high risk population for cardiovascular disease. *Public Health Nutrition* 2000; 3(3):273-283.

(n-3 dose > 6 g)

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(Crossover with < 4 week washout)

List of Acronyms/Abbreviations

Abbreviation	Definition
I	Broadly applicable study
II	Study applicable to sub-group of population
III	Narrowly applicable study
$\Delta\%$	Difference of the marker's profile (post-treatment minus pre-treatment)
A	Alpha linolenic acid or "good" quality study (see Summary Table footnotes)
AA	Arachidonic acid (20:4 n-6)
AC ₅₀	Concentration of collagen giving a 50% decrease in optical density
Ad	Adequate allocation concealment
ADP	Adenosine diphosphate
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate Intake
ALA	Alpha linolenic acid (18:3 n-3)
Allocation Conceal	Allocation concealment
apo	Apolipoprotein
apo A-I	Apolipoprotein A-I
apo B-100	Apolipoprotein B-100
apo B-48	Apolipoprotein B-48
apo C-III	Apolipoprotein C-III
B	Fair quality study
Base	Baseline level in treatment arm
BMI	Body mass index
C	Poor quality study
CAB	Commonwealth Agricultural Bureau
CB	Carotid bifurcation
CCA	Common carotid artery
CI	Confidence interval
Cohort Δ	Difference between cohort and reference cohort (cross-sectional)
CR	Control rate
CRP	C-reactive protein
CSFII	Continuing Food Survey of Intakes by Individuals
CVD	Cardiovascular disease
D	Docosahexaenoic acid
DHA	Docosahexaenoic acid (22:6 n-3)
DM	Diabetes mellitus
DM I	Diabetes mellitus, type 1
DM II	Diabetes mellitus, type 2
DPA	Docosapentaenoic acid (DPA, 22:5 n-3)
DysLip	DysLipidemia
E	Eicosapentaenoic acid
ECG	Electrocardiogram
ED	EPA+DHA
EE	Ethyl ester
ELISA	Enzyme-linked immunosorbent assay
EPA	Eicosapentaenoic acid (20:5 n-3)
EPC	Evidence-based practice center
ERD	Energy-restricted diet
ETT	Exercise tolerance test
FA	Fatty acid
FBS	Fasting blood sugar
GEN	General, healthy population
GLA	Gamma-linolenic acid (18:3 n-6)
HDL	High density lipoprotein
Hgb A _{1c}	Hemoglobin A _{1c}
I _{max}	Maximal velocity
IC ₅₀	Concentration of Iloprost resulting in 50% inhibition of platelet aggregation
ICA	Internal carotid artery

Abbreviation	Definition
IDDM	Insulin dependent diabetes mellitus
IDL	Intermediate density lipoprotein
IL	Interleukin
IMT	Intima-media thickness
In	Inadequate allocation concealment
Jadad	Jadad score (see Methods)
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LA	Linoleic acid (18:2 n-6)
LDL	Low density lipoprotein
LDL apo B	LDL apolipoprotein B
LT	Leukotriene
N	Number of subjects analyzed in study arm
n-3	Omega-3 (fatty acid)
n-6	Omega-6 (fatty acid)
NCEP	National Cholesterol Education Program
NCEP I	National Cholesterol Education Program step I prudent diet
nd	No data
Net % Δ	Net percent difference in change in omega-3 fatty acids arm compared with the change in control arm
Net Δ	Net difference in change in omega-3 fatty acids arm compared with the change in control arm
NHANES III	The third National Health and Nutrition Examination
NIDDM	Non-insulin dependent diabetes mellitus
NIH	National Institutes of Health
NS	Non-significant
P	P value
PAI	Plasminogen activator inhibitor
PG	Prostaglandin
PL	Phospholipids
Pre Post Δ	Change in omega-3 fatty acid arm (no control)
PTCA	Percutaneous transluminal coronary angioplasty
RBC	Red blood cell
RCT	Randomized controlled trial
REM MA	Random effects model meta-analysis
RPP	Rate-pressure product
RR	Relative risk
SD	Standard deviation
SDNN	Standard deviation of the RR interval
SEM	Standard error of the mean
SFA	Saturated fatty acid
Sp.	Species
Summary	Summary quality score (see Methods)
T	Total omega-3 fatty acids
TEP	Technical Expert Panel
Tg	Triglycerides
TNF- α	Tumor necrosis factor α
TPA	Tissue plasminogen activator
TPR	Total peripheral resistance
Tufts-NEMC	Tufts-New England Medical Center
TX	Thromboxane
Un	Unclear allocation concealment
UO	University of Ottawa
USDA	United States Department of Agriculture
V _a	Aggregation velocity
VCAM-1	Vascular cell adhesion molecule 1
VLDL	Very low density lipoprotein
vWF	von Willebrand factor
WBC	White blood cell

Abbreviation

Definition

WMD
Xover

Weight-maintaining diet
Cross-over study

Effects of Omega-3 Fatty Acids on Cardiovascular Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on Effects of Omega-3 Fatty Acids on Cardiovascular Disease was requested and funded by Office of Dietary Supplements, National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.



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Structured Abstract

Context. Epidemiologic studies and clinical trials have reported beneficial effects of fish consumption on several cardiovascular disease (CVD) outcomes, such as all cause mortality, CVD death, cardiac death, sudden death, myocardial infarction and stroke. However, the mechanisms of this benefit are unclear.

Objectives. As the first of a 3-part report on this topic, we analyzed relevant nutrition databases to describe the intake levels of various omega-3 fatty acids in the US population. We also performed a systematic review of the literature to assess the benefits of omega-3 fatty acid supplements or fish consumption on various CVD outcomes and to assess adverse events associated with intake of omega-3 fatty acid supplements.

Data Sources. The Continuing Survey of Food Intakes by Individuals (CSFII) was reviewed and the third National Health and Nutrition Examination Survey (NHANES III) was analyzed for dietary intake. Medline, Embase, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau databases were searched for potentially relevant studies to address the questions on the effects of omega-3 fatty acids.

Study Selection. We screened over 7,464 abstracts and retrieved 768 full text articles. Thirty-nine studies met our inclusion criteria and provided data to address the key questions in this report. We used randomized controlled trials (RCTs) and observational studies that quantified the amount of fish or omega-3 fatty acid intake and that were at least 1 year in duration to assess the effects of omega-3 fatty acid consumption on CVD outcomes on risk of CVD in the general population (those without known CVD) and in populations at high risk due to pre-existing CVD or multiple CVD risk factors.

Data Extraction. From each study that qualified, we extracted information about the study design, population demographics, the prescribed or estimated amount of omega-3 fatty acid supplements or fish consumed, and outcomes. For RCTs, we extracted information about the randomization and blinding techniques to assess methodological quality. For prospective cohort studies, we extracted estimated quantities of fish or fish oil consumed and their associated effect.

Data Synthesis. The intake of omega-3 fatty acids in the population varies. Corrected for energy intake, men consume significantly less alpha-linolenic acid (ALA, 18:3 n-3) than women, adults more than youths, and subjects with a history of CVD less than those without CVD. Based on analyses of a single 24-hour dietary recall in NHANES III, only 25% of the US population reported any amount of daily eicosapentaenoic acid (EPA, 20:5 n-3) or docosahexaenoic acid (DHA, 22:6 n-3) intake.

Eleven RCTs and 1 prospective cohort study reported outcomes on CVD populations. The largest trial reported that fish oil (EPA + DHA) reduces all cause mortality and CVD events, although fish oil has no effect on stroke. Most other studies evaluating either fish oil or ALA supplements reported similar findings. There were few trials of ALA. In the only RCT that directly compared ALA and fish oil, both treatments were efficacious in reducing CVD outcome. No significant difference was found between the 2 supplements.

Twenty-two prospective cohort studies and 1 RCT reported data on general populations. Among the cohort studies there were considerable differences among the populations studied, as well as in the estimates of fish or omega-3 fatty acids consumed. Most of the large cohort studies found fish consumption was associated with lower rates of all cause mortality and CVD outcomes, but several studies reported no significant or negative results for the CVD outcomes. A significant benefit for stroke was reported in 1 study. The single RCT which evaluated ALA in a large general population lasted only 1 year yielding no significant results. Gastrointestinal symptoms associated with fish oil or ALA supplements are the most commonly reported adverse event and may require dose reduction or discontinuation in some individuals. Clinical bleeding is a theoretical concern but this was not borne out by the evidence.

Conclusions. Overall, consumption of omega-3 fatty acids from fish or from supplements of fish oil reduces all cause mortality and various CVD outcomes. The evidence for ALA supplements is sparse and inconclusive. The adverse events due to consumption of fish oil or ALA supplements appear to be minor. Many questions remain. The studies were heterogeneous with regard to the methods of estimating fish or omega-3 fatty acid intake, background diets, settings, and the methods of reporting results. Due to these reasons, the validity of applying the results of studies conducted in countries outside of the US to the US population is uncertain. The optimal quantity and type of omega-3 fatty acid, and the optimal ratio of omega-3 to omega-6 fatty acid (if such an optimal ratio exists), remain undefined. Not much data exists concerning the needs of different subpopulations. Different types of fish and the method of food preparation may have different effects. Future research needs to address these issues.

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Evidence Report

Chapter 1. Introduction

This evidence report is 1 of 3 reports prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the health benefits of omega-3 fatty acids on cardiovascular diseases. These reports are among several that address topics related to omega-3 fatty acids, and that were requested by the Office of Dietary Supplements, National Institutes of Health, through the EPC Program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs — the Tufts-NEMC EPC, the Southern California-RAND EPC, and the University of Ottawa EPC — each produced evidence reports. To ensure consistency of approach, the 3 EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of the reports is to summarize the current evidence on the health effects of omega-3 fatty acids on the following: CVD, cancer, child and maternal health, eye health, gastrointestinal/renal diseases, asthma, autoimmune diseases, immune-mediated diseases, transplantation, mental health, and neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

The focus of this report is on CVD outcomes in humans. The other 2 reports by the Tufts-NEMC EPC focus on risk factors of cardiovascular disease and on arrhythmic electrophysiology in animal and in-vitro studies. In this chapter, the metabolism, physiological functions, and the sources of omega-3 fatty acids are briefly discussed. Subsequent chapters describe the methods used to identify and review studies related to omega-3 fatty acids and CVD — including the analytic framework for this report, findings related to the effects of omega-3 fatty acids on cardiovascular conditions, and recommendations for future research in this area.

Background

Metabolism and Biological Effects of Essential Fatty Acids

Dietary fat is an important source of energy for biological activities in human beings. Dietary fat encompasses saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. Unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Polyunsaturated fatty acids (PUFAs) can be classified on the basis of their chemical structure into two groups: omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. The *omega-3* or *n-3* notation means that the first double bond from the methyl end of the molecule is in the third. The same principle applies to the *omega-6* or *n-6* notation. Despite their differences in structure, all fats contain the same amount of energy (9 kcal/g or 37 kJ/g).

Of all fats found in food, 2 — alpha-linolenic acid (chemical abbreviation: ALA, 18:3 n-3) and linoleic acid (LA, 18:2 n-6) — cannot be synthesized in the human body, yet are necessary for proper physiological functioning. These 2 fats are called essential fatty acids. The essential fatty acids can be converted in the liver to long-chain polyunsaturated fatty acids (LC PUFAs),

which have a higher number of carbon atoms and double bonds. These LC PUFAs retain the omega type (n-3 or n-6) of the parent essential fatty acids.

ALA and LA comprise the bulk of the total PUFAs consumed in a typical North American diet. Typically, LA comprises 89% of the total PUFAs consumed, while ALA comprises 9%. Smaller amounts of other PUFAs make up the remainder¹. Both ALA and LA are present in a variety of foods. For example, LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA, which is consumed in smaller quantities, is present in leafy green vegetables and in some commonly used oils, including canola and soybean oil. Some novelty oils, such as flaxseed oil, contain relatively high concentrations of ALA, but these oils are not commonly found in the food supply.

The Institute of Medicine suggests that, for adults 19 and older, an adequate intake (AI) of ALA is 1.1-1.6 g/day, while an adequate daily intake of LA is 11-17 g/day². Recommendations regarding AI differ by age and gender groups, and for special conditions such as pregnancy and lactation.

As shown in Figure 1.1, EPA and DHA can act as competitors for the same metabolic pathways as AA. In human studies, the analyses of fatty-acid compositions in both blood phospholipids and adipose tissue showed similar competitive relationship between omega-3 LC PUFAs and AA. General scientific agreement supports an increased consumption of omega-3 fatty acids and reduced intake of omega-6 fatty acids to promote good health. However, for omega-3 fatty acid intakes, the specific quantitative recommendations vary widely among countries not only in terms of different units - ratio, gram, total energy intake - but also in quantity³. Furthermore, there remain numerous questions relating to the inherent complexities about omega-3 and omega-6 fatty acid metabolism, in particular regarding the inter-relationships between the 2 fatty acids. For example, it remains unclear to what extent ALA is converted to EPA and DHA in humans, and to what extent high intake of omega-6 fatty acids compromises any benefits of omega-3 fatty acid consumption. Without resolution of these 2 foundational questions, it remains difficult to study the importance of omega-6 to omega-3 fatty acid ratio.

Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids

Omega-3 and omega-6 fatty acids share the same pools of enzymes and go through the same oxidation pathways while being metabolized (Figure 1.1). Once ingested, ALA and LA can be elongated and desaturated into LC PUFAs. LA is converted into gamma-linolenic acid (GLA, 18:3 n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the long-chain omega-6 fatty acid, arachidonic acid (AA, 20:4 n-6). ALA can be converted, to a lesser extent, to the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3). However, the conversion from parent fatty acids into LC PUFAs occurs slowly in humans, and conversion rates are not well understood. Because of the slow rate of conversion and the importance of LC PUFAs to many physiological processes, humans must augment their level of LC PUFAs by consuming foods that are rich in these important compounds. Meat is the primary food source of AA, while fish is the primary food source of EPA.

The specific biological functions of fatty acids depend on the number and position of double bonds and the length of the acyl chain. Both EPA and AA are 20-carbon fatty acids and are precursors for the formation of prostaglandins, thromboxane, and leukotrienes — hormone-like