Chapter 3. Results

In this chapter, we present the results of our review of the effects of omega-3 fatty acids on cardiovascular disease (CVD) outcomes. The chapter is divided into 3 major sections. The first section reports on the dietary intake of omega-3 fatty acids in the US population. The second section reports on the effect of omega-3 fatty acid supplements or fish consumption on all cause mortality and CVD outcomes. The last section describes adverse events and drug interactions in human clinical studies of omega-3 fatty acids. Relevant tables are embedded within, or appear at the end, of each section.

Population Intake of Omega-3 Fatty Acids in the United States

A total of 33,994 persons were interviewed between 1988 and 1994 in the third National Health and Nutrition Examination Survey (NHANES III). The sociodemographic characteristics of the NHANES III sample population are shown in Table 3.1. Because a large number of participants (6%) refused to report their income or income category during the interview, all the analyses on the poverty income ratio (PIR) should be used carefully. In Tables 3.2 to 3.9, results of the mean daily intakes with a standard error of the mean (SEM) are tabulated for linoleic acid (LA, 18:2 n-6), alpha linolenic acid (ALA, 18:3 n-3), eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3) by gender, race/ethnicity, and age groups. Two tables were created for each fatty acid. The first table presents the means and SEMs for the fatty acid from the NHANES III (1988-94) database and the Continuing Survey of Food Intakes by Individuals (CSFII, 1994-96, 1998) database. No statistical test was performed to compare the NHANES III (1988-94) and CSFII (1994-96, 1998) data due to the differences in the dietary survey designs. The second table for each fatty acid shows the means and SEMs for the fatty acid by race/ethnicity groups using NHANES

Table 3.1. The Sociodemographic Characteristics of the Participants in the Third National Health and Nutrition Survey, 1988-94

Sub-populations	Number of participants	Percent
Gender		
- Male	16,295	48%
- Female	17,699	52%
Race/ethnicity		
- Non-Hispanic white	13,085	38%
- Non-Hispanic black	9,627	28%
- Mexican-American	9,751	29%
- Other	1,531	5%
Age groups *		
- 2-6 months	1,076	3%
- 7-12 months	1,129	3%
- 1-3 years	3,189	9%
- 4-8 years	4,271	13%
- 9-13 years	2,744	8%
- 14-18 years	2,183	6%
- 19-30 years	4,550	13%
- 31-50 years	6,307	19%
- 51-70 years	4,678	14%
- 71+ years	3,848	11%
Urbanization of living areas		
- Metro areas	17,183	51%
- Non-metro areas	16,811	49%
Poverty Income Ratio †		
- = 1.3	13,335	39%
- > 1.3	18,509	54%

* Contain small number of missing data.
† 6% (2,150) participants refused to report their income or income category.

III, 1988-94 data only. Additional summary tables present the means and SEMs of LA, ALA, EPA, and DHA by adults vs youths less than 18 years old (Table 3.10), males vs females (Table 3.11), race/ethnicity groups (Table 3.12), urbanization of living area (Table 3.13), and PIR = 1.3 or > 1.3 (Table 3.14).

Average Intake Estimates of ALA, EPA, DHA, and LA in the US Population (Tables 3.2-3.9)

Analyses of intake estimates of ALA, EPA, DHA, and LA in the US population are based on the 29,000+ NHANES III respondents who had a complete and reliable 24-hour dietary recall. This sample is representative of about 200,000,000 non-institutionalized civilians in the United States. The mean intake ± SEM of ALA, EPA, DHA, and LA were 1.33±0.02, 0.04±0.003, 0.07±0.004, and 14.13±0.20 grams per day, respectively. These estimates were equivalent to 0.55±0.004, 0.02±0.001, 0.03±0.002, and 5.79±0.05 percent of total energy intake per day, respectively. The distributions of EPA and DHA intake estimates were very skewed. More than 50% of subjects had less than 0.0001 or zero grams per day of EPA or DHA intake. Therefore, the means and SEMs for EPA and DHA should be used and interpreted with caution.

Consumption Levels of US Subpopulations: Age, Gender, Ethnicity, Socio-economic Status, Urban vs Rural (Tables 3.10-3.14)

In general, the mean intake of ALA and that of LA were highest among adults between age 18 and age 50. The intakes were higher in non-Hispanic blacks and whites than in Mexican Americans and other races/ethnicities. Males consumed more grams per day of ALA and LA than did females. However, an inverse pattern was observed for both ALA and LA when expressed as percent of the total energy intake per day: at the same energy intake level, males consumed less ALA and LA than did females. Results from each table are summarized below.

- Adults vs Youths: Adults consumed significantly more ALA (+0.05±0.01 %kcal/day) and LA (+0.59±0.07 %kcal/day) than did youths (see Table 3.10).
- Males vs Females: Males had a significantly lower intake of ALA (–0.02±0.01 %kcal/day) and LA (–0.28±0.07 %kcal/day) than did females (see Table 3.11).
- Race/Ethnicity Groups: Compared to the reference group, non-Hispanic whites, non-Hispanic blacks, and Mexican Americans all had a significantly higher intake of both ALA and LA on average. The intakes of omega-3 fatty acids among non-Hispanic whites, non-Hispanic blacks, and Mexican Americans were similar. The mean difference ± SED (standard error of the difference) ranged from 0.04±0.01 to 0.09±0.01 (%kcal/day) for ALA, and from 0.43±0.14 to 0.61±0.15 (%kcal/day) for LA (see Table 3.12).
- Urban vs Rural Living Area: No significant differences in the average intake of ALA and LA were found when people living in metro areas were compared to those living in non-metro areas (see Table 3.13).

- Poverty Index Ratio (PIR): People who had a PIR = 1.3 consumed significantly less ALA (–0.04±0.01 %kcal/day) and LA (–0.28±0.06 %kcal/day) than people who had a PIR > 1.3 (see Table 3.14)

Average Intake Estimates of ALA, EPA, DHA, and LA in Individuals with and without Cardiovascular Disease (Tables 3.15-3.19)

A sub-population of NHANES III participants aged 18 and older was used for the analyses of the estimated mean intakes of ALA, EPA, DHA, and LA among individuals with and without a history of CVD (see definition for CVD in Chapter 2). Of the 16,683 adults in NHANES III, 12.7% (2,121) had CVD, while 87.3% (14,562) had no CVD (Table 3.15).

There was no significant difference in the mean intake of LA (%kcal/day) between people with and without CVD (Table 3.16). However, people with CVD consumed significantly less ALA than those without CVD (–0.02±0.01 %kcal/day, $P = .04$) (Table 3.17). The means ± SEMs of EPA and DHA for people with CVD and those without CVD are shown in Table 3.18 and Table 3.19, respectively. The distributions of EPA and DHA intake estimates were very skewed, so the means and SEMs for EPA and DHA should be used and interpreted with caution. For the same reason, no statistical tests for the differences between people with CVD and those without CVD were performed.

The crude means ± SEMs for people with CVD and those without CVD could be misleading because significant differences in the mean intake of ALA and LA were found among gender, age, and race/ethnicity groups. After adjusting for sex, age, and race/ethnicity, people with CVD still had a significantly lower intake of ALA compared to people without CVD (0.54±0.01 vs 0.57±0.01 %kcal/day, respectively, $P = .02$). Based on a typical total energy intake of 2,000 kilocalories per day, our results show that people with CVD consumed 0.67g per day less ALA than people without CVD. We found no significant difference in the mean intake of LA between the 2 groups after adjusting for sex, age, and race/ethnicity. In both ALA and LA models, gender and races were strong predictors of CVD. The regression and least-square results are shown in detail in Appendix D.

Estimates of Average Omega-3 Fatty Acid or Fish Intake in Countries Outside the US

We found no population-based dietary surveys based on single or multiple 24-hour dietary recalls for countries other than the US. However, reports of average fish consumption from the European Investigation into Cancer and Nutrition (EPIC) study provide good estimates for fish intake among the European population[30]. The EPIC study was a cohort study (rather than a population-based survey) on diet and cancer that included more than 480,000 men and women from 10 European countries. The consumption (in grams/day) of total fish and fish products and at least 10 classifications of fish sub-groups was estimated for each country and different geographical areas by gender. The main results demonstrated that fish intake varies greatly throughout Europe, with the highest consumption in centers in Spain (51-120 g/d) and the lowest in centers in Germany (16-24 g/d). The mean daily intake of total fatty fish, which is usually high in omega-3 fatty acids, was the highest in centers in Spain (18-42 g/d) and the lowest in

centers in the Netherlands (6-8 g/d)[31]. We found no report on the estimated amount of omega-3 fatty acids consumed by EPIC study participants.

A few other cross-cultural studies and a household budget survey in Spain estimate per capita intakes of major food groups per day. These studies observed large differences in fish consumption across the 21 countries. Japan was found to have a high per capita fish consumption of about 100 g/capita/day [32]. An increased trend in per capita fish and shellfish consumption (62-88 g/capita/day) was found in Spain between 1964 and 1991 [33].

Table 3.2. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data [§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)	
	Sample Size	Population Size	Mean Intake (g/day)	Mean Intake (%kcal/day)	Sample Size	Mean Intake (g/day)
Both sexes, 0-6 months [¶]	793	1,323,807	6.90	8.32	596	6.70
SEM			0.15	0.14		0.10
Both sexes, 7-12 months	915	1,625,559	5.91	5.28	530	6.90
SEM			0.14	0.12		0.20
Both sexes, 1-3 y	2,734	8,724,437	7.27	4.69	3,949	7.30
SEM			0.14	0.07		0.10
Both sexes, 4-8 y	3,673	17,409,438	10.31	5.16	3,935	10.10
SEM			0.28	0.11		0.10
M, 9-13 y	1,251	9,113,670	13.79	5.09	595	13.40
SEM			0.48	0.11		0.40
M, 14-18 y	925	8,908,287	18.12	5.37	474	16.60
SEM			0.92	0.17		0.50
M, 19-30 y	1,902	21,918,936	19.34	5.60	920	17.60
SEM			0.59	0.13		0.50
M, 31-50 y	2,579	35,368,777	18.90	5.95	1,806	17.00
SEM			0.50	0.09		0.30
M, 51-70 y	1,934	18,623,500	15.37	5.86	1,680	15.30
SEM			0.34	0.09		0.30
M, 71+ y	1,296	6,723,233	12.42	5.69	722	12.20
SEM			0.29	0.09		0.40
F, 9-13 y	1,261	8,888,987	12.23	5.56	606	11.00
SEM			0.41	0.14		0.30
F, 14-18 y	1,062	8,962,331	13.61	5.98	449	11.70
SEM			0.54	0.19		0.50
F, 19-30 y	2,181	22,809,351	13.59	6.13	808	11.80
SEM			0.36	0.11		0.30
F, 31-50 y	3,097	37,172,408	13.44	6.24	1,690	11.70
SEM			0.26	0.10		0.20
F, 51-70 y	2,075	20,961,630	10.62	5.82	1,605	11.00
SEM			0.29	0.13		0.20
F, 71+ y	1,421	9,687,597	9.54	5.92	670	9.30
SEM			0.21	0.10		0.30
All individuals	**29,099**	**238,221,947**	**14.13**	**5.79**	**21,159**	**13.00**
SEM			**0.20**	**0.05**		**0.10**

§ All NHANES III variance estimates were based on Taylor Series (WR) method.
¶ NHANES III data consisted of individuals = 2 months and excluded nursing infants and children.

Table 3.3. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	**10,634**	**14.27**	**0.24**	**8,510**	**14.23**	**0.20**	**8,626**	**14.07**	**0.20**	**1,329**	**12.77**	**0.48**
Both sexes, 2-6 months	444	6.45	0.18	156	7.50	0.40	124	8.03	0.44	69	8.03	0.44
Both sexes, 7-12 months	488	5.36	0.14	156	7.53	0.47	181	6.58	0.38	90	6.58	0.38
Both sexes, 1-3 y	854	7.08	0.20	784	8.78	0.19	962	7.78	0.18	134	7.78	0.18
Both sexes, 4-8 y	989	10.19	0.45	1,179	11.54	0.25	1,322	10.38	0.29	183	10.38	0.29
Both sexes, 9-13 y	646	13.14	0.40	886	13.23	0.39	881	13.21	0.55	99	13.21	0.55
Both sexes, 14-18 y	517	15.58	0.81	714	17.07	0.54	646	14.87	0.56	110	14.87	0.56
Both sexes, 19-30 y	1,065	16.31	0.47	1,314	17.68	0.44	1,533	16.75	0.34	171	16.75	0.34
Both sexes, 31-50 y	1,894	16.45	0.39	1,869	15.54	0.32	1,669	16.07	0.32	244	16.07	0.32
Both sexes, 51-70 y	1,836	13.19	0.29	1,024	11.05	0.35	985	12.18	0.39	164	12.18	0.39
Both sexes, 71+ y	1,901	10.91	0.21	428	9.44	0.51	323	9.79	0.55	65	9.79	0.55
M, Total	**5,028**	**16.70**	**0.34**	**4,001**	**15.87**	**0.25**	**4,264**	**15.84**	**0.25**	**628**	**14.40**	**0.66**
M, 2-6 months	229	6.52	0.23	81	7.57	0.41	66	8.64	0.55	32	8.64	0.55
M, 7-12 months	239	5.38	0.19	78	7.55	0.71	96	6.09	0.44	37	6.09	0.44
M, 1-3 y	421	7.55	0.25	396	9.23	0.27	478	8.04	0.29	81	8.04	0.29
M, 4-8 y	491	11.10	0.72	580	11.71	0.36	627	10.78	0.45	102	10.78	0.45
M, 9-13 y	320	14.07	0.64	440	13.08	0.49	440	13.11	0.65	51	13.11	0.65
M, 14-18 y	228	18.14	1.13	333	18.82	0.74	320	16.13	0.74	44	16.13	0.74
M, 19-30 y	460	19.85	0.76	583	20.33	0.73	776	19.27	0.55	83	19.27	0.55
M, 31-50 y	853	19.22	0.61	826	18.14	0.49	800	18.57	0.38	100	18.57	0.38
M, 51-70 y	895	15.70	0.41	483	12.46	0.61	488	14.72	0.51	68	14.72	0.51
M, 71+	892	12.75	0.29	201	10.35	0.69	173	10.99	0.84	30	10.99	0.84
F, Total	**5,606**	**11.96**	**0.19**	**4,509**	**12.82**	**0.21**	**4,362**	**12.20**	**0.21**	**701**	**11.23**	**0.61**
F, 2-6 months	215	6.37	0.27	75	7.41	0.52	58	7.28	0.46	37	7.28	0.46
F, 7-12 months	249	5.33	0.24	78	7.52	0.42	85	7.16	0.60	53	7.16	0.60
F, 1-3 y	433	6.60	0.25	388	8.34	0.27	484	7.50	0.23	53	7.50	0.23
F, 4-8 y	498	9.15	0.32	599	11.36	0.35	695	10.01	0.37	81	10.01	0.37
F, 9-13 y	326	12.17	0.55	446	13.39	0.55	441	13.32	0.72	48	13.32	0.72
F, 14-18 y	289	12.88	0.70	381	15.32	0.67	326	13.58	0.74	66	13.58	0.74
F, 19-30 y	605	13.03	0.43	731	15.48	0.51	757	13.63	0.35	88	13.63	0.35
F, 31-50 y	1,041	13.71	0.30	1,043	13.38	0.35	869	13.50	0.38	144	13.50	0.38
F, 51-70 y	941	10.93	0.37	541	10.00	0.38	497	9.99	0.51	96	9.99	0.51
F, 71+	1,009	9.65	0.22	227	8.84	0.66	150	8.61	0.75	35	8.61	0.75

Table 3.4. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Alpha Linolenic Acid (ALA, 18:3 n-3), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data [§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)	
	Sample Size	Population Size	Mean Intake (g/day)	Mean Intake (%kcal/day)	Sample Size	Mean Intake (g/day)
Both sexes, 0-6 months [¶]	793	1,323,807	0.62	0.74	596	0.72
SEM			0.02	0.021		0.02
Both sexes, 7-12 months	915	1,625,559	0.60	0.54	530	0.77
SEM			0.02	0.013		0.02
Both sexes, 1-3 y	2,734	8,724,437	0.73	0.48	3,949	0.77
SEM			0.01	0.005		0.01
Both sexes, 4-8 y	3,673	17,409,438	0.98	0.49	3,935	0.97
SEM			0.03	0.010		0.01
M, 9-13 y	1,251	9,113,670	1.29	0.49	595	1.26
SEM			0.05	0.009		0.04
M, 14-18 y	925	8,908,287	1.73	0.52	474	1.65
SEM			0.08	0.018		0.05
M, 19-30 y	1,902	21,918,936	1.80	0.52	920	1.66
SEM			0.05	0.011		0.05
M, 31-50 y	2,579	35,368,777	1.76	0.57	1,806	1.73
SEM			0.04	0.009		0.04
M, 51-70 y	1,934	18,623,500	1.46	0.57	1,680	1.55
SEM			0.03	0.010		0.03
M, 71+ y	1,296	6,723,233	1.18	0.55	722	1.26
SEM			0.03	0.011		0.04
F, 9-13 y	1,261	8,888,987	1.18	0.54	606	1.03
SEM			0.04	0.014		0.02
F, 14-18 y	1,062	8,962,331	1.21	0.53	449	1.13
SEM			0.05	0.016		0.05
F, 19-30 y	2,181	22,809,351	1.25	0.56	808	1.18
SEM			0.04	0.012		0.03
F, 31-50 y	3,097	37,172,408	1.25	0.58	1,690	1.19
SEM			0.03	0.009		0.02
F, 51-70 y	2,075	20,961,630	1.04	0.57	1,605	1.13
SEM			0.03	0.013		0.02
F, 71+ y	1,421	9,687,597	0.92	0.58	670	0.97
SEM			0.02	0.011		0.03
All individuals	**29,099**	**238,221,947**	**1.33**	**0.55**	**21,159**	**1.30**
SEM			**0.02**	**0.004**		**0.01**

§ All NHANES III variance estimates were based on Taylor Series (WR) method.
¶ NHANES III data consisted of individuals = 2 months and excluded nursing infants and children.

Table 3.5. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Alpha Linolenic Acid (ALA, 18:3 n-3) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	**10,634**	**1.37**	**0.02**	**8,510**	**1.27**	**0.02**	**8,626**	**1.20**	**0.02**	**1,329**	**1.12**	**0.04**
Both sexes, 2-6 months	444	0.55	0.02	156	0.71	0.06	124	0.81	0.07	69	0.76	0.08
Both sexes, 7-12 months	488	0.54	0.02	156	0.76	0.04	181	0.65	0.05	90	0.60	0.04
Both sexes, 1-3 y	854	0.73	0.02	784	0.82	0.02	962	0.73	0.01	134	0.64	0.03
Both sexes, 4-8 y	989	0.98	0.04	1,179	1.04	0.02	1,322	0.97	0.03	183	0.87	0.04
Both sexes, 9-13 y	646	1.28	0.05	886	1.18	0.03	881	1.19	0.04	99	1.06	0.08
Both sexes, 14-18 y	517	1.48	0.07	714	1.53	0.06	646	1.30	0.06	110	1.42	0.19
Both sexes, 19-30 y	1,065	1.56	0.04	1,314	1.56	0.04	1,533	1.41	0.03	171	1.27	0.08
Both sexes, 31-50 y	1,894	1.57	0.04	1,869	1.38	0.03	1,669	1.30	0.03	244	1.17	0.08
Both sexes, 51-70 y	1,836	1.28	0.03	1,024	1.02	0.03	985	1.06	0.04	164	1.06	0.08
Both sexes, 71+ y	1,901	1.05	0.02	428	0.87	0.05	323	0.83	0.04	65	0.88	0.15
M, Total	**5,028**	**1.60**	**0.03**	**4,001**	**1.43**	**0.02**	**4,264**	**1.36**	**0.02**	**628**	**1.29**	**0.06**
M, 2-6 months	229	0.56	0.03	81	0.73	0.02	66	0.91	0.08	32	0.77	0.09
M, 7-12 months	239	0.55	0.02	78	0.79	0.06	96	0.63	0.06	37	0.66	0.06
M, 1-3 y	421	0.75	0.02	396	0.85	0.07	478	0.74	0.02	81	0.69	0.03
M, 4-8 y	491	1.08	0.07	580	1.08	0.02	627	0.98	0.03	102	0.87	0.06
M, 9-13 y	320	1.35	0.07	440	1.21	0.03	440	1.21	0.07	51	1.12	0.08
M, 14-18 y	228	1.73	0.09	333	1.70	0.04	320	1.50	0.07	44	2.00	0.46
M, 19-30 y	460	1.89	0.07	583	1.80	0.07	776	1.62	0.06	83	1.35	0.09
M, 31-50 y	853	1.84	0.05	826	1.63	0.06	800	1.49	0.04	100	1.38	0.15
M, 51-70 y	895	1.51	0.04	483	1.11	0.05	488	1.26	0.04	68	1.34	0.11
M, 71+	892	1.22	0.04	201	0.97	0.07	173	0.92	0.07	30	0.94	0.23
F, Total	**5,606**	**1.15**	**0.02**	**4,509**	**1.14**	**0.02**	**4,326**	**1.05**	**0.02**	**701**	**0.97**	**0.04**
F, 2-6 months	215	0.54	0.03	75	0.69	0.08	58	0.68	0.07	37	0.75	0.10
F, 7-12 months	249	0.54	0.03	78	0.72	0.05	85	0.68	0.05	53	0.56	0.05
F, 1-3 y	433	0.71	0.02	388	0.78	0.03	484	0.72	0.02	53	0.58	0.05
F, 4-8 y	498	0.86	0.02	599	1.00	0.02	695	0.96	0.04	81	0.87	0.07
F, 9-13 y	326	1.22	0.06	446	1.15	0.04	441	1.16	0.05	48	0.99	0.17
F, 14-18 y	289	1.22	0.07	381	1.36	0.08	326	1.10	0.05	66	1.03	0.09
F, 19-30 y	605	1.25	0.04	731	1.35	0.05	757	1.15	0.03	88	1.16	0.16
F, 31-50 y	1,041	1.30	0.03	1,043	1.18	0.03	869	1.10	0.03	144	1.01	0.08
F, 51-70 y	941	1.07	0.04	541	0.95	0.03	497	0.90	0.04	96	0.79	0.08
F, 71+	1,009	0.94	0.02	227	0.80	0.05	150	0.75	0.06	35	0.81	0.12

Table 3.6. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Eicosapentaenoic Acid (EPA, 20:5 n-3), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data [§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)‡	
	Sample Size	Population Size	Mean Intake (g/day)	Mean Intake (%kcal/day)	Sample Size	Mean Intake (g/day)
Both sexes, 0-6 months [¶]	793	1,323,807	-	-	578	<0.0005
SEM						
Both sexes, 7-12 months	915	1,625,559	†	†	487	0.002
SEM						
Both sexes, 1-3 y	2,734	8,724,437	†	†	3,777	0.008
SEM						
Both sexes, 4-8 y	3,673	17,409,438	0.010	0.010	3,769	0.012
SEM			0.002	0.002		
M, 9-13 y	1,251	9,113,670	†	†	569	0.016
SEM						
M, 14-18 y	925	8,908,287	†	†	446	0.018
SEM						
M, 19-30 y	1,902	21,918,936	0.040	†	854	0.030
SEM			0.005			
M, 31-50 y	2,579	35,368,777	0.060	0.02	1,684	0.038
SEM			0.007	0.003		
M, 51-70 y	1,934	18,623,500	0.050	0.02	1,606	0.046
SEM			0.005	0.002		
M, 71+ y	1,296	6,723,233	0.050	0.02	674	0.049
SEM			0.006	0.003		
F, 9-13 y	1,261	8,888,987	†	†	580	0.012
SEM						
F, 14-18 y	1,062	8,962,331	0.020	†	436	0.016
SEM			0.003			
F, 19-30 y	2,181	22,809,351	0.030	0.01	760	0.024
SEM			0.005	0.002		
F, 31-50 y	3,097	37,172,408	0.040	0.01	1,614	0.027
SEM			0.005	0.002		
F, 51-70 y	2,075	20,961,630	0.040	0.03	1,539	0.035
SEM			0.005	0.003		
F, 71+ y	1,421	9,687,597	0.030	†	623	0.029
SEM			0.006			
All individuals	**29,099**	**238,221,947**	**0.040**	**0.02**	**20,108**	**0.03**
SEM			**0.003**	**0.001**		

§ All NHANES III variance estimates were based on Taylor Series (WR) method.
‡ EPA estimates of CSFII (1994-96, 98) in the IOM report were calculated using SAS PROC UNIVERIATE, not via JACKKNIFE replication method. SEM data was not available in IOM report.
[¶] NHANES III data consisted of individuals = 2 months and excluded nursing infants and children. Distribution of EPA is very skewed; means and standard errors of the means should be used and interpreted with caution.
- estimate = 0; † Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

Table 3.7. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Eicosapentaenoic Acid (EPA, 20:5 n-3) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	**10,634**	**0.03**	**0.003**	**8,510**	**0.05**	**0.002**	**8,626**	**0.02**	**0.003**	**1,329**	**0.06**	**0.012**
Both sexes, 2-6 months	444	-		156	-		124	-		69	†	
Both sexes, 7-12 months	488	†		156	†	0.001	181	†		90	†	
Both sexes, 1-3 y	854	0.01	0.001	784	0.01	0.001	962	†		134	†	
Both sexes, 4-8 y	989	†		1,179	0.01	0.002	1,322	0.01	0.002	183	†	
Both sexes, 9-13 y	646	†		886	0.02	0.004	881	†		99	†	
Both sexes, 14-18 years	517	†		714	†		646	†		110	†	
Both sexes, 19-30 y	1,065	0.03	0.005	1,314	0.05	0.004	1,533	0.03	0.004	171	†	
Both sexes, 31-50 y	1,894	0.04	0.005	1,869	0.07	0.008	1,669	0.04	0.007	244	†	
Both sexes, 51-70 y	1,836	0.04	0.004	1,024	0.06	0.006	985	0.03	0.004	164	†	
Both sexes, 71+ y	1,901	0.03	0.003	428	†		323	†		65	†	
M, Total	**5,028**	**0.04**	**0.004**	**4,001**	**0.05**	**0.005**	**4,264**	**0.03**	**0.004**	**628**	**0.06**	**0.010**
M, 2-6 months	229	-		81	-		66	-		32	†	
M, 7-12 months	239	†		78	†		96	†		37	†	
M, 1-3 y	421	0.01	0.002	396	0.01	0.001	478	†	0.001	81	†	
M, 4-8 y	491	†		580	0.02	0.003	627	0.01	0.002	102	†	
M, 9-13 y	320	†		440	0.02	0.004	440	†		51	†	
M, 14-18 y	228	†		333	†		320	†		44	†	
M, 19-30 y	460	0.04	0.008	583	0.05	0.008	776	0.03	0.006	83	0.06	0.011
M, 31-50 y	853	0.06	0.009	826	0.09	0.015	800	†		100	†	
M, 51-70 y	895	0.05	0.006	483	0.07	0.013	488	†		68	†	
M, 71+	892	0.05	0.006	201	†		173	†		30	†	
F, Total	**5,606**	**0.03**	**0.003**	**4,509**	**0.04**	**0.002**	**4,362**	**0.02**	**0.003**	**701**	**†**	
F, 2-6 months	215	-		75	-		58	-		37	-	
F, 7-12 months	249	†		78	-		85	-		53	†	
F, 1-3 y	433	†		388	†		484	†		53	†	
F, 4-8 y	498	†		599	†		695	†		81	†	
F, 9-13 y	326	†		446	†		441	†		48	†	
F, 14-18 y	289	†		381	†		326	†		66	†	
F, 19-30 y	605	0.03	0.005	731	0.04	0.005	757	†		88	†	
F, 31-50 y	1,041	0.03	0.004	1,043	0.06	0.006	869	†		144	†	
F, 51-70 y	941	0.04	0.005	541	0.05	0.007	497	†		96	†	
F, 71+	1,009	0.02	0.003	227	†		150	†		35	†	

- estimate = 0; † Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

Table 3.8. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Docosahexaenoic Acid (DHA, 22:6 n-3), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data [§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)	
	Sample Size	Population Size	Mean Intake (g/day)	Mean Intake (%kcal/day)	Sample Size	Mean Intake (g/day)
Both sexes, 0-6 months [¶]	793	1,323,807	-	†	596	<0.0005
SEM						0.001
Both sexes, 7-12 months	915	1,625,559	†	†	530	0.030
SEM						0.008
Both sexes, 1-3 y	2,734	8,724,437	0.020	0.01	3,949	0.032
SEM			0.002	0.001		0.001
Both sexes, 4-8 y	3,673	17,409,438	0.030	0.01	3,935	0.050
SEM			0.003	0.002		0.005
M, 9-13 y	1,251	9,113,670	0.030	0.01	595	0.063
SEM			0.005	0.002		0.010
M, 14-18 y	925	8,908,287	†	†	474	0.072
SEM						0.012
M, 19-30 y	1,902	21,918,936	0.090	0.03	920	0.079
SEM			0.008	0.004		0.006
M, 31-50 y	2,579	35,368,777	0.120	0.04	1,806	0.094
SEM			0.012	0.005		0.006
M, 51-70 y	1,934	18,623,500	0.100	0.04	1,680	0.111
SEM			0.008	0.003		0.007
M, 71+ y	1,296	6,723,233	0.080	0.04	722	0.128
SEM			0.008	0.004		0.019
F, 9-13 y	1,261	8,888,987	0.030	0.02	606	0.055
SEM			0.006	0.003		0.009
F, 14-18 y	1,062	8,962,331	0.030	0.02	449	0.062
SEM			0.004	0.002		0.009
F, 19-30 y	2,181	22,809,351	0.060	0.03	808	0.067
SEM			0.010	0.003		0.006
F, 31-50 y	3,097	37,172,408	0.080	0.03	1,690	0.071
SEM			0.009	0.004		0.009
F, 51-70 y	2,075	20,961,630	0.080	0.04	1,605	0.089
SEM			0.007	0.004		0.006
F, 71+ y	1,421	9,687,597	0.050	0.03	670	0.077
SEM			0.008	0.005		0.010
All individuals	**29,099**	**238,221,947**	**0.070**	**0.03**	**21,159**	**0.057**
SEM			**0.004**	**0.002**		**0.018**

§ All NHANES III variance estimates were based on Taylor Series (WR) method.
¶ NHANES III data consisted of individuals = 2 months and excluded nursing infants and children. Distribution of EPA is very skewed; means and standard errors of the means should be used and interpreted with caution.
- estimate = 0
† Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.
‡ EPA estimates of CSFII (1994-96, 98) in the IOM report were calculated using SAS PROC UNIVERIATE, not via JACKKNIFE replication method. SEM data was not available in IOM report.

Table 3.9. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Docosahexaenoic Acid (DHA, 22:6n-3) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	**10,634**	**0.07**	**0.005**	**8,510**	**0.09**	**0.004**	**8,626**	**0.05**	**0.003**	**1,329**	**0.10**	**0.015**
Both sexes, 2-6 months	444	†		156	-		124	-		69	-	
Both sexes, 7-12 months	488	†		156	*	0.002	181	*	0.002	90	†	
Both sexes, 1-3 y	854	†		784	0.02	0.004	962	0.01	0.002	134	†	
Both sexes, 4-8 y	989	0.02	0.004	1,179	0.03	0.003	1,322	0.03	0.004	183	†	
Both sexes, 9-13 y	646	0.03	0.004	886	0.04	0.005	881	0.03	0.003	99	†	
Both sexes, 14-18 years	517	†		714	0.07	0.012	646	0.03	0.004	110	†	
Both sexes, 19-30 y	1,065	0.07	0.010	1,314	0.10	0.007	1,533	0.06	0.006	171	†	
Both sexes, 31-50 y	1,894	0.09	0.009	1,869	0.13	0.013	1,669	0.07	0.010	244	†	
Both sexes, 51-70 y	1,836	0.08	0.006	1,024	0.10	0.008	985	0.06	0.007	164	0.13	0.024
Both sexes, 71+ y	1,901	0.06	0.004	428	†		323	0.04	0.008	65	†	
M, Total	**5,028**	**0.08**	**0.006**	**4,001**	**0.11**	**0.008**	**4,264**	**0.06**	**0.004**	**628**	**0.10**	**0.012**
M, 2-6 months	229	†		81	-		66	-		32	-	
M, 7-12 months	239	†		78	†		96	*	0.003	37	†	
M, 1-3 y	421	0.02	0.004	396	0.02	0.003	478	0.01	0.002	81	†	
M, 4-8 y	491	0.02	0.004	580	0.03	0.004	627	0.03	0.002	102	†	
M, 9-13 y	320	0.03	0.006	440	0.05	0.006	440	0.03	0.005	51	†	
M, 14-18 y	228	†		333	0.08	0.017	320	0.03	0.004	44	†	
M, 19-30 y	460	0.08	0.012	583	0.13	0.014	776	0.07	0.007	83	0.10	0.011
M, 31-50 y	853	0.11	0.013	826	0.18	0.025	800	0.08	0.015	100	0.14	0.028
M, 51-70 y	895	0.09	0.010	483	0.12	0.015	488	0.08	0.013	68	†	
M, 71+	892	0.08	0.009	201	†		173	0.06	0.016	30	†	
F, Total	**5,606**	**0.05**	**0.005**	**4,509**	**0.07**	**0.003**	**4,326**	**0.04**	**0.004**	**701**	**†**	
F, 2-6 months	215	-		75	-		58	-		37	-	
F, 7-12 months	249	†		78	*	0.001	85	*	0.002	53	†	
F, 1-3 y	433	†		388	†		484	†		53	†	
F, 4-8 y	498	0.03	0.006	599	0.03	0.005	695	†		81	†	
F, 9-13 y	326	0.03	0.006	446	0.04	0.007	441	†		48	†	
F, 14-18 y	289	0.03	0.005	381	0.06	0.011	326	0.03	0.005	66	†	
F, 19-30 y	605	0.06	0.012	731	0.08	0.007	757	0.04	0.006	88	†	
F, 31-50 y	1,041	0.07	0.009	1,043	0.09	0.008	869	0.06	0.009	144	†	
F, 51-70 y	941	0.07	0.008	541	0.08	0.011	497	0.04	0.006	96	†	
F, 71+	1,009	0.04	0.006	227	†		150	†	0.010	35	†	

- estimate = 0; * Value < 0.001 but greater than 0.

† Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

Table 3.10. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) and Omega-3 PUFAs, United States, NHANES III (1988-94), Adults vs. Youths (Age < 18 y)

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d) †					
Total	29,099	238,221,947	14.13	0.1962	9.48
Adults	16,683	175,098,828	14.94	0.2298	7.02
Youths	12,416	63,123,119	11.88	0.2215	6.65
ALA (18:3 n-3) (g/d) †					
Total	29,099	238,221,947	1.33	0.0154	6.81
Adults	16,683	175,098,828	1.40	0.0191	5.59
Youths	12,416	63,123,119	1.13	0.0191	5.97
¶ EPA (20:5 n-3) (g/d)					
Total	29,099	238,221,947	0.04	0.0026	8.57
Adults	16,683	175,098,828	0.04	0.0035	6.99
Youths	12,416	63,123,119	0.01	0.0014	3.90
¶ DHA (22:6 n-3) (g/d)					
Total	29,099	238,221,947	0.07	0.0044	8.69
Adults	16,683	175,098,828	0.08	0.0058	7.40
Youths	12,416	63,123,119	0.03	0.0031	4.18
LA (18:2 n-6) (%kcal/d) †					
Total	29,097	238,218,723	5.79	0.0458	7.29
Adults	16,683	175,098,828	5.95	0.0512	5.06
Youths	12,414	63,119,895	5.36	0.0603	6.19
ALA (18:3 n-3) (%kcal/d) †					
Total	29,097	238,218,723	0.55	0.0041	5.78
Adults	16,683	175,098,828	0.56	0.0049	4.33
Youths	12,414	63,119,895	0.51	0.0047	4.12
¶ EPA (20:5 n-3) (%kcal/d)					
Total	29,097	238,218,723	0.02	0.0011	8.47
Adults	16,683	175,098,828	0.02	0.0014	6.89
Youths	12,414	63,119,895	0.01	0.0006	3.56
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,097	238,218,723	0.03	0.0019	10.67
Adults	16,683	175,098,828	0.04	0.0025	8.52
Youths	12,414	63,119,895	0.01	0.0010	3.97

† $P < .001$ between groups

¶ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.11. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) & Omega-3 PUFAs, United States, NHANES III (1988-94), Males vs. Females

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d) †					
Total	29,105	238,245,897	14.13	0.1962	9.48
Male	13,923	115,778,180	16.36	0.2841	7.48
Female	15,182	122,467,717	12.02	0.1618	5.04
ALA (18:3 n-3) (g/d) †					
Total	29,105	238,245,897	1.33	0.0154	6.81
Male	13,923	115,778,180	1.54	0.0233	6.05
Female	15,182	122,467,717	1.13	0.0134	3.84
¶ EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897	0.04	0.0026	8.57
Male	13,923	115,778,180	0.04	0.0032	4.89
Female	15,182	122,467,717	0.03	0.0031	8.34
¶ DHA (22:6 n-3) (g/d)					
Total	29,105	238,245,897	0.07	0.0044	8.69
Male	13,923	115,778,180	0.08	0.0050	4.36
Female	15,182	122,467,717	0.06	0.0051	8.11
LA (18:2 n-6) (%kcal/d) †					
Total	29,103	238,242,673	5.79	0.0458	7.29
Male	13,922	115,776,672	5.65	0.0526	5.02
Female	15,181	122,466,001	5.93	0.0606	6.22
ALA (18:3 n-3) (%kcal/d) †					
Total	29,103	238,242,673	0.55	0.0041	5.78
Male	13,922	115,776,672	0.54	0.0047	4.05
Female	15,181	122,466,001	0.56	0.0054	4.81
¶ EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.02	0.0011	8.47
Male	13,922	115,776,672	0.02	0.0011	4.67
Female	15,181	122,466,001	0.02	0.0014	7.40
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.03	0.0019	10.67
Male	13,922	115,776,672	0.03	0.0020	5.19
Female	15,181	122,466,001	0.03	0.0023	9.00

† $P < .001$ between groups

¶ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.12. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2n-6) & Omega-3 PUFAs, United States, NHANES III (1988-94), by Race/Ethnicity groups

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d)					
Total	29,105	238,245,897	14.13	0.1962	9.48
* Non-Hispanic white	10,634	174,119,805	14.27	0.2354	5.05
* Non-Hispanic black	8,513	29,355,656	14.23	0.1956	2.55
* Mexican-American	8,627	14,878,866	14.07	0.2025	2.82
Other	1,331	19,891,569	12.77	0.4797	2.78
ALA (18:3 n-3) (g/d)					
Total	29,105	238,245,897	1.33	0.0154	6.81
† Non-Hispanic white	10,634	174,119,805	1.37	0.0192	3.78
* Non-Hispanic black	8,513	29,355,656	1.27	0.0166	2.16
* Mexican-American	8,627	14,878,866	1.20	0.0168	3.04
Other	1,331	19,891,569	1.12	0.0379	2.32
¶ EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897	0.04	0.0026	8.56
Non-Hispanic white	10,634	174,119,805	0.03	0.0026	3.79
Non-Hispanic black	8,513	29,355,656	0.05	0.0024	1.37
Mexican-American	8,627	14,878,866	0.02	0.0026	4.35
Other	1,331	19,891,569	0.06	0.0120	4.60
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,105	238,245,897	0.07	0.0044	8.69
Non-Hispanic white	10,634	174,119,805	0.07	0.0048	3.93
Non-Hispanic black	8,513	29,355,656	0.09	0.0040	1.58
Mexican-American	8,627	14,878,866	0.05	0.0033	4.27
Other	1,331	19,891,569	0.10	0.0153	4.21

(continued to the next page)

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (%kcal/d)					
Total	29,103	238,242,673	5.79	0.0458	7.29
* Non-Hispanic white	10,634	174,119,805	5.79	0.0579	4.38
† Non-Hispanic black	8,512	29,353,940	5.98	0.0592	3.42
† Mexican-American	8,626	14,877,359	5.93	0.0476	2.11
Other	1,331	19,891,569	5.37	0.1279	2.48
ALA (18:3 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.55	0.0041	5.78
† Non-Hispanic white	10,634	174,119,805	0.56	0.0054	3.55
† Non-Hispanic black	8,512	29,353,940	0.54	0.0051	2.77
† Mexican-American	8,626	14,877,359	0.52	0.0063	5.20
Other	1,331	19,891,569	0.48	0.0106	2.23
¶ EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.02	0.0011	8.47
Non-Hispanic white	10,634	174,119,805	0.01	0.0010	3.26
Non-Hispanic black	8,512	29,353,940	0.02	0.0009	1.18
Mexican-American	8,626	14,877,359	0.01	0.0009	3.39
Other	1,331	19,891,569	0.03	0.0057	4.72
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.03	0.0019	10.67
Non-Hispanic white	10,634	174,119,805	0.03	0.0019	4.20
Non-Hispanic black	8,512	29,353,940	0.04	0.0016	1.63
Mexican-American	8,626	14,877,359	0.02	0.0013	3.60
Other	1,331	19,891,569	0.05	0.0079	4.67

Other race/ethnicity group was the reference group.
* $P < .05$ compared to the reference group.
† $P < .001$ compared to the reference group.
¶ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.13. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) and Omega-3 PUFAs, United States, NHANES III (1988-94), Metro vs. Non-metro Areas

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d)					
Total	29,105	238,245,897	14.13	0.1962	9.48
Metro	14,374	114,581,912	14.28	0.2701	8.23
Non-metro	14,731	123,663,985	13.99	0.2479	8.25
ALA (18:3 n-3) (g/d)					
Total	29,105	238,245,897	1.33	0.0154	6.81
Metro	14,374	114,581,912	1.34	0.0250	8.28
Non-metro	14,731	123,663,985	1.32	0.0203	6.39
EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897	0.04	0.0026	8.56
Metro	14,374	114,581,912	0.04	0.0032	6.45
Non-metro	14,731	123,663,985	0.03	0.0040	10.49
DHA (22:6 n-3) (g/d)					
Total	29,105	238,245,897	0.07	0.0044	8.69
Metro	14,374	114,581,912	0.08	0.0056	5.81
Non-metro	14,731	123,663,985	0.06	0.0069	13.43
LA (18:2 n-6) (%kcal/d)					
Total	29,103	238,242,673	5.79	0.0458	7.29
Metro	14,373	114,580,196	5.79	0.0554	5.06
Non-metro	14,730	123,662,477	5.79	0.0629	7.28
ALA (18:3 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.55	0.0041	5.78
Metro	14,373	114,580,196	0.55	0.0066	6.97
Non-metro	14,730	123,662,477	0.55	0.0059	6.29
¶ EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.02	0.0011	8.47
Metro	14,373	114,580,196	0.02	0.0014	6.39
Non-metro	14,730	123,662,477	0.01	0.0017	10.44
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.03	0.0019	10.67
Metro	14,373	114,580,196	0.03	0.0021	5.95
Non-metro	14,730	123,662,477	0.03	0.0032	16.57

¶ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.14. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) & Omega-3 PUFAs, United States, NHANES III (1988-94)*, PIR = 1.3 vs. PIR > 1.3

Poverty Index Ratio (PIR)	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d)					
Total	27,482	226,488,050	14.15	0.2015	9.48
PIR <= 1.3	11,711	53,365,381	12.85	0.2258	5.50
PIR > 1.3	15,771	173,122,669	14.55	0.2289	6.89
ALA (18:3 n-3) (g/d)					
Total	27,482	226,488,050	1.33	0.0160	6.88
PIR <= 1.3	11,711	53,365,381	1.19	0.0191	4.67
PIR > 1.3	15,771	173,122,669	1.38	0.0186	5.22
¶ EPA (20:5 n-3) (g/d)					
Total	27,482	226,488,050	0.04	0.0026	8.03
PIR <= 1.3	11,711	53,365,381	0.03	0.0027	4.67
PIR > 1.3	15,771	173,122,669	0.04	0.0031	6.45
¶ DHA (22:6 n-3) (g/d)					
Total	27,482	226,488,050	0.07	0.0042	7.77
PIR <= 1.3	11,711	53,365,381	0.06	0.0056	5.65
PIR > 1.3	15,771	173,122,669	0.07	0.0050	6.15
LA (18:2 n-6) (%kcal/d)					
Total	27,480	226,484,827	5.79	0.0470	7.27
PIR <= 1.3	11,710	53,363,665	5.58	0.0562	4.35
PIR > 1.3	15,770	173,121,162	5.86	0.0527	5.27
ALA (18:3 n-3) (%kcal/d)					
Total	27,480	226,484,827	0.55	0.0042	5.83
PIR <= 1.3	11,710	53,363,665	0.52	0.0056	4.83
PIR > 1.3	15,770	173,121,162	0.56	0.0047	4.00
¶ EPA (20:5 n-3) (%kcal/d)					
Total	27,480	226,484,827	0.01	0.0011	7.98
PIR <= 1.3	11,710	53,363,665	0.01	0.0009	3.09
PIR > 1.3	15,770	173,121,162	0.02	0.0013	6.68
¶ DHA (22:6 n-3) (%kcal/d)					
Total	27,480	226,484,827	0.03	0.0019	9.97
PIR <= 1.3	11,710	53,363,665	0.02	0.0015	3.41
PIR > 1.3	15,770	173,121,162	0.03	0.0023	7.97

* 6% participants refused to report their income or income category.

¶ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.15.The Demographic Characteristics of Adult Participants With and Without a History of Cardiovascular Diseases, United States, NHANES III (1988-94) §

Gender and Race/Ethnicity Groups	People With a History of CVD		People Without a History of CVD	
	Sample Size	Population Size	Sample Size	Population Size
Total	2,121	14,964,332	14,562	160,134,496
Male	1,136	8,036,546	6,664	75,438,001
Female	985	6,927,787	7,898	84,696,495
Non-Hispanic White				
Total	973	10,966,582	5,771	121,941,462
Male	554	6,165,912	2,567	57,378,183
Female	419	4,800,670	3,204	64,563,276
Non-Hispanic Black				
Total	686	2,445,381	4,033	17,057,068
Male	353	1,175,699	1,777	7,493,735
Female	333	1,269,682	2,256	9,563,333
Mexican-American				
Total	391	502,292	4,176	8,673,940
Male	205	261,129	2,060	4,507,199
Female	186	241,163	2,116	4,166,741
Other				
Total	71	1,050,078	582	12,462,026
Male	24	433,807	260	6,058,884
Female	47	616,271	322	6,403,141

§ All NHANES III variance estimates were based on Taylor Series (WR) method.

Table 3.16. The Mean Intakes ± SEMs of Linoleic Acid (LA, 18:2n-6), Respondents With a History of CVD Compared to Those Without CVD, NHANES III (1988-94)

	Linoleic acid (LA, 18:2n-6)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	12.58	0.4753	15.16	0.2355	5.80	0.0954	5.96	0.0536
Male	15.12	0.8243	17.96	0.3390	5.87	0.1263	5.80	0.0598
Female	9.64	0.2815	12.67	0.1980	5.73	0.1343	6.10	0.0729
Non-Hispanic White								
Total	13.06	0.6196	15.20	0.2798	5.98	0.1178	5.96	0.0663
Male	15.62	1.0596	18.17	0.4158	6.06	0.1699	5.82	0.0739
Female	9.76	0.3733	12.57	0.2245	5.88	0.1803	6.08	0.0844
Non-Hispanic Black								
Total	11.71	0.5201	15.42	0.2521	5.60	0.1378	6.09	0.0687
Male	13.96	0.7583	17.85	0.3712	5.62	0.1692	5.79	0.0613
Female	9.62	0.4955	13.52	0.2714	5.57	0.1811	6.33	0.0999
Mexican-American								
Total	11.36	0.4970	15.92	0.2814	5.79	0.1469	6.16	0.0706
Male	11.28	0.6263	18.57	0.3443	5.17	0.2655	6.06	0.0874
Female	11.44	0.7056	13.05	0.3075	6.46	0.2943	6.26	0.0819
Other								
Total	10.27	1.3049	13.88	0.5446	4.43	0.4121	5.67	0.1486
Male	13.47	2.9402	15.65	0.6688	4.16	0.7905	5.44	0.2131
Female	8.02	0.7190	12.21	0.7737	4.62	0.4265	5.88	0.2396

Table 3.17. The Mean Intakes ± SEMs of Alpha Linolenic Acid (ALA, 18:3 n-3), Respondents With a History of CVD Compared to Those Without CVD, NHANES III (1988-94)

	Alpha Linolenic Acid (ALA, 18:3 n-3)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	1.16	0.0349	1.42	0.0201	0.55 *†	0.0093	0.57 *†	0.0051
Male	1.38	0.0600	1.69	0.0298	0.55	0.0132	0.55	0.0059
Female	0.90	0.0238	1.19	0.0181	0.54	0.0108	0.58	0.0066
Non-Hispanic White								
Total	1.20	0.0399	1.46	0.0253	0.56	0.0105	0.58	0.0069
Male	1.40	0.0651	1.75	0.0368	0.57	0.0148	0.57	0.0075
Female	0.93	0.0305	1.21	0.0224	0.56	0.0132	0.59	0.0089
Non-Hispanic Black								
Total	1.08	0.0456	1.37	0.0222	0.52	0.0115	0.54	0.0057
Male	1.25	0.0684	1.60	0.0389	0.51	0.0141	0.52	0.0067
Female	0.92	0.0552	1.19	0.0224	0.54	0.0192	0.56	0.0079
Mexican-American								
Total	0.96	0.0453	1.32	0.0221	0.49	0.0161	0.52	0.0078
Male	1.04	0.0600	1.53	0.0332	0.47	0.0252	0.50	0.0099
Female	0.87	0.0627	1.09	0.0248	0.52	0.0234	0.53	0.0095
Other								
Total	1.07	0.1754	1.18	0.0453	0.44	0.0370	0.48	0.0167
Male	1.57	0.3688	1.13	0.0701	0.46	0.0820	0.46	0.0244
Female	0.72	0.0584	1.03	0.0724	0.42	0.0314	0.50	0.0233

* Univariate analysis showed significant differences between the CVD groups (*P*=.04)
† Multivariate analysis (adjusted for sex, age, and race/ethnicity) showed significant differences between the CVD groups. The results are shown in Appendix C in detail.

Table 3.18. The Mean Intakes ± SEMs of Eicosapentaenoic Acid (EPA, 20:5 n-3), Respondents with a History of CVD Compared to Those Without CVD, NHANES III (1988-94) §

	Eicosapentaenoic acid (EPA, 20:5 n-3)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	0.04	0.0042	0.04	0.0037	0.02	0.0023	0.02	0.0015
Male	0.05	0.0071	0.05	0.0045	0.02	0.0034	0.02	0.0017
Female	0.04	0.0061	0.04	0.0041	0.03	0.0043	0.02	0.0019
Non-Hispanic White								
Total	0.04	0.0044	0.04	0.0036	0.02	0.0028	0.02	0.0013
Male	0.04	0.0067	0.05	0.0056	0.02	0.0033	0.02	0.0018
Female	0.04	0.0082	0.03	0.0034	0.03	0.0061	0.02	0.0014
Non-Hispanic Black								
Total	0.07	0.0131	0.06	0.0039	0.03	0.0057	0.02	0.0013
Male	0.09	0.0261	0.07	0.0082	0.04	0.0103	0.02	0.0025
Female	0.05	0.0113	0.05	0.0027	0.03	0.0061	0.02	0.0013
Mexican-American								
Total	0.02	0.0064	0.03	0.0039	0.01	0.0030	0.01	0.0014
Male	0.04	0.0117	0.04	0.0058	0.02	0.0053	0.01	0.0019
Female	0.01	0.0040	0.02	0.0039	0.00	0.0014	0.01	0.0017
Other								
Total	0.07	0.0240	0.08	0.0188	0.03	0.0110	0.04	0.0088
Male	0.11	0.0530	0.07	0.0138	0.05	0.0224	0.03	0.0066
Female	0.04	0.0184	0.09	0.0290	0.02	0.0097	0.04	0.0137

§ Distribution of this nutrient is very skewed; means and standard errors of the means should be used and interpreted with caution.

Table 3.19. The Mean Intakes ± SEMs of Docosahexaenoic Acid (DHA, 22:6 n-3), Respondents With a History of CVD Compared to Those Without CVD, NHANES III (1988-94) §

	Docosahexaenoic acid (DHA, 22:6 n-3)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	0.08	0.0050	0.09	0.0062	0.04	0.0032	0.04	0.0026
Male	0.08	0.0085	0.10	0.0074	0.04	0.0042	0.04	0.0031
Female	0.07	0.0103	0.07	0.0067	0.04	0.0066	0.03	0.0029
Non-Hispanic White								
Total	0.07	0.0060	0.08	0.0066	0.04	0.0040	0.03	0.0025
Male	0.07	0.0096	0.10	0.0088	0.03	0.0045	0.03	0.0033
Female	0.06	0.0132	0.06	0.0065	0.04	0.0091	0.03	0.0024
Non-Hispanic Black								
Total	0.12	0.0167	0.12	0.0063	0.06	0.0078	0.05	0.0023
Male	0.14	0.0280	0.15	0.0129	0.06	0.0104	0.05	0.0040
Female	0.09	0.0205	0.09	0.0041	0.06	0.0104	0.04	0.0020
Mexican-American								
Total	0.05	0.0093	0.06	0.0049	0.03	0.0047	0.03	0.0018
Male	0.08	0.0158	0.08	0.0069	0.04	0.0082	0.03	0.0023
Female	0.03	0.0053	0.05	0.0051	0.02	0.0025	0.03	0.0023
Other								
Total	0.11	0.0300	0.13	0.0234	0.05	0.0138	0.06	0.0119
Male	0.14	0.0580	0.13	0.0142	0.06	0.0249	0.05	0.0086
Female	0.08	0.0358	0.14	0.0385	0.04	0.0151	0.07	0.0194

§ Distribution of this nutrient is very skewed; means and standard errors of the means should be used and interpreted with caution.

Effects of Consumption of Omega-3 Fatty Acid from Fish or Overall Diet, or from Supplements of Fish Oil or ALA, on Cardiovascular Disease Outcomes

In this section, we present results from our review of studies that examined the effect of omega-3 fatty acid supplements or fish consumption on all-cause mortality and CVD outcomes. An overview of our literature search is presented first, followed by findings from secondary and primary prevention studies. Specific key questions relating to the efficacy of omega-3 fatty acids on CVD outcomes are also discussed. Relevant summary tables appear at the end of this section.

Summary of Studies Analyzed

We screened over 7,464 abstracts that were indexed as English language articles concerning humans. Based on this initial review, we retrieved and screened 768 full text articles for potentially relevant human data. We subsequently examined 118 articles that passed a screen for studies that might have CVD clinical outcome data. We rejected 80 articles. Thirty of the rejected articles were reviews or commentaries that did not provide primary data. The reasons for rejecting the remaining 50 articles are listed in the section, Excluded Studies.

Thirty-nine unique studies fulfilled our inclusion criteria for reporting mortality or CVD clinical outcomes with a follow-up duration of 1 year or longer (interim reports or articles reporting different outcomes from the same overall study were counted as a single study). The 39

studies included: 12 randomized controlled trials (RCTs), 22 unique prospective cohort studies (including 4 studies that each contributed 2 separate articles on different analyses), 4 case-control studies, and 1 cross-sectional study. We created evidence and summary tables for these studies and included the studies in our analyses. Evidence Table 1 provides detailed information about the RCTs, and Evidence Table 2 describes prospective cohort, case-control, and cross-sectional studies. The summary tables present information about the study population, study design and duration, the frequency or amount of omega-3 fatty acid supplements or fish or fish oil consumed, dietary assessment method, main results, study quality, and study applicability. Studies are ordered by study size in each summary table.

For all practical purposes, CVD populations were studied with RCTs and the general population was studied with prospective cohort and case-control studies. Thus, in this section we first discuss results of the secondary prevention studies (i.e., studies of the CVD population), which are comprised of 11 RCTs and 1 cohort study. This is followed by a discussion of the primary prevention studies (or studies of the general population), which are comprised mostly of prospective cohort studies and 1 RCT.

For the non-randomized studies, data on each outcome are presented in 2 tables. One table presents outcomes based on estimates of omega-3 fatty acid or fish oil consumption, the other presents outcomes based on estimates of fish consumption. Because of the large amount of outcomes data reported in the prospective cohort studies, we created an "overall effect" metric to reduce this volume of information and to help interpret the results of these studies (see Chapter 2, Methods). This metric is used in the summary matrices (Tables 3.40-3.51).

In discussing results for the CVD and general populations, evidence for the following CVD clinical outcomes is presented: all-cause mortality, CVD deaths (deaths due to strokes, cardiac and peripheral vascular diseases), cardiac deaths, sudden death, myocardial infarction (MI), stroke, and all CVD events. It should be noted that different studies reported different combinations of these outcomes, and that the definitions for some of the outcomes varied across studies. For example, coronary deaths, ischemic deaths, cardiac deaths, and fatal myocardial infarction have largely overlapping but not identical meanings, as defined by individual studies. We placed the outcome reported by a study under the most similar common definition, as judged by a clinician-methodologist member of the EPC.

Tables 3.20-3.23 and 3.25 summarize the 12 RCTs. Six of the RCTs were trials of omega-3 fatty acid supplements, and 6 were trials of diets or dietary advice. Only 1 of the 12 trials, a large study that compared linseed oil (ALA) with sunflower oil, was a primary prevention study conducted in the general population. The remaining 11 trials were secondary prevention studies conducted in patients with known CVD. This profile was reversed among the 22 prospective cohort studies (which included 26 separate papers), as all but 1 of the cohort studies were conducted in the general population.

Tables 3.24-3.39 summarize the results of the prospective cohort, case-control, and cross-sectional studies. Studies are ordered by study size in each table. Data on each outcome are presented in 2 tables: 1 table presents outcomes based on estimates of omega-3 fatty acid or fish oil consumption, the other presents outcomes based on estimates of fish consumption. Because of the large amount of data reported in the prospective cohort studies, we created an "overall effect" metric to help in interpreting the results of these studies (see Chapter 2, Methods). This metric is reported by outcome in Tables 3.40-3.51.

Information about omega-3 fatty acid consumption varied across studies. In the RCTs of omega-3 fatty acid supplements, the amount and composition of omega-3 fatty acid is known

and reported, whereas in the diet/dietary advice trials, estimates of the average amount of omega-3 fatty acids consumed by subjects are reported. In the prospective cohort studies, the amount of omega-3 fatty acid was not prescribed. As a result, omega-3 fatty acid intake and the amount or frequency of fish intake were estimated and reported as different quantiles corresponding to the observed relative risk of the outcomes.

Secondary Prevention Studies (Tables 3.20-3.24)

Evidence for the effects of the consumption of omega-3 fatty acids, omega-3 fatty acid supplements, or fish on CVD outcomes in populations known to have CVD was derived from 11 RCTs and 1 prospective cohort study. The 11 RCTs include 5 trials of omega-3 fatty acid supplements and 6 diet or dietary advice trials.

Characteristics of the omega-3 fatty acids supplements trials (Table 3.20-3.21). Of the 5 RCTs of omega-3 fatty acid supplements, 4 examined EPA+DHA supplements, The methodological quality of all 4 RCTs of EPA+DHA supplements was generally good (grade A or B)[34-37]. Data on women are limited. The fifth is the single RCT with both an ALA arm and an EPA+DHA arm and the methodological quality was poor (grade C)[38].

The study populations of these 5 trials were rated as CVD-I (highly applicable) to CVD-II (relevant subgroups). One of the trials, the GISSI-Prevenzione trial, is the largest secondary prevention study with over 11,000 patients randomized [35,39]. The other 3 EPA+DHA trials, combined, contributed fewer than 1,000 patients. The study subjects in these 3 smaller trials were MI survivors, patients with other vascular diseases, or patients with significant CVD risks. Most of the omega-3 fatty acid arms used a combination of EPA+DHA, although the dosages vary from 0.27 g/d to 4.8 g/d. The types of control also varied across the studies. The GISSI study used vitamin E or no vitamin E in a factorial design. Three of the studies used an equivalent amount of non-omega-3 oil as a control. The duration of the trials ranged from 2 to 3.5 years, and most were conducted outside the US.

The ALA trial was conducted in India and had a duration of 1 year. This trial compared 2.9 g/d of ALA in the form of mustard oil in 1 treatment arm and a combination of EPA+DHA in another treatment arm with a non-oil placebo[38]. The methodological quality of this study was poor (grade C).

Table 3.20 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: all cause mortality, CVD death, cardiac death, sudden death (secondary prevention)

Author Year Country	Omega -3 fatty acid		Control		Duration (year)	All cause mortality		CVD death		Cardiac death		Sudden death		Quality			Applicability
	N	Type Dose	N	Type Dose		Control Group Event Rate (%)	RR 95% CI	Control Group Event Rate (%)	RR 95% CI	Control Group Event Rate	RR 95% CI	Control Group Event Rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
EPA + DHA																	
Marchioli 2002 Italy	5665	EPA + DHA (1:2) 0.85 g/d±Vit E	5658	Control ±Vit E	3.5	9.8	0.79[1] 0.66-0.93	6.5	0.70[1] 0.56-0.86	5.4	0.65[1] 0.51-0.82	2.7	0.55[1] 0.39-0.77	B	3	A	CVD I
Nilsen 2001 Norway	150	EPA + DHA (1:2) 1.7 g/d	150	Corn oil 1.7 g/d	1.5	7.3	1.0 0.45-2.2	-	nd	5.3	1.0 0.39-2.6	-	nd.	B	4	U	CVD II
Singh 1997 India	122	EPA + DHA (1:1) 1.8 g/d	118	Non-oil placebo	1	-	nd	-	nd	22	0.52 0.29-0.95	6.6	0.24 0.05-1.1	C	4	I	CVD II
Leng 1998 Scotland	60	EPA 0.27g/d	60	Sun flower seed oil 3 g/d	2	5.0	1.0 0.21-4.8	3.3	1.0 0.15-6.9	-	nd	-	nd.	A	5	A	CVD II
Sacks 1995 US	31	EPA + DHA (3:2) 4.8 g/d	28	Olive Oil	2.4	3.6	0.3 0.01-7.1	3.6	0.3 0.01-7.1	3.6	0.3 0.01-7.1	0	nd	B	3	U	CVD II
ALA																	
Singh 1997 India	120	Mustard Oil ALA 2.9 g/d	118	Non-oil placebo	1	-	nd	-	nd	22	0.61 0.34-1.1	6.6	0.25 0.05-1.1	C	4	I	CVD II

[1] RR adjusted for main confounders as reported in article.
Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data
Applicability is derived from a combination of the target population (GEN or CVD) and the three-level grades (I, II, III). CVD-II represents a relevant subgroup of US subjects with history or risk of CVD. Most studies in this table are graded CVD-II because they are foreign mixed-gender populations with different background diets at risk for CVD.

Table 3.21 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: myocardial infarction, stroke, all CVD events (secondary prevention)

Author Year Country	Omega -3 Fatty acid		Control		Duration (year)	Fatal MI		Non-fatal MI		All strokes		All CVD events		Quality			Applicability
	N	Type Dose	N	Type Dose		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
EPA + DHA																	
Marchioli 2002 Italy	5665	EPA + DHA (1:2) 0.85 g/d±Vit E	5658	Control Or Vit E	3.5	4.6	0.68[1] 0.53-0.88	4.1	0.91[1] 0.70-1.2	1.4	1.2[1] 0.81-1.9	11	0.80[1] 0.68-0.94	B	3	A	CVD I
Nilsen 2001 Norway	150	EPA + DHA (1:2) 1.7 g/d	150	Corn oil 1.7 g/d	1.5	-	nd	10	1.4 0.75-2.6	-	nd	47	1.1 0.84-1.3	B	4	U	CVD II
Singh 1997 India	122	EPA + DHA (1:1) 1.8 g/d	118	Non-oil placebo	1	-	nd	25	0.52 0.3-.0..9	-	nd	35	.0.71 0.48-1.1	C	4	I	CVD II
Leng 1998 Scotland	60	EPA 0.27g/d	60	Sunflower seed oil 3 g/d	2	-	nd	6.7	0.75 0.18-3.2	1.7	Non-fatal stroke 3.0 0.32-28	23	0.86[2] 0.43-1.7	A	5	A	CVD II
Sacks 1995 US	31	EPA + DHA (3:2) 4.8 g/d	28	Olive Oil	2.4	3.6	0.3 0.01-7.1	7.1	0.45 0.04-4.7	0	2.7 0.12-64	-	nd	B	3	U	CVD II
ALA																	
Singh 1997 India	120	Mustard Oil ALA 2.9 g/d	118	Non-oil placebo	1	-	nd	25	0.59 0.35-1.0	-	nd	35	0.82 0.56-1.2	C	4	I	CVD II

[1] RR adjusted for main confounders as reported in article. [2] Includes critical ischemia/amputation, angioplasty and bypass surgery.
Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data
Applicability is derived from a combination of the target population (GEN or CVD) and the three-level grades (I, II, III). CVD-II represents a relevant subgroup of US subjects with history or risk of CVD. Most studies in this table are graded CVD-II because they are foreign mixed-gender populations with different background diets at risk for CVD

Table 3.22 Randomized controlled trials of omega-3 fatty acid diet or dietary advice on cardiovascular disease outcomes: all cause mortality, CVD death, cardiac death, sudden death (secondary prevention)

Author Year Country	Diet / Fish advice		No Diet / No fish advice		Duration (year)	All cause mortality		CVD death		Cardiac death		Sudden death		Quality			Applicability
	N	Estimated omega-3 fatty acid intake	N	Estimated omega-3 fatty acid intake		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
EPA estimate																	
Burr 2003 UK	1571	EPA 2.11-2.65 g/wk	1543	EPA 0.12-0.17 g/wk	5	16	HR 1.15 0.86-1.36	-	-	9	HR 1.26 (1.00-1.58)	3	HR 1.54 (1.06-2.23)	C	2	A	CVD II
Burr 1989 UK	1015	EPA 2.4 g/wk (SD 1.4)	1018	EPA 0.06 g/wk (SD 0.7)	2	13	0.73 0.56-0.93	-	nd	11	0.67 0.51-0.89	-	nd	C	1	U	CVD II
ALA estimate																	
Singh 2002 India	499	Indo Mediterranean diet ALA 1.8 g/d	501	ALA 0.8 g/d	2	8	0.63 0.38-1.04	-	nd	-	nd	3.2	0.38 0.15-0.95	C	3	U	CVD III
Leren 1966 Norway	406	Cholesterol-lowering diet[1] ALA 1-1.9 g/d (soybean oil)	406	Usual diet	5	27	0.75 0.52-1.06	25	0.73 0.50-1.06	-	nd	13	1.00 0.61-1.64	C	2	I	CVD II
DeLorgeril 1999 France	302	Cretan Mediterranean diet[1] ALA 1.9 g/d	303	Prudent diet[2] ALA 0.67 g/d	2.3	7.9	0.44[3] 0.21-0.94	-	nd	6.3	0.35[3] 0.15-0.83	2.6	0.06 0.003-1.02	C	4	A	CVD II
Bemelmans 2002 Netherlands	109	ALA 6.3 g/d	157	ALA 1.0 g/d	2	0.6	4.3 0.46-41	0.6	1.44 0.09-23	-	nd	-	nd	B	3	A	CVD I

[1] ALA=0.84 % energy = calculated from daily nutrient recorded on the final visit in 144 unselected consecutive experimental patients
[2] ALA=0.29% energy = calculated from daily nutrient recorded on the final visit in 83 unselected consecutive control patients
[3] RR adjusted for main confounders as reported in article.
Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data

Table 3.23 Randomized controlled trials of omega-3 fatty acid diet or dietary advice on cardiovascular disease outcomes: myocardial infarction, stroke, all CVD events (secondary prevention)

Author Year Country	Diet / Fish advice		No Diet / No fish advice		Duration (year)	Fatal MI		Non-fatal MI		All strokes		All CVD events		Quality			Applicability
	N	Estimated omega-3 fatty acid intake	N	Estimated omega-3 fatty acid intake		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
EPA estimate																	
Burr 2003 UK	1571	EPA 2.11-2.65 g/wk	1543	EPA 0.12-0.17 g/wk	5	-	nd	-	nd	-	nd	-	nd	C	1	U	CVD II
Burr 1989 UK	1015	EPA 2.4 g/wk	1018	EPA 0.6g/wk (SD 0.7)	2	-	0.7 0.5-0.9	3.2	1.5 0.97-2.3	-	nd	-	nd	C	1	U	CVD II
ALA estimate																	
Singh 2002 India	499	Indo Mediterranean diet ALA 1.8 g/d	501	ALA 0.8 g/d	2	3.4	0.71 0.34-1.5	8.6	0.49 0.30-0.81	2.6	0.54 0.22-1.3	-	nd	C	3	U	CVD II
Leren 1966 Norway	406	Cholesterol-lowering diet ALA 1-1.9 g/d (soybean oil)	406	Usual diet	5	11	0.43 0.21-0.89	15	0.77 0.47-1.27	-	nd	-	nd	C	2	I	CVD II
DeLorgeril 1999 France	302	Cretan Mediterranean diet[1] ALA 1.9 g/d	303	Prudent diet[2] ALA 0.67 g/d	2.3	-	nd	8.3	0.32 0.15-0.70	1.3	0.11 0.01-2.1	59	0.53[3] 0.38-0.74	C	4	A	CVD II
Bemelmans 2002 Netherlands	109	ALA 6.3 g/d	157	ALA 1.0 g/d	2	-	nd	2.5	0.16 0.01-2.9	1.3	0.29 0.01-5.9	5.7	0.16 0.02-1.3	B	3	A	CVD I

[1]ALA = 0.84% daily energy = calculated from daily nutrient recorded on the final visit in 144 unselected consecutive experimental patients
[2] ALA = 0.29% daily energy = calculated from daily nutrient recorded on the final visit in 83 unselected consecutive control patients
[3] Total major and minor endpoints.
Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data

Characteristics of the diet and dietary advice trials. (Tables 3.22-3.23) Evidence for the effects of diet or dietary advice on CVD outcomes in populations known to have CVD was derived from 6 RCTs. About 4,000 patients were studied in the trials, and trial duration ranged from 2 to 5 years.

Two of the trials of diet and dietary advice were conducted among males from the [40,41]. The amount of omega-3 fatty acid consumption in these 2 trials can only be estimated. The methodological quality of the trials was poor (grade C) and the study populations were rated as CVD-II (relevant subgroups). Two other trials reported estimates of EPA intake. The weekly EPA consumption in the first of these trials was 0.6 g in the control group and 2.4 g in the intervention group. Weekly EPA consumption in the second trial was 0.12g in the control group and 2.7 g in the intervention group.

Four trials provided estimates of daily ALA consumption. In the control groups of these trials, estimated ALA consumption ranged from 0.67 g/d to 1 g/d. Estimated ALA intake of the intervention groups was at least double that of the control groups (range 1.8 g/d to 6.3 g/d[42 43-45]. The methodological quality of 3 of the 4 trials was poor (Grade C). The applicability of the trials ranged from CVD-I (highly applicable) to CVD-III (limited applicability). The subjects were mostly MI survivors or those at significant CVD risk. The study by Bemelmans et al. randomized patients in a factorial design to consume a margarine rich in ALA or LA, and to receive nutritional education or not [45]. The amount of margarine prescribed was not fixed, but instead was based on the participants' usual consumption patterns. The study by [44]was conducted among patients in India. Two-thirds of the participants were vegetarians, which limits the applicability of the study results to the US population.

Table 3.24 Association of estimates of fish consumption with all cause mortality, cardiovascular death, and myocardial infarction in prospective cohort studies (secondary prevention)

Author Year Location	N	Duration (year)	Dietary Assessment	Results: Fish consumption (amount or frequency) Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Erkkila 2003 Finland	415	5	4-day food record	0 / 1-57 / >57 g/d All cause mortality 1.0 / 0.50 / 0.37* CV Death 1.0 / 0.64 / 0.45 CAD death or MI 1.0 / 1.0 / 0.49	0.06 NS NS	+ + 0	B	CVD II

There was 1 prospective cohort study[46] (Table 3.24) in a CVD population that associated estimates of daily fish consumption with CVD outcomes. The methodological quality of this study was good (grade B). The study populations were rated as CVD-II (relevant subgroups). This study lasted 5 years and included 415 subjects with known coronary artery disease. A 4-day food record was used to assess the daily fish intake. Fish intake was divided into 3 categories: no intake, below medium consumption (57 g/d), and above medium consumption.

CVD Outcomes of Secondary Prevention Studies

Results from the secondary prevention studies are summarized by outcome, below.

All-cause mortality. Ten RCTs reported all-cause mortality (Tables 3.20-3.23). Of these, 4 [34-37] used omega-3 fatty acid supplements. The quality of the 4 studies was generally good (grade A or B).

The all-cause mortality rate for control groups in the 10 RCTs ranged from 3.6% to 9.8% over a period of 1 to 3.5 years of follow-up. The largest study [35] found significant reduction of all-cause mortality with a relative risk reduction of 21% over 2 to 3.5 years. The amount of omega-3 fatty acid used in the intervention arms of this study was 0.85 g/d of EPA+DHA.

The 2 largest diet/dietary advice trials [41,47] were both of poor quality (Grade C). In the first trial [47], the amount of omega-3 fatty acid in the diet in the intervention arms was 2.4g/week of EPA. This trial found a significant reduction of all-cause mortality with a relative risk of 27% [47]. However, the 10 year follow-up to this trial found no long-term benefit of fish advice in the same group of patients taking a similar amount of EPA [48].

Of the 4 diet/dietary advice trials that provided estimates of ALA consumption [42,43,44,45,] 3 found significant or near-significant reduction of all-cause mortality with a relative risk reduction of 25% to 56% over 2 to 5 years. The quality of these studies were fair to poor (grade B or C). The amount of omega-3 fatty acid in the diet in the intervention arms data ranged from about 1 to 6.3 g/d of ALA. Because these trials were interventions based on diet, the daily variations in the amount of omega-3 fatty acids would make the interpretations of their results difficult.

The single prospective cohort study (Table 3.24) compared subjects who consumed fish to those who did not and reported an at least 50% relative risk reduction in all-cause mortality and CVD death with any amount of fish intake [46].

Sudden death. (Tables 3.20, 3.22, 3.25). Six RCTs reported data on sudden deaths Four studies [35 38,43,44] Singh reported a significant or near-significant large reduction of this outcome (relative risk [RR] 0.06 to 0.55). The reduction of sudden deaths in these studies was observed in both the fish oil group and the ALA oil group. However, of the 4 studies, 3 (a Mediterranean diet study [43] and 2 Indian studies [38,44]) were poorly designed (grade C).

An early trial by Leren [42] randomized 206 men 1-to-2-years post-MI to a cholesterol lowering diet and followed them for 5 years. There were no differences between subjects on the diet and those in the control group. However, a new report by Burr et al [41] found that persons taking fish oil supplements have an increased risk of sudden death risk, although this study is also of poor quality (grade C).

Stroke. (Tables 3.21, 3.23, 3.26). Six trials reported data on stroke Strokes occurred in 0% to 3% of subjects in control groups. Three of the trials [34,35,37] were of fish oil supplements; the methodological quality of these trials was generally good (2 studies of grade B and 1 study of grade A) and each reported trends of increased strokes. However, the 3 diet/dietary advice trials [43 44,45] (which were of poor quality 2 studies of grade C and of 1 grade B) reported trends of fewer strokes. None of the results from the 6 studies were statistically significant.

Other CVD outcomes. One study consistently reported no beneficial effect of omega-3 fatty acids on any CVD outcomes (Tables 3.20 and 3.22) [36]. This study randomized 300 patients to 1.7 g/d of EPA+DHA or an equivalent amount of corn oil and followed subjects for 1.5 years. Of

note, 15% of the study subjects died during the study, and about 40% of the subjects had been taking fish oil before the trial.

Three of the RCTs were too small, with 59 and 120 subjects each[34,37], or had too few CVD events[45] to provide meaningful results.

Reports of other outcomes, such as CVD deaths, cardiac deaths, sudden death, fatal and non-fatal MI, were inconsistently reported. The overall beneficial results were similar across studies.

Table 3.25 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: all cause mortality, CVD death, cardiac death, sudden death (Primary intervention)

Author Year Country	Omega -3 Fatty acid		Control		Duration (year)	All cause mortality		CVD death		Cardiac death		Sudden death		Quality			Applicability
	N	Type Dose	N	Type Dose		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
ALA																	
Natvig 1968 Norway	6716	Linseed oil ALA 5.5 g/d	6690	Sunflower seed oil ALA 0.14 g/d	1	0.6	1.1 0.7-1.6	-	nd	0.4	1.0 0.58-1.7	-	nd	C	4	A	GEN II

Table 3.26 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: myocardial infarction, stroke, all CVD events (Primary intervention)

Author Year Country	Omega -3 Fatty acid		Control		Duration (year)	Fatal MI		Non-fatal MI		All strokes		All CVD events		Quality			Applicability
	N	Type Dose	N	Type Dose		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
ALA																	
Natvig 1968 Norway	6716	Linseed oil ALA 5.5 g/d	6690	Sunflower seed oil ALA 0.14 g/d	1	All MI 0.8	All MI 1.2 (0.84-1.7)			0.13	1.4 0.62-3.4	-	nd	C	4	A	GEN II

Table 3.27 Association of estimates of omega-3 fatty acid consumption with all cause mortality in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results[1] Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)	Trend P-value[2]	Overall effect	Quality	Applicability
Nagata 2002 Japan	29079	7	FFQ	EPA+DHA Men 0.41 0.6 0.79 1.1 1.6 g/d Hazard ratio 1.0 0.82* 0.87 0.88 0.87 Women 0.33 0.49 0.64 0.83 1.3 g/d Hazard ratio 1.0 0.92 0.84 0.90 0.77*	NS 0.01	+ +	A	GEN II
Yuan 2001 China	18244	12	FFQ	EPA+DHA 0.15 0.38 0.65 0.91 1.7 g/wk 1.0 0.79* 0.76* 0.86* 0.79*	0.01	+ +	A	GEN II
Dolecek 1992 US **MRFIT**	6250	10.5	Multiple 24-hr recall	ALA 0.87 1.3 1.6 1.9 2.8 g/d 1.0 0.96 0.69 0.89 0.69 EPA+DHA 0.0 0.009 0.046 0.15 0.66 g/d 1.0 1.1 1.0 0.85 0.76	0.014 0.01	+ +	A	GEN II

The footnotes and abbreviations below apply to summary tables 3.27– 3.39 in this section.

[1] Adjusted results are presented here when reported in original study. See evidence tables for details.
[2] Trend for inverse association. Up arrow indicates a statistically significant positive association (worse outcome).
* Statistically significant p<0.05; numerical p-value reported for p<0.1.

Study acronyms:

ABCC = Alpha-Tocopherol Beta-Carotene Cancer Prevention
ADVENTIST = Adventist Health Study
CHS = Cardiovascular Health Study
HPS = Health Professionals Study
MRFIT = Multiple Risk Factor Intervention Study
NHANES = National Health and Nutrition Examination Study
NHS = Nurses' Health Study
PHS = Physicians' Health Study
WES = Western Electric Company Study

Table 3.28 Association of estimates of fish consumption with all cause mortality in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Fish consumption (amount or frequency) Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Nagata 2002 Japan	29079	7	FFQ	Men 46 68 87 112 158 g/d Hazard ratio 1.0 0.92 0.91 0.90 0.94 Women 37 54 69 88 122 g/d Hazard ratio 1.0 0.93 0.96 0.93 0.86	NS	0	A	GEN II
Albert 1998 US **PHS**	20551	12	FFQ	<1/mo 1-3/mo 1-<2/wk 2-<5/wk =5/wk 1.0 0.79 0.71* 0.70* 0.73*	0.045	+ +	A	GEN II
Yuan 2001 China	18244	12	FFQ	<50 50-100 100-150 150-200 =200 g/wk 1.0 0.79* 0.76* 0.86* 0.79*	0.01	+ +	A	GEN II
Mann 1997 **UK**	10802	13.3	FFQ	0 <1 =1 /wk Death rate ratio 100 97 96	NS	0	B	GEN II
Gillum 2000 US **NHANES**	8825	18.8	FFQ + 24-hr recall	Never <1 1 >1 /wk White Men 1.0 0.88 0.76* 0.85 Black Men 1.0 1.0 1.0 1.1 White Women 1.0 1.0 1.0 0.90 Black Women 1.0 0.77 0.79 0.82	0.01 NS nd nd	+	B	GEN I
Osler 2003 Denmark	8497	18	FFQ	=1/mo 2/mo 1/wk >2/wk Hazard ratio 0.88 0.84* 1.0 (ref) 1.1	0.02 -	–	B	GEN I
Daviglus 1997 US **WES**	1822	30	FFQ	0 1-17 18-34 =35 g/d 1.0 1.02 0.98 0.85	NS	0	A	GEN II
Fraser 1997 US **Adventist**	603	12	FFQ	>84 years old subset of Adventist Health Study <1/wk >1/wk Hazard ratio 1.0 0.98	NS	0	B	GEN III
Kromhout 1995 Holland	272	17	CCD	Non-fish eaters Fish Eaters (24 g/d) 1.0 0.96	NS	0	C	GEN II

Table 3.29 Association of estimates of omega−3 fatty acid consumption with cardiovascular death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Nagata 2002 Japan	29079	7	FFQ	Quintiles (amount not reported) Men 1.0 0.74 0.71 0.82 0.76 Hazard Women 1.0 0.82 0.79 0.86 0.77* ratio	NS NS	+	A	GEN II
Dolecek 1992 US **MRFIT**	6250	10.5	Multiple 24-hr recall	ALA 0.87 1.3 1.6 1.9 2.8 g/d 1.0 0.89 0.64 0.83 0.6 EPA+DHA 0.0 0.009 0.046 0.15 0.66 g/d 1.0 1.06 0.92 0.92 0.59	0.067 0.004	+ +	A	GEN II

Table 3.30 Association of estimates of fish consumption with cardiovascular death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Fish consumption (amount or frequency) Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Albert 1998 US **PHS**	20551	11	FFQ	<1/mo 1-3/mo 1-<2/wk 2-<5/wk =5/wk 1.0 0.96 0.79 0.84 0.81	NS	+	A	GEN II
Gillum 2000 US **NHANES**	8825	***18.8***	FFQ + 24-hr recall	Never <1 1 >1 /wk White men 1.0 0.98 0.87 0.95 Black men 1.0 0.96 0.99 1.1 White women 1.0 1.1 1.1 1.1 Black women 1.0 0.85 0.94 0.99	NS NS nd nd	0	B	GEN II
Daviglus 1997 US **WES**	1822	30	FFQ	0 1-17 18-34 =35 g/d 1.0 0.94 0.89 0.74	0.01	+ +	A	GEN II

Table 3.31 Association of estimates of omega−3 fatty acids with cardiac death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Pietinen 1997 Finland **ABCC**	21930	6.1	FFQ	ALA 0.9 1.2 1.5 1.9 2.5 g/d 1.0 0.94 0.98 1.03 0.99 EPA+DHA 0.2 0.3 0.4 0.5 0.8 g/d 1.0 0.94 1.0 1.1 1.3	NS	0	A	GEN II
Dolecek 1992 US **MRFIT**	6250	10.5	Multiple 24-hr recall	ALA 0.87 1.3 1.6 1.9 2.8 g/d 1.0 0.98 0.57 0.98 0.68 EPA+DHA 0 0.009 0.046 0.15 0.66 g/d 1.0 1.1 0.91 0.88 0.60	NS 0.01	+ +	A	GEN II

Table 3.32 Association of estimates of fish consumption with cardiac death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Fish consumption (amount or frequency) Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Hu 2002, US **NHS**	84688	16	FFQ	<1/mo 1-3/mo 1/wk 2-4/wk >5/wk 1.0 0.80 0.65* 0.72 0.55*	0.01	+ +	A	GEN II
Ascherio 1995, US **HPS**	44895	6	FFQ	*1-3/mo 1/wk 2-3/wk 4-5/wk >6/wk* *0.74 0.86 0.71 0.54* 0.77*	NS	+	A	GEN II
Egeland 2001 Norway	42612	7	Dietary quest-ionnaire	None Cod liver oil Never smoker Hazard ratio 1.0 0.7 Current smoker 1.0 0.8	NS	+	C	GEN II
Fraser 1997, US **Adventist**	26743	6	FFQ	0 <1/wk >1/wk Hazard ratio 1.0 1.1 0.74	nd	0	B	GEN II
Albert 1998, US **PHS**	20551	11	FFQ	<1/mo 1-3/mo 1-<2/wk 2-<5/wk =5/wk 1.0 1.18 0.82 0.91 0.81	NS	+	A	GEN II
Mann 1997 UK	10802	13.3	FFQ	0 <1 =1 /wk Death Rate Ratio 100 121 123	NS	–	B	GEN II
Rodriguez 1996 US **Honolulu**	8006	23	Dietary quest-ionnaire	Cigarettes/d < 2/wk =2/wk Fish consumption <20 0.30 0.42 20-30 0.38 0.45 >30 1.0 0.50*	NS NS nd	+	C	GEN II
Osler 2003 Denmark	8497	18	FFQ	=1/mo 2/mo 1/wk >2/wk Hazard ratio 1.1 0.98 1.0 (ref) 0.98	NS	0	B	GEN I
Mozaffarian 2003 US **CHS**	3910	9.3	FFQ	Tuna/other fish <1/mo 1-3/mo 1/wk 2/wk >3/wk Total IHD death 1.0 0.78 0.77 0.53* 0.47* Fried fish/sand. <1/mo 1-3/mo 1/wk 2/wk >3/wk Total IHD death 1.0 1.2 1.6 1.1 1.4 Hazard ratios	0.002 NS	+ + –	A	GEN II
Oomen 2000 Finland Italy Holland	2738	20	CCD	1-19 20-39 >40 g/d Total fish 0.93 0.95 1.1 Fatty fish 0.57* 0.87(=20 g/d)	NS	+	A	GEN II
Daviglus 1997, US **WES**	1822	30	FFQ	0 1-17 18-34 =35 g/d 1.0 0.88 0.84 0.62*	0.04	+ +	A	GEN II
Kromhout 1985 Holland	852	20	CCD	0 1-14 5-29 30-44 45 g/d 1.0 0.64 0.56 0.36* 0.39	nd	+	B	GEN II
Kromhout 1995 Holland	272	17	CCD	No fish Fish eater 1.0 0.51*	nd	+	C	GEN I

Table 3.33 Association of estimates of omega−3 fatty acids with sudden death in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Prospective cohort								
Albert 1998 US **PHS**	20551	12	FFQ	EPA+DHA <0.3 0.3-2.7 2.7-4.9 4.9-7.4 >7.4 g/mo 1.0 0.58 0.34* 0.60 0.43*	NS	+ +	A	GEN II
Case control								
Siscovick 1995 US	827	na	FFQ	EPA+DHA 0 0.96 2.9 5.5 13.7 g/mo Odds ratio 1.0 0.9* 0.7* 0.5* 0.4*	ND	+ +	A	GEN I

Table 3.34 Association of estimates of fish consumption with sudden death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Fish consumption (amount or frequency) Relative risk	Trend P-value	Overall effect	Quality	Applicability
Albert 1998 US **PHS**	20551	12	FFQ	<1/mo 1-3/mo 1-2/wk 2-5/wk =5/wk 1.0 0.64 0.47* 0.51 0.39*	NS	+ +	A	GEN II
Daviglus 1997 US **WES**	1822	30	FFQ	0 1-17 18-34 =35 g/d 1.0 0.78 0.80 0.68	NS	+	A	GEN II

Table 3.35 Association of estimates of omega-3 fatty acids consumption with myocardial infarction in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Prospective cohort								
Hu 2002 Hu 1999 US **NHS**	84688	16	FFQ	EPA+DHA Median intake (% energy) 0.03 0.05 0.08 0.14 0.24 Nonfatal MI 1.0 0.92 0.83 0.75* 0.69*	<0.001	+ +	A	GEN II
		10		ALA Median intake g/d 0.71 0.86 0.98 1.12 1.36 Fatal IHD 1.0 0.99 0.90 0.67 0.55* Non-fatal MI 1.0 0.92 0.94 1.02 0.85	0.001 0.05	+ +		
Ascherio 1995 US **HPS**	44895	6	FFQ	EPA+DHA <0.11 0.12-0.19 0.20-0.28 0.29-0.41 >0.42 g/d Total MI 1.0 1.0 0.92 0.86 1.1 Nonfatal MI 1.0 0.93 0.89 0.78 1.1	NS NS	+	A	GEN II
Morris 1995 US **PHS**	21185	4	FFQ	EPA+DHA <0.05 0.5-<1.0 1.0-<1.7 1.7-<2.3 >2.3 g/wk Total MI 1.0 1.6 1.4 1.2 1.2 Nonfatal MI 1.0 1.5 1.3 1.2 1.1	NS	–	A	GEN II
Yuan 2001 China	18244	12	FFQ	EPA+DHA <0.27 0.27-0.43 0.44-0.72 0.73-1.1 >1.1 g/wk Fatal MI 1.0 0.39* 0.67 0.53* 0.43*	0.02	+ +	A	GEN II
Oomen 2001 Holland	67	0	CD	ALA (% energy) <0.45 0.45-0.58 >0.58 Fatal and nonfatal CAD 1.0 1.5 1.7 Fatal CAD 1.0 0.99 1.6	NS NS	–	B	GEN III
Case control								
Tavani 2001 Italy	975	na	FFQ	EPA+DHA <0.81 0.81-1.28 >1.28 g/wk Nonfatal MI odds ratio 1.0 0.71* 0.67*	0.03	+ +	B	GEN II

Table 3.36 Association of estimates of fish consumption with myocardial infarction in prospective cohort and case control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Fish consumption (amount or frequency) Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Prospective cohort								
Hu 2002 **NHS**	84688	16	FFQ	1-3/mo 1/wk 2-4/wk >5/wk Nonfatal MI 0.78* 0.74* 0.68* 0.73	0.03	+ +	A	GEN II
Ascherio 1995 US **HPS**	44895	6	FFQ	<1/mo 1-3/mo 1/wk 2-3/wk 4-5/wk >6/wk 0 7 18 37 69 119 g/d MI 1.0 0.66* 0.82 0.69* 0.65* 0.90 Nonfatal MI 1.0 0.62* 0.80 0.67* 0.69 0.96	NS NS	+ +	A	GEN II
Fraser 1992a US **Adventist**	26743	6	FFQ	0 <1 >1 /wk Nonfatal MI 1.0 1.0 1.04	NS	0	B	GEN II
Albert 1998 US **PHS**	20551	11	FFQ	<1/mo 1-3/mo 1-2/wk 2-5/wk >5/wk All MI 1.0 0.91 0.99 1.0 1.0	NS	0	A	GEN II
Yuan 2001 China	18244	12	FFQ	<50 50-100 100-150 150-200 =200 g/wk Fatal MI 1.0 0.55* 0.65 0.66 0.41*	0.03	+ +	A	GEN II
Mozaffarian 2003 US **CHS**	3910	9.3	**FFQ**	Tuna/other fish 1-3/m 1/wk 2/wk >3/wk Nonfatal MI 0.81 0.71 0.75 0.67 Fried fish/sandwich 1-3/m 1/wk 2/wk >3/wk Nonfatal MI 1.3 1.6 1.2 1.9 Hazard ratio	0.10 NS	+ –	A	GEN II
Daviglus 1997 US **WES**	1822	30	FFQ	0 1-17 18-34 =35 g/d All MI 1.0 0.88 0.76 0.56*	0.017	+ +	A	GEN II
Case control								
Tavani, 2001 Italy	975	na	FFQ	<1 1-<2 ≥2 /wk Nonfatal MI odds ratio 1.0 0.79 0.67*	0.02	+ +	B	GEN II
Sasazuki 2001 Japan	1846	na	FFQ	<2 2-3 >4 /wk Nonfatal MI odds ratio Men 1.0 0.6* 0.7* Women 1.0 0.8 1.3	NS 0.09	+	B	GEN II

Table 3.37 Association of estimates of omega-3 fatty acid consumption with stroke in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Assessment	Results Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Prospective cohort								
Iso 2001 US **NHS**	79839	14	FQ	EPA+DHA 0.077 0.12 0.17 0.22 0.48 g/d Ischemic 1.0 0.83 0.67* 0.82 0.71 Hemorrhagic 1.0 0.94 0.66 0.93 0.76	NS NS	+	A	GEN II
He 2002 US **HPS**	43671	12	FQ	EPA+DHA <0.05 0.05-<0.2 0.2-0.4 0.4-<0.6 >0.6 g/d Ischemic 1.0 0.56* 0.63* 0.54* 0.73 Hemorrhagic 1.0 1.3 1.0 0.89 1.1	NS NS	+ +	A	GEN II
Morris 1995 US **PHS**	21185	4	FQ	EPA+DHA <0.5 0.5-<1.0 1.0-<1.7 1.7-<2.3 >2.3 g/wk All strokes 1.0 0.9 1.1 0. 7 1.0	NS	0	A	GEN II
Yuan 2001 China	18244	9	FFQ	EPA+DHA <0.26 0.27-0.43 0.44-0.72 0.73-1.1 ≥1.1 g/wk Fatal strokes 1.0 0.76 0.76* 0.93 1.0	NS	+	A	GEN II
Seino 1997 Japan	2283	15.5	FFQ	n-3 fatty acid 1.8 2.3 2.7 3.2 g/d Ischemic stroke 1.0 0.99 1.6 1.4	NS	–	B	GEN II
Case control								
Caicoya 2002 Spain	913	na	FQ	EPA+DHA <0.12 0.12-0.32 0.32-0.66 >0.66 g/d All strokes odds ratio 1.0 1.1 1.4 1.8	0.01 -	–	A	GEN II

.

Table 3.38 Association of estimates of fish consumption with stroke in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results Fish consumption (amount or frequency) Relative risk (unless stated otherwise)	Trend P-value	Overall effect	Quality	Applicability
Prospective cohort								
Kinjo 1999 Japan	223170	15	1-page quest-ionnarie	>1 1-3 ≥4 /wk Ischemic deaths 1.0 1.05 0.99 Hemorrhagic deaths 1.0 1.02 0.87*	nd nd	0	C	GEN II
Iso 2001 US **NHS**	79839	14	FQ	<1/m 1-3/m 1/wk 2-4/wk >5/wk Ischemic 1.0 0.83 0.69 0.63 0.38 Hemorrhagic 1.0 1.4 1.1 0.93 1.0	0.09 NS	+	A	GEN II
He 2002 US **HPS**	43671	12	FQ	<1/mo 1-3/mo 1/wk 2-4/wk >5/wk Ischemic 1.0 0.57* 0.56* 0.55* 0.54* Hemorrhagic 1.0 1.8 1.4 0.96 1.6	NS NS	+ +	A	GEN II
Morris 1995 US **PHS**	21185	4	FFQ	<1 1 2-4 >5 /wk Non-fatal strokes 1.0 1.3* 1.1 0.9	NS	–	A	GEN II
Yuan 2001 China	18244	9	FQ	<50 50-100 100-150 150-200 =200 g/wk Fatal strokes 1.0 0.93 0.79 1.01 1.11	NS	0	A	GEN II
Gillum 1996 US **NHANES**	5192	12	FFQ	Ischemic stroke 0 <1 1 >1 /wk Women aged 45-74 1.0 0.78 0.77 0.55* Men aged 45-74 1.0 1.3 1.2 0.85 Black men+women Never fish some fish Stroke incidence 1.0 0.51* Stroke death 1.0 0.26*	nd na	+	B	GEN I
Orencia 1996 USA **WES**	1847	30	FFQ / 24-hr recall	0 1-17 18-34 >35 g/d All strokes 1.0 0.94 0.89 1.3 Hazard ratio	NS	0	A	GEN II
Keli 1994 Holland	872	15	CCD	6.3 (<20) 35.4 (≥20) g/d All strokes 1.0 0.49 Hazard ratio	0.06	+	B	GEN II
Case control								
Caicoya 2002 Spain	913	na	FFQ	Total 0 1-22.5 23-45 46-90 >91 g/d Odds ratio 1.0 0.30* 0.44 0.59 0.76 Ischemic 0-11.2 11.3-28.7 28.8-46.5 >46.5 g/d Odds ratio 1.0 1.1 0.90 2.0	nd 0.08 -	+ –	A	GEN II

Table 3.39 Association of estimates of omega-3 fatty acid consumption with all CVD events in cross-sectional study

Author Year Location	N	Duration (year)	Dietary Assessment	Results Estimated omega-3 fatty acid consumption Prevalence odds ratio for all CVD events	Trend P-value	Overall effect	Quality	Applicability
Djousse 2001 US	40 6	n.a	FQ	ALA 0.53 0.67 0.78 0.90 1.1 g/d men 1.0 0.77 0.61* 0.58* 0.60* ALA 0.46 0.58 0.65 0.76 0.96 g/d women 1.0 0.57 0.52 0.30* 0.42*	0.012 0.014	+ +	B	GEN I

Primary Prevention Studies (Tables 3.25-3.39)

Evidence for the effects of the consumption of omega-3 fatty acids, omega-3 fatty acid supplements, or fish on CVD outcomes in the general population is derived from 22 prospective cohort studies, 4 case-control studies, 1 cross-sectional study, and 1 RCT. The methodological quality of most of the studies within their study design category was good (grades A or B); 4 prospective cohort studies were graded as poor (grade C).

We found only 1 RCT that examined omega-3 fatty acid supplements in the general population. (Tables 3.25-3.26) The methodological quality of this study was poor (grade C). The study, which compares linseed oil (5.5 g/d of ALA) with sunflower seed oil (0.14 g/d ALA), was conducted in Norway more than 30 years ago[49] and lasted 1 year. It is the largest of all ALA supplement trials, with over 13,000 subjects. Presumably, subjects had high background omega-3 fatty acid levels because of characteristically large consumption of fish. There were too few all-cause mortality or CVD events in the control group, and it reported no benefit on any of the CVD outcomes. This trial does not contribute substantively to the assessment of the effect of omega-3 fatty acid supplements on CVD outcomes. The major conclusion one can draw from this study is that ALA, given at a dose of 0.14 g/d for 1 year, has no effect on CVD outcomes in the general population with a high fish consumption background diet.

The 22 prospective cohort studies were conducted in many parts of the world, including the US, China, Japan, and countries in the Mediterranean and Northern Europe. Most of the cohorts had several thousand subjects. The majority of the studies received an applicability grade of GEN-II, reflecting either relevant subgroups or differences in the background diet of the study population when compared with the US population. Several of the large population studies conducted in the US were graded as GEN-II because of single sex (male or female) cohorts. If viewed together, however, these studies would provide evidence that is highly applicable to the US population (GEN-I). Study duration in the cohort studies ranged from 4 to 30 years. The number of subjects followed in the cohorts ranged from 272 to as many as 223,170; many of the cohorts had tens of thousands of study subjects.

Most of the studies used the food frequency questionnaire to estimate the dietary fish intake. Most studies provided quantitative estimates of the amount of fish consumed (many also quantified the amount of EPA+DHA intake) and categorized them into various quantiles (e.g.,

tertiles, quartiles, quintiles), although some studies reported only the frequency of fish consumption or simply whether fish was consumed.

CVD Outcomes of Primary Prevention Studies

Results from the primary prevention studies are summarized by outcome, below.

All-cause mortality. Ten studies that followed a total of about 100,000 subjects for an average of over 10 years provided data on all-cause mortality.(Tables 3.27-3.28) Three of the 10 studies provided estimates of fish oil intake, and 9 provided estimates of fish consumption. The studies were conducted in the US, China, Japan, Denmark, Holland, and the UK. All 3 studies that provided estimates of fish oil intake reported a significant reduction (++ overall effect) of all-cause mortality [50-52]. The results of studies reporting estimates of fish intake were heterogeneous — 1 study [53]reported a small but significant increase of all-cause mortality with increasing fish intake, and 5 studies found no benefit [50,54-57]. Of the studies finding no benefit, 1 (by Nagata et al.) reported no benefit using estimates of fish consumption but observed beneficial results using estimates of fish oil. One study showed significant benefit[58], and 1 study showed a trend for benefit[59].

CVD deaths, cardiac deaths, and MI. The outcomes of CVD deaths (Tables 3.29-3.30), cardiac deaths (Tables 3.31-3.32), and MI (Tables 3.35-3.36) were similar. Most of the large cohort studies reported significant reduction of clinical events. Among the large cohort studies, only the Physicians' Health Study (PHS) failed to report a significant beneficial effect of fish consumption [58].

Sudden death. Two prospective cohort studies reported data on sudden death. (Tables 3.33-3.34). These studies provided estimates of both fish and fish oil consumption. The Physicians' Health Study, which followed 20,551 subjects for 12 years, reported an approximately 50% overall relative risk reduction even with a small amount of fish intake (>0.3 g of fish oil per month or eating fish once a month)[58]. A smaller study also found a significant reduction of arrhythmic deaths at higher levels of fish intake [60]. However, in the same study opposite results were seen with consumption of fried fish or fish sandwiches[60]. Another smaller follow-up study of 30 years duration found a significant trend of reduction in sudden death [56]. A case-control study of 827 subjects in the US also reported a significant inverse association of sudden death with increasing fish intake[61].

Stroke. Nine prospective cohort studies and 1 case-control study provided data on stroke. (Tables 3.37-3.38) Five of the cohort studies estimated the amount of fish oil consumed, and 8 estimated fish intake. These studies included the large US cohorts of the Nurses' Health Study (NHS)[62], Health Professionals Study (HPS) [63], and the Physicians' Health Study [64], which followed subjects for 14, 12, and 4 years, respectively. Together, these 3 studies comprised a total of about 145,000 men and women. Only the Health Professionals Study[63]reported a significant reduction of ischemic strokes with any level of fish consumption above the lowest quintile. In the Nurses' Health Study [62], there was a non-significant trend of decreased strokes with increasing fish consumption. Other studies showed a weak benefit, no benefit, or an increased risk of strokes. The fish oil estimates and fish estimates yielded similar results.

Table 3.40 Association of estimates of omega-3 fatty acid consumption with all cause mortality in prospective cohort studies of general population (based on data in Table 3.27)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**			
	II	Study Year N Effect Nagata 2002 29079 ++ Yuan 2001 18244 ++ MRFIT 1992 6250 ++		
	III			

Table 3.41 Association of estimates of fish consumption with all cause mortality in prospective cohort studies of general population (based on data in Table 3.28)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**		**Study Year N Effect** NHANES 2000 8825 + Osler 2003 8487 -	
	II	Study Year N Effect Nagata 2002 29079 0 PHS 1998 20551 ++ Yuan 2001 18244 ++ WES 1997 1822 0	Study Year N Effect Mann 1997 10802 0	Study Year N Effect Kromhout 1995 272 0
	III		Study Year N Effect Adventist 1997 603 0	

Study acronyms (apply to tables 3.40-3.51):

ABCC = Alpha-Tocopherol Beta-Carotene Cancer Prevention
ADVENTIST = Adventist Health Study
CHS = Cardiovascular Health Study
HPS = Health Professionals Study
MRFIT = Multiple Risk Factor Intervention Study
NHANES = National Health and Nutrition Examination Study
NHS = Nurses' Health Study
PHS = Physicians' Health Study
WES = Western Electric Company Study

Table 3.42 Association of estimates of omega-3 fatty acid consumption with cardiovascular death in prospective cohort studies of general population (based on data in Table 3.29)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**			
	II	Study Year N Effect Nagata 2002 29079 + MRFIT 1992 6250 ++		
	III			

Table 3.43 Association of estimates of fish consumption with cardiovascular death in prospective cohort studies of general population (based on data in Table 3.30)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**			
	II	Study Year N Effect PHS 1998 20551 + WES 1997 1822 ++	Study Year N Effect NHANES 2000 8825 0	
	III			

Table 3.44 Association of estimates of omega-3 fatty acid consumption with cardiac death in prospective cohort studies of general population (based on data in Table 3.31)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**			
	II	Study Year N Effect ABCC 1997 21930 0 MRFIT 1992 6250 ++		
	III			

Table 3.45 Association of estimates of fish consumption with cardiac death in prospective cohort studies of general population (based on data in Table 3.32)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**		Study Year N Effect Osler 2003 8497 0	**Study Year N Effect** Kromhout 1985 272 +
	II	Study Year N Effect NHS 2002 84688 ++ HPS 1995 44895 + PHS 1998 20551 + CHS 2003 3910 ++ Oomen 2000 2738 + WES 1997 1822 ++	Study Year N Effect Adventist 1997 26743 0 Mann 1997 10802 - Kromhout 1985 852 +	Study Year N Effect Egeland 2001 42612 + Honolulu 1996 8006 +
	III			

Table 3.46 Association of estimates of omega-3 fatty acid consumption with sudden death in prospective cohort studies of general population (based on data in Table 3.33)

		Methodological Quality		
		A	B	C
Applicability	I			
	II	Study Year N Effect PHS 1998 20551 ++ CHS 2003 3910 +		
	III			

Table 3.47 Association of estimates of fish consumption with sudden death in prospective cohort studies of general population (based on data in Table 3.34)

		Methodological Quality		
		A	B	C
Applicability	I			
	II	Study Year N Effect PHS 1998 20551 ++ CHS 2003 3910 +		
	III			

Table 3.48 Association of estimates of omega-3 fatty acid consumption with myocardial infarction in prospective cohort studies of general population (based on data in Table 3.35)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**			
	II	Study Year N Effect NHS[1] 2002 84688 ++ HPS 1995 44895 + PHS 1995 21185 - Yuan 2001 18244 ++		
	III		Study Year N Effect Oomen 2001 667 -	

[1] Nurses' Health Study analysis using fish oil (EPA+DHA) published in 2002 and analysis using ALA published in 1999 both reported significant beneficial effect on myocardial infarction.

Table 3.49 Association of estimates of fish consumption with myocardial infarction in prospective cohort studies of general population (based on data in Table 3.36)

		Methodological Quality		
		A	**B**	**C**
Applicability	**I**			
	II	Study Year N Effect NHS 2002 84688 ++ HPS 1995 44895 ++ PHS 1998 20551 0 Yuan 2001 18244 ++ CHS 2003 3910 + WES 1997 1822 ++	Study Year N Effect Adventist 1992 26743 0	
	III			

Table 3.50 Association of estimates of omega-3 fatty acid consumption with stroke in prospective cohort studies of general population (based on data in Table 3.37)

		Methodological Quality		
		A	B	C
Applicability	I			
	II	Study Year N Effect NHS 2001 79839 + HPS 2002 43671 ++ PHS 1995 21185 0 Yuan 2001 18244 +	Study Year N Effect Seino 1997 2283 -	
	III			

Table 3.51 Association of estimates of fish consumption with stroke in prospective cohort studies of general population (based on data in Table 3.38)

		Methodological Quality		
		A	B	C
Applicability	I			
	II	Study Year N Effect NHS 2001 79839 + HPS 2002 43671 ++ PHS 1995 21185 - Yuan 2001 18244 + WES 1996 1847 0	Study Year N Effect NHANES 1996 5192 + Keli 1994 872 +	Study Year N Effect Kinjo 1999 223710 0
	III			

Answers to Specific Key Questions

Many of the questions noted below ask about the efficacy of omega-3 fatty acids on CVD outcomes. Efficacy has been defined in an Institute of Medicine report as "what a method can accomplish in expert hands when correctly applied to an appropriate patient."[65]. This is generally interpreted as treatment effect assessed in controlled trial settings. Comparative efficacy among different omega-3 fatty acids can only be assessed reliably within the same or across similarly designed RCTs. Similarly, the comparative effects of omega-3 fatty acids on different subpopulations or different CVD outcomes should be assessed with subgroups within the same trial or across similarly designed RCTs. However, due to the limited availability of RCTs, we

also used prospective cohort studies to answer these questions. Because of the heterogeneity of study design, populations, and settings across the RCTs, and the observational nature of prospective cohort studies, the answers presented here should be interpreted with caution.

What is the efficacy or association of omega-3 fatty acids (DHA, EPA or ALA supplements, and fish consumption) in reducing CVD events (including all-cause mortality, CVD mortality, non-fatal CVD events, and new diagnosis of CVD)?

- *What is the efficacy or association of omega-3 fatty acids in preventing incident CVD events in people without known CVD (primary prevention) and with known CVD (secondary prevention)?*

  One RCT and 22 prospective cohort studies provided data on primary prevention. Among the cohort studies, there were considerable differences among the populations studied and in the estimates of fish or omega-3 fatty acids consumed. Most of the large cohort studies found fish consumption was associated with lower rates of all-cause mortality and CVD events, but several studies reported no significant or negative results for the CVD outcomes. A significant benefit for stroke was reported in 1 study. The single poor-quality RCT, which evaluated ALA in a large general population, lasted only 1 year and yielded no significant results.

  Eleven RCTs and 1 prospective cohort study provided data on secondary prevention. The largest trial reported that fish oil (EPA + DHA) reduces all-cause mortality and CVD events, although it has no effect on stroke. Most other studies evaluating either fish oil or ALA supplements reported similar findings. All the ALA studies were of poor quality and provided weak conclusions.

  These studies were also summarized in previous sections.

- *How does the efficacy or association of omega-3 fatty acids in preventing incident CVD events differ in sub-populations, including men, pre-menopausal women, post-menopausal women, and different age groups?*

  There were no subgroup data from RCTs to address this question. In addition, the proportion of women in these RCTs was small.

  Four cohort studies and 1 case-control study reported data from men and women separately. Overall, no consistent difference in the association of omega-3 fatty acids and CVD outcomes was found between men and women. A report of NHANES I that separately analyzed data for men and women found a trend of decreased stroke with increasing fish consumption for women between ages 45 and 74, but did not find a similar trend for men [66]. The Adventist Health Study did not find a beneficial effect of fish intake on all-cause or coronary disease mortality after grouping subjects into those who ate fish less than once a week and those who ate fish more frequently, and the study found no differences between men and women [67]Osler et al. followed 4,007 men and 3,533 women in Denmark for 18 years. The authors did not find an inverse

association between fish consumption and all-cause mortality or the incidence of coronary heart disease, and trends observed in men and women were not consistently different [53]. Nagata et al. followed a cohort of 13,355 men and 15,742 women in Japan for 7 years. The relationship of soy products and fish intake to all-cause mortality and CVD were evaluated [50]. The association between soy intake and all-cause mortality was significant in women (trend $P = 0.04$) and marginally significant (trend $P = 0.07$) in men. The association between fish oil intake and all-cause mortality was significant for women (trend $P = 0.01$) and non-significant for men (trend $P = 0.38$). A cross-sectional study reported that ALA intake was inversely associated with the prevalence odds ratio of coronary artery disease using age and energy-adjusted quintiles of ALA [68]. Signifcant trends were found for men and women after adjusting for multiple variables.

The Nurses' Health Study, a large prospective cohort study of women, reported no subgroup analyses based on menopausal status or age groups[69] [62]. The Adventist Health Study examined a subgroup of 603 oldest old (≥84 years old) subjects and found no difference in all-cause mortality between those consuming fish less than once a week and those consuming fish more than once a week [57].

- *What are the effects of potential confounders — such as lipid levels, body mass index (BMI), blood pressure, diabetes, aspirin use, hormone replacement therapy, and cardiovascular drugs — on associations found in prospective cohort studies?*

Most prospective cohort studies report multivariate adjusted results, but few studies report results adjusted for individual potential confounders. Iso et al. analyzed subgroups of women in the Nurses' Health Study who took aspirin regularly vs those who did not [62]. Stroke events were reduced in both groups at most levels of fish intake, and a statistically significant trend with increasing fish consumption was found in women who did not take aspirin regularly.

- *What is the relative efficacy of omega-3 fatty acids on different CVD outcomes? Can the CVD outcomes be ordered by strength of treatment effect of omega-3 fatty acids?*

Because of large heterogeneity across studies and inconsistent reporting of outcomes, it is difficult to compare magnitude of the outcomes across studies. Evidence from RCTs is strongest for sudden death, cardiac death (coronary or MI death), all cause mortality, and stroke. All the prospective cohort studies showed a similar order; however, the effect on total mortality (assuming benefits are restricted to CVD) was directly dependent on the proportion of all deaths due to CVD. Given the inconsistent effects in RCTs on stroke, and less consistent effects in cohort studies, the effect on stroke is uncertain.

Omega-3 fatty acid variables and modifiers

- *What is the efficacy or association of specific omega-3 fatty acids (DHA, EPA, ALA), and different ratios of omega-3 fatty acid components in dietary supplements, on CVD outcomes?*

Data on specific omega-3 fatty acids are very limited. The only RCT addressing this question [38] directly compared ALA 2.9 g/d with fish oil (EPA+DHA) 1.8 g/d. The study found both to be efficacious when compared with placebo, and there were no differences in CVD outcomes between the 2 supplements. The study took place in India where background diets and other environmental variables make extrapolation to the US population questionable. In addition, because the study's results contradict other good quality studies, this study is of limited use in assessing the effects of omega-3 fatty acid supplements on CVD events.

- *Does the ratio of omega-6 to omega-3 fatty acid intake affect the efficacy or association of omega-3 fatty acid intake on CVD outcomes?*

Two cohort [52,69] and 1 cross-sectional study [68] reported associations between the omega-3/omega-6 ratio and CVD outcomes. Using data from the Multiple Risk Factor Intervention Study (MRFIT) study, Dolecek divided omega-6/omega-3 ratios into 5 quintiles and reported near significant trends ($P<.10$) for reduction of CVD and all-cause mortality. The mean omega-3/omega-6 ratio for the entire cohort was 0.133, the lowest quintile was 0.086 and the highest was 0.199 [52].

Djousse et al. analyzed the association of omega-6/omega-3 ratios with quintiles of ALA intake on the prevalence odds ratio of coronary artery disease [68]. They reported a near-significant association in the lowest tertile of omega-6/omega-3 ratio (higher ALA intake) with higher levels of ALA intake (trend $P = 0.06$). Near-significant reduction of the prevalence odds ratio of coronary artery disease was also found for the combination of the highest tertile of LA and highest tertile of ALA.

Hu et al. stratified the omega-6/omega-3 ratio into 2 groups (low ratio group, median = 5.9; high ratio group, median = 9.2) and compared the effect of increasing amounts of omega-3 fatty acids (ALA, EPA, DHA). They reported that the inverse association with risk of CVD appeared to be somewhat stronger in the high-ratio group compared to the low-ratio group, but a test for interaction was not statistically significant [69].

- *How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)?*

Determining the comparative efficacy of different sources of omega-3 fatty acids requires direct comparisons. The available studies were too heterogeneous in terms of study design, duration, background diet, methods of assessment, and outcomes to allow even indirect comparisons that were meaningful. Overall, the evidence suggests that fish oil is efficacious, whereas the evidence for ALA is sparse and inconsistent. In the Nurses' Health Study, Hu et al. performed primary analyses of ischemic heart disease outcomes using ALA intake quantified from all sources, and repeated the same analyses using ALA from plant sources only [70]. Results for fatal ischemic heart disease outcomes were similar for the 2 ALA estimates.

- *How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by different ratios of DHA, EPA, and ALA?*

  Comparative efficacy of different ratios of DHA, EPA, and ALA can be reliably assessed only by concurrent multi-arm comparisons in a randomized trial setting. No data were found to answer this question.

- *Is there a threshold or dose-response relationship between omega-3 fatty acids and CVD outcomes?*

  Several RCTs reported beneficial effects from fish oil at a relatively low daily dose. The GISSI trial used a fish oil (EPA+DHA) dose of 0.85 g/d and reported significant beneficial effects on CVD outcomes. Leng et al. found no beneficial effect with a daily EPA dose of 0.27 g/d in a 2-year trial involving 120 CVD patients [34]. Nilsen et al used 1.7 g/d of EPA+DHA and showed no effects on CVD outcomes [36]. Two diet trials [43,44] compared the effects of diets containing ALA to the effects of control diets with lower levels of ALA. DeLorgeril et al. compared estimated ALA intakes of 1.8 g/d and 0.67 g/d, and Singh et al. compared estimated ALA intakes of 1.9 g/d and 0.8 g/d.) Both trials reported that the group with higher ALA intake experienced significant or near-significant beneficial effects on CVD outcomes compared to control.

- *How does the duration of intervention or exposure affect the treatment effect of omega-3 fatty acids on CVD outcomes?*

  The duration of the RCTs in CVD populations ranged from 1.5 to 5 years. The largest RCT (13,000 subjects) had a duration of 1 year and was conducted in the non-CVD population. This RCT found no effect on any of the CVD outcomes[49]. The duration of the prospective cohort studies ranged from 4 to 30 years. Among the cohort studies, those that followed subjects for less than 6 years demonstrated no significant benefit on clinical effects. The Physicians' Health Study reported no significant effect on CVD outcomes after 4 years of follow-up[64].

- *Are treatment effects or the association of omega-3 fatty acids on CVD events sustained after the intervention or exposure stops?*

  Only 1 study [48] a 10-year follow-up to the Diet and Reinfarction Trial addressed whether treatment effects of omega-3 fatty acids on CVD events were sustained after the intervention or exposure stops. This study showed no long-term benefit from being in the fish advice group in the DART study.

- *What is the effect or association of baseline dietary intake of omega-3 fatty acids on the efficacy of omega-3 fatty acid supplements on CVD events?*

  To answer this question, we need studies using the same omega-3 fatty acid treatment in 2 or more groups of subjects who have different baseline diet profiles.

We found no such trials in our search. Several dietary RCTs provide a glimpse of the benefits of adding additional omega-3 fatty acids to baseline intake in comparable populations. As noted above, 2 diet trials[43,44] compared the effects of diets containing ALA to the effects of control diets with lower levels of ALA. Both trials were of 2 years duration, and both reported that the group with the higher ALA intake experienced significant or near significant beneficial effects on multiple CVD outcomes compared to control. In an RCT of dietary fish advice, Burr et al. estimated the amount of EPA in the control group (0.6 g/week) and the intervention group (2.4 g/week) [47] and reported a significant reduction of all cause mortality.

- *Does the use of medications for CVD and/or CVD risk factors (including lipid lowering agents and diabetes medications) affect the efficacy or association of omega-3 fatty acids?*

None of the RCTs were specifically designed to address whether the addition of CVD risk factor medications (lipid lowering agents or diabetes medications) affected the efficacy of omega-3 fatty acids. Among the cohort studies, as well, there were no studies that specifically adjusted for CVD risk factor medications.

Adverse Events Associated with Omega-3 Fatty Acid Consumption

We reviewed 395 clinical articles for potentially relevant human data on adverse events associated with omega-3 fatty acid consumption. These articles included studies of clinical outcomes and risk factors and encompassed RCTs, non-randomized comparison studies, and observational studies in the general and CVD populations.

Adverse events considered in this report are those associated with omega-3 fatty acid supplements, but not fish. As stated in Chapter 1, issues related to mercury toxicity are outside the scope of this report. We also excluded fishy aftertaste as an adverse event.

Of the 395 articles, 247 articles were rejected because they did not provide adverse event information, and 2 additional articles were rejected because of duplicate publications. Of the remaining 148 articles, a variety of adverse events were reported in 71 studies (Tables 3.52-3.53), and 77 studies reported that no adverse events occurred (Tables 3.54-3.55).

Studies that reported adverse events included 54 RCTs and 17 non-randomized comparison studies. Categorizing and reporting of adverse events varied greatly across studies. Only 1 study explicitly defined serious adverse events [34] based on the scale developed by the World Health Organization (WHO). Some studies combined all nausea and vomiting, while others limited reporting to “mild to severe” gastrointestinal (GI) disturbance. In 10 studies, the authors reported that “few,” “some,” or “most” subjects had symptoms, but did not provide any further description. No definitions for clinical bleeding or headache were given. In addition, adverse event rates were reported sometimes as a number and sometimes as a percent of patients with symptoms. In some studies, adverse events were reported without differentiating by treatment assignment, while others studies did not report whether patients who withdrew from the studies experienced adverse events. We grouped the different types of adverse events reported into 4

major categories: clinical bleeding (nasal, hematuria, gastro-intestinal, and other bleeding), GI complaints, withdrawal due to adverse events, and miscellaneous.

No adverse events were reported that associated omega-3 fatty acid consumption with events such as death, life-threatening illness, significant disability, or handicap. However, 4 studies reported that some important bleeding occurred among subjects on fish oil combined with aspirin or warfarin [71, 72, 73, 74].

Studies reporting adverse events are presented in Tables 3.52-3.53. To help readers appreciate the occurrence of adverse events in different populations, we grouped the studies into 5 different categories: general, cardiovascular disease, hyperlipidemia, diabetes, and hypertension.

Overall

We analyzed 148 articles for data on adverse events. These articles represented about 20,000 subjects. About half of these subjects were exposed to omega-3 fatty acid in different forms and dosages and for durations ranging from 1 to 364 weeks. The majority of the studies evaluated a few dozen subjects for less than 6 months. The GISSI-Prevenzione trial, with over 11,000 subjects and a follow-up duration of 182 weeks, reported the largest number of adverse events [39]. This trial contributed about one-third of the total number of GI complaints (in both the omega-3 fatty acid arm and the control arm) from all the studies combined. It also contributed almost all the withdrawals due to adverse events (although the reasons for withdrawals were not given). This discordance suggests that many studies do not adequately report adverse event data, especially data about withdrawals due to adverse events.

GI Complaints

Among the 71 studies that reported adverse events, GI complaints were the most common. They were reported in 6.6% (584/8,805) of subjects in the omega-3 fatty acid arms and 4.3% (381/8680) of subjects in the control arms. The high percentage of GI complaints in the control arms is probably due to the equivalent amounts of non-omega-3 oil that were given to control subjects. In the GISSI study, in which the control arm received either vitamin E or no treatment, the GI complaints in the control group were half that of the fish oil arm. There appears to be more GI complaints with omega-3 fatty acids in the studies of the diabetes population [75-78 79-81] but the total number of events and total number of subjects evaluated in these studies was too small to draw meaningful conclusions. There was no significant difference in other categories of study populations.

Clinical Bleeding

Clinical bleeding was reported almost exclusively in the CVD study populations. Overall, there was no difference in the frequency of bleeding events between the omega-3 fatty acid and control arms. Because of the lack of uniform definitions for the severity and seriousness of clinical bleeding, case descriptions from 5 RCTs [74,82 83 84 85] that reported clinical bleeding are noteworthy. Together, the RCTs involved a total of 125 subjects (57 in omega-3 fatty acid arms, 68 in control arms). There were no significant differences between omega-3 fatty acid and control groups in the 5 studies. All of the subjects in these studies took warfarin or 200-325 mg

of aspirin daily. Severe bleeding was reported in 2 of the 5 studies. Eritsland randomized 511 patients [82] and reported an intrathoracic postoperative bleeding event that required transfusion and re-operation; however, it was not mentioned whether this patient received fish oil. This study also reported that bleeding complications were the reason for 9 of the withdrawals (5 from the fish oil group and four from the olive oil group). Similarly, in a large study, Reis [74] compared 6g of omega-3 fatty acid daily with the same amount of olive oil and reported that important bleeding occurred in 4 patients on fish oil and none on placebo. Two of the patients had severe bleeding at the site of a femoral puncture and 1 required surgical repair. The other 2 patients experienced GI bleeding during follow-up. One of these patients required hospital admission and transfusion, and the other had a heme-positive stool. Cairns [84] found that most bleeding was mild, leading to permanent discontinuation of the study medication in only 6 patients (0.9%). No transfusions were required, and bleeding was less frequent in patients taking fish oil compared to those taking placebo. Leaf [83] reported that 3% of patients in each treatment group experienced bleeding episodes[85] noted 1 patient with chronic lower GI bleeding.

Studies that Reported that No Adverse Events Occurred

In addition to studies that reported adverse events, we reviewed 77 studies (51 RCTs and 26 non-randomized comparison studies) that reported there were no adverse events associated with the omega-3 fatty acid supplements used (Table 3.54-3.55). Together, these studies involved 2,325 subjects in omega-3 fatty acid arms. Study duration ranged from 1 to 364 weeks, and the EPA and DHA dosage ranged from 0.3 to 8 g/d.

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
Wander 1996	24	EPA+DHA 4.3	24	Soybean oil 4 capsules	36			1	0			Post-menopausal women
Hamazaki 1996	13	DHA 1.5-1.8	11	Soybean oil ND	13			2	3			1 weight gain in each group
Kaminski 1993	7	EPA+DHA 5.8	7	ND	6			"some"				
Allard 1997	35	EPA+DHA 5.4	37	Olive oil 6.3	6			3	0	3	0	
Hawkes 2002	40	EPA+DHA 0.74	40	Placebo oil 2.0	4			4				1 skin rash in n-3 FA
	40	EPA+DHA 0.37										
Stark 2000	18	EPA+DHA 4.0	17	Primrose oil 8 capsules	4			2				Post-menopausal women
Harris 1993	4	EPA+DHA 0.64	4	Olive oil ND	4			1				1 headache in n-3 FA
Mueller 1991	6	n-3 FA 8.0 + EPA 3.5	6	Olive oil 8 capsules	3			3	3			1 constipation, 1 weight gain, 1 headache in n-3 FA 1 diarrhea in olive oil
Total	187		146					16	6	3	0	
Cardiovascular disease population												
GISSI-P 2001	5665	EPA+DHA 0.85±VitE	5658	Vit E or Control	182			179	93	215	119	
Sacks 1995	31	EPA+DHA 4.8	28	Olive oil ND	112			3		3	0	≥93% in both groups took antiplatelet agents
Von Schacky 1999	111	EPA+DHA 3.5 to1.7	112	Blend of fish oil	104			4	3	4	3	1 rash in n-3 FA
Leng 1998	60	GLA 1.7 + EPA 0.27	60	Sunflower seed oil 3.0	104			30	19			47 vs 40% on aspirin
Kaul 1992	58	EPA+DHA 3.0	49	Calcium blocker	48	0	0	2	0			All on aspirin
Borchgrevink 1966	100	Linseed oil 10 ml	100	Corn oil 10 ml	40			7	7	3	0	All taking anticoagulants
Eritsland 1995	119	EPA+DHA [2] and Aspirin	106	Aspirin	36	10	8	34		5	4	See footnote 2

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
	132	EPA+DHA [2] and Warfarin	154	Warfarin		17	14					
Maresta 2002	125	EPA+DHA 5.1	132	Olive oil	26	0	0	2	2			All on aspirin
Leaf 1994	226	EPA+DHA 6.9	221	Corn oil	24	8	8	19	22	3	8	All on aspirin, 4% (11) infections in each group
Johansen 1999	196	EPA+DHA 5.1	192	Corn oil 5.1	24			3	2			71 vs 67 % on Aspirin 18 % vs 16 on Warfarin
Reis 1989	124	n-3 FA 6.0 + aspirin	62	Olive oil	24	4[3]	0	59	11	46		n-3 vs olive Weight gain: 6 vs 3 (5% in each group) Diarrhea: 15 vs 4
Milner 1989	95	EPA+DHA 4.5	99	Olive oil	24	1[4]	0	24				1 insomnia, 1 headache in n-3 FA
Bairati 1992	59	EPA+DHA 4.5	60	Olive oil 15	24			29	30			All on aspirin
Bellamy 1992	60	EPA+DHA 3.0	53	ND	24			4	0			1 diarrhea with n-3 FA, 96% of all on aspirin
Dehmer 1988	43	EPA+DHA 5.4	39	ND	24	0	0	7	3			All on aspirin + dipyridamole
Cairns 1996	325	EPA+DHA 5.4	328	Corn oil	18	17	38	122	101	3	3	All on aspirin See footnote 5
Franzen 1993	92	n-3 FA 3.2	83	Olive oil 9 capsules	16	0	0	13	5	13		All on aspirin
Berrettini 1996	20	EPA+DHA 2.6	19	Corn oil 3.0	16				1	0	1	> 2/3 on aspirin
Berg 1965	42	Linseed oil 10 - 30 ml	37	Corn oil 10 – 30 ml	12			5		0	0	Diarrhea: 5 in n-3 FA, all on anticoagulants
Berg 1988	14	EPA+DHA 4.5	16	Vegetable oil 15 capsules	12			0	1	0	1	
Davidson 1989	15	EPA+DHA 3.6 EPA+DHA 2.4	15	Olive oil 20 capsules	4							1 diarrhea in olive oil
Total	**7712**		**7623**			**57**	**68**	**512**	**300**	**236**	**139**	
Hyperlipdemia population												

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
Sirtori 1997	470	EPA+DHA 2.5 to 1.7	465	Olive oil ND	24			18	21			
Harris 1997	22	EPA+DHA 3.4	20	Corn oil ND	16			4	3	0	0	
Boberg 1986	7	EPA+DHA 3.0	7	Olive oil ND	16			"some"				1 skin rash in n-3 FA
Grundt 1995	28	EPA+DHA 3.4	29	Corn oil 4.0	12			"some"				
Alaswad 1999	11	EPA+DHA 3.4	42	Placebo	12	1 nose	0					
Bonaa 1992	72	EPA+DHA 5.1	74	Corn oil 6.0	10			10	7			
Wilt 1989	19	EPA+DHA 6.0	19	Placebo	12			8	8			
Silva, 1996	20	EPA+DHA 3.6	15	Soya oil 12 capsules	8			4		4		
Mori 1999a	36	EPA+DHA 4.0	20	Olive oil 4.0	6			1		1		
Mori 2000a	26	EPA+DHA 4.0	14	Olive oil 4.0	6			1		1		
Davidson 1997	18	DHA 1.25 or 2.5	8	Corn and soybean oil 12 capsules	6			"some"				
Contacos 1993	10	EPA+DHA 3.0	11	Placebo	6			1				
Brox 1983	7	Cod liver oil 30 ml	11	ND	6			2	0			
Demke 1988	13	EPA+DHA 1.7	18	Safflower oil 5.0	4			"some"				Some diarrhea and headache
Subtotal	**759**		**753**			**1**	**0**	**34**	**31**			
Diabetes population												
Myrup 2001	14	EPA+DHA 4.6	15	Olive oil 21 ml	52			3	1	3	0	
Rossing 1996	14	EPA+DHA 4.6	15	Olive oil 21 ml	52			2	0	2	0	
Schect-man 1988	13	EPA+DHA 4.0	13	Safflower oil 12	24			1	0	1	0	
Vessby 1990	5	EPA+DHA 3.0	9	Olive oil 10	8			"some"		0	1	
Hendra 1990	40	EPA+DHA 3.0	40	Olive oil 5 capsules	6			1	0	1	0	
Mori 1991	9	EPA+DHA 5.2	9	Olive oil ND	3			"some"				

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
Fasching 1996	5	EPA+DHA 4.7	5	Gemfibrozil (0.9)	2			2	0			
Subtotal	**100**		**106**					**9**	**1**	**7**	**1**	
Hypertension population												
Margolin 1991	22	n-3 FA 4.7	24	Corn oil 9.0	8	1		4				1.8% dizziness 5.1% diarrhea, 1 skin rash in n-3 FA
Gray 1996	9	EPA+DHA 3.4	10	Corn oil 1 capsule	8			0	3	0	0	4 headaches in n-3 FA
Levinson 1990	8	EPA+DHA 15	8	Vegetable oil 50	6			2	1	1	0	
Landmark 1993	8	EPA+DHA 4.6	10	Olive oil 5 capsules	4			2	1	0	0	No diarrhea
Subtotal	**47**		**52**					**4**	**5**	**1**	**0**	
All Studies												
Total	**8805**		**8680**			**58**	**68**	**575**	**373**	**247**	**140**	

AE= Adverse Events; C=Control; ND= No data

[1] Serious adverse events defined by Scotia Pharmaceuticals based on a WHO scale, including death, life-threatening illness, significant disability on handicap and in –patient hospitalization for any reason.

[2] Only bleeding episodes detected clinically were recorded. One bleeding episode required transfusion and operation, the other episodes were minor. In addition, a bleeding complication was the reason for withdrawal in 9 out of the 66 patients.

[3] Important bleeding occurred in 4 patients on fish oil and none on placebo. Two patients had severe bleeding at the site of femoral puncture.

[4] one patient with chronic lower GI bleeding + and a known diagnosis of diverticulosis required partial colectomy.

[5] Most bleeding was mild, leading to permanent discontinuation of study medication in 6 patients.

Table 3.53. Adverse Events Reported in Non-randomized Studies of Omega-3 Fatty Acid Supplements

Author Year	n	Omega-3 fatty acids (g/d)	Duration (weeks)	Clinical bleeding	GI complaints	Withdrawal due to AE	Comments
General population							
Schmidt 1992a	24	EPA+DHA 3.2	36		"some"		
Berg 1990	10	n-3 FA 1.3 - 9	18		"some"		
Brown 1991	12	n-3 FA 5.0	6			5	1 weight gain after 2 wk
Mortensen 1983	20	n-3 FA 4.0	4		1		
Wojenski 1991	9	EPA+DHA 3.0	4		4		
Subtotal	**75**				**4**	**5**	
Cardiovascular disease population							
Bowles 1991	85	EPA 2.8	24		28		"Considerable symptoms" and some diarrhea
Verheugt 1986	5	n-3 FA 3.0	24		1		
Smith 1989	22	EPA+DHA 3.4	4	1 nose	3		
Kahl 1987	16	n-3 FA 8.1	2		10		4 increased appetite
Subtotal	**128**			**1**	**42**		
Hyperlipdemia population							
Dallongeville 1991	18	EPA+DHA 4.8	12		6	0	
Schectman 1989	16	EPA+DHA 6.0	12		18	1	**3 diarrhea**
Pichter 1992	12	EPA+DHA 3.6	12				Inverse in blood glucose from 97-249 mg/dl, HbA from 5.5 to 7.1%, after removal of n-3 fatty acids, blood glucose normalized.
Otto 1996	23	EPA+DHA 1.5 to 3.0	8		1		
Schmidt 1989a	17	EPA+DHA 5.1	6		"some"		
Subtotal	**86**				**25**	**1**	
Diabetes population							
Tamura 1987	62	EPA 1.8 to 2.7	16		1 or 2		
Mori 1989	10	EPA+DHA 4.3	3		2		
Fasching 1991	8	EPA+DHA 6.3	2		2		

Author Year	n	Omega-3 fatty acids (g/d)	Duration (weeks)	Clinical bleeding	GI complaints	Withdrawal due to AE	Comments
Subtotal	**80**				**5 - 6**		

GI = Gastrointestinal (not including liver inflammation). AE= Adverse Events

Table 3.54. Randomized Trials of Omega-3 Fatty Acid Supplements that Reported No Adverse Events

Author, Year	N	Omega-3 Fatty Acids (g/d)	*Duration (Weeks)*
Nilsen, 2001	150	EPA+DHA 1.7	104
Brox, 2001	36	EPA+DHA 2.6	56
Eritsland,1994	260	EPA+DHA 3.4	36
Satterfield, 1991	175	n-3 FA 3.0	24
Hamazaki 1996	16	EPA 1.8	24
Radack, 1990	17	n-3 FA 1.1 - 2.2	20
Toft, 1997	38	EPA+DHA 3.4	16
Gans, 1990	16	EPA+DHA 3.0	16
Goodfellow, 2000	15	EPA+DHA 3.4	16
Prisco, 1994	10	EPA+DHA 3.4	16
Prisco, 1995	10	EPA+DHA 3.4	16
Prisco, 1998	8	EPA+DHA 3.4	16
Schmidt, 1988	18	n-3 FA 4.5	12
Radack, 1991	16	n-3 FA 2.0	12
Vandongen, 1993	17	EPA 1.3 – 2.6	12
Nenseter, 2000	34	Fish powder 10	12
Yam, 2002	34	n-3 FA 7.0	12
Adler, 1997	10	n-3 FA 3.6	12
Morris, 1993	12	n-3 FA 3.0 – 6.0	12
Salanchas, 1994	20	EPA+DHA 4.0	12
Warner, 1989	7	Max EPA 50ml	12
Solomon, 1990	5	EPA+DHA 4.6	12
Mehta, 1988	8	EPA+DHA 5.4	12
Calabresi, 2000	14	EPA+DHA 3.4	8
Schmidt, 1992	11	n-3 FA 2.0 – 9.0	8
Steiner, 1989	3	EPA+DHA 1.6	8
Wing, 1990	20	EPA+DHA 4.5	8
Luo , 1998	6	EPA+DHA 1.8	8
Grimsgaard, 1998	147	EPA+DHA 4.0	7
Hansen, 1993	11	EPA+DHA 3.4 to 3.6	7
Grimsgaard 1997	147	EPA 4, DHA 4	7
Honstra, 1990	40	n-3 FA 1.7	6
Van Houwelingen, 1988	40	EPA+DHA 4.7	6
Howe, 1994	28	n-3 FA 5.0	6
Chan, 2003a	25	EPA+DHA 3.4	6
Pirich, 1999	13	EPA+DHA 0.4	6
Chan, 2002	12	EPA+DHA 3.4	6
Conquer, 1999	10	EPA+DHA 3.0	6
Vericel, 1999	10	EPA+DHA 0.2	6
Axelrod, 1994	9	EPA+DHA 2.6	6
Brox, 1981	6	Cod liver oil 25 ml	6
Chan 2002b	25	EPA+DHA 3.4	6
Balestieri, 1996	8	n-3 FA 5.1	4
Baumann, 1999	7	EPA+DHA 4.6	4
Freese, 1997	24	EPA+DHA 5.2	4

Author, Year	N	Omega-3 Fatty Acids (g/d)	*Duration (Weeks)*
Mori, 1992	15	EPA+DHA 4.6	4
Nozaki, 1991	12	EPA+DHA 8.0	4
Davi, 1990	10	EPA 1.8	4
Harris, 1991	16	EPA+DHA 2.2	4
Villa, 2002	10	n-3 FA 3.0 – 6.0	4
Swails, 1993	7	EPA+DHA 1.6	1
Total	**1,618**		

Table: 3.55. Non-Randomized Studies of Omega-3 Fatty Acid Supplements that Reported No Adverse Events

Author, Year	N	Omega-3 Fatty Acid (g/d)	*Duration (week)*
Saynor, 1992	365	EPA+DHA 1.1 – 1.8	4-364
Shinozaki, 1996	16	EPA 1.8	96
Blok, 1997	44	EPA+DHA 1.0 – 2.9	52
Rhodes, 1994	15	EPA+DHA 3.0	24
Von Schacky, 1985	6	Cod liver oil 10 - 40 ml	20
Nelson, 1997	10	DHA 6.0	17
Russo, 1995	24	EPA+DHA 2.6	16
Meydani, 1991	25	EPA+DHA 2.4	12
Bagdade, 1990	8	EPA+DHA 6.0	12
Nau, 1991	14	EPA+DHA 1.0	8
Toth, 1995	10	n-3 FA 0.2	8
Bonanome, 1996	12	n-3 FA 2.5	8
Bagdade, 1996	9	EPA+DHA 4.6	8
Berg, 1989	10	EPA+DHA 0.7	6
Schmidt, 1991	10	EPA+DHA 0.7	6
Schmidt, 1990	10	EPA+DHA 2.1	6
Schmidt, 1989	10	n-3 FA 4.0	6
Berg, 1989	17	EPA+DHA 5.1	6
Haglund, 1990	13	EPA 2.7 – 5.4	4
Glauber, 1988	6	EPA+DHA 5.5	4
Suehiro, 1994	27	EPA 1.8	4
Harris , 1983	12	n-3 FA 20 - 29	4
Owens, 1990	6	EPA+DHA 4.5	4
Kasim-Karakas, 1995	14	EPA+DHA 3.3	4
Terano, 1983	8	EPA+DHA 0.3	4
Nordoy, 1994	6	EPA+DHA 4.8	3
Total	**707**		