Effect of Fish Oil on Heart Rate in Humans : A Meta-Analysis of Randomized Controlled Trials

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Background—The effect of fish oil on heart rate (HR), a major risk factor for sudden death, is not well established. We calculated this effect in a meta-analysis of randomized, double-blind, placebo-controlled trials in humans.

Methods and Results—Randomized trials of fish oil that evaluated HR were identified through MEDLINE (1966 through January 2005), hand-searching of references, and contact with investigators for unpublished results. Two investigators independently extracted trial data. A pooled estimate was calculated from random-effects meta-analysis. Predefined stratified meta-analyses and meta-regression were used to explore potential heterogeneity. Of 197 identified articles, 30 met inclusion criteria. Evidence for publication bias was not present. In the overall pooled estimate, fish oil decreased HR by 1.6 bpm (95% CI, 0.6 to 2.5; $P=0.002$) compared with placebo. Between-trial heterogeneity was evident (Q test, $P<0.001$). Fish oil reduced HR by 2.5 bpm ($P<0.001$) in trials with baseline HR ≥69 bpm (median) but had little effect (0.04-bpm reduction; $P=0.56$) in trials with baseline HR <69 bpm (P for interaction=0.03). Fish oil reduced HR by 2.5 bpm ($P<0.001$) in trials with duration ≥12 weeks but had less effect (0.7-bpm reduction; $P=0.27$) in trials with duration <12 weeks (P for interaction=0.07). HR reduction with fish oil intake did not significantly vary by fish oil dose (range, 0.81 to 15 g/d), type of HR measure, population age, population health, parallel versus crossover design, type of control oil, or study quality by Delphi criteria (P for interaction >0.25 for each).

Conclusions—In randomized controlled trials in humans, fish oil reduces HR, particularly in those with higher baseline HR or longer treatment duration. These findings provide firm evidence that fish oil consumption directly or indirectly affects cardiac electrophysiology in humans. Potential mechanisms such as effects on the sinus node, ventricular efficiency, or autonomic function deserve further investigation. **(*Circulation*. 2005;112:1945-1952.)**

Key Words: heart rate ■ fatty acids, omega-3 ■ fish oil ■ meta-analysis ■ randomized controlled trials

Fatty fish and fish oil intake is associated with lower risk of cardiac arrhythmias, including sudden death, arrhythmic coronary heart disease death, and atrial fibrillation.[1–8] Experimental studies in isolated rat myocytes, exercising dogs, and nonhuman primates suggest that fish oil has direct cardiac electrophysiological effects, including slowing of the heart rate (HR).[9–11] However, such effects are not well established in humans. Because higher HR is a major independent risk factor for cardiovascular death, particularly sudden death,[12–18] an effect of fish oil on HR would both confirm an influence on cardiac electrophysiology in humans and indicate a plausible potential mechanism for observed relations between fish intake and arrhythmic events. We therefore performed a meta-analysis of randomized placebo-controlled clinical trials to determine the effect of fish oil consumption on HR in humans.

Methods

Selection of Randomized Trials

We followed the Quality of Reporting of Meta-Analyses (QUOROM) standards[19] during all phases of the design and implementation of this analysis. Randomized clinical trials of fish oil that included evaluation of HR were identified through MEDLINE (1966 through February 2005), including fish oil trials designed primarily to evaluate other outcomes such as blood pressure or coronary restenosis,* hand-searching of reference lists of obtained articles, and contacting investigators for unreported HR data in published trials or for HR data from unpublished trials. To minimize publication bias, we attempted to identify all fish oil trials that may have measured and reported HR data, rather than limiting our search to trials designed primarily to evaluate HR. English-language trials in human subjects >18 years of age were included if oral fish oil supplementation was randomized and changes in HR or baseline and follow-up HR were measured; trials with organ transplant subjects, cointerventions that could not be separated from fish oil treatment,

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*Medline search criteria included (*heart rate* or *blood pressure* or *restenosis*) and (*fish oil* or *n-3 fatty acids* or *omega-3* or *eicosapentaenoic* or *docosahexaenoic*). Limits were adults ≥19 years of age, English language, clinical trial, and humans.

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no placebo control, nonblinding of participants, or duration <2 weeks were excluded.

Trial Review

When potentially relevant trials were identified, abstracts and, if necessary, original articles were screened for obvious exclusions by an investigator. Of 197 identified trials, 161 were excluded for not being a randomized trial of fish oil (n=28), for having no available HR data (n=75), for occurring in organ transplant recipients (n=12), for having no placebo control (n=29), for having a cointervention that could not be separated from fish oil treatment (n=6), or for being a duplicate publication from the same study (n=11). The identified trials included 10 published and 2 unpublished trials for which we contacted the authors to determine whether unreported HR data might be available. A list of all reviewed trials and reasons for exclusion is available by request from the investigators. For the remaining 36 trials not excluded during initial screening, each original article was independently reviewed for inclusion by 2 investigators. Six of these trials were excluded for no placebo control (n=2), no follow-up HR data (n=2), duration <2 weeks (n=1), or being a duplicate publication from the same study (n=1). Thirty trials met inclusion and exclusion criteria, including 2 trials for which unpublished HR data were obtained from the authors (personal communications, William Harris, February 18, 2005, and Ingrid Toft, March 4, 2005).[20–49] Concordance on inclusion and exclusion decisions was 100%.

Data Extraction

For each of the articles meeting inclusion and exclusion criteria, data were independently extracted by 2 investigators on study design; population; sample size and dropout; fish oil type, dose, and duration; method of HR assessment; change in HR or baseline and follow-up HR values; and HR variance measures. For studies reporting RR interval values (duration of 1 heartbeat in milliseconds), HR was calculated and its corresponding variance was estimated proportionally to the RR interval variance. Study quality was also independently assessed by 2 investigators according to the criteria for quality assessment of randomized clinical trials developed by Delphi consensus.[50] The 9 criteria (1a, 1b, and 2 through 8) include, for example, whether a method of randomization was performed, whether the treatment groups were similar at baseline with regard to the most important prognostic indicators, and whether the analysis was of intention-to-treat design. For the last criterion, we considered analyses as having intention-to-treat design if all subjects not lost to follow-up were analyzed according to their original randomization group; exclusions were not made for noncompliance. We assessed the validity of data extraction by comparing the independently abstracted results for concordance, and any discrepancies were resolved by discussion and review of the original manuscript by the 2 investigators who extracted the data or, if necessary, a committee comprising all the investigators. When necessary, missing information (type of control oil, mean age of participants, etc) was obtained by direct contact with the original authors. We attempted to minimize clinical heterogeneity by excluding studies in children, in organ transplant recipients, or with duration <2 weeks. Remaining clinical heterogeneity was evaluated qualitatively by comparing the mean age, gender distribution, and general health of the study populations; the doses and durations of fish oil treatment; and the methods of HR assessment. Clinical heterogeneity was assessed quantitatively in prespecified stratified analyses (see Statistical Analysis).

Statistical Analysis

Our primary outcome was the change in HR resulting from fish oil treatment. For parallel-design trials, the HR change from baseline to study end in the control group was subtracted from the HR change from baseline to study end in the treatment group. For crossover design trials, the HR at the end of the control period was subtracted from the HR at the end of the treatment period. Within-individual changes were used when available; otherwise, group means were used. SEs were abstracted or, if not reported, derived from SDs, CIs, or probability values. The pooled variance for the net HR change resulting from fish oil treatment was calculated as (1) $SE^2_T+SE^2_C-2(r)(SE_T)(SE_C)$ for crossover design trials, where SE_T and SE_C are the SE of the treatment and control period HR values, respectively, and r is the within-individual correlation between the treatment and control period HR values, and (2) $SE^2_{TG}+SE^2_{CG}$ for parallel-design trials, where SE_{TG} and SE_{CG} are the SE of the HR change from baseline to study end in the treatment and control groups, respectively. For parallel-design trials that reported precision of baseline and final HR values (n=18) rather than HR changes, SE_{TG} and SE_{CG} were calculated according to the method of Follmann et al,[51] which involves making an assumption for the unreported within-individual correlation between baseline and final HR values. On the basis of measured correlations in fish oil trials (Anouk Geelen, personal communication, January 27, 2005), the within-individual correlation between HR values was estimated to be 0.60 for trials using a single HR measure, 0.80 for trials using the average of multiple measures, and 0.85 for trials using a 24-hour measure, with the higher correlations consistent with less random error in the HR measurement. Sensitivity analyses were performed assuming a within-individual correlation of 0.60 for all trials. Data for the calculation of the change in HR and the variance of this change were not missing from any trial.

Pooled estimates of the effect of fish oil on HR were calculated through the use of random-effects meta-analysis, which accounts for heterogeneity in treatment effects among trials, using the method of DerSimonian and Laird[52] with inverse-variance (SE) weighting. Because some trials compared multiple intervention groups with a single control group (n=7), we performed sensitivity analyses in which separate pooled estimates and variances for the effect of fish oil on HR were calculated using separate meta-analyses for each of these trials; these trial-specific estimates then were used in a second meta-analysis evaluating all trials. Heterogeneity between studies was tested with the DerSimonian and Laird Q statistic.[52,53] To assess publication bias, a funnel plot of the treatment effect versus SE was visually inspected.[54] Potential publication bias was also evaluated with the Begg adjusted-rank correlation test,[55] a statistical analog of the visual funnel graph, and the regression asymmetry test according to the method of Egger et al.[54]

We performed predefined stratified meta-analyses to explore potential heterogeneity by dose of eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA) (at the median), duration of treatment (≥12 weeks versus less), type of HR measure (single measure, average of multiple resting measures, or 24-hour measure), baseline HR (at the median), type of control oil (olive oil versus other), population age (at the median), general health (healthy versus otherwise), study design (parallel versus crossover), and study quality (meeting at least 8 Delphi criteria versus fewer). We used meta-regression to test for heterogeneity of the pooled treatment effect by these factors,[56] testing for significance of the stratifying variable by using the Wald test in a mixed-effects meta-regression model. We also performed sensitivity analyses excluding trials with ≥20% dropout of randomized participants at baseline. All analyses were performed with Stata version 8.2 (Stata Corp). Statistical significance was defined as 2-tailed α <0.05.

Results

Overview of Trials

Of the 30 trials meeting inclusion and exclusion criteria, 6 had 2 separate intervention groups, and 1 had 3 separate intervention groups, for a total of 38 intervention groups in the 30 trials (Table 1). Although single-blind trials were acceptable, all were double-blind trials. Eight were crossover design trials, and 22 were parallel-design trials. Median study size was 30 participants; in total, this meta-analysis included 1678 individuals treated with fish oil or placebo for 27 615 person-weeks. The mean ages of the study populations ranged

TABLE 1. Characteristics of the 38 Intervention Groups (30 Trials) Included in the Meta-Analysis

Study	Design	Mean Age, y*	Male, %	General Health	Fish Oil, n†	Control, n†	EPA+DHA, g/d‡	Duration, wk	Control Oil	HR Measure	Dropout, %	Delphi Criteria§
Bairati et al,[20] 1992	Parallel	54	80	CAD	66	59	4.5	26	Olive	Single	39	9
Christensen et al,[21] 1999	Parallel	38	58	Healthy	20	20	1.7	12	Olive	24-h continuous	0	8
Christensen et al,[21] 1999 (group 2)	Parallel	38	58	Healthy	20	20	5.9	12	Olive	24-h continuous	0	8
Christensen et al,[21] 1998	Parallel	52	59	Renal failure	11	6	4.2	12	Olive	24-h continuous	41	8
Christensen et al,[22] 1996	Parallel	No data	No data	CAD, EF <40	26	23	4.3	12	Olive	24-h continuous	11	9
Conquer and Holub[24] 1999	Parallel	30	100	Healthy	9	10	3.0	6	n-6	Single	5	7
Deslypere,[25] 1992	Parallel	56	100	Healthy	15	14	1.0	52	Oleic	Multiple average	0	6
Deslypere,[25] 1992 (group 2)	Parallel	56	100	Healthy	15	14	1.9	52	Oleic	Multiple average	0	6
Deslypere,[25] 1992 (group 3)	Parallel	56	100	Healthy	14	14	2.9	52	Oleic	Multiple average	0	6
Dyerberget et al,[26] 2004	Parallel	39	100	Healthy	24	25	3.2	8	Palmitic	24-h continuous	10	8
Geelen et al,[27] 2003	Parallel	59	49	Healthy	39	35	1.3	12	Oleic	Multiple average	2	9
Geelen et al,[28] 2005	Parallel	64	60	Frequent PVCs	41	43	1.3	14	Oleic	24-h continuous	9	9
Gray et al,[29] 1996	Parallel	56	100	HTN	9	10	3.5	8	Corn	Multiple average	10	9
Grimsgaard et al,[30] 1998	Parallel	44	100	Healthy	72	77	3.8	7	Corn	Multiple average	4	9
Grimsgaard et al,[30] 1998 (group 2)	Parallel	44	100	Healthy	75	77	3.6	7	Corn	Multiple average	4	9
Landmark et al,[31] 1993	Crossover	42	100	HTN, Hyperlipidemia	18	...	4.6	4	Olive	Single	0	9
Leaf et al,[32] 1994	Parallel	63	79	CAD	201	205	6.9	26	Corn	Single	26	9
Levinson et al,[33] 1990	Parallel	56	81	HTN	8	8	15.0	6	Palm, corn	Multiple average	6	9
McVeigh et al,[34] 1994	Crossover	53	80	NIDDM	20	...	3.0	6	Olive	Single	0	9
Mehta et al,[35] 1988	Crossover	63	100	CAD	8	...	5.5	4	No data	Single	0	9
Mills et al,[36] 1990	Parallel	23	100	Healthy	10	10	1.3	4	Safflower	Multiple average	9	7
Mills et al,[37] 1989	Parallel	28	100	Healthy	10	10	2.6	4	Olive	Single	0	7
Miyajima et al,[38] 2001	Crossover	45	100	HTN	17	...	2.7	4	Linoleic	Multiple average	0	9
Monahan et al,[39] 2004	Parallel	25	56	Healthy	9	9	5.0	4.3	Olive	Single	0	9
Mori et al,[40] 1999	Parallel	49	100	Overweight, Hyperlipidemia	19	20	3.8	6	Olive	24-h ambulatory	5	9
Mori et al,[40] 1999 (group2)	Parallel	49	100	Overweight, Hyperlipidemia	17	20	3.7	6	Olive	24-h ambulatory	5	9
Nestel et al,[41] 2002	Parallel	58	55	Hyperlipidemia	12	14	3.0	7	Olive	Single	7	9
Nestel et al,[41] 2002 (group2)	Parallel	58	55	Hyperlipidemia	12	14	2.8	7	Olive	Single	7	9
O'Keefe et al,[42] 2005	Crossover	68	100	CAD, EF <40%	18	...	0.8	16	Corn, olive	1-h continuous	44	9
Solomon et al,[43] 1990	Parallel	56	80	CAD	5	5	4.6	12	Olive	Single	0	9
Stark and Holub,[44] 2004	Crossover	57	0	Healthy	32	...	2.8	4	Corn, soy	Multiple average	16	8
Toft et al,[45] 1995	Parallel	54	64	HTN	37	39	3.4	16	Corn	Single	10	8
Vacek et al,[46] 1989	Crossover	54	63	CAD	6	...	9.0	6	Palm, cottonseed	Single	25	8
Vandongen et al,[47] 1993	Parallel	46	100	Healthy	17	18	2.2	12	Olive, palm, safflower	Multiple average	13	5
Vandongen et al,[47] 1993 (group2)	Parallel	46	100	Healthy	16	18	4.3	12	Olive, palm, safflower	Multiple average	13	5
Wing et al,[48] 1990	Crossover	61	35	HTN	20	...	4.5	8	Olive	Multiple average	17	9
Woodman et al,[49] 2002	Parallel	61	76	NIDDM	17	16	3.8	6	Olive	24-h ambulatory	15	9
Woodman et al,[49] 2002 (group2)	Parallel	61	76	NIDDM	17	16	3.7	6	Olive	24-hour ambulatory	15	9

CAD indicates coronary artery disease; EF, ejection fraction; PVC premature ventricular contractions; HTN, hypertension; and NIDDM, non–insulin-dependent diabetes mellitus.

*When mean age was not specified, the median age or age range midpoint was used.

†Subjects who completed the trial (ie, after dropout).

‡For 2 studies, the dose of EPA and DHA was estimated as 80% of the n-3 polyunsaturated fatty acid dose.

§Number of Delphi criteria met of a total of 9 (1a, 1b, 2 through 8).

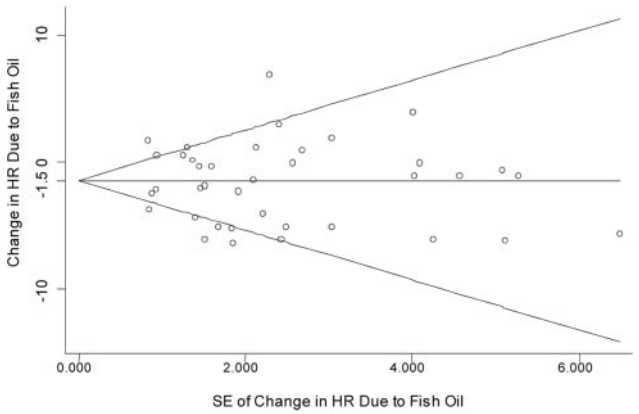

Figure 1. Funnel plot with pseudo–95% CIs of the 38 intervention groups included in the meta-analysis.

from 23 to 68 years (median, 54 years). Sixteen intervention groups were made up of generally healthy populations; 22 comprised individuals with ≥1 underlying chronic condition. The median EPA+DHA dose was 3.5 g/d (range, 0.81 to 15 g/d), and the median treatment duration was 8 weeks (range, 4 to 52 weeks). Thirteen intervention groups assessed HR with a single resting measure; 14 used the average of 2 or 3 resting measures; and 11 used the average of ambulatory or continuous monitoring. Twenty-five trials (30 intervention groups) met at least 8 Delphi criteria for study quality; 5 trials (8 intervention groups) met <8.

Our broad search methods appeared to be successful in minimizing the effect of publication bias. Among the 30 included trials, 12 reported HR findings in the abstract (7 reporting an effect, 5 reporting the absence of an effect); 10 reported HR findings in the results text but not the abstract (5 reporting an effect, 5 reporting the absence of an effect); 6 presented HR findings in a table only (all 6 showing no significant effect); and 2 constituted unpublished results. Little evidence for publication bias was present by visual inspection of a funnel plot (Figure 1), Begg's test (P=0.87), or Egger's test (P=0.69).

Effect of Fish Oil on HR

The individual trial results and the pooled estimate are presented in Figure 2. In the overall pooled estimate, fish oil decreased HR by 1.6 bpm (95% CI, 0.6 to 2.5; P=0.002) compared with placebo. Exclusion of trials with ≥20% dropout (n=5) had little effect on the pooled estimate, with fish oil decreasing HR by 1.3 bpm (95% CI, 0.3 to 2.4; P=0.009). Assuming a within-individual HR correlation of

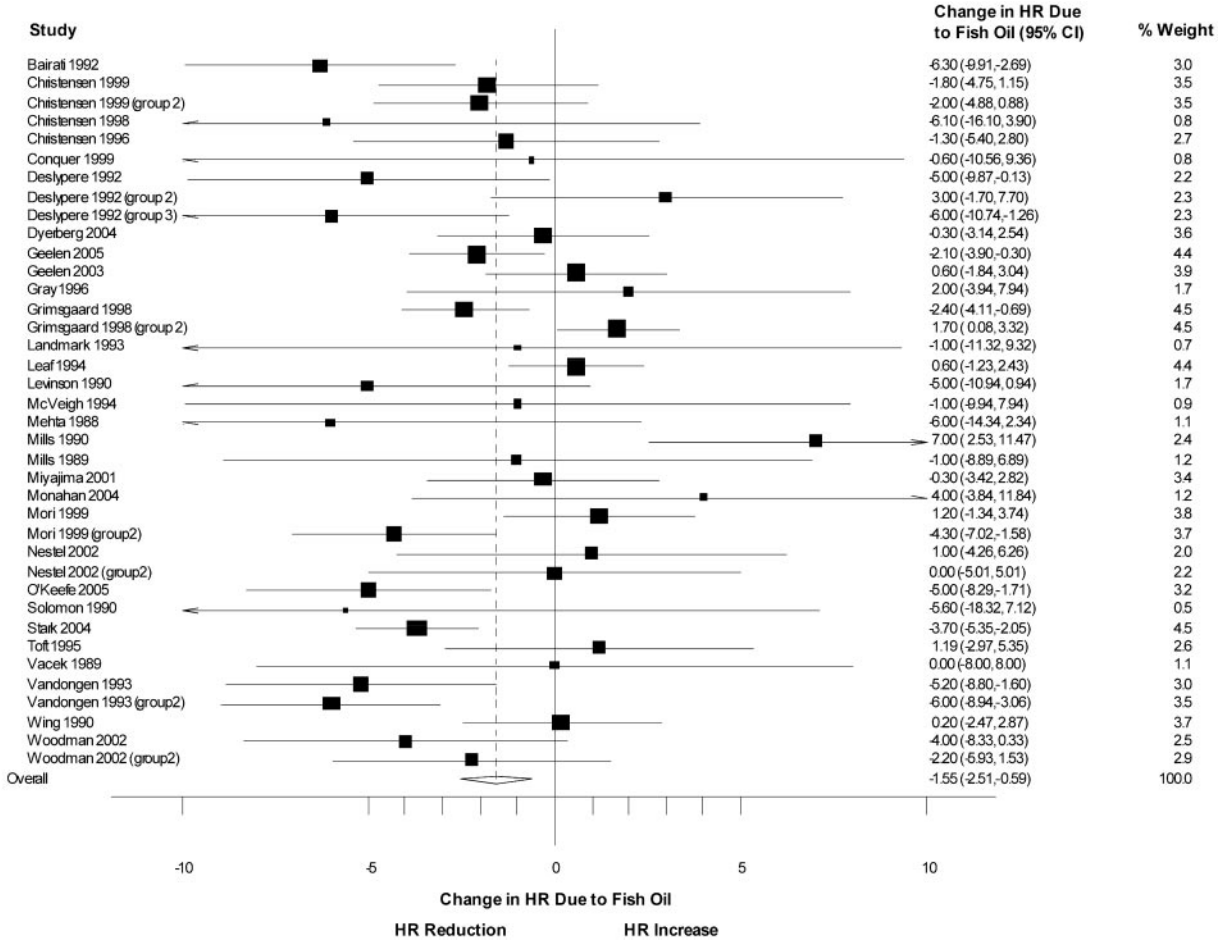

Figure 2. Change in HR resulting from fish oil consumption. Shaded squares indicate the point estimate for each trial, with the size of the square proportional to the contribution (inverse variance random effects weight) of the study to the overall estimate. The overall pooled estimate and 95% CI are indicated by the dotted line and clear diamond, respectively.

TABLE 2. Effect of Fish Oil on HR According to Prespecified Study Characteristics

Characteristic	Intervention Groups, n	Effect of Fish Oil on HR (95% CI)	*P* for Interaction*
Design			
Parallel	30	−1.4 (−2.5–−0.3)	
Crossover	8	−2.3 (−4.0–−0.5)	0.54
Mean age, y†			
<55	20	−1.3 (−2.8–0.2)	
≥55	17	−1.8 (−3.1–−0.5)	0.61
Health			
Generally healthy	16	−1.4 (−3.0–0.3)	
Chronic condition‡	22	−1.6 (−2.7–−0.5)	0.78
CAD§			
No	30	−1.3 (−2.4–−0.2)	
Yes	8	−2.7 (−4.8–−0.6)	0.26
Baseline HR, bpm			
<69	19	−0.4 (−1.9–1.0)	
≥69	19	−2.5 (−3.5–−1.4)	0.03
EPA+DHA, g/d			
<3.5	19	−1.4 (−2.8–0.0)	
≥3.5	19	−1.7 (−3.1–−0.3)	0.72
Duration, wk			
<12	22	−0.7 (−2.0–0.6)	
≥12	16	−2.5 (−4.0–−1.1)	0.07
HR measure			
Single	13	−0.8 (−2.6–1.0)	
Average of 2 or 3	14	−1.4 (−3.2–0.4)	0.32
Ambulatory/continuous	11	−2.0 (−2.9–−1.1)	
Control oil†			
Olive	17	−1.7 (−2.9–−0.5)	
Mixed/other	20	−1.4 (−2.7–−0.0)	0.74
Delphi criteria			
≥8	30	−1.4 (−2.3–−0.5)	
<8	8	−1.9 (−5.6–1.8)	0.56

*Testing for significance of the stratifying variable by using the Wald test in a mixed-effects meta-regression model.

†One trial was not included in this subgroup analysis because of missing data on this covariate.

‡Such as coronary artery disease (CAD), diabetes mellitus, hyperlipidemia, or hypertension.

§Secondary analysis; not prespecified.

0.60 for all trials also had little effect, with fish oil decreasing HR by 1.5 bpm (95% CI, 0.5 to 2.5; $P=0.003$). The pooled estimate was also similar in sensitivity analyses accounting for multiple intervention groups in some trials, with fish oil decreasing HR by 1.4 bpm (95% CI, 0.4 to 2.5; $P=0.007$).

Between-trial heterogeneity was evident (Q test, $P<0.001$). We evaluated prespecified study characteristics to explore reasons for potential heterogeneity (Table 2). The HR reduction with fish oil consumption was greater in study populations with a mean baseline HR ≥69 bpm (*P* for interaction=0.03), among whom fish oil reduced HR by 2.5 bpm (95% CI, 1.4 to 3.5; $P<0.001$), and in study populations receiving ≥12 weeks of fish oil treatment (*P* for interaction=0.07), among whom fish oil reduced HR by 2.5 bpm (95% CI, 1.1 to 4.0; $P=0.001$). Although other differences related to study characteristics were not statistically significant (Table 2), several findings were consistent with intuition; eg, the effect of fish oil on HR appeared possibly greater with increasing precision of the measurement method used (single versus average of 2 or 3 measures versus ambulatory/continuous), consistent with reduced measurement error reducing bias toward the null.

Little evidence was present for a dose-response effect. Stratified at the median dose of fish oil (3.5 g/d), the reduction in HR was not significantly different at higher versus lower doses (each compared with placebo) (*P* for interaction=0.72) (Table 2). Similarly, stratified into quartiles of fish oil dose, HR was reduced by 1.1 (95% CI, −0.9 to 3.1), 1.8 (95% CI, −0.1 to 3.6), 1.9 (95% CI, 0.1 to 3.8), and 1.5 (95% CI, −0.6 to 3.6) bpm in quartiles 1 through 4, respectively, compared with placebo (*P* for ordinal interaction=0.72). Evaluated continuously, the dose of fish oil was not a predictor of treatment effect ($P=0.63$), above and beyond being on fish oil treatment (yes/no). In the 2 trials with EPA+DHA doses ≤1 g/d, HR was reduced by 5.0 bpm (95% CI, 2.3 to 7.7; $P<0.001$) compared with 1.4 bpm in the trials with EPA+DHA doses >1 g/d (95% CI, 0.4 to 2.3; $P<0.001$).

When we evaluated different factors simultaneously in the meta-regression model, there appeared to be potential independent heterogeneity related to both baseline HR (*P* for interaction=0.04) and treatment duration (*P* for interaction=0.09). Among the 9 trials with mean baseline HR ≥69 bpm and treatment duration ≥12 weeks, fish oil reduced HR by 2.9 bpm (95% CI, 1.5 to 4.4; $P<0.001$) compared with placebo, without significant between-trial heterogeneity (Q test, $P>0.05$).

Discussion

In this meta-analysis of randomized, double-blind, placebo-controlled clinical trials, fish oil consumption reduced HR in humans. Although the overall effect was modest (1.6-bpm reduction), on a population level, even modest differences in risk factors can have a significant impact on health. These findings provide firm evidence for an effect of fish oil consumption on cardiac electrophysiology in humans.

The regulation of HR is a complex physiological process, with components related to vagal tone, sympathetic input, responsiveness of the sinus node, and systolic and diastolic left ventricular function. The decrease in HR with fish oil consumption indicates that marine n-3 fatty acids influence at least 1 of these parameters. The n-3 fatty acids are incorporated into myocyte membranes and may influence ion channel function[9,10]; this could directly alter the automaticity or responsiveness of the sinus node. Fish oil also lowers blood pressure in humans,[57] possibly by reducing systemic vascular resistance.[58] In one observational study, such an effect was apparent at dietary levels of fish intake.[58] Such a decrease in systemic vascular resistance would reduce left ventricular afterload and improve diastolic function, which could indirectly reduce HR as a result of better ventricular efficiency.

Experimental studies in nonhuman primates support the hypothesis that fish oil consumption improves left ventricular efficiency.[59,60] Intake of n-3 fatty acid may also improve measures of HR variability,[21–23,27] suggesting a potential effect on autonomic tone. Our findings substantiate an electrophysiological effect of fish oil in humans and support the need for further investigation of these potential mechanisms.

Higher HR is associated with increased cardiovascular risk, including greater risk of sudden death,[12–15,17] coronary heart disease death,[13,14] and cardiovascular death.[16] A higher HR could directly increase cardiovascular risk, eg, by increasing myocardial vulnerability to ischemia or arrhythmia. On the basis of work by Jouven et al,[17] our finding of a 1.6-bpm HR reduction with fish oil consumption would correspond to an ≈5% lower risk of sudden death. Thus, in addition to effects on HR, other mechanisms are likely to contribute to the reductions in sudden death risk with fish or fish oil consumption seen in observational studies and randomized trials. A higher HR may indicate less optimal underlying cardiovascular health as manifested by increased sympathetic tone, decreased vagal tone, or decreased ventricular efficiency. The HR reduction with fish oil consumption could therefore indicate beneficial effects of fish oil on these other physiological parameters that might reduce cardiovascular risk to a greater extent than that resulting from the change in HR alone.

Our exploration of heterogeneity revealed several interesting findings. First, the reduction in HR appeared larger in trials with longer duration of intake (≥12 weeks). This may relate in part to the time needed for EPA and DHA to be incorporated into the tissues where they exert their effects and suggests that regular consumption over time may have greater effects than short-term intake. Second, HR was reduced to a greater extent in populations with higher baseline HR. Because fish oil was compared with placebo in each trial, this result would not be due to regression toward the mean. This finding suggests that fish oil may have greater effects on HR in populations with higher intrinsic sinus node automaticity, greater sympathetic tone, lower vagal tone, or lower ventricular efficiency. Third, although power was insufficient to prove equivalence of different doses, very high consumption of fish oil did not appear to have substantially greater effects than modest consumption. This is consistent with observational studies and randomized trials indicating clinical benefits of fatty fish or fish oil consumption at relatively modest intake, ≈1 to 2 servings per week or 500 to 1000 mg/d EPA+DHA, respectively.[1–8] In the present meta-analysis, the lowest EPA+DHA doses were ≈1 g/d, and it is possible that a dose-response effect may exist at lower (eg, dietary) levels of intake, as suggested by one observational analysis.[58] Finally, although the differences were not statistically significant, the HR reduction was smaller in trials using a single resting measure of HR, intermediate in trials using the average of 2 or 3 resting measures, and greatest in trials using ambulatory or continuous measures. This is consistent with a greater degree of misclassification (random measurement error) when only a single or a few resting measures were used, suggesting that such trials may underestimate the true effect of fish oil on HR. Alternatively, the results of trials using ambulatory and continuous monitoring represent the averaged effect of fish oil consumption on both resting and activity-related HR responses, which may be somewhat greater than effects on resting HR alone.

Publication bias is a major potential limitation of meta-analyses. Our broad, prespecified search methods and contacting of investigators for unpublished results appeared to be successful in minimizing the effect of publication bias; in only a minority of included trials was a significant HR effect prominently reported, and little evidence was present for publication bias in the final included studies. Additionally, given the large number of included trials, it is unlikely that the results of even several additional studies would greatly alter the pooled estimate. Between-trial heterogeneity may limit the generalizability of the overall pooled estimate; we attempted to account for potential heterogeneity by using a random-effects model and by assessing factors that may explain between-trial differences.

In this meta-analysis of randomized, double-blind, placebo-controlled clinical trials, fish oil reduced HR, particularly with higher baseline HR or longer durations of treatment. These results provide strong evidence that fish oil consumption directly or indirectly influences cardiac electrophysiology in humans. This effect may directly account for part of the observed benefits of fish intake on cardiovascular risk, particularly risk of arrhythmic events, and may indicate favorable effects on physiological systems such as on autonomic tone, vascular resistance, or ventricular efficiency that improve cardiovascular health.

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