Does Fish Oil Lower Blood Pressure?

A Meta-Analysis of Controlled Trials

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Background. **In a meta-analysis of 31 placebo-controlled trials on 1356 subjects, we examined the effect of ω-3 fatty acids in fish oil on blood pressure by grouping studies that were similar in fish oil dose, length of treatment, health of the subjects, or study design.**

Methods and Results. **The mean reduction in blood pressure caused by fish oil for the 31 studies was −3.0/−1.5 mm Hg (95% confidence intervals: systolic blood pressure: −4.5,−1.5; diastolic blood pressure: −2.2,−0.8). There was a statistically significant dose-response effect when studies were grouped by ω-3 fatty acid dose: −1.3/−0.7 mm Hg at doses ≤3 g/d, −2.9/−1.6 mm Hg at 3.3 to 7 g/d, and −8.1/−5.8 mm Hg at 15 g/d. Both eicosapentaenoic acid and docosahexaenoic acid were significantly related to blood pressure response. There was no effect on blood pressure in eight studies of "healthy" persons (mean reduction, −0.4/−0.7 mm Hg) at an overall mean dose of 4.2 g ω-3 fatty acids/d. By contrast, there was a significant effect of −3.4/−2.0 mm Hg in the group of hypertensive studies with a mean fish oil dose of 5.6 g/d and on systolic blood pressure only in six studies of hypercholesterolemic patients (−4.4/−1.1 mm Hg) with a mean dose of 4.0 g/d. A nonsignificant decrease in blood pressure was observed in four studies of patients with atherosclerotic cardiovascular disease (−6.3/−2.9 mm Hg). Variations in the length of treatment (from 3 to 24 weeks), type of placebo, and study design (crossover or parallel groups) did not appear to account for inconsistent findings among studies.**

Conclusions. **There is a dose-response effect of fish oil on blood pressure of −0.66/−0.35 mm Hg/g ω-3 fatty acids. The hypotensive effect may be strongest in hypertensive subjects and those with clinical atherosclerotic disease or hypercholesterolemia. (*Circulation* 1993;88:523-533)**

KEY WORDS • **fish oil** • **fatty acids** • **blood pressure** • **trials**

Despite many clinical studies, the evidence for a fish oil effect on blood pressure is inconclusive. From results of animal and clinical studies, it is theorized that the ω-3 fatty acids in fish oil have hypotensive properties through stimulation of the prostaglandins that control sodium and water excretion, cause vasodilation and inhibition of the vasoconstrictor thromboxane, regulate renin release, and decrease the response to vasopressor hormones.[1] However, many studies do not report significant decreases in blood pressure.

There are a number of plausible explanations for the inconsistent findings. For example, many studies are based on small samples and may lack the statistical power to detect a modest effect. The blood pressure response to fish oil also may vary depending on ω-3 fatty acid dose or length of treatment or may occur only in certain types of subjects, such as patients with hypertension or various cardiovascular diseases. Study design may contribute to biased results through carryover of treatment effects in crossover studies or imbalance in baseline characteristics in parallel group studies. One might argue that certain placebos also bias results, since the three types currently in use (ω-6 polyunsaturated, monounsaturated, and saturated fatty acids) have all been investigated for their own blood pressure effects, even if the evidence is unconvincing.[2]

Two recent reviews[3,4] noted weaknesses of many studies of fish oil and blood pressure, including the absence of placebo controls, unblinded blood pressure observers, and measurement error. However, neither review assessed how differences in dose, type of subject, or study design may account for variations in a fish oil effect. We explored these issues through a meta-analysis in an attempt to provide a useful summary of the data accumulated thus far.

Methods

We conducted an extensive literature search using *Index Medicus* for references of all publications on ω-3 fatty acids from fish oil, including fish oil supplements (in the form of emulsions or capsules) and fish diets. All clinical trials on human subjects that reported the effect of fish oil on blood pressure were reviewed. We also received permission to include results of a multicenter trial that were unpublished at the time of this analysis.[5]

The only criteria for trial inclusion in the meta-analysis were use of a placebo control and report of pretreatment and posttreatment blood pressure measurements.

We computed overall summary estimates of a blood pressure effect from fish oil by combining the mean

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estimates of effect reported by individual studies weighted by the inverse of the individual and between study variance according to a random effects model.[6] All summary estimates of effect are presented with 95% confidence intervals (CI) based on the estimated variances (see "Appendix": Calculation of the Summary Estimate of Effect and 95% CI).

The blood pressure effect attributed to fish oil treatment was calculated differently for parallel group and crossover study designs to reflect the intergroup and intragroup comparisons. In the case of a parallel group design, blood pressure effect was calculated by subtracting the mean change among controls from that in the fish oil group; in crossover studies, the estimate represents the difference in posttreatment blood pressures for the fish oil and placebo periods. We included the adjusted rather than crude effects for the two studies[7,8] that controlled for differences among treatment and control groups.

We were unable to derive the correct within-study variances (S_i^2) for more than two thirds of the trials based on the published data (few reported exact probability values or confidence intervals for the group differences described above). As an alternative, we computed our own estimates using the data and formula for blood pressure variance published by Rosner and Polk.[9] These authors described the variance of individual mean blood pressure, measured through standard sphygmomanometers, as a function of within- and between-visit measurement error and reported these two variance components for different age, sex, and race categories for a large screening population. We computed variance estimates for each study in the meta-analysis using these published estimates of the variance components and information that the studies provided on subject characteristics, number of blood pressure measurements (taken on different visits and within one visit), and number of subjects (see "Appendix": Calculation of Within-Study Variance). In one study,[10] where blood pressure was measured 20 times over a 12-hour period using an ambulatory device, the variance estimates were not directly applicable; thus, we assumed the equivalent of 10 standard measurements taken at each of two visits for the variance calculations.

We assessed the homogeneity of study estimates of effect by the Q test,[6] where $Q > \chi^2_{k-1,.975}$ indicated that the individual estimates for k studies were not estimators of one underlying effect (see "Appendix": Calculation of Q).

For each meta-analysis, we selected one set of blood pressure results from any particular study to avoid undue weighting by that study in the summary estimates. Selection criteria were designed to maximize similarity among studies; therefore, blood pressure measurements taken with the subject in the sitting position took precedence (followed by supine, then standing), as did those from standard sphygmomanometers (followed by random-zero and ambulatory devices). When results for more than one dose level[10,11] or length of treatment[11-14] were reported, we selected effects of the dose and treatment length closest to the mean for all studies in the overall analyses (4.8 g ω-3 fatty acids/d and 7 weeks). However, these studies were represented in every category for which they had information in subgroup analyses.

Weighted least squares regression was used to test for a dose-response effect on blood pressure, with individual study effects weighted by the inverse of the estimated variance. For these analyses, we included all available data for different dose levels, which meant that two studies[10,11] each reporting the effect of two doses of ω-3 fatty acids were represented twice in the regression models, once for each dose level.

Differences in effect between groups of studies were assessed by the two-sample standard normal test and, where appropriate, analysis of covariance to adjust for dose of ω-3 fatty acids. The two-sided t test was used to test for statistical significance of the β-coefficients with the standard error of β divided by the square root of the error mean squared.[15] All tests were performed at the .05 level of significance (see "Appendix" for details).

Results

We reviewed 52 clinical studies reporting the effect of fish oil on blood pressure.[5,7,8,10-14,16-58] Twenty-one publications did not meet the criteria for inclusion in the meta-analysis including three studies that did not report blood pressure data for both fish oil and placebo groups[32-34]; one study that used a diet supplement of eggs from chickens fed fish oil[35]; one that reported only mean arterial pressure,[36] a legitimate representation but incompatible with our definition of fish oil effect; one study with a randomized block design of fish oil and sodium restriction that reported data for the combination of treatments only[37]; and 15 studies that did not use a placebo control comparison.[17-31] Of the five controlled trials with insufficient numerical data for this meta-analysis, four reported no effect on blood pressure[32-34,37] and one reported a significant decrease.[36] The diet study using eggs enriched with fish oil reported a significant decrease in blood pressure with consumption of the treatment eggs but not with the control eggs.

There were 31 placebo-controlled trials that reported mean blood pressure data for both placebo and fish oil treatment groups[5,7,8,10-14,16,38-58] (Table 1). Most studies used encapsulated fish oil; only Cobiac et al[16] and v Houwelingen et al[43] examined the effects of a fish diet. Since Cobiac et al also included groups receiving fish oil and placebo supplements, we used the data for the fish oil group in the meta-analyses. Blood pressure results from the three experimental sites in the study by v Houwelingen et al were included in the analyses as separate studies. The crossover studies of Margolin et al[38] and Radack et al[58] used parallel group analysis of the first period only because of the presence of a treatment by period statistical interaction; we also used the data from the first period in the meta-analyses. Two studies, one with a parallel group design[16] and one crossover study,[39] did not use random assignment to the treatment and control periods. Twenty of the 31 studies reported that both participants and blood pressure observers were blinded to treatment status; four reported single blinding either of participants[41] or of blood pressure observers[43]; three were unblinded[10,12,16]; and four did not state whether blinding was part of the design[7,45,54,56] (Table 1). Eight studies measured blood pressure with automated[7,10,16] or random-zero[5,11,12,49,51] devices to reduce observer bias. About half (15) of the studies used multiple readings to account for natural

within-person variations in blood pressure, but only three[5,11,50] of these averaged the measurements over multiple visits, a more accurate estimate of the overall mean (Table 1).

For individual studies, the changes in blood pressure associated with fish oil ranged from −16.8 to +9.0 mm Hg for systolic blood pressure (SBP) and −9.6 to +1.7 mm Hg for diastolic blood pressure (DBP), with the largest decreases occurring in the smallest studies. Using the estimated variances to construct 95% CIs around the effect estimates, nine studies (29%) showed significant decreases in SBP and five (16%) in DBP, with just one of the 31 studies[7] showing significant decreases in both (Fig 1).

Overall Meta-Analysis

In the overall meta-analysis of 31 studies representing 1356 participants, the mean reduction in blood pressure caused by fish oil was −3.0/−1.5 mm Hg (95% CI: SBP: −4.5,−1.5; DBP: −2.2,−0.8) (Table 2). Individual study estimates of the fish oil effect on diastolic blood pressure had low variability (Q=34, P=.28). The estimates for SBP, however, were highly variable across studies (Q=79, P<.001), indicating that the response to fish oil may be better characterized by separate estimates of effect for groups of studies similar in design or subject characteristics.

Subgroup Analyses by Dose

When we grouped studies according to dose of ω-3 fatty acids, we observed greater decreases in blood pressure with increasing dose; there was little change in blood pressure at the lowest doses ≤3 g/d (−1.3/−0.7 mm Hg), a significant moderate decrease with doses from 3.3 to 7 g/d (−2.9/−1.6 mm Hg), and a significant substantial decrease at the highest dose of 15 g/d (−8.1/−5.8 mm Hg) (Table 3). No study investigated doses between 7 and 15 g.

We used weighted least squares regression to test for a dose-response effect on blood pressure with each study assigned the mean value (2.6 g, 4.8 g, or 15 g) of its corresponding dose category. The dose-response effect was statistically significant for both SBP (P=.005) and DBP (P=.0082). We reanalyzed the data with each study represented by its actual dose of ω-3 fatty acids to assure that the relation was not merely an artifact of the arbitrarily defined dose categories. The relation remained significant although slightly reduced; per 1.0 g increase in dose there was a 0.66 mm Hg decrease in SBP (P=.002) and 0.35 mm Hg decrease in DBP (P=.026) (Fig 2). We conducted further analyses excluding the highest dose of 15 g/d, which, based on just two small studies, provided a highly unstable estimate. Without this extreme category, the dose-response relation <15 g/d remained statistically significant for SBP, with a decrease of 0.78 mm Hg per gram increase of ω-3 fatty acids (P=.02) but not for DBP (−0.24 mm Hg per gram, P=.32). The dose-response effect was also evident when dose was represented by either of the primary ω-3 fatty acids, eicosapentaenoic acid (−0.93/−0.53 mm Hg per gram increase in dose, P=.009/.046), or docosahexaenoic acid (−1.5/−0.77 mm Hg per gram, P=.001/.021).

Subgroup Analyses by Treatment Length

There were similar mean decreases in blood pressure with 3 to 4 weeks, 5 to 6 weeks, and 8 to 10 weeks of treatment (Table 3). The blood pressure decrease in the longest duration trials of 12 to 24 weeks was less than in the trials of shorter duration but not significantly so. When we eliminated the largest trial (TOHP,[5] which used a low dose of 2.4 g ω-3 fatty acids/d), the estimate of effect of 12 to 24 weeks of fish oil treatment increased slightly to −2.0/−2.0 mm Hg. Therefore, the effect of fish oil on blood pressure manifests fully after 3 to 4 weeks.

Subgroup Analyses by Subject Type

We identified eight studies that targeted "healthy" persons with no clinical manifestations of disease.[5,13,39,41,43,45] In all except one of these studies[13] in which the mean total cholesterol at baseline was 6.0 mmol/L, blood pressure and total cholesterol were within normal ranges (SBP/DBP <140/90 mm Hg and cholesterol <5.5 mmol/L). The mean reduction in blood pressure for this group of studies was close to zero (−0.4/−0.7 mm Hg), with no indication that the individual study estimates were not consistent (Q tests for homogeneity: P=.32/.67, SBP/DBP).

Nine studies selected hypertensive samples through screening or patient clinics.[7,10,11,14,38,40,44,52,58] The hypertensive samples had a significant overall mean reduction in blood pressure caused by fish oil of −3.4/−2.0 mm Hg, but the average ω-3 fatty acid dose for this group was higher than for other types of subjects, and the individual study estimates were highly variable for systolic blood pressure (Q=17.4, P=.03) (Table 3). When we controlled for dose using analysis of covariance, the mean effect for hypertensives was not significantly different from the healthy group; the adjusted mean difference between the groups was −0.95 mm Hg for SBP (P=.32) and −0.22 mm Hg for DBP (P=.75). We repeated the analysis on studies of stable hypertensives only, which meant dropping two trials[11,52] in which the mean DBP was <90 mm Hg during the baseline or placebo periods. For this group, the summary estimate of effect was −4.5/−2.5 mm Hg (95% CI: SBP: −7.8,−1.2; DBP: −4.4,−0.6), whereas there was still variability among individual study estimates of the SBP effect (Q=12.2, P=.06). When we adjusted for ω-3 fatty acid dose, the difference in mean effects between the groups of stable hypertensives and healthy subjects was statistically significant for SBP (β=−3.6 mm Hg, P=.02) but not for DBP (β=−1.6 mm Hg, P=.14).

Six studies recruited hypercholesterolemic patients or used screening to select persons with high cholesterol levels.[16,46,48,50,54,56] For this group, there was a statistically significant effect of fish oil treatment on SBP of −4.4 mm Hg (95% CI: −6.6,−2.2) but not for DBP. Individual estimates of effect were consistent among the studies (SBP: Q=6.2, P=.29; DBP: Q=4.6, P=.47). The SBP effect for hypercholesterolemic studies was significantly greater than the effect for healthy subjects by 4 mm Hg (P=.0008), but the effects on DBP did not differ. The doses were similar for the two groups, 4.0 g and 4.2 g, respectively.

The largest effect, although not statistically significant, was observed among patients with cardiovascular diseases, where three of the four studies[47,49,51,57] had

TABLE 1. Characteristics of the 31 Trials Included in the Meta-Analysis

Reference No.	Study Design	No. of subjects*	Type of subject†	TC (mmol/L) BP (mm Hg)‡	Blinding		No. of BPs /Device‖
					Participant	Observer§	
39	Mortensen et al 1983/crossover	20 Fish oil 20 Mixed oil	Healthy men (25-40 y)	TC: 5.0 BP: 120/76	+	+	1 BP Standard
41	Bruckner et al 1987/parallel group	10 Fish oil 11 Olive oil	Healthy men (19-40 y)	TC: 4.3 BP: 119/80	+	−	2 BPs Standard
43	v Houwelingen et al 1987/parallel group						
	Maastricht	19 Fish 20 Meat	Healthy men (20-45 y)	TC: 4.9 BP: 121/77	−	+	1 BP NS
	Tromso	11 Fish 12 Meat	Healthy men (20-45 y)	TC: 4.9 BP: 118/77	−	+	1 BP NS
	Zeist	10 Fish 10 Meat	Healthy men (20-45 y)	TC: 4.1 BP: 115/73	−	+	1 BP NS
13	Flaten et al 1990/parallel group	27 Fish oil 29 Olive oil	Healthy men (35-45 y)	TC: 6.0 BP: 119/80	+	+	2 BPs Standard
45	Ryu et al 1990/parallel group	10 Fish oil 10 Wheat germ	Healthy men (20-39 y)	TC: NS BP: 124/73	NS		BP NS NS
5	TOHP 1992/parallel group	175 Fish oil 175 Olive oil	Healthy men and women (30-54 y)	TC: NS BP: 123/81	+	+	3*3 BPs R-Z
40	Norris et al 1986/crossover	16 Fish oil 16 Placebo	Hypertensive men and women (45-74 y)	TC: NS BP: 161/95	+	+	2 BPs NS
10	Knapp et al 1989/parallel group	8 Fish oil 8 Saturated mix	Hypertensive men (age NS)	TC: NS BP: 137/94	−	−	20 BPs Automated
44	Meland et al 1989/parallel group	20 Fish oil 20 Mixed oil	Hypertensive men (26-66 y)	TC: 6.4 BP: 149/101	+	+	3 BPs Standard
7	Bonaa et al 1990/parallel group	78 Fish oil 78 Corn oil	Hypertensive men and women (34-60 y)	TC: 6.6 BP: 144/95	NS		2 BPs Automated
14	Levinson et al 1990/parallel group	8 Fish oil 8 Saturated mix	Hypertensive men and women (18-75 y)	TC: 5.6 BP: 147/94	+	+	3 BPs Standard
52	Wing et al 1990/crossover	20 Fish oil 20 Olive oil	Hypertensive men and women (32-75 y)	TC: 6.6 BP: 139/81	+	+	2 BPs NS
58	Radack et al 1991/parallel group	16 Fish oil 17 Safflower	Hypertensive men and women (mean, 46 y)	TC: 5.5 BP: 136/95	+	+	3 BPs Standard
38	Margolin et al 1991/parallel group	22 Fish oil 24 Corn oil	Hypertensive men and women (60-80 y)	TC: 5.7 BP: 164/94	+	+	3 BPs Standard
11	Morris et al 1992/crossover	18 Fish oil 18 Olive oil	Hypertensive men and women (32-64 y)	TC: 5.8 BP: 130/87	+	+	3*3 BPs R-Z
46	Demke et al 1988/parallel group	13 Fish oil 18 Safflower	Hypercholesterol, men and women (18-60 y)	TC: 7.5 BP: 119/74	+	+	BP NS NS
48	Bach et al 1989/parallel group	30 Total saturated	Hypercholesterol, men and women (mean, 31 y)	TC: 5.6 BP: 130/85	+	+	BP NS NS
56	Dart et al 1989/crossover	21 Fish oil 21 Olive oil	Hypercholesterol, men and women (mean, 46 y)	TC: 9.7 BP: 125/77	NS		BP NS NS
54, 55	Wilt et al 1989/crossover	38 Fish oil 38 Safflower	Hypercholesterol, men (mean, 42 y)	TC: 6.2 BP: 124/84	NS		3 BPs Standard
50	Kestin et al 1990/parallel group	11 Fish oil 11 Linoleic	Hypercholesterol, men (mean, 46 y)	TC: 6.3 BP: 124/75	+	+	3*4 BPs Standard
16	Cobiac et al 1991/parallel group	12 Fish 13 Fish oil 6 Saturated mix	Hypercholesterol, men (30-60 y)	TC: 6.8 BP: 128/79	−	−	12 BPs Automated
57	Davidson et al 1986/parallel group	30 Total olive oil	CHD Age, sex NS	TC: 8.0 BP: 142/88	+	+	BP NS NS
47	Mehta et al 1988/crossover	8 Fish oil 8 Placebo	CHD, men (52-73 y)	TC: 5.9 BP: 138/80	+	+	BP NS NS

*The number of subjects in each treatment period is listed for crossover studies. The number of subjects in each treatment group was not reported for References 57 and 48. Saturated mix is a mixture of saturated and other oils; mixed oil is a mixture of corn and olive oils.

†NS, not specified. Mixed sample indicates that there were no inclusion criteria for health of the sample. CHD, Coronary heart disease.

‡TC, total cholesterol at baseline; BP, average blood pressure at baseline for active and control groups for parallel group studies and BP during the placebo period for crossover studies.

§Blinded to treatment status.

‖One number represents the number of BPs used to measure BP at one visit; otherwise, the first number represents the number of measurements at one visit and the second number represents the number of measurement visits. Device, type of sphygmomanometer; R-Z, random zero; NS, device not specified.

TABLE 1. Continued

Reference No.	Study Design	No. of subjects*	Type of subject†	TC (mmol/L) BP (mm Hg)‡	Blinding		No. of BPs /Device‖
					Participant	Observer§	
51	Solomon et al 1990/parallel group	5 Fish oil 5 Olive oil	Stable angina, men and women (42-64 y)	TC: NS BP: 142/87	+	+	BP NS R-Z
49	Gans et al 1990/parallel group	16 Fish oil 16 Corn oil	Claudication, men and women (mean, 66 y)	TC: 6.6 BP: 148/80	+	+	BP NS R-Z
12	Haines et al 1986/parallel group	19 Fish oil 22 Olive oil	Diabetics, men and women (30-59 y)	TC: 5.0 BP: 136/82	−	−	BP NS R-Z
53	Jensen et al 1989/crossover	18 Fish oil 18 Olive oil	Diabetics, men and women (22-47 y)	TC: 5.7 BP: 148/89	+	+	BP NS Standard
8	Hendra et al 1990/parallel group	40 Fish oil 40 Olive oil	Diabetics, men and women (mean, 56 y)	TC: 6.0 BP: 143/83	+	+	BP NS NS
42	Rogers et al 1987/parallel group	30 Fish oil 30 Olive oil	Mixed sample, men (22-65 y)	TC: 5.2 BP: 130/76	+	+	BP NS Standard

decreases in blood pressure ranging from −10 to −17 mm Hg for SBP and −3 to −10 mm Hg for DBP. The estimate of effect for the three studies of diabetic patients[8,12,53] was small and nonsignificant. Since the estimates of effect for diabetic and cardiovascular disease patients are based on only a few studies, these results should be viewed with caution.

Given the observed association between ω-3 fatty acid dose and blood pressure effect in the overall analyses, we examined the dose-response relation within subgroups of subject type. There was no evidence of a dose-response effect of fish oil among the group of healthy subjects (SBP: β=0.5, P=.63; DBP: β=0.3, P=.42), nor among hypercholesterolemics (SBP: β=0.7, P=.35; DBP: β=−0.2, P=.76). There was a statistically significant dose-response effect among the hypertensive studies of −0.7/−0.5 mm Hg per gram increase in ω-3 fatty acids (P=.02/.04 for SBP/DBP) that was not evident when we restricted the analysis to ω-3 fatty acid doses of 2 to 6 g/d, a range similar to that of the groups of healthy and hypercholesterolemic studies (within the range of 2 to 6 g ω-3 fatty acids/d SBP: β=−1.0, P=.14; DBP: β=−0.2, P=.52). There was also no dose-response relation among stable hypertensives in this dose range (SBP: β=0.8, P=.49; DBP: β=0.7, P=.43).

Subgroup Analyses by Study Design

Comparison of the fish oil effect on blood pressure by study design indicated a greater decrease (by −2.5/−1.0 mm Hg) among crossover than parallel group designs, but when we controlled for dose, the adjusted difference of −0.62/−0.19 mm Hg was not statistically significant (probability values for SBP/DBP, .76/.77, respectively).

Subgroup Analyses by Placebo

The magnitude of the crude blood pressure effect for fish oil versus placebo was virtually the same regardless of which placebo was used (Table 3). The group of studies using ω-6 polyunsaturated oils for placebo administered a lower mean fish oil dose (3.6 g/d) than either of the groups using olive oil (4.5 g/d) or saturated oil placebos (4.6 g/d). Further analyses controlling for fish oil dose showed a small but significantly greater effect for SBP in the group of studies using ω-6 polyunsaturated oils for placebo when compared with the olive oil group (SBP/DBP: β=2.3/0.6 mm Hg, P=.04/.43). Missing from this subanalysis by placebo type were two studies that used a mixture of corn and olive oils[39,44] and two others that did not report the type of placebo.[40,47]

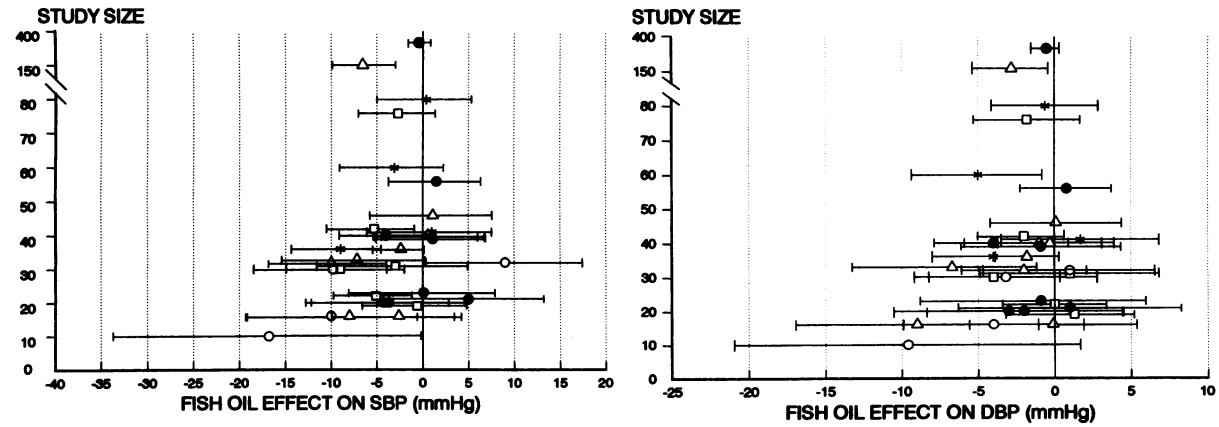

FIG 1. *Graphs show effects of fish oil on systolic blood pressure (SBP) and diastolic blood pressure (DBP) with 95% confidence intervals for the 31 studies in this meta-analysis. For each study, the mean difference in blood pressure is plotted against the number of subjects in each treatment. Symbols indicate health of study sample: ●, healthy; △, hypertensive; □, hypercholesterolemic; *, diabetic/mixed; ○, cardiovascular disease.*

TABLE 2. Overall Meta-Analysis on 31 Studies of Fish Oil and Blood Pressure

Reference No.	Study	ω-3 Dose* (g/d)	Treatment length (wk)	Variance†		BP Effect	
				SBP	DBP	SBP	DBP
Healthy subjects							
39	Mortensen et al	3.3	4	5.12	3.75	−4.0	−4.0
41	Bruckner et al	3.9	3	15.88	12.08	5.0	1.0
43	v Houwelingen et al						
	Maastricht	4.7	6	8.54	6.50	1.1	−0.9
	Tromso	4.7	6	14.49	11.03	0.1	−0.9
	Zeist	4.7	6	16.64	12.66	−3.7	−3.0
13	Flaten et al	6.5	6	5.95	2.18	1.5	0.8
45	Ryu et al	3.0	4	12.63	9.34	−4.3	−2.0
5	TOHP	2.4	24	0.36	0.23	−0.2	−0.6
Hypertensive subjects							
40	Norris et al	NS	6	9.17	4.09	−10.0	−2.0
10	Knapp et al	3.0	4	10.87	6.6	−2.6	−0.1
44	Meland et al	6.0	6	8.93	5.82	1.0	−1.0
7	Bonaa et al	5.1	10	2.81	1.50	−6.4	−2.8
14	Levinson et al	15.0	6	25.46	13.65	−8.0	−9.0
52	Wing et al	4.5	8	5.48	2.83	0.6	−0.3
58	Radack et al	2.0	12	14.16	7.35	−7.2	−6.7
38	Margolin et al	4.7	8	10.51	4.52	1.1	0.1
11	Morris et al	4.8	6	1.82	1.02	−2.4	−1.8
Hypercholesterolemic subjects							
46	Demke et al	1.7	4	15.67	8.22	−3.0	1.0
48	Bach et al	2.5	5	6.92	4.41	−9.0	−4.0
56	Dart et al	6.0	8	5.54	3.09	−5.3	−2.0
54	Wilt et al	6.0	12	4.41	3.12	−2.7	−1.8
50	Kestin et al	3.4	6	4.09	2.61	−5.1	0.0
16	Cobiac et al	4.5	5	7.01	4.59	−0.6	1.3
Cardiovascular disease subjects							
57	Davidson et al	6.0	4	15.77	8.66	−9.8	−3.2
47	Mehta et al	5.4	4	16.30	7.70	−10.0	−4.0
51	Solomon et al	4.6	12	51.27	25.12	−16.8	−9.6
49	Gans et al	3.0	16	17.13	7.67	9.0	1.0
Diabetic subjects							
12	Haines et al	4.6	6	10.97	6.49	1.0	1.7
53	Jensen et al	4.6	8	5.57	3.82	−9.0	−4.0
8	Hendra et al	3.0	6	6.30	3.16	0.4	−0.6
Mixed sample							
42	Rogers et al	3.3	4	7.26	4.52	−3.1	−5.0
Overall		4.8			−3.0 SBP		−1.5 DBP
95% Confidence intervals					−4.5,−1.5		−2.2,−0.8
Additional findings from the 31 studies used in analyses by dose							
10	Knapp et al	15.0	4	10.87	6.6	−8.2	−4.1
11	Morris et al	2.4	6	1.82	1.02	1.4	0.9
Additional findings from the 31 studies used in analyses by treatment length							
13	Flaten et al	6.5	3	5.95	2.18	−0.2	−1.0
14	Levinson et al	15.0	4	25.46	13.65	−7.0	−7.0
11	Morris et al	4.8	12	5.46	3.07	0.7	0.9
12	Haines et al	4.6	3	10.97	6.49	3.0	−2.0

SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; NS, not specified.

*ω-3 Dose represents eicosapentaenoic acid plus docosahexaenoic acid. The ω-3 dose for Bruckner et al, reported as 1.5 g/10 kg body wt, is estimated based on a mean weight of 85 kg.

†Estimated within-study variances (S_i^2) (see text).

‡Change in BP attributed to fish oil treatment (see text).

TABLE 3. Meta-Analyses by Subgroup: Dose, Length of Treatment, Subject Type, Study Design, and Placebo

Subgroup*	n	ω-3 Dose (g/d)	SBP (mm Hg)			DBP (mm Hg)		
			Q†	BP effect	95% CI	Q	BP effect	95% CI
ω-3 Fatty acid dose								
≤3 g/d	9	2.6	23.2†	−1.3	−4.8, 2.2	10.1	−0.7	−1.9, 0.5
>3-7 g/d	21	4.8	40.8†	−2.9	−4.5, −1.3	19.5	−1.6	−2.4, −0.8
15 g/d	2	15.0	<1	−8.1	−13, −2.7	1.2	−5.8	−10, −1.2
Treatment length								
3-4 Wk	11	5.1	15.5	−2.9	−5.5, −0.4	8.2	−2.3	−3.7, −0.9
5-6 Wk	13	5.4	24.2†	−2.4	−4.5, −0.3	12.1	−1.1	−2.2, −0.1
8-10 Wk	5	5.0	12.7†	−4.1	−7.7, −0.5	3.5	−2.0	−3.5, −0.6
12-24 Wk	6	3.8	15.7†	−1.3	−4.8, 2.2	9.1	−1.4	−3.4, 0.6
Subject type								
Healthy	8	4.2	9.2	−0.4	−1.6, 0.8	5.8	−0.7	−1.5, 0.1
Hypertensive	9	5.6	17.4†	−3.4	−5.9, −0.9	9.8	−2.0	−3.3, −0.7
Hypercholesterolemic	6	4.0	6.2	−4.4	−6.6, −2.2	4.6	−1.1	−2.7, 0.5
CVD	4	4.8	17.2†	−6.3	−17, 4.5	3.9	−2.9	−6.4, 0.6
Diabetic	3	4.1	9.7†	−2.7	−9.4, 4.0	3.5	−1.2	−4.3, 1.9
Study design								
Parallel group	23	4.5	53.0†	−2.2	−3.9, −0.5	27.4	−1.2	−2.1, −0.3
Crossover	8	4.9	16.6†	−4.7	−7.2, −2.2	3.6	−2.2	−3.4, −1.1
Placebo								
ω-6 Fatty acids	8	3.6	15.8†	−3.0	−5.9, −0.8	7.9	−1.5	−2.9, −0.1
Olive oil	12	4.5	32.5†	−2.2	−4.4, −0.4	14.2	−1.2	−2.4, −0.2
Saturated oil	7	4.6	9.7	−3.0	−6.1, 0.1	2.1	−1.9	−4.2, 0.4

SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CI, confidence intervals; CVD, cardiovascular disease.
*Studies included in subgroup analyses by length of treatment are 3-4 wk (References 10, 12-14, 39, 41, 42, 45-47, 57); 5-6 wk (References 8, 11-14, 16, 40, 43, 44, 48, 50); 8-10 wk (References 7, 38, 52, 53, 56); 12-24 wk (References 5, 11, 49, 51, 54, 58). Studies in subgroup analyses by dose of ω-3 fatty acids are ≤3 g/d (References 5, 8, 10, 11, 45, 46, 48, 49, 58); 4-7 g/d (References 7, 11-13, 16, 38, 39, 41-44, 50-54, 56, 57); 15 g/d (References 10, 14).
†Statistically significant at $P<.05$ (see "Appendix": Calculation of Q Test for Homogeneity).

Discussion

We conducted a meta-analysis of 31 controlled trials that showed a small, statistically significant effect of fish oil on blood pressure of −3.0/−1.5 mm Hg at an overall mean dose of 4.8 g ω-3 fatty acids/d. The narrow confidence intervals for the overall effect indicated that this finding probably was not due to chance and provided evidence for a biological relation that was heretofore unresolved because of inconsistent findings among studies. We did, however, observe substantial heterogeneity among individual study estimates for SBP, which suggested that the effect was not uniform.

Subgroup analyses showed that some of the discrepancies in study results may be explained by differences in the dose of ω-3 fatty acids administered to subjects and the presence of a weak but real dose-response effect. Health status of the study samples also appeared to account in part for the inconsistencies, since there was no evidence of an effect of fish oil among healthy subjects but moderate effects among hypercholesterolemics and stable hypertensives. The presence of a dose-response effect only within the subgroup of hypertensive subjects and only when the two studies using the highest dose of 15 g ω-3 fatty acids/d were included in the analysis may be due to the restricted dose ranges used in studies of hypercholesterolemics and healthy subjects or to the small number of studies used to detect small changes in effect and thus insufficient statistical power. It is also possible that among hypercholesterolemic patients, the blood pressure response to fish oil plateaus at a low dose.

The most consistent blood pressure responses to fish oil occurred among hypercholesterolemics, in which all six studies reported decreases in SBP, and in coronary heart disease patients, in which three of four studies reported large decreases in blood pressure. There is less certainty about the response to fish oil among hypertensives, where even among stable hypertensives the estimates for SBP were highly variable. Differences in dose appeared to account for some of this variation, but limited data prevented further investigation of, for example, the coexistence of hypercholesterolemia among hypertensives.

We were able to rule out other features of trial design as important sources of variation among trial results. The fish oil effects on blood pressure appeared to be fairly constant with varying lengths of treatment, except for a nonsignificant reduction in effect for treatment periods greater than 10 weeks, a likely consequence of diminished compliance with pill taking. There was also little evidence that the different types of placebo used by the studies could account for the divergent results: In analyses controlling for dose, the group using olive oil placebos had a significantly smaller effect on SBP than those using ω-6 polyunsaturated oils, but this was not substantiated in the comparison with studies using

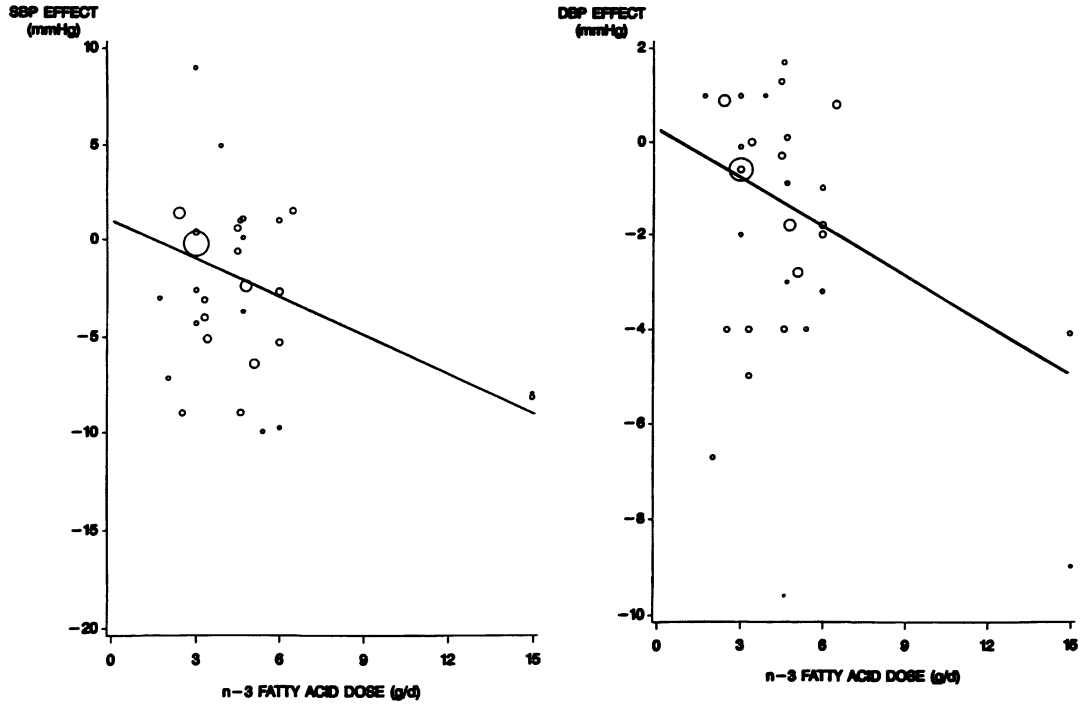

FIG 2. *Plots show inverse associations between dose of ω-3 fatty acids and mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) caused by fish oil. For each study, the mean difference in blood pressure changes between fish oil and placebo treatment groups is plotted against dose in weighted least squares regression. The weight of each study effect is indicated by the size of the circle.*

saturated fats and oils. The smaller reduction in blood pressure may be due to chance or to the fact that a greater number of the olive oil studies were of healthy or diabetic samples, groups with comparatively smaller estimates of effect. We also observed a greater blood pressure response in studies using a crossover design when compared with that of parallel group studies, a finding that refutes the contention by some[3] that crossover studies yield null results because of carryover of treatment effects into the placebo period.

The overall effects from the meta-analysis could be an overestimate by publication bias of the true blood pressure response to fish oil (see Fig 1). Notably, effects of ≥3 mm Hg in either SBP or DBP are reported in all six studies (100%) with sample sizes of 20 or less compared with 10 of 21 studies (45%) with samples ranging from 21 to 60 and just one (25%) of the four largest studies. However, the degree of bias should be minimal in that the smallest samples are generally given the least weight in the meta-analysis.

Our procedure for estimating the variance of individual studies produced weights favoring large samples, the crossover design (through the absence of intersubject variability), and multiple measurements of blood pressure, particularly the number of separate measurement occasions. This method appeared to provide good approximations of the actual study variances: Statistical significance of SBP and DBP changes based on the estimated variances were in agreement with investigators' reports of statistical significance in 92% of the cases (61 of 66 effects for 33 doses in 31 studies), and four of the five disagreements were cases of borderline significance.

Although we did not weight studies by scores of their scientific merit, a critical review of their methods did not reveal any shortcomings that would substantially alter the meta-analysis results. For example, one crossover study[39] failed to use random assignment, but in the absence of carryover effects, this should not affect the results; only the study by Cobiac et al, which was primarily designed to compare groups receiving fish oil or a fish diet, used questionable randomization to the control group.[16] Also, although few reports presented more than limited information on characteristics of the treatment and placebo groups, one study[51] did show substantial imbalances that could point to biased blood pressure effects, but this study received negligible weight in the meta-analysis. Neither could we find evidence for bias caused by low compliance or failure to blind the staff and/or participants. Compliance reports were generally excellent: Sixteen studies using biochemical measures of compliance showed appropriate increases in the ω-3 fatty acids, and six others reported a high percentage (>90%) of pills taken. All seven of the remaining studies, including one with 78% compliance[43] and six others with no compliance report, had blood pressure effects >3 mm Hg. Of the 11 studies that did not blind both participants and staff to treatment status, less than half (5) reported effects >2 mm Hg, and two of these used automatic devices to measure blood pressure.

Our finding of no fish oil effect on blood pressure in studies using low doses of ω-3 fatty acids of 3 g/d or less is supported by a number of population studies[59-63] that observed no correlation between blood pressure and fish consumption or biochemical levels of ω-3 fatty acids in cross-sectional analyses.

The predominant theory attributes the hypotensive effect of fish oil to the ω-3 fatty acid eicosapentaenoic acid (EPA), primarily to its ability to stimulate the synthesis of prostacyclin (a vasodilator) and inhibit thromboxane (a vasoconstrictor), although recent evidence from human studies indicates that the hypothesis of altered prostanoid synthesis has limitations as an explanation of lowered blood pressure.[1] The association between EPA and blood pressure response was supported by our meta-analysis. Although less is known about the hypotensive effects of docosahexaenoic acid (DHA), this was also significantly associated with blood pressure reduction.

Our analysis revealed that hypercholesterolemics and patients with cardiovascular disease had the largest blood pressure response to fish oil, which is consistent with a recent review[1] suggesting that the antihypertensive effects caused by inhibition of thromboxane synthesis are most likely to occur in those with initially high levels of thromboxane, such as in patients with atherosclerosis.

Insufficient data precluded our investigating the possibility of effect modification by dietary consumption of fish or sodium. In a trial of 157 hypertensives, Bonaa et al[7] found that fish oil lowered blood pressure only among those who consumed less than three fish meals per week, whereas Cobiac et al[37] reported a fish oil effect in those on sodium-restricted diets but not in other subjects.

We conclude that there is a dose-response hypotensive effect of fish oil in hypertensive patients but little or no effect among healthy normotensives, at least at clinically feasible dose levels. There also may be moderate effects on blood pressure among hypercholesterolemics and possibly larger effects in patients with cardiovascular disease. The hypotensive effect of fish oil may be related to the presence of atherosclerosis.

Fish oil is unlikely to be of benefit to healthy subjects for the prevention of hypertension or to treat hypertensive patients, given the uncertainty of a response and the large dose required to elicit small changes in blood pressure. Based on regression analysis of the nine controlled studies of hypertensive subjects, 7.7 g ω-3 fatty acids/d (about 15 capsules/d) is required for a blood pressure reduction of $-4/-3$ mm Hg. The data do suggest that fish oil may have a moderate, clinically meaningful effect in atherosclerotic patients. However, in view of the small numbers of subjects in previous trials, a larger trial would be needed to test this hypothesis.

Appendix

Calculation of the Summary Estimate of Effect and 95% Confidence Intervals

To calculate the summary estimate of effect for k studies, the ith individual study estimate y_i was multiplied by the inverse of the between- and within-study variance, $w_i=(1/[\sigma_k^2+S_i^2])$. The weighted estimates were summed over the k studies and divided by the sum of the weights:

$$\bar{Y}=\frac{\sum_{i=1}^{k} w_i y_i}{\sum_{i=1}^{k} w_i}$$

We used the $var(\bar{Y})=(\Sigma w_i)^{-1}$ to obtain 95% CI for the estimates of effect:

$$\bar{Y}\pm 1.96\sqrt{var(\bar{Y})}$$

Calculation of Within-Study Variance (S_i^2)

Given that $\bar{X}_{ijl}$ is group mean blood pressure for measurement period l of treatment group j in the ith individual study, $Var(\bar{X}_{ijl})$ is a function of the number of subjects as well as the number of blood pressure readings taken at one or more visits.

$$Var(\bar{X}_{ijl})=\frac{(\sigma^2_A/R_{jl}+\sigma^2_W/R_{jl}V_{jl})}{P_{jl}}$$

where σ_A^2 is the between-visit component and σ_W^2 is the within-visit component of variance for R_{jl} readings taken at each of V_{jl} visits for P_{jl} number of subjects.

The individual study estimates of blood pressure variance, σ_A^2 and σ_W^2, were obtained from a large screening study[9] of subjects grouped by age (30 to 49 years and 50 to 69 years), race (white and black), and sex, using information from the individual studies on the proportion of subjects within these categories. We first computed the weighted average variance over the two age categories within sex and race categories (step 1 in the example below), followed by computation of the weighted average variance for race within the sex category (step 2), and finally, computation of the weighted average variance over men and women (step 3). For studies where no information was provided on the sex, age, or race of the subjects, we assumed proportions equivalent to those of all studies combined: 78% were men, 50% in each age category, and white race. We also assumed that blood pressure was measured once at one visit for each measurement period ($R_{jl}=V_{jl}=1$) when this information was not reported.

Presented below are computations for the within-visit (σ_W^2) and between-visit (σ_A^2) variance estimates for SBP for the fish oil group of TOHP.[5]

Step 1. Calculate the weighted average variance over age categories given data on the age distribution of the TOHP study sample (83% 30 to 49 years and 17% 50 to 69 years) and the variance estimates provided by Rosner and Polk[9] for these age categories by race and sex (numbers within parentheses).

	White men	Black men
σ_A^2:	.83(34.6)+.17(49.5)=37.13	.83(56.2)+.17(73.6)=59.16
σ_w^2:	.83(14.0)+.17(15.7)=14.29	.83(15.0)+.17(18.6)=15.61
	White women	Black women
σ_A^2:	.83(42.90)+.17(64.80)=46.6	.83(56.20)+.17(73.30)=59.11
σ_W^2:	.83(12.80)+.17(13.50)=12.92	.83(11.20)+.17(18.80)=12.49

Step 2. Calculate the weighted average variance over race categories given data on the race distribution of the TOHP study sample (88% white and 12% black) and the weighted average variances computed in step 1 (numbers within parentheses).

	Men	Women
σ_A^2:	.88(37.13)+.12(59.16)=39.77	.88(46.60)+.12(59.11)=48.10
σ_W^2:	.88(14.29)+.12(15.61)=14.45	.88(12.92)+.12(12.49)=12.87

Step 3. Calculate the weighted average variance over sex categories given data on the sex distribution of the TOHP study sample (70.9% men and 29.1% women) and the

weighted average variances computed in step 2 (the numbers within parentheses).

$$\sigma_A^2: .709(39.77)+.291(48.10)=42.19$$

$$\sigma_W^2: .709(14.45)+.291(12.87)=13.99$$

For the parallel group study design, the blood pressure effect for individual studies is measured by calculating the difference between the blood pressure changes for the fish oil and placebo treatment groups. If $\bar{X}_{ijl}$ is the mean blood pressure for the jth treatment group (j=1, fish oil; 2, placebo) at the lth measurement period (l=1, pretreatment; 2, posttreatment), then the change in blood pressure is denoted by $d_{ij}=\bar{X}_{j2}-\bar{X}_{j1}$, and $var(d_{ij})=var(\bar{X}_{j2})+\text{var}(\bar{X}_{j1})$.

The blood pressure effect for the ith parallel study is $y_i=d_{i1}-d_{i2}$, and $S_i^2=var(y_i)=var(\bar{X}_{11})+\text{var}(\bar{X}_{12})+\text{var}(\bar{X}_{21})+\text{var}(\bar{X}_{22})$.

With the crossover design, the blood pressure effect is computed as the difference between posttreatment blood pressure measurements (l=2) for the fish oil (j=1) and placebo (j=2) treatment groups, disregarding any pretreatment blood pressure measurements: $y_i=\bar{X}_{12}-\bar{X}_{22}$, and $S_i^2=var(y_i)=var(\bar{X}_{12})+\text{var}(\bar{X}_{22})$.

Calculation of Q *and the Between-Study Variance* σ^2 *for* k *Studies*

The estimate of between-study variance (σ^2) for k studies was based on the Q statistic:

$$Q=\sum a_i(y_i-\bar{Y})^2$$

$$\sigma^2=\frac{Q-(k-1)}{\sum a_i-\sum a_i^2/\sum a_i}$$

where $a_i=(S_i^2)^{-1}$ for the ith study. When $Q-(k-1)<0$, then $\sigma^2=0$.[6]

Comparison of Adjusted Estimates of Effect for Two Groups of Studies

We compared the estimates of effect for two subgroups of studies using the standard normal test for the difference between means: $Z=(\bar{Y}_1-\bar{Y}_2)/[var(\bar{Y}_1)+\text{var}(\bar{Y}_2)]^{1/2}$.

Regression Analyses Controlling for ω-3 Fatty Acid Dose

We used analysis of covariance and the t test to test for the statistical significance of the difference between estimates of effect controlling for dose. The standard error of the β-coefficients, SE(β), was adjusted for the error mean squared produced by the regression model:

$$t=\frac{\beta}{SE(\beta)/\sqrt{MSE}}$$

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