Does Fish Oil Lower Blood Pressure?
A Meta-Analysis of Controlled Trials

Martha Clare Morris, ScD; Frank Sacks, MD; Bernard Rosner, PhD

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 vasconstrictor thromboxane, regulate renin release, and decrease the response to vasopressor hormones. 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. Two recent reviews 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. 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...
estimates of effect reported by individual studies weighted by the inverse of the individual and between
study variance according to a random effects model. 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 repre-
sents the difference in posttreatment blood pressures
for the fish oil and placebo periods. We included the
adjusted rather than crude effects for the two studies7,8
that controlled for differences among treatment and
control groups.

We were unable to derive the correct within-study variances ($\sigma^2$) for more than two thirds of the trials
based on the published data (few reported exact prob-
ability 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 individ-
ual mean blood pressure, measured through standard
sphygmomanometers, as a function of within- and be-
tween-visit measurement error and reported these two
variance components for different age, sex, and race
categories for a large screening population. We com-
puted 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”: Calcu-
ation 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 esti-
mates 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 $Q>\chi^2_{0.05,1,975}$ indicated that
the individual estimates for $k$ studies were not estima-
tors of one underlying effect (see “Appendix”: Calcu-
ation 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 esti-
mates. 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 sphygmoman-
ometers (followed by random-zero and ambulatory devic-
es). When results for more than one dose level10,11 or
length of treatment11-14 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 $\omega$-3
fatty acids/d and 7 weeks). However, these studies were
represented in every category for which they had infor-
mation in subgroup analyses.

Weighted least squares regression was used to test for
dose-response effect on blood pressure, with individ-
ual study effects weighted by the inverse of the esti-
mated variance. For these analyses, we included all
available data for different dose levels, which meant that
two studies10,11 each reporting the effect of two
doses of $\omega$-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 $\omega$-3 fatty acids. The two-sided $t$ test was used to
test for statistical significance of the $\beta$-coefficients with
the standard error of $\beta$ 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 pub-
llications 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
groups52-54; one study that used a diet supplement of
eggs from chickens fed fish oil55; one that reported only
mean arterial pressure,56 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 combina-
tion of treatments only57; 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 pressure32-34,37
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 re-
ported mean blood pressure data for both placebo and
fish oil treatment groups5,7,8,10-14,16-58 (Table 1). Most
studies used encapsulated fish oil; only Cobiac et al16
and v Houwelingen et al14 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 al38 and Radack et al38 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 design14 and one crossover study,39 did not use
random assignment to the treatment and control pe-
riods. Twenty of the 31 studies reported that both partic-
ipants and blood pressure observers were
blinded to treatment status; four reported single blind-
ing either of participants41 or of blood pressure ob-
servers43; three were unblinded10,12,16; and four did not
state whether blinding was part of the design,7,45,54,56 (Table 1). Eight studies measured blood
pressure with automated7,10,16 or random-zero5,11,12,49,51
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\textsuperscript{5,13,50} 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\textsuperscript{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 \(\omega-3\) 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 \(\omega-3\) 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 \(\omega-3\) 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 \(\omega-3\) 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,\textsuperscript{3} which used a low dose of 2.4 g \(\omega-3\) 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.\textsuperscript{5,13,39,41,43,45} In all except one of these studies\textsuperscript{5} 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.\textsuperscript{7,10,11,14,38,40,44,52,56} 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 \(\omega-3\) 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\textsuperscript{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 \(\omega-3\) 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.\textsuperscript{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\textsuperscript{47,49,51,57} had
<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Study Design</th>
<th>No. of subjects*</th>
<th>Type of subject†</th>
<th>TC (mmol/L)</th>
<th>Blinding</th>
<th>Observer§</th>
<th>No. of BPs / Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>Mortensen et al 1983/crossover</td>
<td>20 Fish oil</td>
<td>Healthy men (25-40 y)</td>
<td>TC: 5.0</td>
<td>+</td>
<td>+</td>
<td>1 BP</td>
</tr>
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<td>41</td>
<td>Bruckner et al 1987/parallel group</td>
<td>10 Fish oil</td>
<td>Healthy men (19-40 y)</td>
<td>TC: 4.3</td>
<td>+</td>
<td>-</td>
<td>2 BPs</td>
</tr>
<tr>
<td>43</td>
<td>v Houwelingen et al 1987/parallel group</td>
<td>19 Fish</td>
<td>Healthy men (20-45 y)</td>
<td>TC: 4.9</td>
<td>-</td>
<td>+</td>
<td>1 BP</td>
</tr>
<tr>
<td>13</td>
<td>Flaten et al 1990/parallel group</td>
<td>27 Fish oil</td>
<td>Healthy men (35-45 y)</td>
<td>TC: 6.0</td>
<td>+</td>
<td>+</td>
<td>2 BPs</td>
</tr>
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<td>45</td>
<td>Ryu et al 1990/parallel group</td>
<td>10 Fish oil</td>
<td>Healthy men (20-39 y)</td>
<td>TC: NS</td>
<td>NS</td>
<td>BP NS</td>
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<td>5</td>
<td>TOHP 1992/parallel group</td>
<td>175 Fish oil</td>
<td>Healthy men and women (30-54 y)</td>
<td>TC: NS</td>
<td>+</td>
<td>+</td>
<td>3+3 BPs</td>
</tr>
<tr>
<td>40</td>
<td>Norris et al 1986/crossover</td>
<td>16 Fish oil</td>
<td>Hypertensive men and women (45-74 y)</td>
<td>TC: NS</td>
<td>+</td>
<td>+</td>
<td>2 BPs</td>
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<tr>
<td>10</td>
<td>Knapp et al 1989/parallel group</td>
<td>8 Fish oil</td>
<td>Hypertensive men (age NS)</td>
<td>TC: NS</td>
<td>-</td>
<td>-</td>
<td>20 BPs</td>
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<tr>
<td>44</td>
<td>Meland et al 1989/parallel group</td>
<td>20 Fish oil</td>
<td>Hypertensive men (26-66 y)</td>
<td>TC: 6.4</td>
<td>+</td>
<td>+</td>
<td>3 BPs</td>
</tr>
<tr>
<td>7</td>
<td>Bonata et al 1990/parallel group</td>
<td>78 Fish oil</td>
<td>Hypertensive men and women (34-60 y)</td>
<td>TC: 6.6</td>
<td>NS</td>
<td>Automated</td>
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<td>14</td>
<td>Levinson et al 1990/parallel group</td>
<td>8 Fish oil</td>
<td>Hypertensive men and women (18-75 y)</td>
<td>TC: 5.6</td>
<td>+</td>
<td>+</td>
<td>3 BPs</td>
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<tr>
<td>52</td>
<td>Wing et al 1990/crossover</td>
<td>20 Fish oil</td>
<td>Hypertensive men and women (32-75 y)</td>
<td>TC: 6.6</td>
<td>+</td>
<td>+</td>
<td>2 BPs</td>
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<tr>
<td>58</td>
<td>Raddack et al 1991/parallel group</td>
<td>16 Fish oil</td>
<td>Hypertensive men and women (mean, 46 y)</td>
<td>TC: 5.5</td>
<td>-</td>
<td>-</td>
<td>3 BPs</td>
</tr>
<tr>
<td>38</td>
<td>Margolin et al 1991/parallel group</td>
<td>22 Fish oil</td>
<td>Hypertensive men and women (60-80 y)</td>
<td>TC: 5.7</td>
<td>+</td>
<td>+</td>
<td>3 BPs</td>
</tr>
<tr>
<td>11</td>
<td>Morris et al 1992/crossover</td>
<td>18 Fish oil</td>
<td>Hypertensive men and women (32-64 y)</td>
<td>TC: 5.8</td>
<td>+</td>
<td>+</td>
<td>3+3 BPs</td>
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<tr>
<td>46</td>
<td>Demke et al 1988/parallel group</td>
<td>13 Fish oil</td>
<td>Hypercholesterolemia, men and women (18-60 y)</td>
<td>TC: 7.5</td>
<td>+</td>
<td>+</td>
<td>BP NS</td>
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<tr>
<td>48</td>
<td>Bach et al 1989/parallel group</td>
<td>30 Total saturated</td>
<td>Hypercholesterolemia, men and women (mean, 31 y)</td>
<td>TC: 5.6</td>
<td>+</td>
<td>+</td>
<td>BP NS</td>
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<tr>
<td>56</td>
<td>Dart et al 1989/crossover</td>
<td>21 Fish oil</td>
<td>Hypercholesterolemia, men and women (mean, 46 y)</td>
<td>TC: 9.7</td>
<td>NS</td>
<td>BP NS</td>
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<tr>
<td>54, 55</td>
<td>Wilt et al 1989/crossover</td>
<td>38 Fish oil</td>
<td>Hypercholesterolemia, men (mean, 42 y)</td>
<td>TC: 6.2</td>
<td>NS</td>
<td>3 BPs</td>
<td></td>
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<tr>
<td>50</td>
<td>Kestin et al 1990/parallel group</td>
<td>11 Fish oil</td>
<td>Hypercholesterolemia, men (mean, 46 y)</td>
<td>TC: 6.3</td>
<td>+</td>
<td>+</td>
<td>3+4 BPs</td>
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<td>16</td>
<td>Cobiac et al 1991/parallel group</td>
<td>12 Fish</td>
<td>Hypercholesterolemia, men (30-60 y)</td>
<td>TC: 6.8</td>
<td>-</td>
<td>-</td>
<td>12 BPs</td>
</tr>
<tr>
<td>57</td>
<td>Davidson et al 1986/parallel group</td>
<td>30 Total olive oil</td>
<td>CHD</td>
<td>TC: 8.0</td>
<td>+</td>
<td>+</td>
<td>BP NS</td>
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<tr>
<td>47</td>
<td>Mehta et al 1988/crossover</td>
<td>8 Fish oil</td>
<td>CHD, men (52-73 y)</td>
<td>TC: 5.9</td>
<td>+</td>
<td>+</td>
<td>BP NS</td>
</tr>
</tbody>
</table>

*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) | Blinding | No. of BP/s
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<tbody>
<tr>
<td>51 Soloman et al 1990/parallel group 5 Fish oil Stable angina, men and women (42-64 y) TC: NS BP: 142/87 + + BP NS</td>
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<tr>
<td>49 Gans et al 1990/parallel group 16 Fish oil Claudication, men and women (mean, 66 y) TC: 6.6 BP: 148/80 + + BP NS</td>
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<tr>
<td>12 Haines et al 1986/parallel group 19 Fish oil Diabetics, men and women (30-59 y) TC: 5.0 BP: 136/82 - - BP NS</td>
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<tr>
<td>53 Jensen et al 1989/crossover 18 Olive oil Diabetics, men and women (22-47 y) TC: 5.7 BP: 148/89 + + BP NS</td>
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<tr>
<td>8 Hendra et al 1990/parallel group 40 Olive oil Diabetics, men and women (mean, 56 y) TC: 6.0 BP: 143/83 + + BP NS</td>
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</tr>
<tr>
<td>42 Rogers et al 1987/parallel group 30 Fish oil Mixed sample, men (22-65 y) TC: 5.2 BP: 130/76 + + BP NS</td>
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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 oils30,44 and two others that did not report the type of placebo.40,47

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 patients8,12,23 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).

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

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Study</th>
<th>Dose$^*$ (g/d)</th>
<th>Treatment length (wk)</th>
<th>Variance† SBP</th>
<th>Variance† DBP</th>
<th>BP Effect SBP</th>
<th>BP Effect DBP</th>
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<tr>
<td>39</td>
<td>Mortensen et al</td>
<td>3.3</td>
<td>4</td>
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<td>41</td>
<td>Bruckner et al</td>
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<td>15.88</td>
<td>12.08</td>
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<td>1.0</td>
</tr>
<tr>
<td>43</td>
<td>v Houwelingen et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Maastricht</td>
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<td>6</td>
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<tr>
<td></td>
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<td>11.03</td>
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<td>5.95</td>
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<td>1.5</td>
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<td>4</td>
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<td>4</td>
<td>10.87</td>
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<td>-1.0</td>
</tr>
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<td>Bonan et al</td>
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<td>-7.2</td>
<td>-6.7</td>
</tr>
<tr>
<td>38</td>
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<td>0.1</td>
</tr>
<tr>
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<td>1.82</td>
<td>1.02</td>
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<td>-1.8</td>
</tr>
<tr>
<td>46</td>
<td>Demke et al</td>
<td>1.7</td>
<td>4</td>
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<td>8.22</td>
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<td>1.0</td>
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<tr>
<td>48</td>
<td>Bach et al</td>
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<td>6.92</td>
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<td>Dart et al</td>
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</tr>
<tr>
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<td>6.0</td>
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<td>4.41</td>
<td>3.12</td>
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<tr>
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<td>6</td>
<td>4.09</td>
<td>2.61</td>
<td>-5.1</td>
<td>0.0</td>
</tr>
<tr>
<td>16</td>
<td>Cobi et al</td>
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<td>5</td>
<td>7.01</td>
<td>4.59</td>
<td>-0.6</td>
<td>1.3</td>
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<tr>
<td>57</td>
<td>Davidson et al</td>
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<td>4</td>
<td>15.77</td>
<td>8.66</td>
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<td>47</td>
<td>Mehta et al</td>
<td>5.4</td>
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<td>16.30</td>
<td>7.70</td>
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<tr>
<td>51</td>
<td>Solomon et al</td>
<td>4.6</td>
<td>12</td>
<td>51.27</td>
<td>25.12</td>
<td>-16.8</td>
<td>-9.6</td>
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<tr>
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<td>Gans et al</td>
<td>3.0</td>
<td>16</td>
<td>17.13</td>
<td>7.67</td>
<td>9.0</td>
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<tr>
<td>12</td>
<td>Haines et al</td>
<td>4.6</td>
<td>6</td>
<td>10.97</td>
<td>6.49</td>
<td>1.0</td>
<td>1.7</td>
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<tr>
<td>53</td>
<td>Jensen et al</td>
<td>4.6</td>
<td>8</td>
<td>5.57</td>
<td>3.82</td>
<td>-9.0</td>
<td>-4.0</td>
</tr>
<tr>
<td>8</td>
<td>Hendra et al</td>
<td>3.0</td>
<td>6</td>
<td>6.30</td>
<td>3.16</td>
<td>0.4</td>
<td>-0.6</td>
</tr>
<tr>
<td>42</td>
<td>Rogers et al</td>
<td>3.3</td>
<td>4</td>
<td>7.26</td>
<td>4.52</td>
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<td>-5.0</td>
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<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-3.0 SBP</td>
<td>-1.5 DBP</td>
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<tr>
<td>95% Confidence intervals</td>
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<td>-4.5, -1.5</td>
<td>-2.2, -0.8</td>
</tr>
</tbody>
</table>

**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 (S²) (see text).

$^\dagger$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

<table>
<thead>
<tr>
<th>Subgroup*</th>
<th>n</th>
<th>ω-3 Dose (g/d)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q† BP effect</td>
<td>95% CI</td>
</tr>
<tr>
<td>ω-3 Fatty acid dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 g/d</td>
<td>9</td>
<td>2.6</td>
<td>23.2† -1.3</td>
<td>-4.8, 2.2</td>
</tr>
<tr>
<td>&gt;3-7 g/d</td>
<td>21</td>
<td>4.8</td>
<td>40.8† -2.9</td>
<td>-4.5, -1.3</td>
</tr>
<tr>
<td>15 g/d</td>
<td>2</td>
<td>15.0</td>
<td>&lt;1 -8.1</td>
<td>-13, -2.7</td>
</tr>
</tbody>
</table>

**Treatment length**

|          |   |                |             |         |             |         |
|          | n |                | Q† BP effect | 95% CI | Q† BP effect | 95% CI |
| 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**

|          |   |                |             |         |             |         |
|          | n |                | Q† BP effect | 95% CI | Q† BP effect | 95% CI |
| 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 |
| Hypercholesteremic | 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**

|          |   |                |             |         |             |         |
|          | n |                | Q† BP effect | 95% CI | Q† BP effect | 95% CI |
| 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, 50); 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 hitherto 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 hypercholesterolemic 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 hypercholesterolemic 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 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 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. Also, although few reports presented more than limited information on characteristics of the treatment and placebo groups, one study 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 used 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, 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 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. 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 hypercholesterolemic patients with cardiovascular disease had the largest blood pressure response to fish oil, which is consistent with a recent review 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. found that fish oil lowered blood pressure only among those who consumed less than three fish meals per week, whereas Cobić et al. 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 hypercholesterolemic 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 yi was multiplied by the inverse of the between- and within-study variance, wi = 1/[wi2+Si2]. 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})=(\sum w_i)^{-1} to obtain 95% CI for the estimates of effect:

\[ \bar{Y} \pm 1.96\sqrt{\text{var}(\bar{Y})} \]

Calculation of Within-Study Variance (Si2)

Given that \( X_{ij} \) is group mean blood pressure for measurement period i of treatment group j in the ith individual study, \( \text{Var}(X_{ij}) \) is a function of the number of subjects as well as the number of blood pressure readings taken at one or more visits.

\[ \text{Var}(X_{ij}) = (\sigma_i^2+\sigma_w^2) \]

where \( \sigma_i^2 \) is the between-visit component and \( \sigma_w^2 \) is the within-visit component of variance for \( R_i \) readings taken at each of \( V_j \) visits for \( P_j \) number of subjects.

The individual study estimates of blood pressure variance, \( \sigma_i^2 \) and \( \sigma_w^2 \), were obtained from a large screening study 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 (\( R_w=V_w=1 \)) when this information was not reported.

Presented below are computations for the within-visit (\( \sigma_i^2 \)) and between-visit (\( \sigma_w^2 \)) variance estimates for SBP for the fish oil group of TOHP. 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 Polsky for these age categories by race and sex (numbers within parentheses).

<table>
<thead>
<tr>
<th>White men</th>
<th>Black men</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_i^2: .83(34.6)+.17(49.5)=37.13 )</td>
<td>( .83(56.2)+.17(73.6)=59.16 )</td>
</tr>
<tr>
<td>( \sigma_w: .83(14.0)+.17(15.7)=14.29 )</td>
<td>( .83(15.0)+.17(18.6)=15.61 )</td>
</tr>
</tbody>
</table>

Step 2. Calculate the weighted average variance for 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).

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_i^2: .83(42.9)+.17(64.8)=46.6 )</td>
<td>( .83(56.20)+.17(73.30)=59.11 )</td>
</tr>
<tr>
<td>( \sigma_w^2: .83(28.8)+.17(35.5)=12.92 )</td>
<td>( .83(11.20)+.17(18.80)=12.49 )</td>
</tr>
</tbody>
</table>

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).

\[ \sigma^2 = 0.709(39.77) + 0.291(48.10) = 42.19 \]

\[ \sigma^2_N = 0.709(14.45) + 0.291(12.87) = 13.99 \]

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 \( X_1 \) is the mean blood pressure for the jth treatment group (j=1, fish oil; 2, placebo) at the jth measurement period (t=1, pretreatment; 2, posttreatment), then the change in blood pressure is denoted by \( d_j = X_{1j} - X_{2j} \), and \( var(d_j) = var(X_{1j}) + var(X_{2j}) \).

The blood pressure effect for the ith parallel study is \( y_{ij} = d_{ij} - d_{0j} \), and \( S^2 = var(y_{ij}) = var(X_{1ij}) + var(X_{2ij}) + var(X_{2ij}) + var(X_{2ij}) \).

With the crossover design, the blood pressure effect is computed as the difference between posttreatment blood pressure measurements (t=2) for the fish oil (j=1) and placebo (j=2) treatment groups, disregarding any pretreatment blood pressure measurements: \( y_{ij} = X_{1i2} - X_{2i2} \), and \( S^2 = var(y_{ij}) = var(X_{1i2}) + var(X_{2i2}) + var(X_{2i2}) \).

**Calculation of Q and the Between-Study Variance \( \sigma^2 \) for k Studies**

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

\[ Q = \sum a_i(y_{ij} - \bar{Y}_j)^2 \]

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

where \( a_i = (S^2_i)^{-1} \) 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: \( Z = (\bar{Y}_1 - \bar{Y}_2) / [var(\bar{Y}_1) + var(\bar{Y}_2)]^{1/2} \).

**Regression Analyses Controlling for \( \omega-3 \) 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 \( \beta \)-coefficients, SE(\( \beta \)), was adjusted for the error mean squared produced by the regression model:

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

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**References**


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