Chapter 3. Results

Results of Literature Search

Figure 3.1 displays the flow of the literature review. The University of Ottawa EPC e-mailed us a total of 4,212 citations as a result of their computerized library searches. Our two reviewers considered 1,384 of these article titles to be relevant to our research topics. Of these, a senior researcher rejected 347 titles as not being relevant. We also received 25 citations from the literature searches conducted by New England Medical Center (NEMC) EPC, and we identified 42 articles by hand searching the reference lists of articles that we reviewed. Thus, we identified a total of 1,105 relevant article titles. We were able to retrieve all but 8 of these articles.

Of the 1,097 articles retrieved, 115 were accepted for further review, because they reported on results from randomized clinical trials or controlled clinical trials of omega-3 fatty acids in the treatment of RA, IBD, diabetes, renal disease, and SLE or reported results from randomized clinical trials, controlled clinical trials, or case series of omega-3 fatty acids on the effects on bone mineral metabolism. Of those articles that were rejected at this stage, 149 reported on a condition other than those of interest, 301 reported on a topic other than omega-3 fatty acids, 22 did not report on a population of interest, and 504 were rejected for study design (i.e., descriptive studies or editorials/commentaries, previous reviews or meta-analyses, and observational studies in all topic areas except bone mineral metabolism). Three articles were duplicates of articles already on file, and four were not reviewed due to language.

Of the 115 articles that went to further review, 10 were rejected because they did not report on outcomes of interest, 15 because they did not report a difference in omega-3 content among study arms, and 7 because they were duplicate reports of the same trial. Thus, a total of 83 articles were accepted for supplementary analysis. Of these, 21 articles reported on RA, 13 articles reported on IBD, 34 articles reported on diabetes, 9 articles reported on renal, 3 articles reported on lupus, and 4 articles reported on bone mineral metabolism. One article reported outcomes for both SLE and renal disease.

Due to the limited number of articles found for renal failure, SLE, and bone mineral metabolism, these outcomes are discussed qualitatively.

Ten trials[16-25] were included in the meta-analysis of RA outcomes (not all trials were included for each outcome). Eleven trials were not included in meta-analysis for the following reasons: insufficient statistics[26-35] and no outcome of interest.[38]

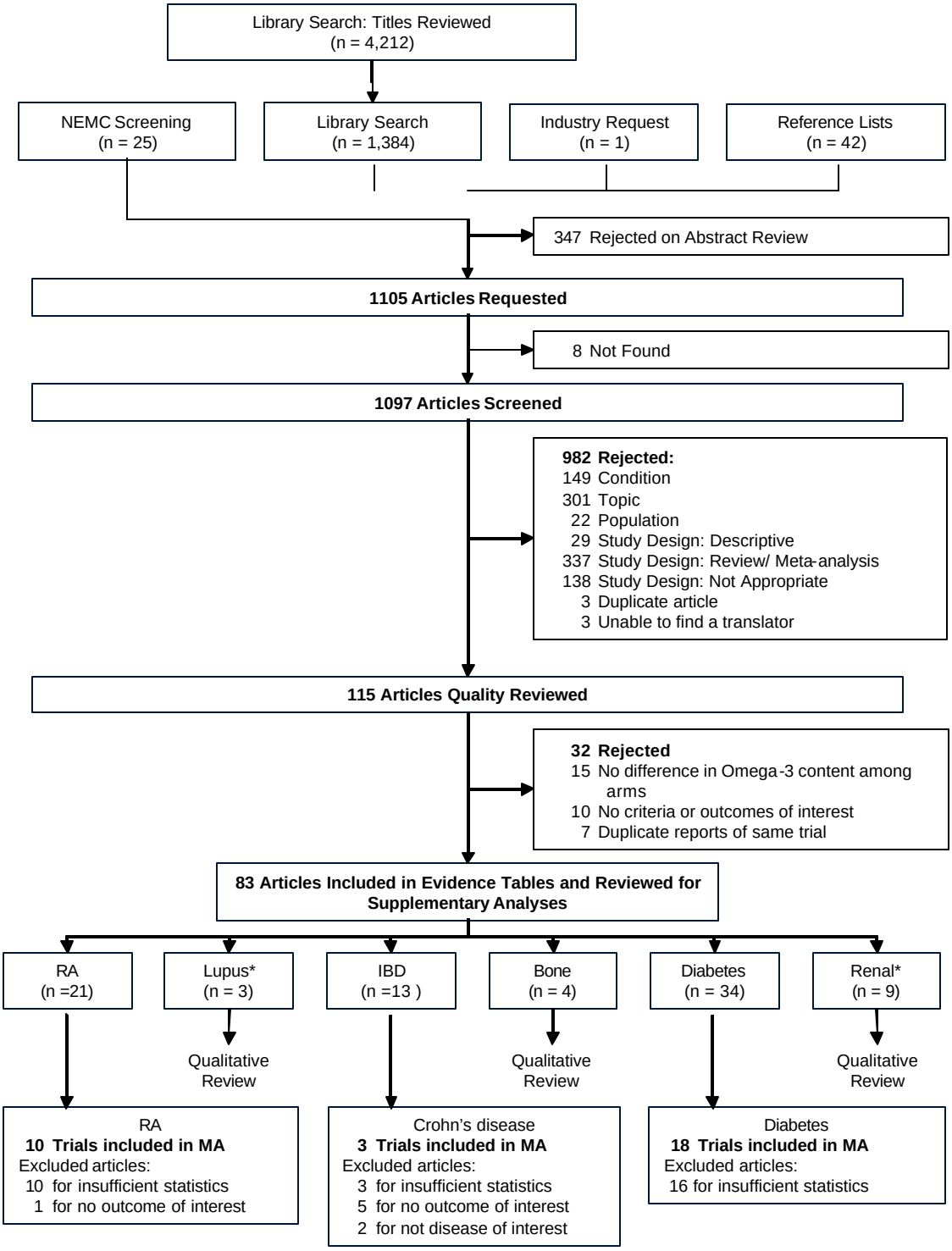
Three trials[39-41] were included in the meta-analysis of remission/relapse in ulcerative colitis. Ten trials were not included in meta-analysis for the following reasons: insufficient statistics,[42, 43,95] no outcome of interest,[44,46,52,53,94] and wrong disease (Crohn's disease, not ulcerative colitis).[54, 55]

Eighteen trials[56-73] were included in the meta-analysis of diabetes outcomes (not all trials were included for each outcome). Sixteen articles were not included in meta-analysis for insufficient statistics.[74-83,86-91]

In addition, as a result of our request to industry experts for unpublished data, Herbert Woolf, Technical Marketing Manager for BASF Corporation, sent us the following document: "Food Labeling: Health Claims and Label Statement – Omega-3 Fatty Acids and Coronary Heart Disease," prepared by members of the Joint Task Group (CHPA, CRN, NFI), FDA Docket No: 91N-0103.[15]

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm

Figure 3.1. Literature flow.



* One article reported both lupus and renal outcomes.

DIABETES

Summaries of all evaluated diabetes studies can be found in appendix C.1.

Diabetes: Total Cholesterol

Overall effect. We identified 32 studies[56-72, 75-83, 86-91] that evaluated the effect to of omega-3 fatty acids on total cholesterol in type II diabetics. Among these, 14 contained sufficient data to be included in a meta-analysis. (Table 3.1) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for total cholesterol is 0.72 mg/dl (95% CI, -5.90, 7.33) (Table 3.1 and Figure 3.2). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

Sub-populations. None of the studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study[58] assessed the effects of fish oil alone, atorvastatin alone, and combined fish oil and atorvastatin. Both atorvastatin alone and combined fish oil and atorvastatin reduced total cholesterol significantly, relative to placebo; there was an insignificant reduction with fish oil alone. The reduction for atorvastatin alone was greater than that for the other groups, although statistical testing was not reported.

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 stratified analysis of source, the pooled random effects estimates of the mean difference between omega-3 fatty acids and placebo, for studies using a fish-oil and studies using a plant source, respectively, were 1.21 mg/dl (95% CI, -6.51, 8.49) and –1.82 (95% CI, -5.87, 12.20).

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

Quality and applicability. Among studies that entered the meta-analysis, 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) (Table 3.2). 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 were identified that assessed the effect of omega-3 fatty acids among children with type II diabetes.

Table 3.1. Diabetes: mean difference for total cholesterol.

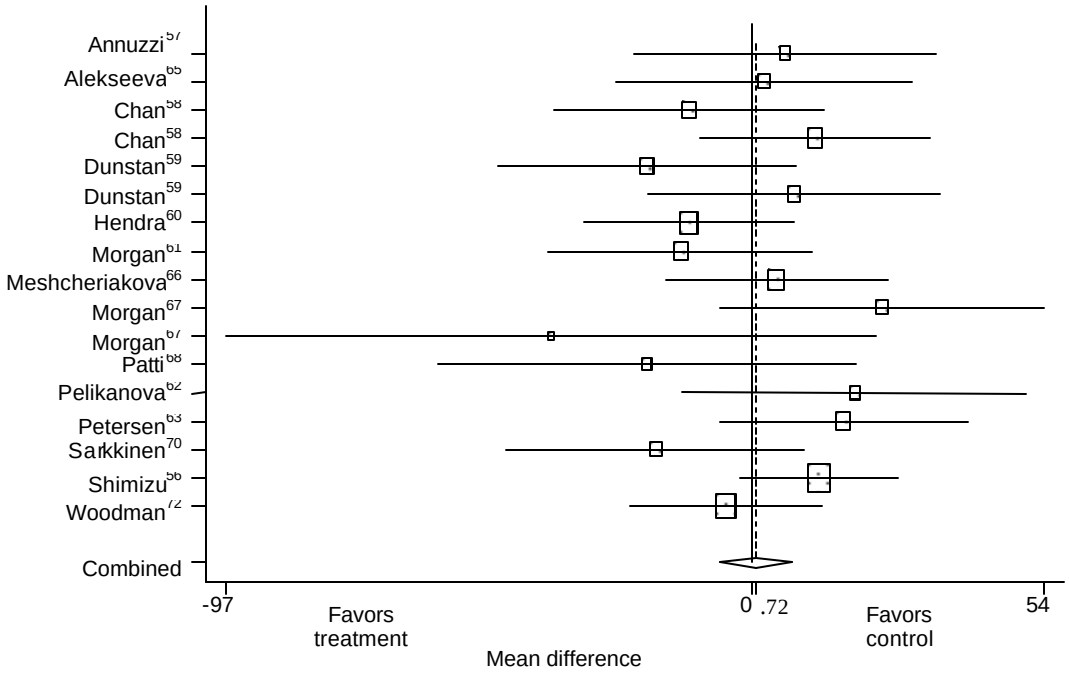
	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Alekseeva[65]	Linseed oil	30	Placebo	30	2.32	(-24.97, 29.60)
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	6.80	(-21.65, 34.00)
Chan[58]	Omacor	12	Placebo	13	-11.58	(-36.35, 13.19)
	Omacor/Atorvastatin	11	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									

Figure 3.2. Diabetes: total cholesterol.



Diabetes: HDL Cholesterol

Overall effect. We identified 30 studies[56-61, 63,64,67-73, 75-83, 86-91] that evaluated the effect to of omega-3 fatty acids on HDL cholesterol in type II diabetics. Among these studies, 12 contained sufficient data to be included in a meta-analysis. (Table 3.4) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for HDL cholesterol is 1.17 mg/dl (95% CI, -1.08, 3.42) (Table 3.3 and Figure 3.3). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis[116] studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study assessed the effects of fish oil alone, atorvastatin alone, and combined fish oil and atorvastatin.[58] There was an insignificant increase and decrease in HDL with atorvastatin alone and fish oil alone, respectively, and a significant increase with a combination of fish oil and atorvastatin.

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. In one study, plants were the source of omega-3 fatty acids. In this study,[70] the mean difference between omega-3 fatty acids and placebo for HDL cholesterol was –3.09 mg/dl (95% CI, -9.84, 3.67). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for HDL cholesterol was 1.53 mg/dl (95% CI, -0.82, 3.87).

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

Quality and applicability. Among studies that entered the meta-analysis, 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) (Table 3.4). 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 were identified that assessed the effect of omega-3 fatty acids among children with type II diabetes.

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

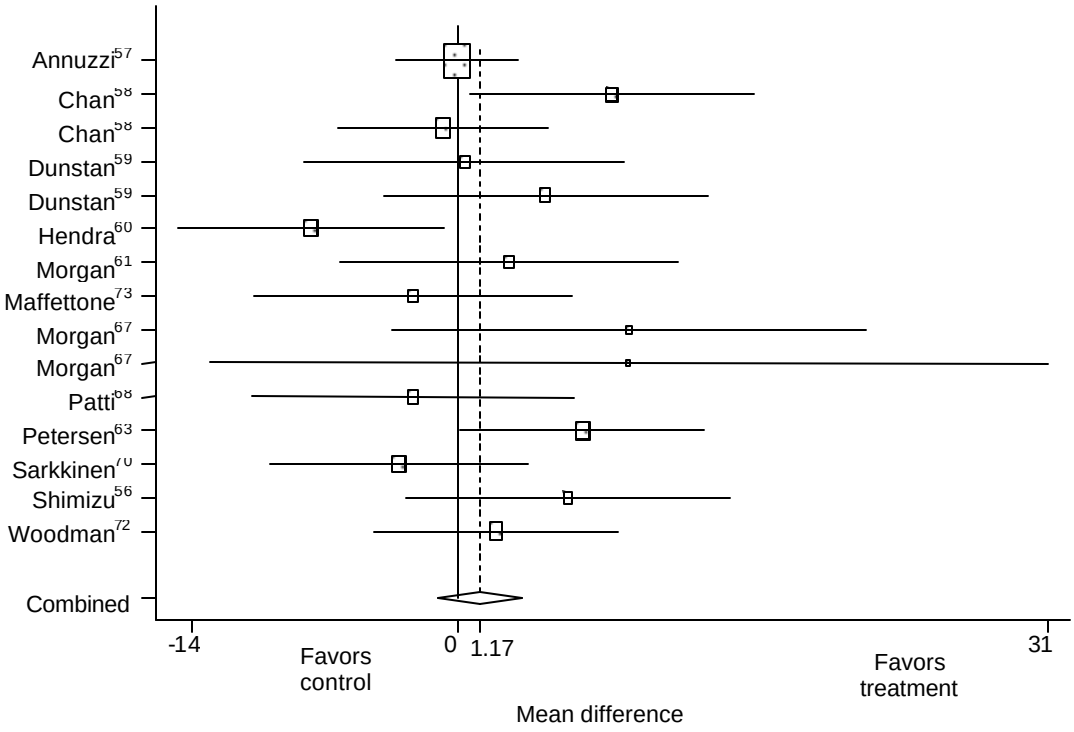
	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	0.00	(-3.21, 3.21)
Chan[58]	Omacor	12	Placebo	13	-0.77	(-6.33, 4.78)
	Omacor/Atorvastatin	11	Atorvastatin	13	8.11	(0.63, 15.59)
Dunstan[59]	Fish oil/light exercise	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									

Figure 3.3. Diabetes: high density lipoprotein (HDL).



Diabetes: LDL Cholesterol

Overall effect. We identified 28 studies that evaluated the effect of omega-3 fatty acids on LDL cholesterol in type II diabetics[57-61, 63,64,67, 69-73, 75-83, 86-91]. Among these, 11 contained sufficient data to be included in a meta-analysis. (Table 3.5) The pooled random effects estimate of the effect of omega-3 fatty acids on LDL cholesterol is 5.12 mg/dl (95% CI, -1.02, 11.25) (Table 3.5 and Figure 3.4). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here, although the results in the other meta-analysis were statistically significant.

Sub-populations. None of the studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study[58] assessed the effects of fish oil alone, atorvastatin alone, and a combination of fish oil and atorvastatin. Atorvastatin alone and combined fish oil and atorvastatin reduced LDL cholesterol with significantly relative to placebo; fish oil alone reduced LDL cholesterol relative to placebo, though not significantly. The reduction was greatest for atorvastatin alone, although statistical testing between atorvastatin and fish oil groups was not reported.

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. In one study, plants were the source of omega-3 fatty acids. In this study,[70] the mean difference between omega-3 fatty acids and placebo for LDL cholesterol was –10.04 mg/dl (95% CI, -37.38, 17.30). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for LDL cholesterol was 5.92 mg/dl (95% CI, -0.38, 12.22).

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

Quality and applicability. Among studies that entered the meta-analysis, 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) (Table 3.6). 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 were identified that assessed the effect of omega-3 fatty acids among children with type II diabetes.

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

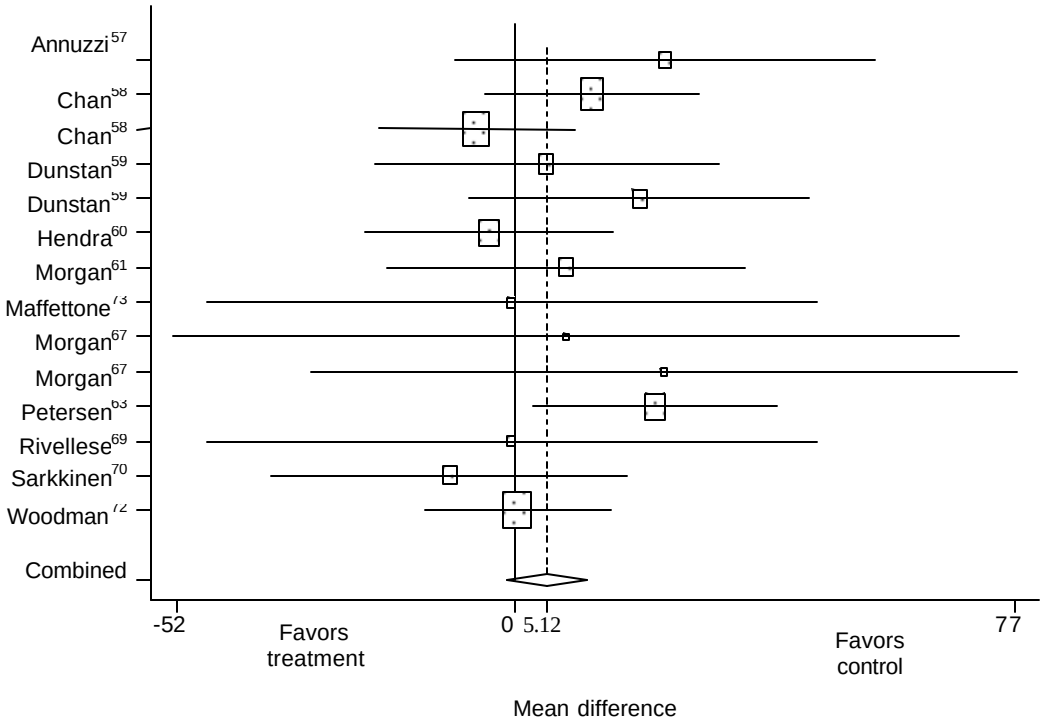
	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	23.17	(-9.22, 55.56)
Chan[58]	Omacor	12	Placebo	13	-5.79	(-20.88, 9.29)
	Omacor/Atorvastatin	11	Atorvastatin	13	11.97	(-4.51, 28.45)
Dunstan[59]	Fish oil/light 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									

Figure 3.4. Diabetes: low density lipoprotein (LDL).



Diabetes: Triglycerides

Overall effect. We identified 33 studies that evaluated the effect to of omega-3 fatty acids on triglycerides in type II diabetics.[56-72, 74-83, 86-91] Among these, 14 contained sufficient data to be included in a meta-analysis. (Table 3.7) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for triglycerides is -31.61 mg/dl (95% CI, -49.58, -13.64) (Table 3.7 and Figure 3.5). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

Sub-populations. None of the studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study[58] assessed the effects of fish oil alone, atorvastatin alone and combined fish oil and atorvastatin. Fish oil alone, atorvastatin alone and combined fish oil and atorvastatin reduced triglycerides significantly relative to placebo. The reduction for combined atorvastatin and fish oil was greater that for either drug alone, although statistical testing was not reported.

One study assessed the independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control.[93] There was a significant reduction in triglycerides and an increase in glycosylated hemoglobin with a diet high in fish. With combined moderate exercise and the fish diet, reduction in triglycerides was maintained and glycosylated hemoglobin did not increase.

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 stratified analysis of source, the pooled random effects estimates of the mean difference between omega-3 fatty acids and placebo, for studies using a fish-oil and studies using a plant source, respectively, were –35.93 mg/dl (95% CI, -56.02, -15.83) and –12.08 (95% CI, -56.90, 32.73).

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, 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) (Table 3.8). 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 3.7. Diabetes: mean difference for triglycerides.

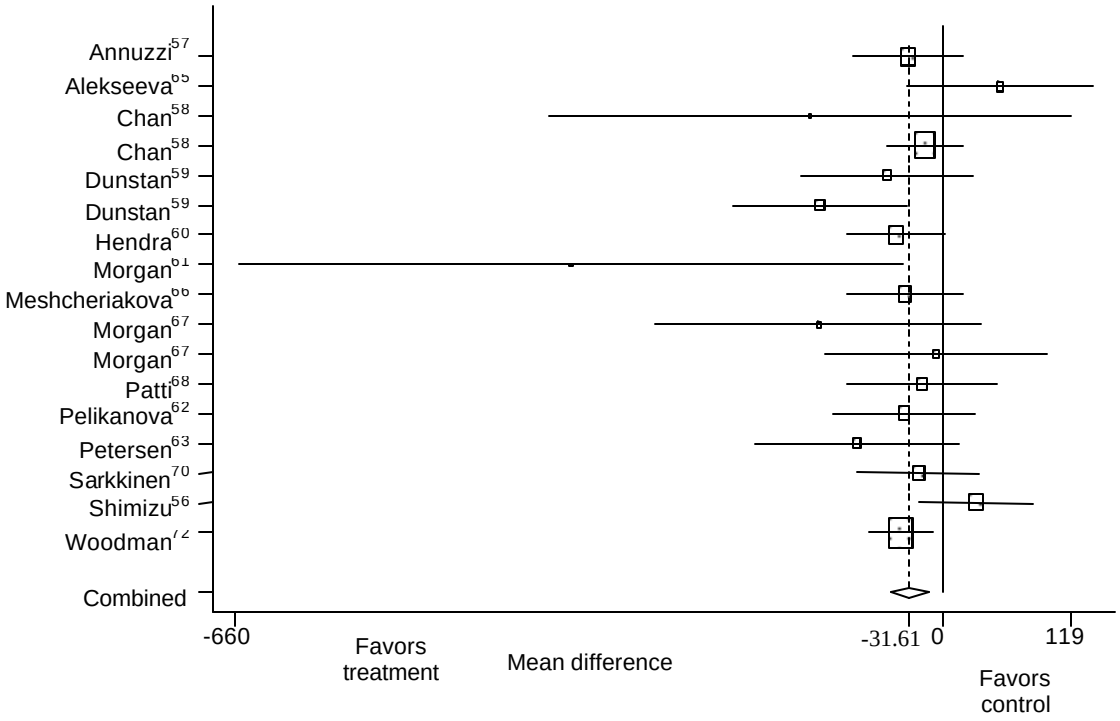
	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	-32.74	(-84.25, 18.77)
Alekseeva[65]	Linseed oil	30	Placebo	30	53.10	(-33.54, 139.74)
Chan[58]	Omacor	12	Placebo	13	-123.89	(-366.93, 119.14)
	Omacor/Atorvastatin	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									

Figure 3.5. Diabetes: triglycerides.



Diabetes: Insulin Sensitivity/Glycemic Control

Overall effect. We identified 3 studies that evaluated the effect to of omega-3 fatty acids on plasma insulin in type II diabetics,[57, 82, 93] and 1 that evaluated this effect in the metabolic syndrome.[92] We did not perform meta-analysis because the outcomes used for measuring plasma insulin in these studies were sufficiently different to preclude pooling across studies.

In one study among type II diabetics, glucose-stimulated plasma insulin response during a hyperglycemic clamp was not influenced by fish oil.[57] In the second study, there was no effect on fasting serum insulin or insulin as measured by area under the curve during a fasting glucose tolerance test.[93] In the third study, there was no difference in insulin suppression of hepatic glucose production or in insulin stimulation of whole-body glucose disposal measured by the euglycemic-hyperinsulinemic clamp.[82]

In the study of metabolic syndrome, fish oil had no effect on insulin resistance estimated by Homeostatic Model Assessment.[92]

We identified 26 studies that evaluated the effect of omega-3 fatty acids on fasting blood sugar in type II diabetics.[57, 59-61, 63-65,67-72, 75-83,86,87, 89-91] Among these, 9 contained sufficient data to be included in a meta-analysis. (Table 3.9) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for fasting blood sugar is 5.87 mg/dl (95% CI, -0.15, 11.88) (Table 3.9 and Figure 3.6). Although a large number of the studies identified with this outcome were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

We identified 23 studies that evaluated the effect of omega-3 fatty acids on glycosylated hemoglobin in type II diabetics.[56,57, 61-64, 67-69, 71,72,74-76, 78,79, 80-83, 86,87,90,91] Among these 8 contained sufficient data to be included in a meta-analysis. (Table 3.11) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for glycosylated hemoglobin is 0.21 (%) (95% CI, -0.01, 0.44) (Table 3.11 and Figure 3.12). Although a large number of the studies identified with this outcome were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

Sub-populations. The effects of omega-3 fatty acids on insulin were assessed in type II diabetes and metabolic syndrome.

Covariates. One study assessed the effects of fish oil alone, atorvastatin alone and combined fish oil and atorvastatin.[92] There were increases in HOMA scores with fish oil alone, atorvastatin alone and combined fish oil and atorvastatin relative to placebo, though none were significant. Statistical testing was not reported, except the comparisons with placebo.

One study assessed the independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control.[93] There was a significant reduction in triglycerides and an increase in glycosylated hemoglobin with fish diet. With a combination of moderate exercise and fish diet, reduction in triglycerides was maintained and glycosylated hemoglobin did not increase.

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.

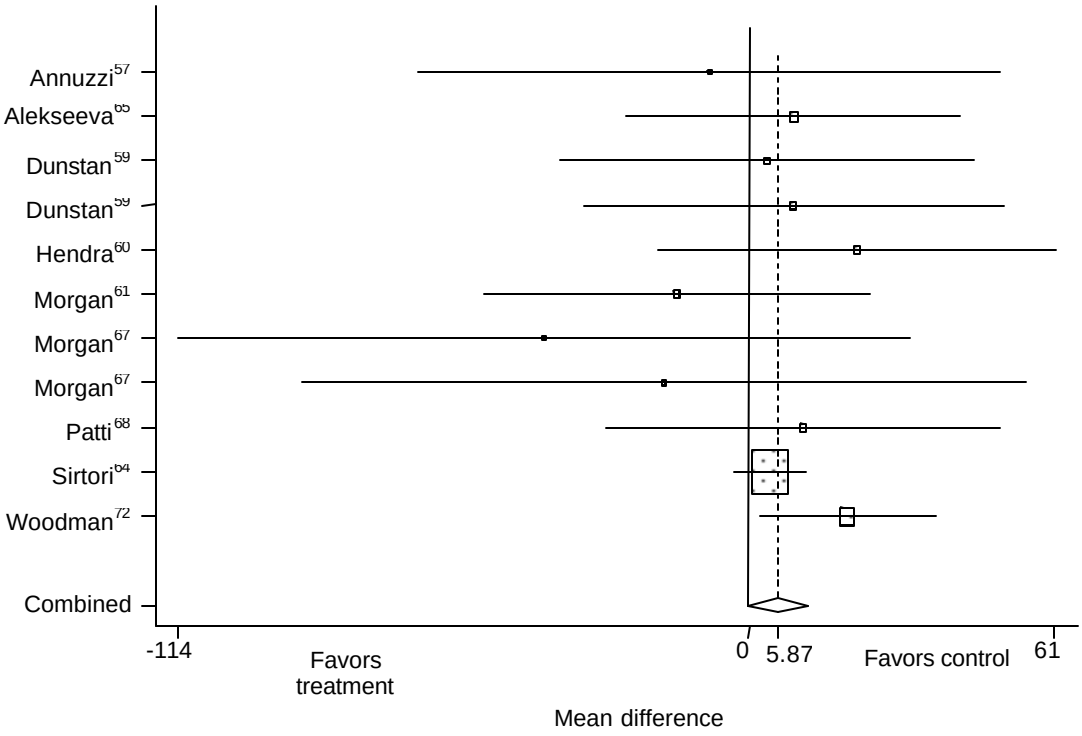


Table 3.11. Diabetes: effect size of hemoglobin A1c (HbA1c).

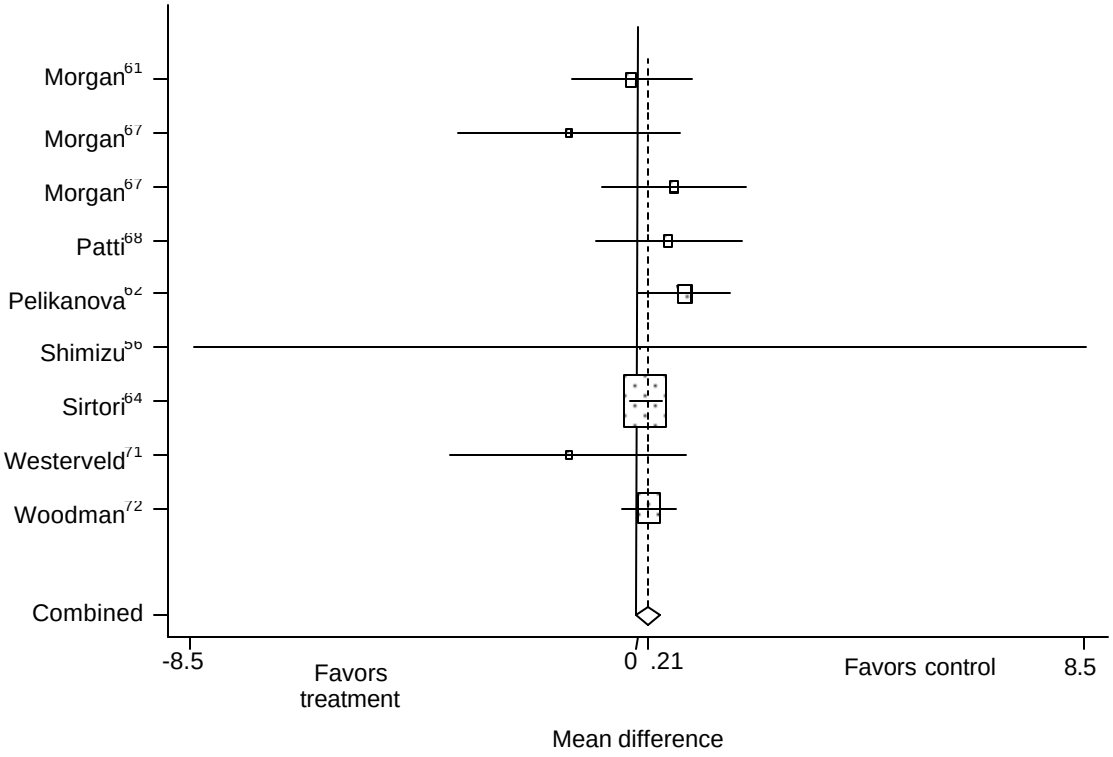
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**(%) (95% CI)**
Morgan[61]	Fish oil	10	Placebo	10	-0.10 (-1.25, 1.05)
	Fish oil	10	Placebo	10	
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-1.30 (-3.42, 0.82)
	High dosage Fish oil	6	Placebo	6	0.70 (-0.68, 2.08)
Patti[68]	Fish oil	8	Placebo	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								

Figure 3.7. Diabetes: hemoglobin A1$_c$ (HgA1$_c$).



INFLAMMATORY BOWEL DISEASE

Summaries of all inflammatory bowel disease studies that were evaluated can be found in appendix C.2.

Inflammatory Bowel Disease: Clinical Effect

Overall effect. The effect of omega-3 fatty acids on each of the following outcomes was assessed: clinical score, sigmoidoscopic score, histologic score, induced remission and relapse. In total, 13 studies described in 14 reports were identified that reported these outcomes. All outcomes were assessed separately for ulcerative colitis and Crohn's disease. There were sufficient data to perform meta-analysis only for relapse and only for ulcerative colitis. Clinical score was described for ulcerative colitis in 5 studies; two reported no effect[39, 52] and three reported statistically significant improvement with omega-3 fatty acids.[44, 46, 94] Clinical score was described for Crohn's disease in only 1 study, which reported no effect.[52]

Sigmoidoscopic score was reported for ulcerative colitis in 3 studies,[44, 52, 94] each of which reported a statistically significant improvement with omega-3 fatty acids. Sigmoidoscopic score was reported for Crohn's disease in 1 study,[52] which showed a statistically significant improvement with omega-3 fatty acids. Histologic score was reported for ulcerative colitis in 3 studies; 2 reported no effect[42, 46] and 1 statistically significant improvement.[44] Histologic score was not reported in any of the studies of Crohn's disease.

Induction of remission was reported for ulcerative colitis in 2 studies,[44, 95] both of which showed improvement with omega-3 fatty acids. However, neither was statistically significant, and in one study,[44] comparable data for the placebo group was not reported. Induction of remission was not reported in the studies of Crohn's disease.

Relapse was described for ulcerative colitis in 5 studies, 3 of which could be used for meta-analysis. Among these studies, 1 reported a lower relapse rate with omega-3 fatty acids than with placebo,[42] 2 found no difference and 2 reported an increased rate of relapse.[39, 43] However, the results were not statistically significant in any of these studies. The pooled random effect estimate of the risk of relapse for omega-3 fatty acids relative to placebo for ulcerative colitis was 1.13 (95% CI: 0.81, 1.57) (Table 3.13, Figure 3.7). The data yield an average control group risk of 38% (all studies weighted equally). Combining these yields a NNH of 21. So the number of patients needed to treat on average to result in one relapse is 21. Among the studies not included in the meta-analysis, one reported a lower relapse rate and one reported a higher relapse rate with omega-3 fatty acids.

Relapse was described for Crohn's disease in two studies; one reported a significantly lower relapse rate with omega-3 fatty acids than with placebo.[54]

Sub-populations. Among the 13 studies identified, the study sample was restricted to patients with ulcerative colitis in 10[39-44, 46, 53, 94, 95] and to Crohn's disease in two;[54, 55] one study included both patients with ulcerative colitis and those with Crohn's disease and reported data separately for each disease.[52] In this study, the effect of omega-3 fatty acids on clinical score was the same for subjects with ulcerative colitis and Crohn's disease (no effect). The effect on histologic score was also the same; however the improvement reached statistical significance only when diseases were pooled.

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.

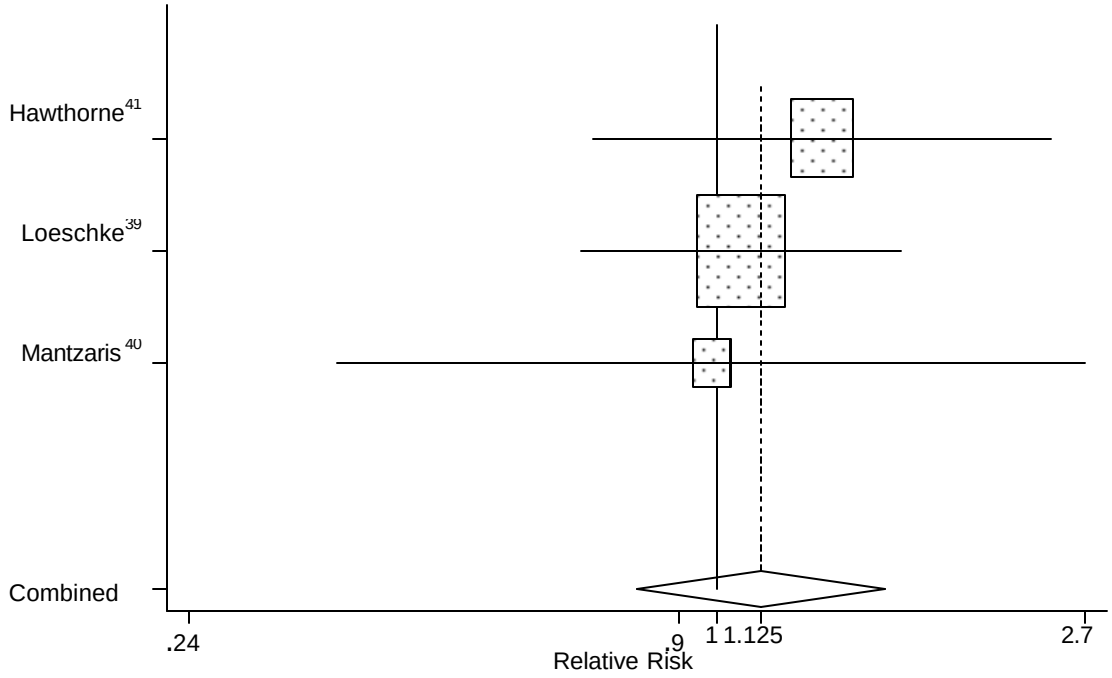
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Relative Risk (95% CI)**
Hawthorne[41]	Hi EPA	35	Placebo	34	1.32 (0.71, 2.46)
Loeschke[39]	Fish oil	31	Placebo	33	1.06 (0.69, 1.64)
Mantzaris[40]	Max EPA (fish oil)	22	Placebo	18	0.98 (0.36, 2.70)
Pooled Random Effects Estimate*					1.13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



Inflammatory Bowel Disease: Effect on Requirement for Steroids/Other Immunosuppressive Drugs

Overall effect. We identified only 2 studies that assessed the effect of omega-3 fatty acids on requirements for corticosteroids or other immunosuppressive agents, both of which assessed the effect on corticosteroid requirement.[44, 53] Both of these studies found a reduced requirement for corticosteroids with omega-3 fatty acid treatment relative to placebo, but the differences were not statistically significant. Sustainment of effect after discontinuation of the omega-3 fatty acids was not assessed.

We found no data on the effect of omega-3 fatty acids on requirements for steroids and other immunosuppressive drugs for different subpopulations, doses, exposures and sources.

RHEUMATOID ARTHRITIS

Summaries of all rheumatoid arthritis studies we evaluated can be found in Appendix C.3.

Rheumatoid Arthritis: Pain

Overall effect. The effect of omega-3 fatty acids on patient-assessed pain in rheumatoid arthritis was described in 19 studies, 9 of which could be used for meta-analysis. Among these studies, 3 reported significant improvement relative to placebo,[17, 29, 34] and 4 reported significant improvement from baseline.[16, 21, 26, 30] There were no significant effects in twelve studies.[18, 19, 22-25, 28, 31-33, 35, 38] The pooled random estimate of effect size for the effect of omega-3 fatty acids on pain relative to placebo is -0.19 (95% CI, -0.43, 0.06) (Table 3.15, Figure 3.8). An effect size of 1.0 is equivalent to 2.72 cm units on the Visual Analogue Scale. Hence, an effect size of -0.19 translates to a 0.52 cm decrease on the visual analog scale. Of note, among the 10 studies that were not included in the meta-analysis, 8 did not demonstrate a significant effect from omega-3 fatty acids, and 2 did demonstrate such an effect.[29, 34]

Sub-populations. None of the studies assessed the effects of omega-3 fatty acids on different subpopulations of patients with RA.

Covariates. One study assessed the effect of different diets (Western versus modified lacto-vegetarian) combined with omega-3 fatty acids on pain in RA.[26] In this study, among subjects treated with fish oil, there was a reduction in pain among patients on a modified lacto-vegetarian diet relative to a Western diet ($P<0.01$)

Effects of dose, source, and exposure duration. One study assessed the effect of different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, the effect of fish oil on pain did not differ among doses. There were insufficient data across studies to perform a pooled analysis of dose or source effect.

In 1 study, plants were the source of omega-3 fatty acids. In this study[23] the effect size for omega-3 fatty acids for pain was -0.21 (95% CI, -1.04, 0.63). Restricting the pooled analysis to

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.

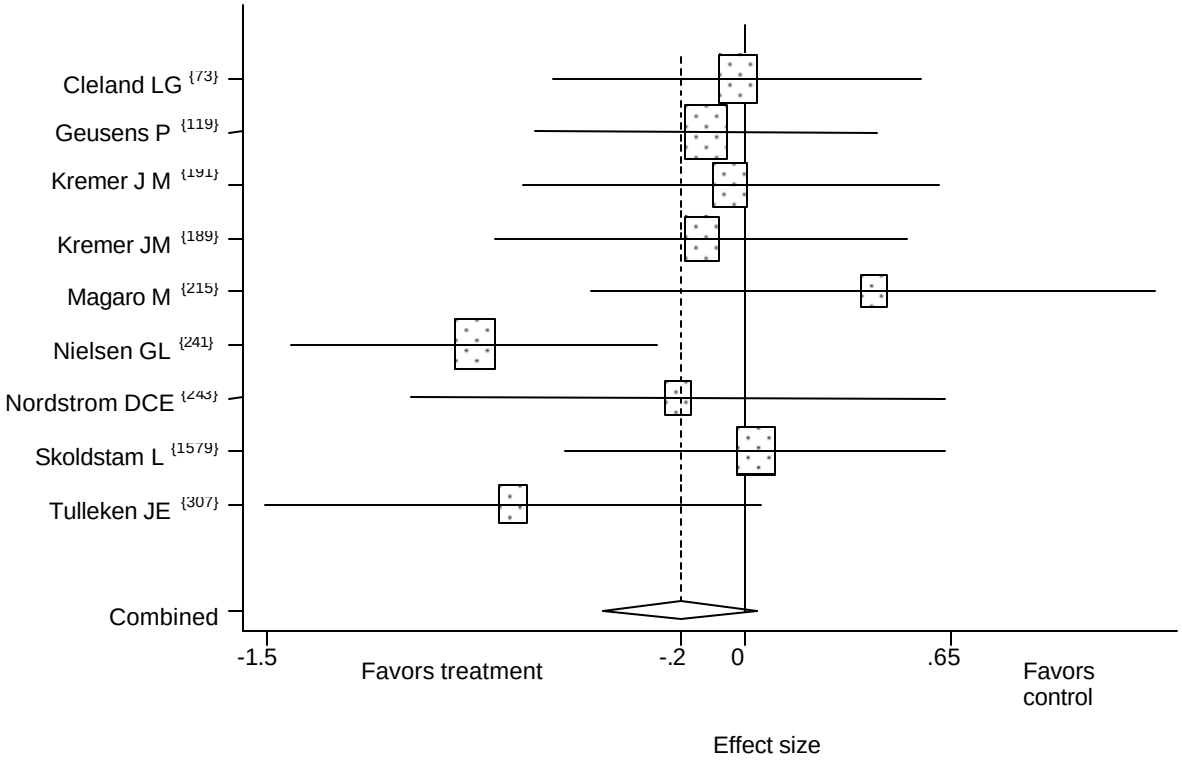
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Cleland[16]	Max EPA (fish oil)	23	Placebo	23	-0.02 (-0.60, 0.56)
Geusens[17]	Fish oil	21	Placebo	20	-0.04 (-0.57, 0.50)
	Fish oil	19			
Kremer[19]	Fish oil	20	Placebo	12	-0.04 (-0.69, 0.61)
	Fish oil	17			
Kremer[18]	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.



Rheumatoid Arthritis: Swollen Joints

Overall effect. The effect of omega-3 fatty acids on swollen joint count in RA was described in 15 studies, 6 of which could be included in meta-analysis. Among these studies, 2 reported significant improvement relative to placebo[29, 33] and 4 reported significant improvement from baseline.[19, 25, 26, 30] There were no significant effects in 9 studies.[18, 22-24, 28, 31, 35, 38] In one study, swollen joint count was significantly worse with omega-3 treatment relative to placebo.[16] The pooled random effect estimate for the effect of omega-3 fatty acids on swollen joint count relative to placebo is -0.13 (95% CI, -0.35, 0.08 (Table 3.17, Figure 3.9). In this analysis, an effect size of 1.0 is equivalent to 3.21 swollen joints. So an effect size of –0.13 is equivalent to a reduction in the swollen joint count by 0.42 joints. Among the 9 studies that were excluded from meta-analysis, 2 reported statistically significant improvements with omega-3 fatty acids and 7 did not. Among the 2 that reported significant improvements, one[29] was of poor methodologic quality (Jadad score =1, concealment of allocation not reported) and the other, [33] although of good methodologic quality (Jadad score = 4, concealment of allocation not reported) was a cross-over study and did not include a wash-out period.

The effect of omega-3 fatty acids on swollen joints in rheumatoid arthritis has also been assessed in a previously published meta-analysis. [97] This meta-analysis reported improvement favoring fish oil over placebo that was not statistically significant (estimate not reported).

Sub-populations. No studies assessed the effect on specific subpopulations.

Covariates. One study assessed the effect of two different diets (Western versus modified lacto-vegetarian) combined with omega-3 fatty acids on joint swelling in RA.[26] In this study, among subjects treated with fish oil, there was a reduction in the number of swollen joints among patients on a modified lacto-vegetarian diet relative to a Western diet ($p < 0.01$)

Effects of dose, source, and exposure duration. One study assessed the effect of two different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, there was a significant improvement in the number of swollen joints at 24 and 36 weeks relative to baseline for subjects treated with a lower dose of fish oil. Among patients treated with a higher dose of fish oil, the improvement relative to baseline was significant only at 24 weeks. There were insufficient data across studies to perform a pooled analysis of dose effect.

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 swollen joints was -0.06 (95% CI, -0.90, 0.77). Restricting the pooled analysis to the remaining studies, which a fish source, the pooled random effects estimate of the effect size for swollen joints unchanged at –0.14 (95% CI, -0.36, 0.09).

Sustainment of effect. Two studies assessed the sustainment of effects of omega-3 fatty acids on outcomes in RA.[18, 28] In one study, there was no change in swollen joint count in a fish oil-treated arm 1-2 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 3.18). 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.

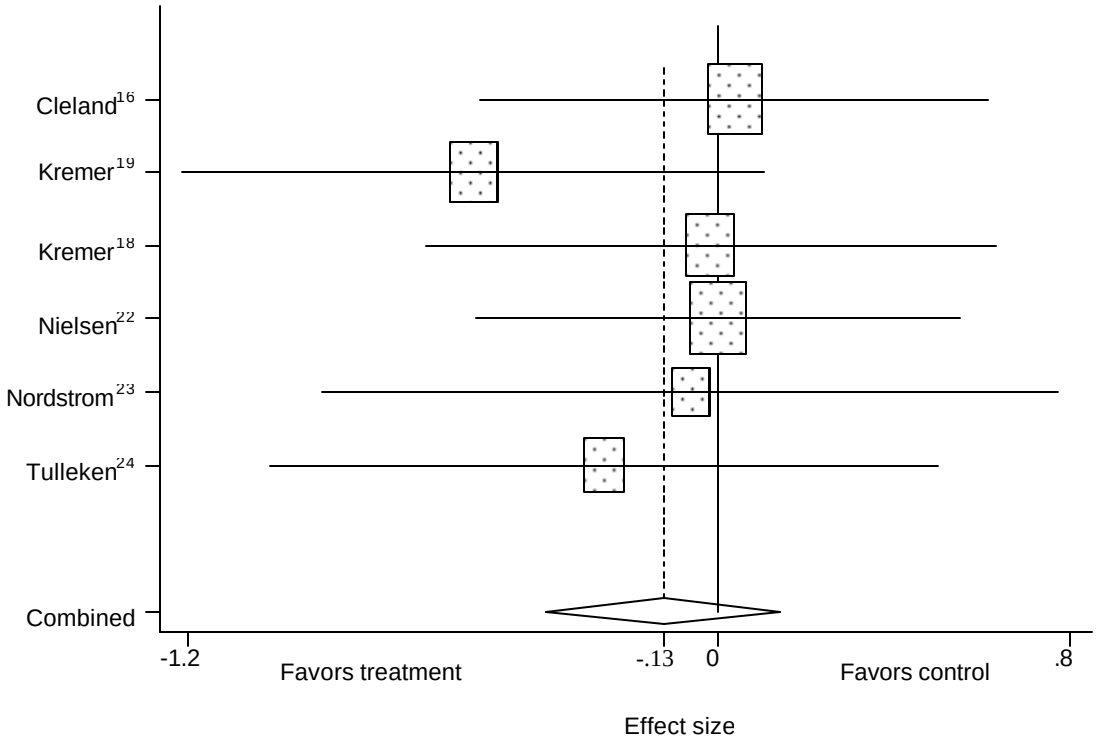
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Cleland[16]	Max EPA (fish oil)	23	Placebo	23	0.04 (-0.54, 0.62)
Kremer[19]	Fish oil	20	Placebo	12	-0.63 (-1.30, 0.03)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.02 (-0.66, 0.63)
Magalish[20]	Omega-3 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								

Figure 3.10. RA: swollen joint count.



Rheumatoid Arthritis: Disease Activity (Erythrocyte Sedimentation Rate)

Overall effect. The effect of omega-3 fatty acids on disease activity (Erythrocyte Sedimentation Rate [ESR]) in rheumatoid arthritis was described in 16 studies, 6 of which could be used for meta-analysis. Among these studies, 1 (in which the population had JRA) reported significant improvement relative to placebo[27] and 1 reported significant improvement from baseline.[21] There were no significant effects in 13 studies. [16, 18, 19, 22-24, 25, 28, 29, 32-35, 38] The pooled random effect estimate for the effect of omega-3 fatty acids on ESR relative to placebo is -0.32 (95% CI, -0.83, 0.19) (Table 3.19, Figure 3.10). In this analysis and effect size of 1.0 is equivalent to 23.79 mm/hr. So, an effect size of –0.32 is equivalent to a reduction in ESR by 7.6 mm/hr. Among the studies excluded from the meta-analysis, one reported a benefit for omega-3 relative to placebo, but in a special population, JRA; none of the remaining studies reported a significant benefit relative to placebo.

Of note, there was significant heterogeneity among these studies (chi-squared test of heterogeneity =0.01). Visual inspection of the Forest plot identified one outlier study.[24] With this study removed from the pooled analysis, the pooled random effects estimate for the effect of omega-3 fatty acids on ESR relative to placebo is -0.07 (95% CI, -0.37, 0.23), and the chi-squared test for heterogeneity is not significant (p = .77). The outlier study is similar to the other studies in the pooled analysis in terms of study design, source, dose, and duration of omega-3 fatty acid treatment. The characteristics of the study population in the outlier study are also similar to those of the other studies in the pooled analysis in terms of age, disease duration, number of swollen joints, and number of tender joints. However, the baseline ESR and C-Reactive Protein (CRP) values for the control group in the outlier study were significantly higher than for the experimental group ($p<0.05$). This observation suggests that the disease activity may have been higher in the control group than in the experimental group, which could bias toward a more favorable estimate of the effect of omega-3 fatty acids.

The effect of omega-3 fatty acids on ESR in rheumatoid arthritis has also been assessed in a previously published meta-analysis. [97] This meta-analysis reported improvement with fish oil relative to placebo; however, this improvement was not statistically significant (estimate not reported).

Sub-populations. One study assessed the effect of cod liver oil on ESR among children with JRA. This study demonstrated a significant reduction in ESR for cod liver oil relative to placebo.[27]

Covariates. The effect of covariates on the efficacy of omega-3 fatty acids was not specifically assessed in any of the studies identified.

Effects of dose, source, and exposure duration. One study assessed the effect of two different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, there was a significant improvement in ESR at 24 and 36 weeks relative to baseline for subjects treated with a lower dose of fish oil. Among patients treated with a higher dose of fish oil, the improvement relative to baseline was significant only at 24 weeks. There were insufficient data across studies to perform a pooled analysis of dose or source effect.

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.

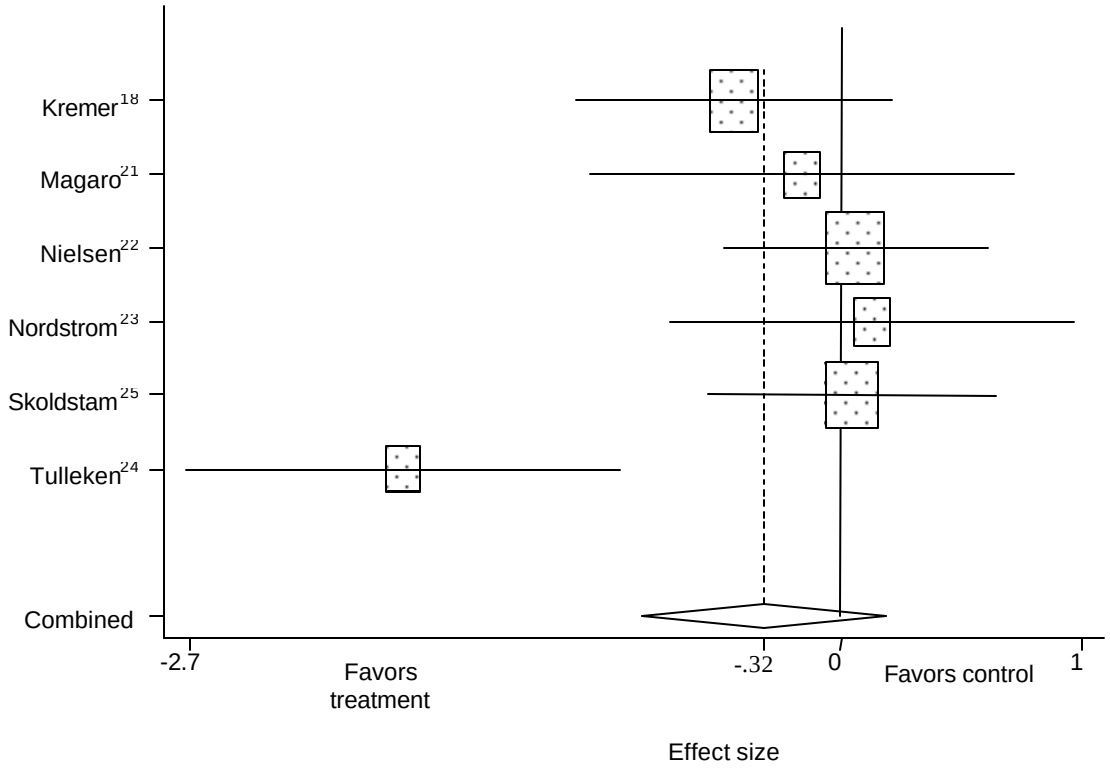
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.44 (-1.1, 0.21)
Magaro[21]	Max EPA (fish oil)	10	Placebo	10	-0.16 (-1.04, 0.72)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	0.06 (-0.49, 0.61)
Nordstrom[23]	Flaxseed 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.



Rheumatoid Arthritis: Patient's Global Assessment

Overall effect. The effect of omega-3 fatty acids on patient's global assessment in RA was described in 8 studies, 5 of which could be used for meta-analysis. Among these studies, 1 reported significant improvement relative to placebo,[17] and 3 reported significant improvement from baseline.[25, 26, 30] There were no significant effects in 4 studies.[16, 18, 19, 31] The pooled random effect estimate for the effect of omega-3 fatty acids on patient's global assessment relative to placebo is -0.30 (95% CI, -0.90, 0.30) (Table 3.21, Figure 3.11). In this analysis, an effect size of 1.0 is equivalent to 0.7 units on the patient global assessment scale. So, an effect size of –0.30 is equivalent to a decrease on the scale by 0.21 units. None of the studies that were excluded from the meta-analysis demonstrated a significant of omega-3 fatty acids on patient's global assessment.

Of note, there was significant heterogeneity among these studies (chi-squared test of heterogeneity =0.002). Visual inspection of the Forest plot identified one outlier study.[17] With this study removed from the pooled analysis, the pooled random effect estimate for the effect of omega-3 fatty acids on patient global assessment relative to placebo is -0.02 (95% CI, -0.36, 0.31) and the chi-squared test for heterogeneity is not significant (p = .76). On qualitative review of the outlier study, we could find no characteristics that differed from the other studies. The outlier study is similar to the other studies in the pooled analysis in terms of study design, source, and dose of omega-3 fatty acid. The characteristics of the study population in the outlier study are similar to those of the other studies in the pooled analysis in terms of age, disease duration, number of swollen joints, and number of tender joints. Although the study duration is longer (12 months) in the outlier study than in the other studies (3-9 months), a common time point for assessment (3 months) was used in the pooled analysis.

The effect of omega-3 fatty acids on patient's global assessments in RA has also been assessed in a previously published meta-analysis.[97] This meta-analysis reported improvement with fish oil relative to placebo; however, this improvement was not statistically significant (estimate not reported).

Sub-populations. No studies assessed the effects across sub-populations.

Covariates. One study assessed the effect of combining different diets (Western versus modified lacto-vegetarian) with omega-3 fatty acids on patient's global assessment in RA.[26] In this study, among subjects treated with fish oil, there was a reduction in patient's global assessment among patients on a modified lacto-vegetarian diet relative to a Western diet ($p<0.01$)

Effects of dose, source, and exposure duration. One study assessed the effect of different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, the effect of fish oil on patient's global assessment did not differ between doses. There were insufficient data across studies to perform a pooled analysis of dose or source effect.

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 patient global assessment was 0.26 (95% CI, -0.58, 1.10). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the effect size for patient global assessment was –0.42 (95% CI, -1.09, 0.26).

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.

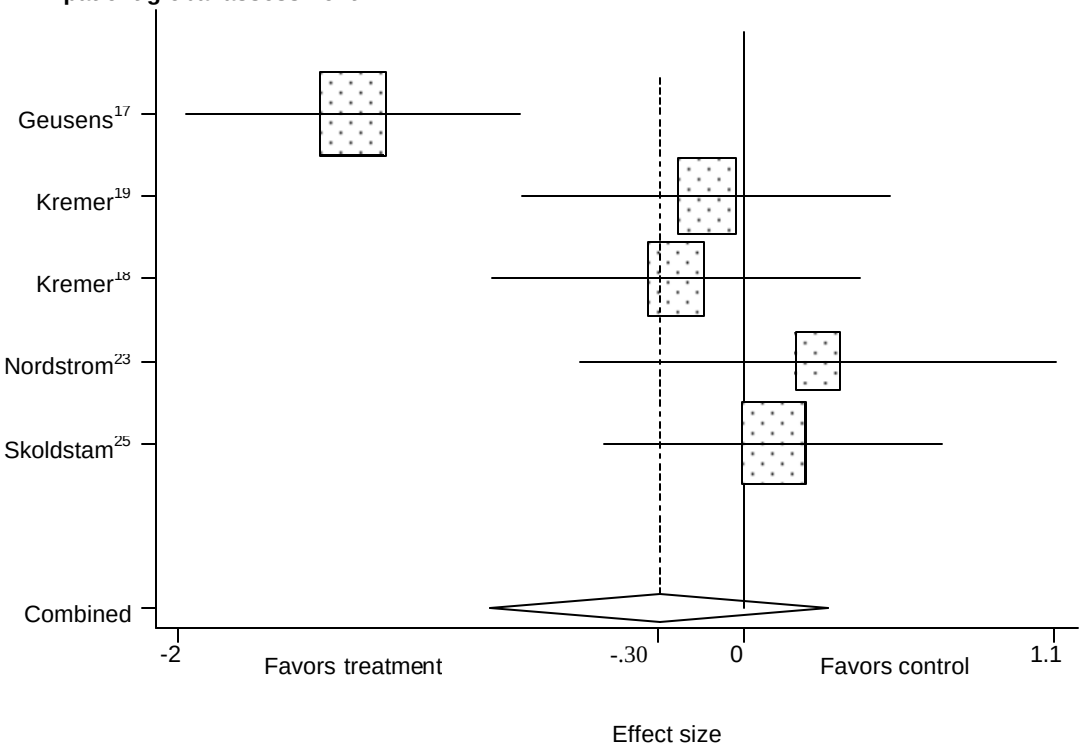
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Geusens[17]	Fish oil	21	Placebo	20	-1.38 (-1.97, -0.79)
	Fish oil	19			
Kremer[19]	Fish oil	20	Placebo	12	-0.13 (-0.78, 0.52)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.24 (-0.89, 0.41)
Nordstrom[23]	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								

Figure 3.12. RA: patient global assessment.



Rheumatoid Arthritis: Joint Damage

Overall effect. We identified one study that assessed the effect of omega-3 fatty acids on joint damage in RA.[29] In this study, the Larsen score of radiographic damage was not affected by administering the omega-3 fatty acids in the form of a diet high in fish.

Rheumatoid Arthritis: Tender Joint Count

Overall effect. The effect of omega-3 fatty acids on tender joint count in RA has been assessed in a previously published meta-analysis. [97] Inclusion criteria for this meta-analysis were 1) double blind, placebo controlled trial, 2) use of at least one of seven predetermined outcome measures, including tender joint count, 3) results reported for both placebo and treatment groups at baseline and follow-up, 4) randomization, and 5) parallel or cross-over design. A Medline search through 1991 identified 10 trials that met the inclusion criteria, 6 of which were analyzed for tender joint count. The rate difference between fish oil and placebo for tender joint count was –2.9 (95% CI, -3.8, -2.1).

Analysis of subpopulations and covariates, effects of dose, source, and exposure duration, and sustainment of effect were not addressed in this meta-analysis.

Rheumatoid Arthritis: Effect on Anti-inflammatory/ Immunosuppressive Drug Requirement

Overall effect. We identified 7 studies that assessed the effect of omega-3 fatty acids on anti-inflammatory and/or immunosuppressive drug requirements among patients with RA. All 7 studies assessed the effect on requirement for anti-inflammatory drugs. Among these studies, there was significant improvement relative to placebo for omega-3 treated subjects in 3,[30-32] significant improvement relative to baseline requirements in 3,[25, 26, 28] and no difference in NSAID requirement in 1.[29] One study, which assessed the effect of omega-3 fatty acids on steroid requirements, demonstrated significant improvement relative to placebo.[30] We did not identify any studies that assessed the effect of omega-3 fatty acids on disease modifying antirheumatic drug (DMARD) requirement.

Sub-populations. Not assessed in any identified studies.

Covariates. Not assessed in any identified studies.

Effects of dose, source, and exposure duration. The effects of dose, source, and exposure duration were not specifically assessed in any of the studies.

Sustainment of effect. Two studies demonstrated that the effect of omega-3 fatty acids on the requirement for NSAIDs in RA was not sustained.[30, 31]

RENAL DISEASE

Summaries of all renal disease studies we evaluated can be found in Appendix C.4.

Renal Disease: Clinical Effect

Overall effect. The effect of omega-3 fatty acids on each of the following was assessed in patients with renal disease: serum creatinine, creatinine clearance, progression to end stage renal disease (ESRD), hemodialysis graft thrombosis/patency, and mortality. A total of studies were identified that reported these outcomes. There were insufficient data to perform meta-analysis on any of the outcomes.

Effects on serum creatinine were described in 4 studies: 1 reported a statistically significant improvement with fish oil relative to placebo,[98] 1 reported no effect,[99] and 2 reported worsening.[100, 101] Among the studies that reported worsening, neither reported testing of statistical significance between the omega-3 and control arms, and in one, there was worsening for both the omega-3 and control group.

Creatinine clearance was reported in 3 studies: 1 reported a statistically significant improvement with fish oil relative to placebo,[98] and 2 reported worsening.[100, 101] Among the studies that reported worsening, neither reported testing of statistical significance between the omega-3 and control arms, and in one, there was worsening for both the omega-3 and control groups.

Progression to ESRD was reported in 2 studies:[98, 100] one demonstrated a favorable effect for fish oil relative to placebo,[98] and the other demonstrated no effect.

Hemodialysis graft thrombosis/patency was described in 2 studies.[102, 103] In one, graft patency was significantly better for fish oil than for placebo.[102] There were no graft thromboses in either the omega-3 fatty acid or the control groups.[103]

Mortality was reported in two studies.[98, 104] Statistical testing for between group mortality rates was not reported in either. In one, mortality over 5 years was 2.0% in the placebo group and 1.8% in the omega-3 group;[98] in the other, the mortality over 5 years was zero in a low-dose fish oil group and 6% in a high-dose fish oil group.[104]

Meta-Analysis. Across the studies identified, only three were sufficiently homogeneous in terms of the population studies and the outcomes reported to consider for meta-analysis. These studies evaluated the effects of omega-3 fatty acids on Immunoglobulin A(IgA) nephropathy.[98, 100, 101] These studies, along with two other studies[117,118] that were identified but not included in this report because they did not meet our inclusion criteria, have been evaluated in a previously published meta-analysis.[105] This meta-analysis calculated effect sizes for treatment effect based on either serum creatinine concentration or creatinine clearance. Although the pooled effect size for the five studies was positive (i.e. favoring treatment over control), it was small (0.25) and not statistically significant (p=0.27).

Sub-populations. No studies that assessed the differential effect of omega-3 fatty acids across distinct subpopulations of renal disease were identified. Among the studies identified, the renal disease in the study sample was IgA nephropathy in four,[98, 100, 101, 104] lupus nephritis in one,[99] glomerular disease in one,[106] and ESRD requiring dialysis in two.[102, 103]

Covariates. The effect of omega-3 fatty acids on covariates was not assessed in any of the identified studies.

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.

Renal Disease: Effect on Corticosteroid/Other Immunosuppressive Drug Requirement

We did not identify any studies that assessed the effects of omega-3 fatty acids on requirements for corticosteroids or other immunosuppressive drugs.

SYSTEMIC LUPUS ERYTHEMATOSUS

Summaries of all systemic lupus erythematosus studies we evaluated can be found in Appendix C.5.

Systemic Lupus Erythematosus: Clinical Effect

Overall effect. The effect of omega-3 fatty acids on each of the following was assessed in patients with SLE: disease activity, damage, and patient perception of disease. A total of 3 studies was identified that reported disease activity;[99, 107, 108] no studies that assessed the other outcomes were identified. There were insufficient data to perform meta-analysis on disease activity.

Disease activity was described using clinical and laboratory scores. Improvement in disease activity was reported in one study, which used a clinical score developed for that study (validity of score not described).[107] The other studies reported no effect on the SLE Disease Activity Index (SLEDAI)[99] or on another clinical score developed for the study (validity of instrument not described).[108] Levels of anti-DNA antibodies and complement levels were assessed in two of the studies;[99, 108] neither demonstrated an omega-3 fatty acid effect. No studies were identified that assessed effect on damage or patient perception of disease.

Sub-populations. No studies that assessed the differential effect of omega-3 fatty acids across distinct subpopulations of SLE were identified.

Covariates. The effect of omega-3 fatty acids on covariates were not assessed in any of the identified studies.

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. One study was designed to evaluate for sustainment of effect after discontinuation of omega-3 fatty acids.[108] However, in this study, no main effect was demonstrated before discontinuation of the omega-3 fatty acid.

Systemic Lupus Erythematosus: Effect on Steroid/Other Immunosuppressive Drug Requirement

We identified one study that assessed the effects of omega-3 fatty acids on requirements for corticosteroids.[99] In this study, omega-3 fatty acids had no effect on steroid requirements. We identified no studies that assessed the effects of omega-3 fatty acids on requirements for other immunosuppressive drugs.

BONE DENSITY/OSTEOPOROSIS

Summaries of all bone density/osteoporosis studies evaluated can be found in Appendix C.6.

Bone Density/Osteoporosis: Clinical Effect

Overall effect. The effects of omega-3 fatty acids on bone mineral density and fracture rate were assessed. In total, 5 studies described in 4 reports were identified that reported bone mineral density;[109-112] no studies of fracture rate were identified. There were insufficient data to perform meta-analysis on bone mineral density.

Improvement in bone mineral density for omega-3 fatty acids relative to placebo was described in one study;[111] improvement relative to baseline was described in one study.[110] In two studies, omega-3 fatty acids had no effect on bone mineral density.[109, 112]

Sub-populations. One report described separate studies performed in pre-menopausal and post-menopausal women. No effect was seen in either population.

Covariates. The effect of omega-3 fatty acids on covariates was not assessed in any of the identified studies.

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.