

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Bernasconi, Aldo A.; Wiest, Michelle M.; Lavie, Carl J.; Milani, Richard V.;
Laukkanen, Jari A.

Title: Effect of Omega-3 Dosage on Cardiovascular Outcomes : An Updated Meta-Analysis and
Meta-Regression of Interventional Trials

Year: 2021

Version: Accepted version (Final draft)

Copyright: © 2020 Mayo Foundation for Medical Education and Research. Published by Elsev

Rights: CC BY-NC-ND 4.0

Rights url: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Please cite the original version:

Bernasconi, A. A., Wiest, M. M., Lavie, C. J., Milani, R. V., & Laukkanen, J. A. (2021). Effect of Omega-3 Dosage on Cardiovascular Outcomes : An Updated Meta-Analysis and Meta-Regression of Interventional Trials. *Mayo Clinic Proceedings*, 96(2), 304-313.
<https://doi.org/10.1016/j.mayocp.2020.08.034>

Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials

Aldo A. Bernasconi, PhD; Michelle M. Wiest, PhD; Carl J. Lavie, MD; Richard V. Milani, MD; and Jari A. Laukkanen, MD, PhD

Abstract

Objectives: To quantify the effect of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on cardiovascular disease (CVD) prevention and the effect of dosage.

Methods: This study is designed as a random effects meta-analysis and meta-regression of randomized control trials with EPA/DHA supplementation. This is an update and expanded analysis of a previously published meta-analysis which covers all randomized control trials with EPA/DHA interventions and cardiovascular outcomes published before August 2019. The outcomes included are myocardial infarction (MI), coronary heart disease (CHD) events, CVD events (a composite of MI, angina, stroke, heart failure, peripheral arterial disease, sudden death, and non-scheduled cardiovascular surgical interventions), CHD mortality and fatal MI. The strength of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation framework.

Results: A total of 40 studies with a combined 135,267 participants were included. Supplementation was associated with reduced risk of MI (relative risk [RR], 0.87; 95% CI, 0.80 to 0.96), high certainty number needed to treat (NNT) of 272; CHD events (RR, 0.90; 95% CI, 0.84 to 0.97), high certainty NNT of 192; fatal MI (RR, 0.65; 95% CI, 0.46 to 0.91), moderate certainty NNT = 128; and CHD mortality (RR, 0.91; 95% CI, 0.85 to 0.98), low certainty NNT = 431, but not CVD events (RR, 0.95; 95% CI, 0.90 to 1.00). The effect is dose dependent for CVD events and MI.

Conclusion: Cardiovascular disease remains the leading cause of death worldwide. Supplementation with EPA and DHA is an effective lifestyle strategy for CVD prevention, and the protective effect probably increases with dosage.

© 2020 Mayo Foundation for Medical Education and Research. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) ■ Mayo Clin Proc. 2020;■(■):1-10

Despite significant advances in the prevention and treatment of cardiovascular diseases (CVDs), they remain the leading cause of mortality in the United States and most of the world. According to the Centers for Disease Control and Prevention, diseases of the heart accounted for 23.1% and cerebrovascular diseases for 5.2% of all deaths in the United States in 2017.¹

Eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, the two main omega-3 long-chain polyunsaturated fatty acids of marine origin, have shown promise for the prevention of CVD outcomes in animal

studies and epidemiologic studies as previously reviewed in detail.² However, randomized control trials (RCTs) have found inconsistent results.^{2,3} Whether a study finds a significant protective effect is not purely a function of study size or quality. Three large studies⁴⁻⁶ whose primary outcome was the occurrence of CVD events were published in 2018, and they reached diverging conclusions. A Study of Cardiovascular Events in Diabetes (ASCEND)⁴ (n=15,480), a study on primary prevention in diabetics, found no reduction in CVD risk. Vitamin D and Omega-3 Trial (VITAL)⁵ (n=25,871), the



From the Global Organization for EPA and DHA Omega-3s (GOED), Salt Lake City, UT (A.A.B.); the Department of Statistical Science, University of Idaho, Moscow, ID (M.M.W.); the Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of

Affiliations continued at the end of this article.

first primary prevention study on healthy adults, found a non-statistically significant 7% reduction in the risk of CVD events, and an unexpectedly high 28% reduction in the risk of myocardial infarction (MI), a pre-specified secondary outcome. Finally, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)⁶ (n=8179), a trial that studied the effect of Vascepa (icosapent ethyl), a highly concentrated ethyl ester form of EPA on patients with mostly borderline and mildly high triglycerides who were taking statins, found a statistically significant 25% reduction in the risk of the primary endpoint, as well as risk reductions of similar magnitudes in multiple secondary endpoints.

The results of meta-analyses are equally inconsistent. Three recent analyses of the effect of EPA and DHA on multiple CVD outcomes reached entirely different conclusions. For example, for coronary heart disease (CHD) mortality, Abdelhamid et al⁷ finds low certainty of a possible protective effect; Rizos et al⁸ finds a protective effect when using the usual *P* value cutoff of .05, but dismisses it as uncertain after using a very conservative multiple hypothesis correction; and Maki et al⁹ finds a statistically significant 8.0% risk reduction. The limitations of these analyses form the basis and rationale for our more extensive evaluation of the evidence.

The reasons for this variability among the results of RCTs are not well understood, and although a number of possible explanations have been proposed, there is a dearth of data to support them. The explanations proposed range from differences in results depending on the year of publication (earlier trials, presumably being more likely to find positive results),^{5,7,10,11} the natural variability to be expected in insufficiently powered trials, potential interference in the omega-3 mechanisms of action by modern CVD prevention and treatment (especially use of statins and statin doses), differences in omega-3 baseline status and treatment compliance, baseline risk and dosage (11), and whether the study intervention included EPA alone or both EPA and DHA.⁶

A recent meta-analysis¹² used meta-regression to study the effect of dosage on

CVD outcomes and suggested significant protective effects of omega-3 against CVD events, but they restricted the analysis to only the 13 largest RCTs to date. Previous meta-analyses have compared the effect of dosages greater than or less than 1000 mg/day,^{7,9} but reducing the existing dosage information in this manner using what is an arbitrary cutoff is not an efficient use of existing information, and does not allow for a proper quantification of the dose-effect relationship. In 2006, Mozaffarian and Rimm¹³ observed that for multiple CVD outcomes, a higher dosage was associated with increased protection, and quantified this effect, but their estimates were based on an unweighted combination of interventional and observational studies, and inclusion of the latter may have introduced confounders and biased the results.

The current analysis builds on the work of Abdelhamid et al⁷ but differs in the choice of what trials to include, focusing only on studies for which the intervention is EPA/DHA supplementation, and not dietary advice. This addresses more directly the question of what the effect is of long-chain omega-3 supplementation on CVD outcomes. Trials on dietary advice are important for designing efficient public health recommendations, but their results are confounded by problems in compliance and by the differences in EPA/DHA content of common foods. Unlike previous research,¹² our work uses the totality of available evidence in measuring the effect of dosage. The larger study number and wider range of dosages allows for more precise and more robust estimates of the dose-effect relationship. Finally, the current study is the first to use meta-regression to examine other often cited potential sources of heterogeneity in the results from existing research.

Given the prevalence of CVD, and their human and financial costs, it is important to determine which lifestyle modifications (and under what conditions) may provide some protection against these various CVD conditions. The use of fish oils and other products containing long-chain omega-3 fatty acids is a popular patient strategy to reduce CVD

risk, and a nuanced understanding of why some clinical trials yield positive results and others fail to do so is a fundamental step in the correct evaluation of the risks and benefits of this supplementation to adequately inform both clinicians and the public about the potential benefits or lack of efficacy.

The current review focuses on determining whether supplementation with EPA and DHA results in reduced CVD risk, and in quantifying the relationship between dosage and other predictors and the risk of CVD outcomes.

METHODS

Study Inclusion

A recent comprehensive meta-analysis by Abdelhamid et al.⁷ identified and extracted data published before August 2019 for all RCTs that reported CVD outcomes. The current study relies on the event count extracted as part of that meta-analysis and expands on its analysis. This review focuses on the following outcomes: CVD events (defined as a composite outcome including MI, angina, stroke, heart failure, peripheral arterial disease, sudden death, and non-scheduled cardiovascular surgical interventions), MI, and CHD events. Because considerable attention has focused on the effect of EPA and DHA on the risk of CVD mortality, we also examined fatal MI and CHD mortality. Characteristics of included studies are reported on [Supplementary Table 1](#) (available online at <http://www.mayoclinicproceedings.org>).

We restricted the review to only RCTs where the intervention consisted exclusively of dietary supplementation, and not dietary advice. The exclusion of dietary advice trials (four studies, n=5639) is the only difference between our inclusion criteria and those of Abdelhamid et al.⁷ Different foods contain widely varying amounts of EPA and DHA per serving, and this makes estimating the average within-study long-chain omega-3 intake particularly problematic.

Risk of Bias and Strength of Evidence

The risk of bias for each study is reported in [Supplementary Figure 1](#) (available online at

<http://www.mayoclinicproceedings.org>) using the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions*¹⁴, and for each individual study the assessment was based on the decisions in Abdelhamid et al.⁷

The overall strength of evidence was assessed for each outcome according to the guidelines developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group¹⁵ ([Supplementary Tables 2 and 3](#), available online at <http://www.mayoclinicproceedings.org>).

Statistical Analysis

For all outcomes, pooled relative risks (RRs) were calculated with a DerSimonian-Laird random effects model using the R statistical framework, version 3.5.2,¹⁶ and the meta package, v4.9-5.¹⁷ Results are summarized by means of the pooled RR estimate (and 95% CI interval) and number needed to treat (NNT), and the heterogeneity measured by means of the I² statistic. Asymmetry of the funnel plot, which would indicate the possibility of publication bias, is evaluated using the weighted linear regression method of Egger et al.¹⁸

For each outcome, the log-RR modeled as a linear function for which the y-axis intercept and slope(s) are reported, along with their P value testing the hypothesis that they are different than zero.

Each outcome is modeled as a function of: the EPA+DHA dosage, the year of publication, and the risk in the control group, which is used as a proxy for the baseline population risk in the absence of the intervention. Each model was fitted both before and after controlling for the effect of dosage.

RESULTS

Characteristics of Included Studies

The dosage of supplementary EPA+DHA in the treated groups of the 40 included studies varied from 400 mg/day to 5500 mg/day. Of the included studies, 5 (combined n=8036) were conducted with dosages lower than 800 mg/day, 10 (n=94,936) with dosages between 800 and 1200 mg/day, and 25

TABLE 1. Statistics From Random Effect Meta-Analysis of Each Studied Outcome^a

Outcome	Studies	Pooled RR (95% CI)	Heterogeneity (I ²)	Funnel plot asymmetry (P value)
CVD events	39 (n=134,843)	0.95 (0.90-1.00)	41% moderate	.36
MI	24 (n=130,487)	0.87 (0.80-0.96)	28% low	.35
CHD events	28 (n=131,306)	0.90 (0.84-0.97)	40% moderate	.15
Fatal MI	14 (n=78,981)	0.65 (0.46-0.91)	29% low	.42
CHD mortality	22 (n=122,231)	0.91 (0.85-0.98)	2% low	.03

^aCHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; RR = relative risk.

(n=32,295) with higher dosages. The (weighted) average dosage received was 1221 mg/day of EPA+DHA.

Pooled Results From Meta-Analysis

For all outcomes, except CVD events, supplementation with EPA+DHA results in a statistically significant risk reduction. Statistics summarizing the results of these random-effects meta-analyses are presented in Table 1 and Figure 1.

Supplementation was not associated with a statistically significant reduction in the risk of CVD events (RR, 0.95; 95% CI, 0.90 to 1.00), in line with Abdelhamid et al.⁷ It was associated with statistically significant reductions in the risk of MI (RR, 0.87; 95% CI, 0.80 to 0.96), high GRADE certainty,¹⁵ NNT of 272; CHD events (RR, 0.90; 95% CI, 0.84 to 0.97), high certainty NNT of 192; fatal MI (RR, 0.65; 95% CI, 0.46 to 0.91), moderate certainty NNT of 128 and CHD mortality

(RR, 0.91; 95% CI, 0.85 to 0.98), and low certainty NNT of 431. Heterogeneity was moderate¹⁴ for CVD events (I² = 41%) and CHD events (I² = 40%), and low for all other outcomes. Funnel and forest plots for all outcomes are included in Supplementary Figures 2 through 11 (available online at <http://www.mayoclinicproceedings.org>).

We performed leave-one-out sensitivity analysis and found that the removal of some studies would change the statistical significance of our findings for CVD events, fatal MI, and CHD death, but not for MI or CHD events. For rare outcomes whose occurrence rate in the control group was under 5% (MI, fatal MI and CHD death), we performed sensitivity analysis using Peto's odd ratios and found that it made no difference in the statistical significance of the results.

The results of our meta-analyses differ from those of previous reviews, likely because differences in inclusion criteria can have a dramatic impact. Abdelhamid et al,⁷ for example, includes trials whose intervention consists of dietary advice rather than EPA+DHA supplementation, but dietary advice often consists of multiple recommendations (not only to eat more fish), and it is difficult to estimate dosage and monitor compliance.

There was evidence of asymmetry of the funnel plot (see Table 1) only for CHD mortality. Such asymmetry is frequently an indication of publication bias, and previous meta-analyses on the effect of long-chain omega-3s have used visual inspection to conclude that publication bias exists. A more reliable method, such as the weighted linear regression method from Egger et al¹⁸

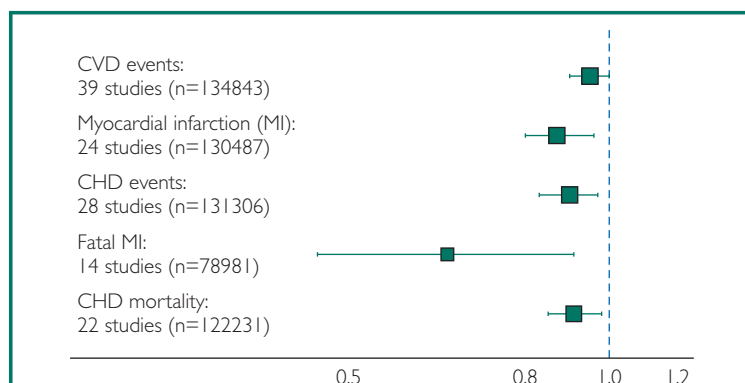


FIGURE 1. Pooled results from meta-analysis. The figure shows the pooled estimate of relative risk (RR) and 95% CI, as well as the number of studies and combined number of participants. CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction.

used in our analysis, finds no evidence of it for four of five outcomes.

Meta-Regression

The results of a meta-regression modeling the log-RR for each outcome as a function of EPA+DHA dosage are summarized in Table 2. Figure 2 shows the dose-effect relationship between EPA+DHA supplementation and the incidence of CVD events. Similar plots for the remaining outcomes are available in Supplemental Figures 12 through 16 (available online at <http://www.mayoclinicproceedings.org>).

For CVD events and MI, the slope is negative and significantly non-zero ($P < .01$), indicating that higher dosages (within the range of dosages used in the included studies) are associated with increased protection. The estimated slope for CVD events, describing the log-RR as a function of EPA+DHA dosage, was -6.0×10^{-2} (-1.0×10^{-1} ; -1.6×10^{-2} ; $P < .01$). These estimates for the slope translate to a risk reduction of 5.8% (1.6%; -9.9%) for each additional 1 g/day of intake. For MI, the slope estimate was -9.4×10^{-2} (-1.5×10^{-1} ; -3.9×10^{-2} ; $P < .001$), corresponding to a risk reduction of 9.0% (3.8% to 13.9%). We performed sensitivity analysis, and the removal of any one included study does not affect the slope sign or statistical significance.

For MI, fatal MI, and CHD mortality, we did not find a linear relationship. For these

outcomes, the pooled RR estimates from our meta-analysis showed a statistically significant risk reduction, raising the possibility of a nonlinear dose-response curve.

Similar models failed to find a relationship between the year of publication and the log-RR. These findings are maintained after correcting for the effect of dosage (Supplementary Table 4, available online at <http://www.mayoclinicproceedings.org>). For the relationship between baseline risk and effect, a statistically significant ($P < .05$) result was found for MI (Supplementary Table 5, available online at <http://www.mayoclinicproceedings.org>) only after correcting for the effect of dosage. The estimated slope is positive, suggesting that, for equal dosages, EPA+DHA supplementation is more effective for MI prevention in lower risk populations, as shown in the results of the VITAL trial (5). For fatal MI, a statistically significant finding of a negative slope was found, both before and after correcting for the effect of dosage, indicating that it is possible that EPA/DHA are more effective in preventing this outcome in higher-risk populations. More research is necessary to confirm these findings.

EPA Compared with EPA+DHA

One important question is whether EPA, DHA, or some combination of both is more effective in preventing CVD outcomes. For each outcome we modeled the log-RR as a

TABLE 2. Meta-Regression Coefficients for Log-RR as a Linear Model With EPA+DHA Dosage as Predictor^{a,b}

Outcome	Slope ^{c,d}	Intercept	Equivalent risk change per 1 g/day
CVD events	-6.0×10^{-2} (-1.0×10^{-1} to -1.6×10^{-2}) ^e	2.4×10^{-2} (-4.3×10^{-2} to 9.0×10^{-2})	-5.8% (-9.9% to -1.6%)
MI	-9.4×10^{-2} (-1.5×10^{-1} to -3.9×10^{-2}) ^f	3.7×10^{-3} (-9.8×10^{-2} to 1.0×10^{-1})	-9.0% (-13.9% to -3.8%)
CHD events	-5.5×10^{-2} (-1.2×10^{-1} to 6.4×10^{-3})	-2.4×10^{-2} (-1.3×10^{-1} to 8.0×10^{-2})	N/A
Fatal MI	3.8×10^{-1} (-3.1×10^{-3} to 7.6×10^{-1})	-8.6×10^{-1} (-1.3×10^0 to -4.2×10^{-1}) ^f	N/A
CHD mortality	2.2×10^{-2} (-2.0×10^{-1} to 2.4×10^{-1})	-1.2×10^{-1} [-3.3×10^{-1} , 9.5×10^{-2}]	N/A

^aCHD = coronary heart disease; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MI = myocardial infarction; N/A = not applicable; RR = relative risk.

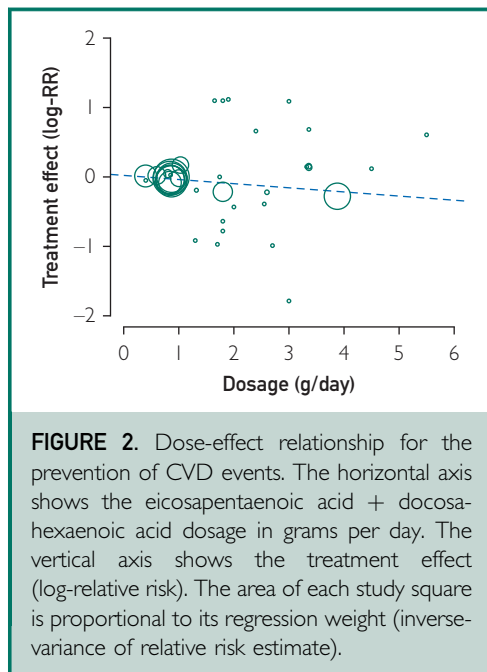
^bLog-RR modeled as a function of daily EPA+DHA dosage, in g/day.

^cFor outcomes for which the slope is significantly non-zero, the change in risk for that outcome associated with each additional 1 g/day of EPA+DHA is reported.

^dEstimates and 95% CIs are reported for slope and intercept.

^e $P < .01$.

^f $P < .001$.



linear function of dosage and an interaction term between the dosage and a Boolean variable, indicating whether the intervention consisted a combination of EPA and DHA versus uniquely of EPA. The interaction term, which measures whether the slope of the dose-response lines for trials with EPA is different from the slope for all other trials, was not significantly different from zero for any of the outcomes. We are unable to conclude that EPA alone is a more effective agent for CVD prevention than EPA+DHA,⁶ at least for the outcomes covered in this review, from the currently available evidence.

DISCUSSION

The use of EPA+DHA was found to significantly reduce the risk of all outcomes considered in this study, with the exception of CVD events. For CVD and MI, the protective effect increased significantly with dosage. The combined results of our meta-analysis and meta-regressions provide strong evidence of the effectiveness of EPA+DHA intake in the prevention of adverse CVD outcomes, particularly CHD events and MI.

Protective Effects and Their Relationship With Dosage

Supplementation was associated with a small, although nonsignificant, reduction in the risk of CVD events (RR, 0.95; 95% CI, 0.90 to 1.00). The heterogeneity for this outcome is moderate (41%), indicating that a substantial percentage of the variance in this meta-analysis is due to between-study differences.¹⁹ Meta-regression analysis finds that this heterogeneity is partially due to differences in dosage — increasing intake by 1 g/day is significantly associated ($P < .01$) with a reduction of 5.8% in the risk of CVD events. The low residual heterogeneity (23%) is likely due to factors such as differences in study design (including the baseline characteristics of the studied populations), as well as inconsistencies in the definitions used across studies for what constitutes a CVD event.

Use of EPA and DHA was also associated with a statistically significant ($P < .001$) lower risk of CHD events and MI with equivalent risk reductions of 9% (95% CI, -16% or -3%) and 13% (-20%; -4%), respectively. In the case of MI, this risk reduction is dose-dependent, and each additional 1 g/day is associated with a significant risk reduction of 9.0%. These findings indicate that long-chain marine omega-3s are an effective strategy for the prevention of CHD events, and especially protective against MI.

One recent study, VITAL (5), the first large-scale RCT aimed at studying the role of EPA+DHA supplementation in primary CVD prevention, found a nonsignificant 8% risk reduction in the risk of major adverse CVD events (a composite endpoint combining stroke, MI, and death from CVD causes), its primary outcome. The relatively low dose used (840 mg/day) was associated with a significant 28% reduction in the risk of MI, a secondary outcome. The implications of this finding, however, have generated some controversy. Results from secondary outcomes need to be interpreted with caution²⁰ because too many outcomes increase the risk of finding a false-positive result. Such findings must be subjected to more strict significance criteria (correcting for multiple

hypothesis testing) or confirmed with other studies. This result is already in line with an existing body of research indicating a protective effect of EPA and DHA against MI, as shown by our analysis. According to our meta-regression—derived model, 840 mg/day should reduce the risk of MI by 7.6%, and VITAL found an effect more than three times larger. The remaining question is not whether the finding in VITAL proves that EPA and DHA reduces the risk of MI, but rather why the effect observed was so large—whether it is a numerical artifact, or some characteristics of the studied population that makes long-chain marine omega-3s particularly protective. If the latter, this would have profound implications in devising primary preventative care strategies.

Based on our meta-analysis, supplementation with EPA and DHA was also associated with significant reductions in the risk of CVD death: a 35% reduction in the risk of fatal MI, and a 9% reduction in the risk of CHD mortality. Meta-regression shows that the slope of the log-RR as a function of dosage is not significantly non-zero. This is consistent with the hypothesis that CHD mortality and fatal MI prevention can be achieved with little EPA+DHA (less than the 800 to 1200 mg/day that constitute most of the existing evidence), and that the protective effect quickly plateaus with increasing dosages. This agrees with the conclusions reached by Mozaffarian and Rimm¹³ that most of the protection against CHD mortality is achieved with dosages less than 500 mg/day.

Year of Publication

A commonly held belief is that earlier interventional trials found larger CVD protective effects for EPA and DHA, but that later studies have found smaller risk reductions, if they found a reduction at all.^{7,11} The interpretation of this putative finding varies. Some researchers attribute this to the fact that newer trials benefit from advances in study design and that more carefully planned trials would find null results. Others observe that the treatment and prevention of CVD has changed dramatically in the last three decades, and that modern medications,

particularly statins and statins at higher doses, may interfere with the mechanisms of action of EPA and DHA, reducing the effect magnitude. There is, in fact, evidence of complex interactions (both synergistic and antagonistic) between statins and long chain omega-3s.²¹ Results from our meta-regressions using the year of publication as a predictor (either correcting for the effect or dosage or not) fail to find a significant relationship. Although it is possible that populations that receive different forms of CVD care may benefit differently from EPA/DHA supplementation, there is no evidence that the effect magnitude for any of the outcomes covered in this study has changed over time.

Primary Versus Secondary Prevention

Finally, an important question is whether EPA+DHA supplementation is more effective for primary or secondary prevention, a challenging question because of the paucity of primary prevention studies. We addressed a related question: Does the EPA+DHA supplementation effectiveness change depending on the baseline risk of the population? For each outcome, we used the event risk in the placebo or untreated group as a proxy for the population risk. Most of the existing research has been conducted on populations at high risk (people with established CVD, diabetes, or a history of CVD events), and we could only find that EPA+DHA is more effective in higher-risk populations for MI, and only after correcting for the effect of dosage. The fact that the effect of supplementation does not increase with baseline risk provides some confidence that findings about effectiveness can be generalized to prevention in lower-risk populations.

EPA Compared With EPA+DHA

It has been observed that DHA supplementation can increase low-density lipoprotein cholesterol (LDL-C), and some researchers believe that omega-3 supplementation would be safer if it consisted primarily of EPA.²² But LDL-C is an imperfect marker of CVD risk, and although DHA increases LDL-C, it

does not change apolipoprotein B.²³⁻²⁵ This is consistent with shifting LDL particles to a larger, less atherogenic profile.

There is a lack of data to address this question. Because there is the belief that EPA is better for CVD prevention, most of the information available for larger dosages has been obtained using highly concentrated forms of EPA, and the range of DHA dosages across studies is small. Based on our analysis, we are unable to conclude that EPA alone is any more or less effective for CVD prevention than EPA+DHA.⁶

To our knowledge, this is only the second study to estimate the relationship between EPA+DHA dosage and the effect of supplementation on selected CVD outcomes using the meta-regression methodology, the first to do so using the totality of available evidence from interventional trials, and the first to address the effect of other numeric variables.

Study Limitations

One weakness of our study is that we only considered linear models. It is possible that the real relationship is nonlinear, with threshold and plateau effects, and our analysis assumes that the dosages used in existing interventional studies correspond to the central part of the dose-effect curve, where the relationship is approximately linear. We decided not to include nonlinear terms in our meta-regression models out of concerns that doing so may lead to overfitting. Depending on the outcome, our assumption may be more or less correct, and more research is needed to address this issue. However, our results suggest that there may be some dose-dependent relationship between EPA/DHA doses and major clinical events.

A second weakness derives from the fact that we were unable to assess whether there was a higher prevalence of negative side effects in the treated group. Side effects have already been studied extensively and been generally found to be rare and/or not particularly serious.²⁶⁻²⁸ Because serious side effects are rare, their reporting is not consistent across studies, which makes

meta-analysis and meta-regression less accurate techniques to address this question.

VITAL⁵ found a higher risk reduction in subpopulations who eat less fish — this is consistent with a nonlinear dose-effect curve, where a possible protective effect reaches a plateau at high enough doses. A third weakness of our study is the lack of data to address whether this is the case. Fish intake is rarely declared in trials, and varies depending on multiple cultural, socioeconomic, and demographic variables. The only way to answer this question is through subgroup analysis of the individual patient data for each trial.

A final limitation derives from the fact that there is insufficient research on the effect of EPA/DHA supplementation on primary cardiovascular prevention. Only two trials have been conducted in populations without a previous history of CVD: VITAL⁵ and ASCEND.⁴ This makes the use of subgroup analysis for a direct comparison between primary and secondary prevention trials impossible. Abdelhamid et al⁷ addressed this limitation by comparing secondary and primary/mixed research, but the majority of the mixed trials include a majority of patients with previous events or at very high risk. Our approach consisted of modeling the risk reduction as a function of the baseline risk and found little evidence that EPA/DHA are more or less preventive in populations at different risk.

CONCLUSION

The current study presents strong evidence that EPA+DHA supplementation is an effective strategy for the prevention of certain CVD outcomes, and that for CVD events and MI the protective effect appears to increase with dosage. Authoritative bodies issuing intake recommendations and health care providers need to consider taking these results into account. Considering the relatively low costs and side effect profiles of omega-3 supplementation and the low drug-drug interactions with other standard therapies used in primary and secondary CVD prevention, clinicians and patients should consider the potential benefits of

omega-3 (EPA/DHA) supplementation, especially using 1000 to 2000 mg/day dosages, which are rarely obtained in most Westernized diets, even those including some routine fish consumption.

SUPPLEMENTAL ONLINE MATERIAL APPENDIX

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: CHD = coronary heart disease; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MACE = major adverse cardiovascular events; MI = myocardial infarction; RCT = randomized control trial

Affiliations (Continued from the first page of this article.): Medicine, New Orleans, LA (C.J.L., R.V.M.); and the Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland; Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland; Department of Medicine, Central Finland Health Care District, Jyväskylä, Finland (J.A.L.).

Potential Competing Interests: Dr Bemasconi is an employee of the Global Organization for EPA and DHA Omega-3s (GOED), a 501(c)6 not-for profit trade association. GOED's goals are to increase consumption of omega-3s to adequate levels around the world and to ensure that the industry is producing quality omega-3 products that consumers can trust. Dr Wiest has been a guest speaker with travel sponsored by DSM Nutritional Products and the Global Organization for EPA and DHA Omega-3s (GOED); and has received funding from GOED to conduct a meta-analysis on omega-3 fatty acids. Dr Lavie has been a speaker for Amarin Corporation on Vascepa, has consulted for DSM Nutritional Products, and has made an omega-3 educational video at the American Heart Association meeting on November 14, 2016, for the Global Organization for EPA and DHA Omega-3s and also gave a presentation at a GOED-hosted omega-3 conference in Barcelona, Spain, in February 2020. The remaining authors report no potential competing interests.

Grant Support: This study was supported by a grant from the Global Organization for EPA and DHA Omega-3s (GOED), Salt Lake City, UT.

Correspondence: Address to Aldo A. Bemasconi, PhD, Global Organization for EPA and DHA Omega-3s (GOED), 1075 Hollywood Ave, Salt Lake City, UT 84105 (aldo@goedomega3.com).

ORCID

Aldo A. Bemasconi: <https://orcid.org/0000-0002-7170-4799>; Carl J. Lavie: <https://orcid.org/0000-0003-3906-1911>; Jari A. Laukkanen: <https://orcid.org/0000-0002-3738-1586>

REFERENCES

- Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. *NCHS Data Brief*. 2018;328:1-8.
- Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58(20):2047-2067.
- Rizos EC, Elisaf MS. Does supplementation with omega-3 PUFAs add to the prevention of cardiovascular disease? *Curr Cardiol Rep*. 2017;19(6):47.
- Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379(16):1540-1550.
- Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380(1):23-32.
- Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.
- Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2020;3(2):CD003177. pub5.
- Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308(10):1024-1033.
- Maki KC, Palacios OM, Bell M, Toth PP. Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: an updated meta-analysis and review of research gaps. *J Clin Lipidol*. 2017;11(5):1152-1160.e2.
- Abbasi J. Another nail in the coffin for fish oil supplements. *JAMA*. 2018;319(18):1851-1852.
- Rice HB, Bemasconi A, Maki KC, Harris WS, Von Schacky C, Calder PC. Conducting omega-3 clinical trials with cardiovascular outcomes: proceedings of a workshop held at ISS-FAL 2014. *Prostaglandins Leukot Essent Fatty Acids*. 2016;107:30-42.
- Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: an updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. *J Am Heart Assoc*. 2019;8(19):e013543.
- Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*. 2006;296(15):1885-1899.
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. www.training.cochrane.org/handbook. Accessed September 8, 2020.
- Schünemann H, Brożek J, Guyatt G, Oxman A. *GRADE handbook for grading quality of evidence and strength of recommendations*. Updated October 2013. The GRADE Working Group, 2013. guidelinedevelopment.org/handbook. Accessed September 8, 2020.
- R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>. Accessed September 8, 2020.
- Schwarzer G. meta: an R package for meta-analysis. *R News*. 2007;7(3):40-45.
- Egger M, Davey smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
20. Keaney JF, Rosen CJ. VITAL Signs for dietary supplementation to prevent cancer and heart disease. *N Engl J Med*. 2019;380(1):91-93.
21. Bird JK, Calder PC, Eggersdorfer M. The role of -3 long chain polyunsaturated fatty acids in cardiovascular disease prevention, and interactions with statins. *Nutrients*. 2018;10(6):775.
22. Brinton EA, Mason RP. Prescription omega-3 fatty acid products containing highly purified eicosapentaenoic acid (EPA). *Lipids Health Dis*. 2017;16(1):23.
23. Skulas-ray AC, Wilson PWF, Harris WS, et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. *Circulation*. 2019;140(12):e673-e691.
24. Barter PJ, Ballantyne CM, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259(3):247-258.
25. Sniderman AD, Furberg CD, Keech A, et al. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet*. 2003;361(9359):777-780.
26. Norwegian Scientific Committee for Food Safety (VKM) (2011). Evaluation of negative and positive health effects of n-3 fatty acids as constituents of food supplements and fortified foods. Norwegian Scientific Committee for Food Safety. <https://www.vkm.no/english/riskassessments/allpublications/evaluationofnegativeandpositivehealtheffectsofn3fattyacidsasconstituentsoffoodsupplementsandfortifiedfoods.4.72c3261615e09f2472f47636.html>. Accessed September 8, 2020.
27. EFSA Panel on Dietetic Products, Nutrition and Allergies (2012). Scientific opinion on the tolerable upper intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). *EFSA J*. 2012; 10(7):2815.
28. Letter Responding to Health Claim Petition dated April 24, 2014: "Eicosapentaenoic Acid and Docosahexaenoic Acid and Reduction of Blood Pressure in the General Population" (June 19, 2019). https://www.fda.gov/media/128043/download?utm_campaign=CFSANCU%20-%20FDA%20Announces%20New%20Qualified%20Health%20Claims%20for%20EPA%20and%20DHA%20Omega-3&utm_medium=email&utm_source=Eloqua. Accessed September 8, 2020.