temperature. The term “saturation” refers to a chemical structure in which each carbon atom in the fatty acyl chain is bound to (saturated with) four other atoms, these carbons are linked by single bonds, and no other atoms or molecules can attach; unsaturated fatty acids contain at least one pair of carbon atoms linked by a double bond, which allows the attachment of additional atoms to those carbons (resulting in saturation). Despite their differences in structure, all fats contain approximately the same amount of energy (37 kilojoules/gram, or 9 kilocalories/gram).

The class of unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Monounsaturated fatty acids (the primary constituents of olive and canola oils) contain only one double bond. Polyunsaturated fatty acids (PUFAs) (the primary constituents of corn, sunflower, flax seed and many other vegetable oils) contain more than one double bond. Fatty acids are often referred to using the number of carbon atoms in the acyl chain, followed by a colon, followed by the number of double bonds in the chain (e.g., 18:1 refers to the 18-carbon monounsaturated fatty acid, oleic acid; 18:3 refers to any 18-carbon PUFA with three double bonds).

PUFAs are further categorized on the basis of the location of their double bonds. An omega or n notation indicates the number of carbon atoms from the methyl end of the acyl chain to the first double bond. Thus, for example, in the omega-3 (n-3) family of PUFAs, the first double bond is 3 carbons from the methyl end of the molecule. The trivial names, chemical names and abbreviations for the omega-3 fatty acids are detailed in Table 1.1.

Finally, PUFAs can be categorized according to their chain length. The 18-carbon n-3 and n-6 short-chain PUFAs are precursors to the longer 20- and 22-carbon PUFAs, called long-chain PUFAs (LCPUFAs).

Table 1.1. Nomenclature of omega-3 fatty acids.

Names		Abbreviations		
Trivial	IUPAC*	Carboxyl-reference	Omega-reference	Other
Linolenic acid	9,12,15-octadecenoic acid	$18{:}3\Delta^{9\ 12\ 15}$	18:3n-3 18:3 (ω-3)	ALA α-LA LNA α-LNA
Docosahexaenoic acid	4,8,12,15,19- docosahexaenoic acid	$22{:}6\Delta^{4\ 8\ 12\ 15\ 19}$	22:6n-3 22:6 (ω-3)	DHA
Docosapentaenoic acid	7,10,13,16,19-docosapentaenoic acid	$22{:}5\Delta^{7\ 10\ 13\ 16\ 19}$	22:5n-3 22:5 (ω-3)	DPA
Eicosapentaenoic acid Icosapentaenoic acid Timnodonic acid	5,8,11,14,17- eicosapentaenoic acid	$20{:}5\Delta^{5\ 8\ 11\ 14\ 17}$	20:5n-3 20:5 (ω-3)	EPA

*IUPAC=International Union of Pure and Applied Chemistry

Fatty Acid Metabolism

Mammalian cells can introduce double bonds into all positions on the fatty acid chain except the n-3 and n-6 position. Thus, the short-chain alpha-linolenic acid (ALA, chemical abbreviation: 18:3n-3) and linoleic acid (LA, chemical abbreviation: 18:2n-6) are essential fatty acids. No other fatty acids found in food are considered ‘essential’ for humans, because they can all be synthesized from the short chain fatty acids.

Table 1.2. Sources and proportions of omega-3 fatty acids in common foods and supplements.

Food/supplement	EPA 20:5n-3	DHA 22:6n-3	DPA 22:5n-3	ALA 18:3n-3
Foods in which Total Omega-3 Fatty Acids account for more than 50% of Total PUFA				
Fish				
Anchovy	v	v	v	
Halibut	v	v	v	
Herring	v	v	v	
Mackerel	v	v	v	
Salmon	v	v	v	
Sardine	v	v	v	
Tuna				
Canned, waterpacked	v	v	v	
Fresh Bluefin	v	v	v	
Oils/Supplements				
Cod liver oils	v	v	v	
Coromega *	v	v		
Fish oil capsules*	v	v		
*Flaxseed/linseed oil**				v
Herring oil	v	v	v	
MaxEPA*	v	v		
Menhaden oil	v	v	v	
Neuromins*		v		
Omacor*	v	v		
Ropufa*	v	v	v	
Salmon oil	v	v	v	
Sardine oil	v	v	v	
Seeds				
Flaxseeds/Linseeds				v
Foods/Supplements in which total Omega 3 fatty acids are 10-50% of total PUFA				
Oils				
Black currant oil				v
Canola oil**				v
Mustard seed oils				v
Soybean oil				v
Walnut oil				v
Wheat germ oil				v
Other foods				
Wheat germ				v
Human milk				v
Foods/Supplements in which total Omega 3 fatty acids are less than 10% of total PUFA				
Efamol Marine*	v	v		
Soybeans				v
Walnuts				v

* Dietary Supplement
** Also called rapeseed oil

Several lines of research have suggested that the high ratio of omega 6s to omega 3s currently consumed in the U.S. promotes a number of chronic diseases.[4] Because of the slow rate of elongation and further desaturation of the essential FA, the importance of LC PUFAs to many physiological processes, and the overwhelming ratio of omega 6s to omega 3s in the average U.S. diet, nutrition experts are increasingly recognizing the need for humans to augment the body's synthesis of omega 3 LC PUFAs by consuming foods that are rich in these compounds. According to data from two population-based surveys, the major dietary sources of LC omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements, and the primary dietary sources of omega-6 LC PUFAs are meats and dairy products. These surveys, the Continuing Food Survey of Intakes by Individuals 1994-98 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988-94 surveys, are the main sources of dietary intake data for the U.S. population. The CSFII has the advantage of collecting dietary recall data over a period of several days, which may permit estimates of omega-3 intake that more accurately reflect individual intakes than do those of NHANES. However, NHANES intake data have the advantage of being able to be linked to health outcomes. Table 1.3 provides a list of food sources of omega-3 fatty acids.

Table 1.3. Good food sources* of omega 3 fatty acids.

	EPA+DHA	ALA		EPA+DHA	ALA
Fish (3oz. Cooked)			**Oils (1 Tbs.)**		
Anchovy	v		Canola		v
Halibut	v		Cod liver	v	
Herring, Atlantic	v		Flaxseed/linseed		v
Pacific	v		Herring	v	
Mackerel, Atlantic	v		Menhaden	v	
Pacific	v		Salmon	v	
Salmon, Atlantic**	v		Sardine	v	
Sardines	v		Soybean		v
Trout, Rainbow	v		Walnut		v
Tuna, Albacore	v		Wheat germ		v
Canned light, water-packed	v				
Canned white, water-packed	v				
Fresh Bluefin	v				
Organ Meats (3 oz. Cooked)			**Seeds**		
Brain, lamb	v		Flaxseeds/linseeds (1 Tbs.)		v
Brain, pork	v				
Thymus, calf		v			
Other Foods					
Caviar (1 oz.)#	v				
Human breast milk (1c)#		v			
Soybeans, cooked (1/2c)		v			
Tofu, regular (1/2c)		v			
Walnuts (1/4c)		v			
Wheat germ (1/4c)#		v			

Source: Figures adapted from USDA, 2003; *Foods that provide (per serving) 10% or more of the Adequate Intake (AI) for ALA or the Acceptable Macronutrient Distribution Range (AMDR) for EPA and DHA (10% of the AMDR for ALA); an AI is a recommended average daily intake level based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people (thus, assumed to be adequate) when an RDA cannot be determined; an AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients."[5]

Standard serving size not established; **Farm-raised Atlantic salmon have nearly identical omega-3 fatty acid levels to wild Atlantic salmon and significantly more omega-3 fatty acids than wild Pacific salmon.

Table 1.4 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by NHANES III.[1] Table 1.5 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by CSFII.

Table 1.4. Estimates of the mean intake of LA, ALA, EPA, and DHA in the U.S. Population from analysis of NHANES III data.*

	Grams/day		Percent energy intake/day	
	Mean ± SEM	Median (range)**	Mean ± SEM	Median (range)**
LA (18:2n-6)	14.1 ± 0.2	9.9 (0 - 168)	5.79 ± 0.05	5.30 (0 - 39.4)
ALA (18:3n-3)	1.33 ± 0.02	0.90 (0 - 17)	0.55 ± 0.004	0.48 (0 - 4.98)
EPA (20:5n-3)	0.04 ± 0.003	0.00 (0 - 4.1)	0.02 ± 0.001	0.00 (0 - 0.61)
DHA (22:6n-3)	0.07 ± 0.004	0.00 (0 - 7.8)	0.03 ± 0.002	0.00 (0 - 2.86)

*Based on analysis of a single 24-hour dietary recall from NHANES III data; **Distributions are not adjusted for the over-sampling of Mexican –Americans, non-Hispanic African Americans, children 5 years old and under, and adults 60 years and over in the NHANES III dataset.

Table 1.5. Mean, range, and median usual daily Intakes (ranges) of n-6 and n-3 PUFAs, in the U.S. population, from analysis of CSFII data (1994 to 1998).*

	Mean (gms/d) (± SEM)**	Range of Means (gms/d) (±SEM)	Median (gms/d) (± SEM)**
LA (18:2n-6)	13.0 ± 0.1	6.7 ± 0.1-17.6 ± 0.5	12.0 ± 0.1
Total n-3 FA	1.40 ± 0.01	0.72 ± 0.02 - 1.86 ± 0.04	1.30 ± 0.01
ALA (18:3n-3)	1.30 ± 0.01	0.72 ± 0.02 - 1.73 ± 0.04	1.21 ± 0.01
EPA (20:5n-3)	0.028	0.002 - 0.049	0.004
DPA (22:5n-3)	0.013	0.001 - 0.019	0.005
DHA (22:6n-3)	0.057 ± 0.018	< 0.0005 ± 0.001	0.046 ± 0.013

Source: Adapted from Dietary Reference Intakes Report;[5] *Estimates are based on respondents' intakes on the first day of survey and were adjusted using the Iowa State University method; **For all individuals.

Lacking sufficient evidence from research on the effects or correction of dietary deficiencies to establish Recommended Dietary Allowances (RDAs) for the essential fatty acids, the Food and Nutrition Board (FNB) of the Institute of Medicine[5] has set adequate intakes[2] (AI) for the essential fatty acids, based on the average intakes of healthy CSFII participants. The AIs for the essential fatty acids vary by age group and sex, as well as for particular conditions such as pregnancy and breastfeeding. For ALA, the AI for men 19 and older, is 1.6 grams/day and the AI for (non-pregnant, non-breastfeeding) women is 1.1 grams/day. The AI for LA is 17 grams/day for men and 11 grams/day for women.

Based on evidence suggesting a role in prevention or treatment of some chronic diseases, the FNB has also established Acceptable Macronutrient Distribution Ranges (AMDR) for the essential fatty acids. An AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of

[1] The population represented by NHANES III includes individuals ages 2 months and older. Mexican Americans and non-Hispanic African-Americans, children 5 years old and younger, and adults 60 years of age and over were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall data. The NHANES III also included a physical examination and health survey of each participant.

[2] An Adequate Intake (AI) is defined as "the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake, by a group (or groups) of apparently healthy people, that are assumed to be adequate – used when a recommended dietary allowance cannot be determined."[5] An AI is set when data are insufficient or inadequate to establish an Estimated Average Requirement, on which the RDA is based, and indicate the need for more and better research. The EAR is "the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group," based on a specific indicator or criterion of adequacy.

Table 1.6. The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, and fish oils, and nuts and seeds, and plant oils that contain at least 5 g omega-3 fatty acids per 100 g.

Food item	EPA	DHA	ALA	Food item	EPA	DHA	ALA
Fish (Raw [a])				**Fish, continued**			
Anchovy, European	0.6	0.9	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.2	0.4	0.1	Tuna, Light, Canned in Oil [e]	trace	0.1	trace
Bass, Striped	0.2	0.6	trace	Tuna, Light, Canned in Water [e]	trace	0.2	trace
Bluefish	0.2	0.5	-	Tuna, White, Canned in Oil [e]	trace	0.2	0.2
Carp	0.2	0.1	0.3	Tuna, White, Canned in Water [e]	0.2	0.6	trace
Catfish, Channel	trace	0.2	0.1	Whitefish, Mixed Sp.	0.3	0.9	0.2
Cod, Atlantic	trace	0.1	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	trace	0.1	trace	Wolf fish, Atlantic	0.4	0.3	trace
Eel, Mixed Sp.	trace	trace	0.4				
Flounder & Sole Sp.	trace	0.1	trace				
Grouper, Mixed Sp.	trace	0.2	trace	**Shellfish (Raw)**			
Haddock	trace	0.1	trace	Abalone, Mixed Sp.	trace	-	-
Halibut, Atlantic and Pacific	trace	0.3	trace	Clam, Mixed Sp.	trace	trace	trace
Halibut, Greenland	0.5	0.4	trace	Crab, Blue	0.2	0.2	-
Herring, Atlantic	0.7	0.9	0.1	Crayfish, Mixed Sp., Farmed	trace	0.1	trace
Herring, Pacific	1.0	0.7	trace	Lobster, Northern	-	-	-
Mackerel, Atlantic	0.9	1.4	0.2	Mussel, Blue	0.2	0.3	trace
Mackerel, Pacific and Jack	0.6	0.9	trace	Oyster, Eastern, Farmed	0.2	0.2	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Eastern, Wild	0.3	0.3	trace
Ocean Perch, Atlantic	trace	0.2	trace	Oyster, Pacific	0.4	0.3	trace

Table 3.1. Diabetes: mean difference for total cholesterol.

	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Alekseeva[65]	Linseed oil	30	Placebo	30	2.32	(-24.97, 29.60)
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	6.80	(-21.65, 34.00)
Chan[58]	Omacor	12	Placebo	13	-11.58	(-36.35, 13.19)
	Omacor/Atorvastatin	11	Atorvastatin	13	11.58	(-9.59, 32.76)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	-19.31	(-46.67, 8.06)
	Fish/moderate exercise	14	Placebo	11	7.72	(-19.28, 34.73)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-11.58	(-30.89, 7.72)
Meshcheriakova[66]	Linseed oil/Eiconol	60	Low-fat/Low sodium diet	60	4.63	(-15.75, 25.01)
Morgan[61]	Fish oil	10	Placebo	10	-13.13	(-37.43, 11.18)
	Fish oil	10	Placebo	10		
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-37.00	(-96.98, 22.98)
	High dosage Fish oil	6	Placebo	6	24.00	(-5.75, 53.75)
Patti[68]	Fish oil	8	Placebo	8	-19.31	(-57.98, 19.37)
Pelikanova[62]	Fish oil	10	Placebo	10	18.92	(-12.96, 50.80)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	16.99	(-5.97, 39.95)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-17.76	(-45.21, 9.69)
Shimizu[56]	EPA-E	29	Placebo	16	12.40	(-2.30, 27.10)
Woodman[72]	EPA	17	Placebo	16	-4.75	(-22.48, 12.97)
	DHA	18				
Pooled Random Effects Estimate*					0.72	(-5.90, 7.33)

*Chi-squared test of heterogeneity p-value = 0.22

Table 3.2. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on total cholesterol among people with type II diabetes.

		Methodological Quality							
		A	B				C			
	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
Applicability			Hendra[60]	80	-11.58	(-30.89, 7.72)	Shimizu[56]	45	12.40	(-2.30, 27.10)
			Morgan[67]	13	-37.00	(-96.98, 22.98)	Morgan[61]	40	-13.13	(-37.43, 11.18)
				12	24.00	(-5.75, 53.75)				
			Petersen[63]	42	16.99	(-5.97, 39.95)	Patti[68]	16	-19.31	(-57.98, 19.37)
							Sarkkinen[70]	31	-17.76	(-45.21, 9.69)
	II		Chan[58]	25	-11.58	(-36.35, 13.19)	Annuzzi[57]	8	6.18	(-21.65, 34.00)
				24	11.58	(-9.59, 32.76)				
			Woodman[72]	51	-4.75	(-22.48, 12.97)	Dunstan[59]	24	-19.31	(-46.67, 8.06)
								25	7.72	(-19.28, 34.73)
							Pelikanova[62]	20	18.92	(-12.96, 50.80)
	III									

Table 3.3. Diabetes: mean difference for high-density lipoprotein (HDL).

	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	0.00	(-3.21, 3.21)
Chan[58]	Omacor	12	Placebo	13	-0.77	(-6.33, 4.78)
	Omacor/Atorvastatin	11	Atorvastatin	13	8.11	(0.63, 15.59)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	4.63	(-3.90, 13.16)
	Fish oil/mod. exercise	14	Placebo	11	0.39	(-8.03, 8.80)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-7.72	(-14.68, -0.76)
Morgan[61]	Fish oil	10	Placebo	10	2.70	(-6.18, 11.58)
	Fish oil	10	Placebo	10		
Maffettone[73]	Fish oil	8	Placebo	8	-2.32	(-10.69, 6.06)
Morgan[67]	Low dosage Fish oil	7	Placebo	6	9.00	(-3.49, 21.49)
	High dosage Fish oil	6	Placebo	6	9.00	(-13.03, 31.03)
Patti[68]	Fish oil	8	Placebo	8	-2.32	(-10.78, 6.14)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	6.56	(0.13, 13.00)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-3.09	(-9.84, 3.67)
Shimizu[56]	EPA-E	29	Placebo	16	5.80	(-2.70, 14.30)
Woodman[72]	EPA	17	Placebo	16	2.02	(-4.44, 8.48)
	DHA	18				
Pooled Random Effects Estimate*					1.17	(-1.08, 3.42)

*Chi-squared test of heterogeneity p-value = 0.13

Table 3.4. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on HDL among people with type II diabetes.

		Methodological Quality							
		A	B				C			
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
			Hendra[60]	80	-7.72	(-14.68, -0.76)	Shimizu[56]	45	5.80	(-2.70, 14.30)
			Morgan[67]	13	9.00	(-3.49, 21.49)	Morgan[61]	40	2.70	(-6.18, 11.58)
				12	9.00	(-13.03, 31.03)				
			Petersen[63]	42	6.56	(0.13, 13.00)	Patti[68]	14	-2.32	(-10.78, 6.14)
							Sarkkinen[70]	31	-3.09	(-9.84, 3.67)
	II		Chan[58]	25	-0.77	(-6.33, 4.78)	Annuzzi[57]	8	0.00	(-3.21, 3.21)
				24	8.11	(0.63, 15.59)				
			Woodman[72]	51	2.02	(-4.44, 8.48)	Dunstan[59]	24	4.63	(-3.90, 13.16)
								25	0.39	(-8.03, 8.80)
	III									

Table 3.5. Diabetes: mean difference for low-density lipoprotein (LDL).

	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	23.17	(-9.22, 55.56)
Chan[58]	Omacor	12	Placebo	13	-5.79	(-20.88, 9.29)
	Omacor/Atorvastatin	11	Atorvastatin	13	11.97	(-4.51, 28.45)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	5.02	(-21.44, 31.48)
	Fish oil/mod. exercise	14	Placebo	11	19.31	(-6.81, 45.42)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-3.86	(-22.97, 15.25)
Morgan[61]	Fish oil	10	Placebo	10	8.11	(-19.46, 35.67)
	Fish oil	10	Placebo	10		
Maffettone[73]	Fish oil	8	Placebo	8	-0.39	(-47.32, 46.55)
Morgan[67]	Low dosage Fish oil	7	Placebo	6	8.00	(-52.53, 68.53)
	High dosage Fish oil	6	Placebo	6	23.00	(-31.39, 77.39)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	21.62	(2.79, 40.45)
Rivellese[69]	Fish oil	8	Placebo	8	-0.39	(-47.31, 46.54)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-10.04	(-37.38, 17.30)
Woodman[72]	EPA	17	Placebo	16	0.50	(-13.80, 14.79)
	DHA	18				
Pooled Random Effects Estimate*					5.12	(-1.02, 11.25)

*Chi-squared test of heterogeneity p-value = 0.62

Table 3.6. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on LDL among people with type II diabetes.

		Methodological Quality							
		A	B				C			
	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
Applicability			Hendra[60]	80	-3.86	(-22.97, 15.25)	Morgan[61]	40	8.11	(-19.46, 35.67)
			Morgan[67]	13	8.00	(-52.53, 68.53)	Rivallese[69]	16	-0.39	(-47.31, 46.54)
				12	23.00	(-31.39, 77.39)				
			Petersen[63]	42	21.62	(2.79, 40.45)	Sarkkinen[70]	31	-10.04	(-37.38, 17.30)
	II		Chan[58]	25	-5.79	(-20.88, 9.29)	Annuzzi[57]	8	23.17	(-9.22, 55.56)
				24	11.97	(-4.51, 28.45)				
			Woodman[72]	51	0.50	(-13.80, 14.79)	Dunstan[59]	24	5.02	(-21.44, 31.48)
								25	19.31	(-6.81, 45.42)
	III									

Table 3.7. Diabetes: mean difference for triglycerides.

	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	-32.74	(-84.25, 18.77)
Alekseeva[65]	Linseed oil	30	Placebo	30	53.10	(-33.54, 139.74)
Chan[58]	Omacor	12	Placebo	13	-123.89	(-366.93, 119.14)
	Omacor/Atorvastatin	11	Atorvastatin	13	-17.70	(-52.99, 17.59)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	-115.04	(-195.84, -34.24)
	Fish oil/moderate exercise	14	Placebo	11	-53.10	(-132.84, 26.65)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-44.25	(-89.80, 1.31)
Meshcheriakova[66]	Linseed oil/Eiconol	60	Low-fat/Low sodium diet	60	-35.40	(-88.83, 18.03)
Morgan[61]	Fish oil	10	Placebo	10	-346.90	(-656.00, -37.81)
	Fish oil	10	Placebo	10		
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-116.00	(-267.44, 35.44)
	High dosage Fish oil	6	Placebo	6	-7.00	(-110.19, 96.19)
Patti[68]	Fish oil	8	Placebo	8	-19.47	(-89.24, 50.30)
Pelikanova[62]	Fish oil	10	Placebo	10	-36.28	(-101.90, 29.33)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	-80.53	(-175.69, 14.63)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-23.01	(-80.05, 34.03)
Shimizu[56]	EPA-E	29	Placebo	16	30.40	(-23.37, 84.17)
Woodman[72]	EPA	17	Placebo	16	-39.52	(-68.98, -10.06)
	DHA	18				
Pooled Random Effects Estimate*					-31.61	(-49.58, -13.64)

*Chi-squared test of heterogeneity p-value = 0.16

Table 3.8. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on triglycerides among people with type II diabetes.

		Methodological Quality							
		A	B				C		
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
			Hendra[60]	80	-44.25	(-89.80, 1.31)	Shimizu[56]	45	30.40	(-23.37, 84.17)
			Morgan[67]	13	-116.00	(-267.44, 35.44)	Morgan[61]	40	-346.90	(-656.00, -37.81)
				12	-7.00	(-110.19, 96.19)				
			Petersen[63]	42	-80.53	(-175.69, 14.63)	Patti[68]	14	-19.47	(-89.24, 50.30)
							Sarkkinen[70]	31	-23.01	(-80.05, 34.03)
	II		Chan[58]	25	-123.89	(-366.93, 119.14)	Annuzzi[57]	8	-32.74	(-84.25, 18.77)
				24	-17.70	(-42.99, 17.59)				
			Woodman[72]	51	-39.52	(-68.98, -10.06)	Dunstan[59]	24	-115.04	(-195.84, -34.24)
								25	-53.10	(-132.84, 26.65)
							Pelikanova[62]	20	-36.28	(-101.90, 29.33)
	III									

Effects of dose, source, and exposure duration. None of the studies specifically assessed the effects of dose, source, or exposure duration. A pooled analysis of dose effect using meta-regression revealed no significant dose effect on fasting blood glucose or glycosylated hemoglobin. No studies were identified that assessed the effects of omega-3 fatty acids from a plant source on insulin sensitivity or glycemic control.

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Among studies that were included in the meta-analysis for fasting blood glucose and glycosylated hemoglobin, none had both an applicability rating of I (representative of general adult population with type II diabetes), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Tables 3.10 and 3.12). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with type II diabetes. Of note, no studies that assessed the effect of omega-3 fatty acids among children with type II diabetes were identified.

Table 3.9. Diabetes: mean difference of fasting blood glucose.

	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	-7.93	(-66.18, 50.32)
Alekseeva[65]	Linseed oil	30	Placebo	30	9.01	(-24.30, 42.32)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	9.01	(-33.00, 51.02)
	Fish oil/mod. exercise	14	Placebo	11	3.60	(-37.85, 45.06)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	21.62	(-18.06, 61.3)
Morgan[61]	Fish oil	10	Placebo	10	-14.41	(-52.95, 24.12)
	Fish oil	10	Placebo	10		
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-41.00	(-114.16, 32.16)
	High dosage Fish oil	6	Placebo	6	-17.00	(-89.43, 55.43)
Patti[68]	Fish oil	8	Placebo	8	10.81	(-28.67, 50.29)
Sirtori[64]	Esepent (fish oil)	203	Placebo	211	4.30	(-2.82, 11.42)
Woodman[72]	EPA	17	Placebo	16	19.81	(2.25, 37.37)
	DHA	18				
Pooled Random Effects Estimate*					5.87	(-0.15, 11.88)

*Chi-squared test of heterogeneity p-value = 0.76

Table 3.10. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on fasting blood sugar among people with type II diabetes.

		Methodological Quality								
		A	B				C			
	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
Applicability			Hendra[60]	80	21.62	(-18.06, 61.30)	Morgan[61]	40	-14.41	(-52.95, 24.12)
			Morgan[67]	13 12	-41.00 -17.00	(-114.16, 32.16) (-89.43, 55.43)	Patti[68]	16	10.81	(-28.67, 50.29)
			Sirtori[64]	414	4.30	(-2.82, 11.42)				
	II		Woodman[72]	51	19.81	(2.25, 37.37)	Annuzzi[57]	8	-7.93	(-66.18, 50.32)
							Dunstan[59]	24 25	9.01 3.60	(-33.00, 51.02) (-37.85, 45.06)
	III									

Figure 3.6. Diabetes: fasting blood glucose.

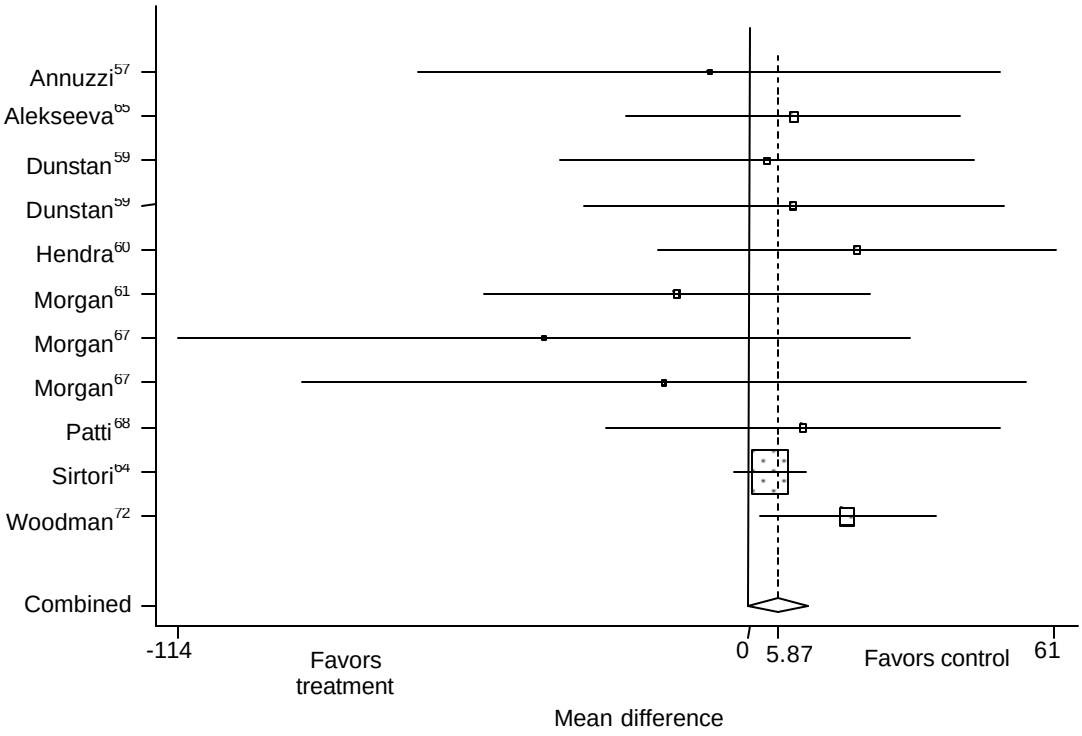


Table 3.11. Diabetes: effect size of hemoglobin A1c (HbA1c).

	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**(%) (95% CI)**
Morgan[61]	Fish oil	10	Placebo	10	-0.10 (-1.25, 1.05)
	Fish oil	10	Placebo	10	
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-1.30 (-3.42, 0.82)
	High dosage Fish oil	6	Placebo	6	0.70 (-0.68, 2.08)
Patti[68]	Fish oil	8	Placebo	8	0.60 (-0.79, 1.99)
Pelikanova[62]	Fish oil	10	Placebo	10	0.90 (0.02, 1.78)
Shimizu[56]	EPA-E	29	Placebo	16	0.06 (-8.44, 8.56)
Sirtori[64]	Esepent (fish oil)	203	Placebo	211	0.17 (-0.12, 0.46)
Westerveld[71]	EPA-E	8	Placebo	8	-1.30 (-3.55, 0.95)
	EPA-E	8			
Woodman[72]	EPA	17	Placebo	16	0.23 (-0.28, 0.75)
	DHA	18			
Pooled Random Effects Estimate*					0.21 (-0.01, 0.44)

*Chi-squared test of heterogeneity p-value = 0.52

Table 3.12. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on glycosylated hemoglobin among people with type II diabetes.

		Methodological Quality							
		A	B				C		
			Study	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**
Applicability	I		Morgan[67]	13	-1.30	(-3.42, 0.82)	Morgan[61]	40	-0.10 (-1.25, 1.05)
				12	0.70	(-0.68, 2.08)			
			Sirtori[64]	414	0.17	(-0.12, 0.46)	Patti[68]	16	0.60 (-0.79, 1.99)
			Westerveld [71]	24	1.30	(-3.55, 0.95)			
	II		Woodman[72]	51	0.23	(-0.28, 0.75)	Pelikanova[62]	20	0.90 (0.02, 1.78)
	III								

Covariates. Reported covariates included use of other drugs, previous surgery and presence of fistulae. However, no comparisons of the effects of covariates on outcomes were identified.

Effects of dose, source, and exposure duration. All studies identified used fish oil as the source of omega-3 fatty acids. No studies compared the effect of different doses of omega-3 fatty acids. There were too few studies that assessed the effects of any single outcome to perform a pooled analysis of dose effect.

Of note, one study administered the fish oil via an enteric-coated capsule, which was designed to deliver the omega-3 fatty acids to the small bowel. [54] This study, which included only patients with Crohn's disease, demonstrated a reduced relapse rate relative to placebo.

Duration of exposure varied from 2 to 24 months across the studies. Too few studies assessed any single outcome across similar time periods to analyze the effect of duration of exposure.

Sustainment of effect. Sustainment of the assessed effects was not evaluated in any of the studies.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general population with IBD) and a summary quality score of A (Jadad score = 5 with concealment of allocation). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with IBD. Of note, no studies that assessed the effect of omega-3 fatty acids among children with IBD were identified.

Table 3.13. Ulcerative colitis disease: relative risk of relapse.

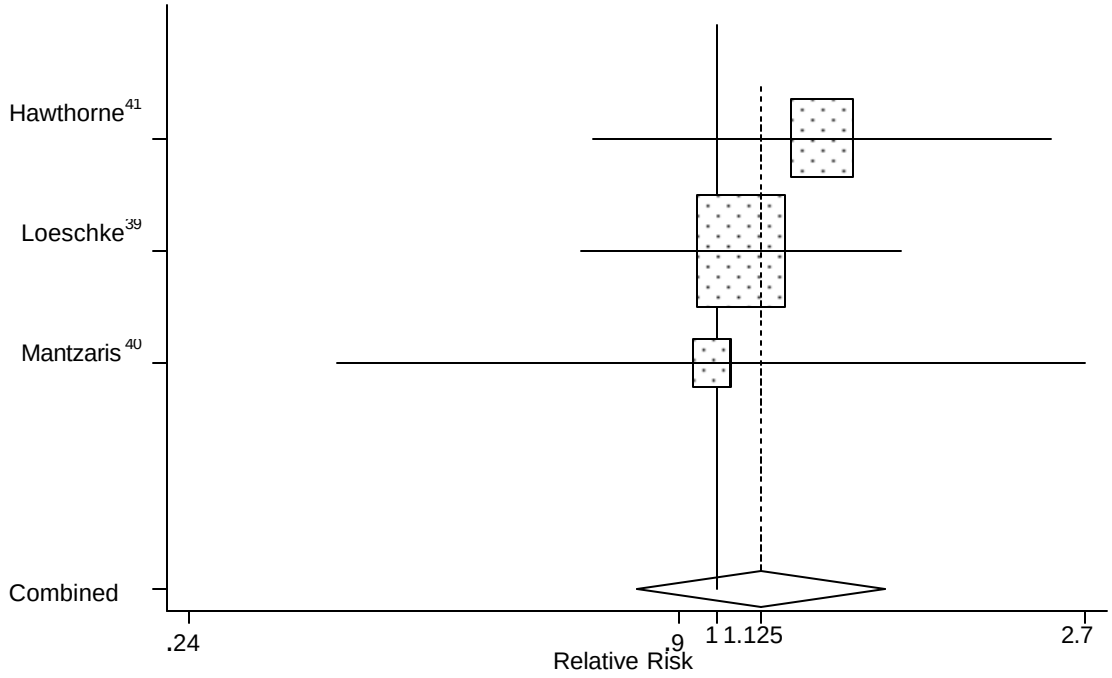
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Relative Risk (95% CI)**
Hawthorne[41]	Hi EPA	35	Placebo	34	1.32 (0.71, 2.46)
Loeschke[39]	Fish oil	31	Placebo	33	1.06 (0.69, 1.64)
Mantzaris[40]	Max EPA (fish oil)	22	Placebo	18	0.98 (0.36, 2.70)
Pooled Random Effects Estimate*					1.13 (0.81, 1.57)

*Chi-squared test of heterogeneity p-value = 0.82

Table 3.14. Relationship between methodological quality and applicability for estimates of effect of omega-3 fatty acid consumption with ulcerative colitis disease for relapse/remission.

		Methodological Quality					
		A	B				C
Applicability	I		**Study**	**n**	**Relative Risk (95%, CI)**		
			Loeschke[39]	64	1.06	(0.69, 1.64)	
			Mantzaris[40]	40	0.98	(0.36, 2.70)	
	II						
	III		Hawthorne[96]	69	1.32	(0.71, 2.46)	

Figure 3.8. Ulcerative colitis disease: relative risk of relapse.



the remaining studies, which used a fish source, the pooled random effects estimate of the effect size for pain is unchanged at –0.19 (95% CI, -0.46, 0.09).

Only 1 study assessed the effects of different durations of exposure on outcomes in RA.[19] In this study, there was no effect on pain at 24 and 36 weeks, although statistical testing of the effect between these time points was not performed. There were insufficient data across studies to perform a pooled analysis of exposure duration effect.

Sustainment of effect. Two studies assessed the sustainment of effects of omega-3 fatty acids on outcomes in RA.[18, 28] In 1 study, pain worsened in a fish oil-treated arm 3 months after discontinuation of the fish oil ($p<0.05$). In the other study, 100% of the control arm (evening primrose oil) and 80% of the fish oil group "returned to baseline or became worse." Although pain, joint swelling, and acute phase reactants were assessed in this study, the parameters on which this assessment was made were not specified. There were insufficient data across studies to perform a pooled analysis of sustainment of effect.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.16). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, no studies that assessed the effect of omega-3 fatty acids on pain among children with Juvenile RA (JRA) were identified.

Table 3.15. RA: effect size for patient assessment of pain.

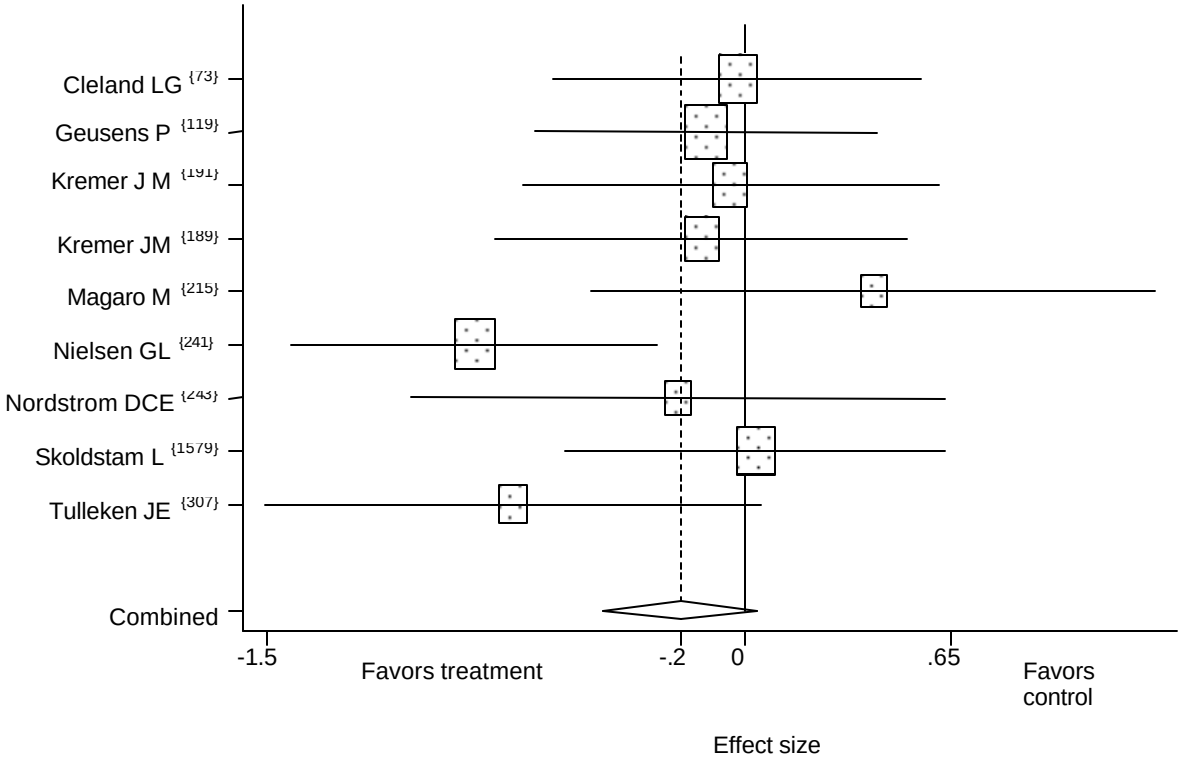
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Cleland[16]	Max EPA (fish oil)	23	Placebo	23	-0.02 (-0.60, 0.56)
Geusens[17]	Fish oil	21	Placebo	20	-0.04 (-0.57, 0.50)
	Fish oil	19			
Kremer[19]	Fish oil	20	Placebo	12	-0.04 (-0.69, 0.61)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.13 (-0.78, 0.51)
Magaro[21]	Max EPA (fish oil)	10	Placebo	10	0.41 (-0.48, 1.29)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	-0.85 (-1.42, -0.27)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	-0.21 (-1.04, 0.63)
Skoldstam[25]	Max EPA (fish oil)	22	Placebo	21	0.04 (-0.56, 0.63)
Tulleken[24]	Fish oil	13	Placebo	14	-0.72 (-1.5, 0.06)
Pooled Random Effects Estimate*					-0.19 (-0.43, 0.06)

*Chi-squared test of heterogeneity p-value = 0.23

Table 3.16. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on pain among people with rheumatoid arthritis.

		Methodological Quality							
		A	B				C		
			Study	**n**	**Effect Size(95% CI)**		**Study**	**n**	**Effect Size(95% CI)**
Applicability	I		Cleland[16]	46	-0.02	(-0.60, 0.56)	Kremer[19]	49	-0.04 (-0.69, 0.61)
			Geusens[17]	60	-0.04	(-0.57, 0.50)			
			Kremer[18]	37	-0.13	(-0.78, 0.51)			
			Skoldstam[25]	43	0.04	(-0.56, 0.63)			
	II		Tulleken[24]	27	-0.72	(-1.5, 0.06)	Magaro[21]	20	0.41 (-0.48, 1.29)
	III								

Figure 3.9. RA: patient assessment of pain.



Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.18). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, no studies that assessed the effect of omega-3 fatty acids on swollen joints among children with JRA were identified.

Table 3.17. RA: effect size for swollen joint count.

	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Cleland[16]	Max EPA (fish oil)	23	Placebo	23	0.04 (-0.54, 0.62)
Kremer[19]	Fish oil	20	Placebo	12	-0.63 (-1.30, 0.03)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.02 (-0.66, 0.63)
Magalish[20]	Omega-3 fatty acid (source not specified)	65	Placebo	47	-0.13 (-0.51, 0.25)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	0.00 (-0.55, 0.55)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	-0.06 (-0.90, 0.77)
Tulleken[24]	Fish oil	13	Placebo	14	-0.26 (-1.02, 0.50)
Pooled Random Effects Estimate					-0.13 (-0.35, 0.08)

*Chi-squared test of heterogeneity p-value = 0.81

Table 3.18. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on swollen joints among people with rheumatoid arthritis.

		Methodological Quality							
		A	B				C		
			Study	**n**	**Effect Size (95% CI)**		**Study**	**n**	**Effect Size (95% CI)**
Applicability	I		Cleland[16]	46	0.04	(-0.54, 0.62)	Kremer[19]	49	-0.63 (-1.30, 0.03)
			Kremer[18]	37	-0.02	(-0.66, 0.63)			
	II		Tulleken[24]	27	-0.26	(-1.02, 0.50)			
	III								

In one study, plants were the source of omega-3 fatty acids. In this study,[23] the effect size of omega-3 fatty acids for ESR was 0.13 (95% CI, -0.71, 0.96). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the effect size for ESR was –0.41 (95% CI, -0.99, 0.18).

Sustainment of effect. The sustainment of effects of omega-3 fatty acids on ESR or CRP in RA was not clearly described in any studies. In one study,[28] 100% of the control arm (evening primrose oil) and 80% of the fish oil group "returned to baseline or became worse." Although pain, joint swelling, and ESR were assessed in this study, the parameters on which this assessment was made were not specified.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.20). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, one study that assessed the effect of omega-3 fatty acids on ESR among children with JRA was identified.

Table 3.19. RA: effect size for ESR.

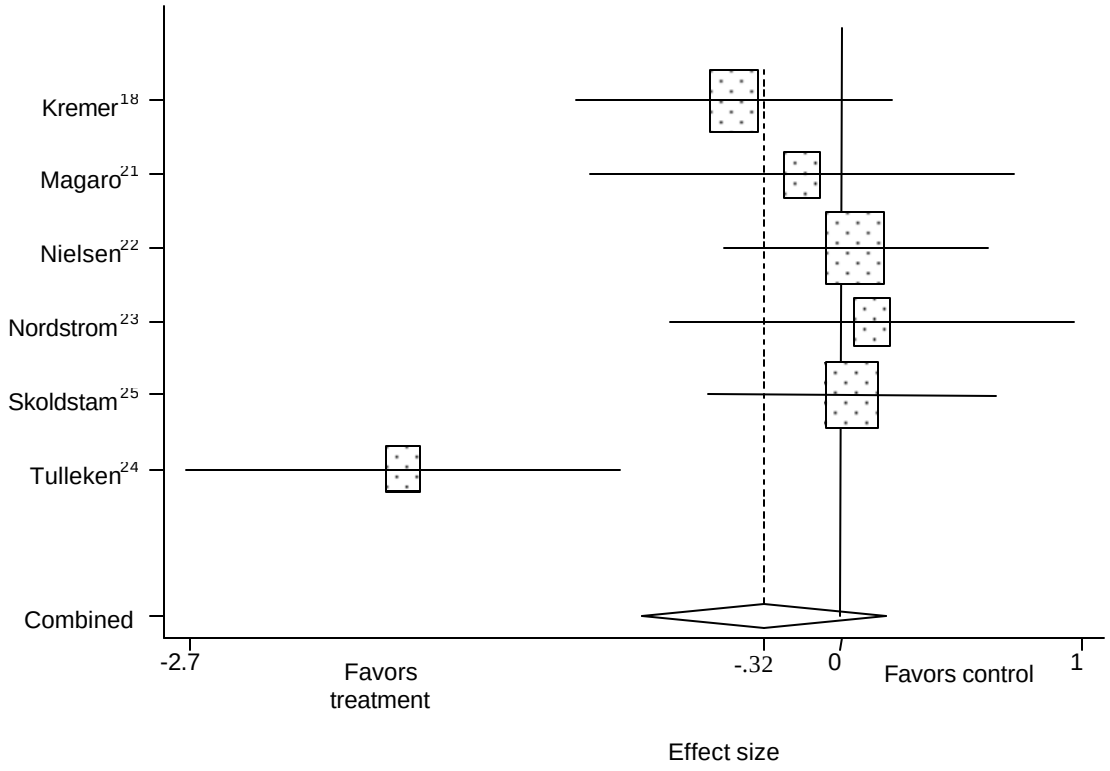
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.44 (-1.1, 0.21)
Magaro[21]	Max EPA (fish oil)	10	Placebo	10	-0.16 (-1.04, 0.72)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	0.06 (-0.49, 0.61)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	0.13 (-0.71, 0.96)
Skoldstam[25]	Max EPA (fish oil)	22	Placebo	21	0.04 (-0.55, 0.64)
Tulleken[24]	Fish oil	13	Placebo	14	-1.82 (-2.71, -0.92)
Pooled Random Effects Estimate					-0.32 (-0.83, 0.19)

*Chi-squared test of heterogeneity p-value = 0.01

Table 3.20. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on ESR among people with rheumatoid arthritis.

		Methodological Quality							
		A	B				C		
	I		**Study**	**n**	**Effect Size(95% CI)**		**Study**	**n**	**Effect Size(95% CI)**
			Kremer[18]	37	-0.44	(-1.10, 0.21)			
			Skoldstam[25]	43	0.04	(-0.55, 0.64)			
Applicability	II		Tulleken[24]	27	-1.82	(-2.71, -0.92)	Magaro[21]	20	-0.16 (-1.04, 0.72)
	III								

Figure 3.11. RA: ESR.



One study assessed the effects of omega-3 fatty acids on outcomes in RA for different durations of exposure.[19] In this study, there was no effect on patient's global assessment at 24 and 36 weeks, although statistical testing of the effect between these time points was not performed.

Sustainment of effect. One study assessed the sustainment of effects of omega-3 fatty acids on patient's global assessment in RA.[18] In this study, patient's global assessment worsened in a group that had been in a fish oil-treated arm, 3 months after discontinuation of the fish oil ($p<0.05$).

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.22). Similarly there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, no studies that assessed the effect of omega-3 fatty acids on patient's global assessment among children with JRA were identified.

Table 3.21. RA: effect size for patient global assessment.

	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Geusens[17]	Fish oil	21	Placebo	20	-1.38 (-1.97, -0.79)
	Fish oil	19			
Kremer[19]	Fish oil	20	Placebo	12	-0.13 (-0.78, 0.52)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.24 (-0.89, 0.41)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	0.26 (-0.58, 1.10)
Skoldstam[25]	Max EPA (fish oil)	22	Placebo	21	0.11 (-0.49, 0.71)
Pooled Random Effects Estimate					-0.30 (-0.90, 0.30)

*Chi-squared test of heterogeneity p-value = 0.002

Table 3.22. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on global assessment among people with rheumatoid arthritis.

		Methodological Quality							
		A	B				C		
	I		**Study**	**n**	**Effect Size (95% CI)**		**Study**	**n**	**Effect Size(95% Ci)**
Applicability			Geusens[17]	60	-1.38	(-1.97, -0.79)	Kremer[19]	49	-0.13 (-0.78, 0.52)
			Kremer[18]	37	-0.24	(-0.89, 0.41)			
			Skoldstam[25]	43	0.11	(-0.49, 0.71)			
	II								
	III								

Dose and source effect. Dose and source effects of omega-3 fatty acids were not assessed in any of the identified studies.

Exposure duration. Effect of exposure duration of omega-3 fatty acids was not assessed in any of the identified studies.

Sustainment of effect. Sustainment of effect after discontinuation of omega-3 fatty acids was not assessed in any of the identified studies.

Publication Bias

There was no evidence of publication bias on the funnel plots and adjusted rank correlation testing (not shown) performed for studies that entered meta-analysis.

Adverse Events

Among 83 articles across the six topic areas of this report that were reviewed for adverse events, 28 reported adverse events, which are summarized in Table 3.22.

Table 3.23. Summary of reported adverse events.*

Adverse Event	Total # of studies	Sample size		Adverse event count		Adverse event rate Omega 3	Adverse event rate Placebo
		N for Omega 3	N for Placebo/ Control	N for Omega 3	N for Placebo/ Control		
Clinical bleeding	1	73	NR**	2	0	2.74%	----
GI complaint or nausea	13	885	685	72	34	8.14%	4.96%
Diarrhea	3	159	104	11	5	6.92%	4.81%
Headaches	2	31	26	2	0	6.45%	0.00%
Withdrawal due to adverse event	10	353	228	13	9	3.68%	3.95%
Dermatological	4	190	159	5	10	2.63%	6.29%

- N = number of individuals with an adverse event. **Not reported. No placebo arm reported on clinical bleeding.