Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events

A Systematic Review and Meta-analysis

Evangelos C. Rizos, MD, PhD
Evangelia E. Ntzani, MD, PhD
Eftychia Bika, MD
Michael S. Kostapanos, MD
Moses S. Elisaf, MD, PhD, FASA, FRSH

Context Considerable controversy exists regarding the association of omega-3 polyunsaturated fatty acids (PUFAs) and major cardiovascular end points.

Objective To assess the role of omega-3 supplementation on major cardiovascular outcomes.

Data Sources MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through August 2012.

Study Selection Randomized clinical trials evaluating the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke.

Data Extraction Descriptive and quantitative information was extracted; absolute and relative risk (RR) estimates were synthesized under a random-effects model. Heterogeneity was assessed using the *Q* statistic and I^2. Subgroup analyses were performed for the presence of blinding, the prevention settings, and patients with implantable cardioverter-defibrillators, and meta-regression analyses were performed for the omega-3 dose. A statistical significance threshold of .0063 was assumed after adjustment for multiple comparisons.

Data Synthesis Of the 3635 citations retrieved, 20 studies of 68 680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; risk reduction [RD] –0.004, 95% CI, –0.01 to 0.02), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; RD, –0.01; 95% CI, –0.02 to 0.00), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, –0.003; 95% CI, –0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, –0.002; 95% CI, –0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, –0.002 to 0.004) when all supplement studies were considered.

Conclusion Overall, omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.

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TREATMENT WITH MARINE-derived omega-3 polyunsaturated fatty acids (PUFAs) for the prevention of major cardiovascular adverse outcomes has been supported by a number of randomized clinical trials (RCTs) and refuted by others.[1-5] Although their mechanism of action is not clear, their postulated effect on cardiovascular outcomes may be due to their ability to lower triglyceride levels, prevent serious arrhythmias, or even decrease platelet aggregation and lower blood pressure.[6] Current guidelines issued by major societies recommend their use, either as supplements or through dietary counseling, for patients after myocardial infarction (MI),[7,8] whereas the US Food and Drug Administration has approved their administration only as triglyceride-lowering agents in patients with overt hypertriglyceridemia,[9] and some (but not all) European national regulatory agencies have approved the omega-3 administration for cardiovascular risk modification.[10]

The controversy stemming from the varying labeling indications causes confusion in everyday clinical practice about whether to use these agents for cardiovascular protection.

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Author Affiliations: Lipid Disorders Clinic, Department of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece (Dr Rizos, Bika, Kostapanos, and Elisaf); and Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina (Dr Ntzani).
Corresponding Author: Moses S. Elisaf, MD, PhD, FASA, FRSH, Department of Internal Medicine, University Hospital of Ioannina, Ioannina 45110, Greece (egepi@cc.uoi.gr).

Systematic reviews and meta-analyses of RCTs published in the field add further to the existing controversy because they report conflicting findings[6,11-16]; other than the emergence of new evidence, reasons include the appraisal of a single outcome, the inclusion of double-blind–only RCTs, the inclusion of supplements only, or the exclusion of populations with specific clinical characteristics.

In the present study, we attempted a large-scale synthesis of the available randomized evidence under 1 updated systematic review and meta-analysis to determine the association between omega-3 PUFAs and major patient-important cardiovascular outcomes.

METHODS

We considered all randomized trials evaluating omega-3 PUFA supplementation in adult participants. Eligible outcomes included all-cause mortality, cardiac death, sudden death, MI, and all types of stroke. Omega-3 administration could be achieved either through diet or supplements. Trials were eligible if they were randomized, controlled using another diet or placebo, and implemented in primary or secondary cardiovascular disease (CVD) prevention settings. We excluded studies with treatment duration less than 1 year, allowing for enough time for the treatment to prove efficacy on CVD prevention. Whenever reports pertained to the same patients at different follow-up periods, we retained the one with the longer follow-up to avoid data duplication.

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (up to August 2012) using a predefined algorithm (eMethods, available at http://www.jama.com). Moreover, we screened references included in pertinent systematic reviews.

Data Extraction

We recorded information on study characteristics and demographics such as authors, publication year and journal, per-group sample size, population characteristics, treatment indication, omega-3 dose and mode of administration, study duration, CVD-related outcome and definition thereof, relative risk and 95% CI, as well as information regarding randomization mode, allocation concealment, blinding, loss to follow-up, and intention-to-treat analysis. Data extraction was performed independently by 2 investigators and discrepancies were resolved by another.

Assessment of Methodological Quality

We assessed the methodological quality of the included trials and the risk of bias conferred by using elements of the Cochrane collaboration tool for assessing risk of bias.[17] The domains used in the present systematic review pertained to randomization and allocation concealment (selection bias), blinding (performance and detection bias), and loss to follow-up and adherence to the intention-to-treat principle (attrition bias). Among the established strategies, we chose to present the meta-analysis of all studies while providing a summary of the risk of bias across studies. We then performed a sensitivity analysis excluding open-label studies.

Main and Subgroup Analyses

Given the dose standardization issues, we chose to analyze separately studies in which the omega-3 administration was achieved through dietary counseling from those in which omega-3 was administered as supplements. We also analyzed separately each major outcome.

We further assessed potential associations of the treatment effect with study-level variables in subgroup analyses and meta-regression analyses. Prespecified subgroup analyses were performed based on the patient history of CVD (primary vs secondary CVD prevention setting) and the presence of implantable cardioverter-defibrillator (ICD). Meta-regression analyses considered the administered omega-3 dose (continuous variable).

Statistical Analyses

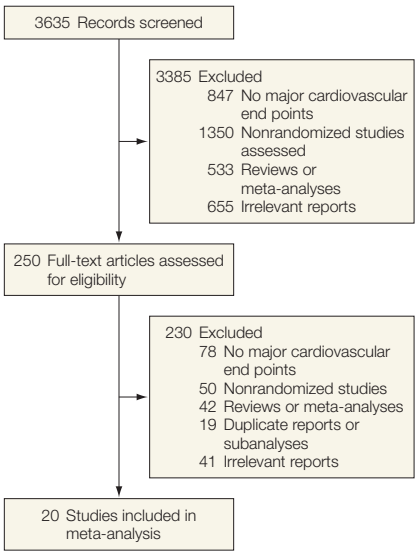
The principal summary measures were the relative risk (RR) and the absolute risk reduction (RD). For each trial, we retrieved or calculated the crude RR and RD estimates and corresponding 95% CIs for the assessed outcomes. The presence of statistically significant heterogeneity was assessed by the Q statistic (significant at $P<.10$) and the extent of the observed heterogeneity was assessed by the I^2 (ranging from 0% to 100%).[18] We summarized RR and RD estimates using random-effects models.[19] Fixed-effects models assume that there is a common underlying effect and the variability observed is attributed to chance alone; random-effects models acknowledge that true between-study heterogeneity exists and take into account the presence of heterogeneity into their calculations. In the absence of heterogeneity, fixed- and random-effects models yield the same results.

We examined whether the subgroup-specific effects were significantly different beyond chance by using a z score.[20] To detect publication bias, we visually examined funnel plots per assessed outcome and further assessed asymmetry by using the Begg-Mazumbar test.[21] In addition, the trim-and-fill approach was used to obtain an adjusted effect size that takes into account publication bias. Finally, we performed a cumulative meta-analysis to assess the evolution of the observed effects over time.[22]

Analyses were performed in RevMan version 5 (Cochrane Collaboration, 2010) and Stata version 10 (StataCorp). All P values are 2-tailed. Within each assessed outcome, we adopted a level of statistical significance adjusted for multiple comparisons testing by a factor of 8 equaling

the number of overall and subgroup analyses performed using the 2 measures of effect (RR and RD); thus, statistical significance was assumed at a *P* value threshold of .0063. The study is reported according to the PRISMA checklist.[23]

Figure 1. Flowchart for the Selection of Eligible Studies



RESULTS

Of the retrieved 3635 citations, 20 studies of 68 680 randomized patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 MIs, and 1490 strokes[1-5,24-38] (FIGURE 1).

Summary and study-specific characteristics are shown in TABLE 1 and TABLE 2. Trials were published as early as 1989, and half of the included trials had been conducted during the period where statins were routinely recommended for cardiovascular risk modification (1998 or later). The majority of the randomized participants had European ancestral backgrounds (15 studies, 49 134 participants), and the largest trial included 18 645 Japanese participants.[3] With the exception of 2 trials where omega-3 administration was based on dietary counselling,[30,31] omega-3 PUFA supplements were used; the mean omega-3 dose was 1.51 g per day (0.77-g/d eicosapentaenoic acid [EPA], 0.60-g/d docosahexaenoic acid [DHA]), while 10 studies used an omega-3 dose of 1 g or greater per day. The median treatment duration was 2 years (maximum, 6.2 years[5]), and usually omega-3 PUFAs were administered for secondary CVD prevention (13 studies[1,4,24-32,36,38]). All-cause mortality, cardiac death, and MI were the outcomes more extensively assessed (19, 15, and 14 studies, respectively); MI refers to nonfatal MI, except for 4 studies.[5,32,33,35] Most studies were of high methodological quality (eTable 1); 16 studies used an intention-to-treat analysis and 16 studies were double-blind, although methods used to ensure adequate allocation concealment were not always clearly reported.

Table 1. Summary Characteristics of the Eligible Randomized Clinical Trials

	Eligible Studies
No. of unique trials	20
Total No. of participants	68 680
Median (IQR)	555 (210-4582)
Publication year, median (IQR)	2006 (1999-2010)
Median age (range), y	68 (49-70)
Administration mode, No. of studies	
Diet	2
Supplements	18
Omega-3 PUFA dose, median (IQR), g/d	
EPA+DHA	1.0 (0.53-1.80)
EPA	0.46 (0.28-1.09)
DHA	0.43 (0.21-0.70)
Treatment duration, median (range), y	2 (1.0-6.2)
Indication/setting	
Primary prevention	0
Secondary prevention	13[a]
Mixed primary/secondary	4
ICD	3
Outcome, No. of studies (No. of participants)	
All-cause mortality	19 (68 426)
Cardiac mortality	15 (61 554)
Sudden death	8 (44 865)
Myocardial infarction	14 (55 908)
Stroke	9 (52 589)

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PUFA, polyunsaturated fatty acid.
[a] One hemodialysis trial included.

Assessed Outcomes and Evidence Synthesis

Omega-3 PUFA Administration Through Diet. The available randomized evidence indicates a knowledge gap regarding the administration of omega-3 PUFAs through dietary counseling. Omega-3–targeted dietary counseling was assessed in 2 studies on 5147 randomized patients of European ancestry reporting 749 deaths, 513 cardiac deaths, 120 sudden deaths, and 82 non-fatal MIs.[30,31] For the 2 outcomes that were assessed in both studies (all-cause mortality and cardiac death), these 2 studies showed associations of opposite direction that differed beyond chance (FIGURE 2). Study-specific characteristics could not explain the observed discrepancy; both studies were open-label, conducted by the same research group in participants of European ancestry, using omega-3 PUFA doses greater than 1 g for secondary prevention. Due to the observed discrepancies, a quantitative synthesis of these trials was not deemed informative and therefore was not conducted.

Omega-3 PUFA Supplements. For all-cause mortality, 17 studies were included, reporting 6295 events among 63 279 participants (FIGURE 3). Overall, omega-3 PUFA supplements were not statistically significantly associated with a reduced all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; *P*=.17;

Table 2. Characteristics of the Eligible Randomized Clinical Trials

Source (Country)	Age, Median (Range), y	Omega-3 Dose, g/d[a]	EPA, g/d	DHA, g/d	Control	Duration, y	Indication	No. of Participants, Treatment/ Control	Outcomes Assessed	Funding Source[b]
Burr et al (DART1),[31] 1989 (UK)	57 (NR)	0.24 (D), 0.86 (S)	0.24 (D), 0.51 (S)	0.35 (S)	Non–fish oil diet	2	Secondary	1015/1018	All-cause mortality, cardiac death, MI	Mixed
Sacks et al,[27] 1995 (US)	62 (30-75)	6	2.9	1.9	Placebo (olive oil)	2.3	Secondary	31/28	All-cause mortality, cardiac death, MI, stroke	Mixed
Singh et al,[28] 1997 (India)	49 (NR)	1.8	1.08	0.72	Placebo (nonoil)	1	Secondary	122/118	Cardiac death, sudden death, MI	NR
Leng et al,[26] 1998 (UK)	66 (NR)	0.27	0.27	0	Placebo (sunflower seed oil)	2	Secondary	60/60	All-cause mortality, cardiac death, MI, stroke	NR
von Schacky et al,[25] 1999 (Germany)	58 (18-75)	3.3 (3 mo), 1.7 (21 mo)			Placebo (nonmarine fatty acids)	2	Secondary	112/111	All-cause mortality, cardiac death, MI, stroke	Mixed
Marchioli et al (GISSI),[1] 1999 (Italy)	60 (NR)	0.85	0.28	0.57	None	3.5	Secondary	5666/5658	All-cause mortality, cardiac death, sudden death, MI, stroke	Industry
Nilsen et al,[24] 2001 (Norway)	64 (29-88)	3.4	1.1	2.3	Placebo (corn oil)	1.5	Secondary	150/150	All-cause mortality, cardiac death, MI	Industry
Burr et al (DART2),[30] 2003 (UK)	61 (NR)	0.34 (D), 0.86 (S)	0.51 (S)	0.35 (S)	Non–fish oil diet	5	Secondary	1571/1543	All-cause mortality, cardiac death, sudden death	Mixed
Leaf et al,[34] 2005 (US)[c]	65 (NR)	2.6			Placebo (olive oil)	1	ICD	200/202	All-cause mortality, cardiac death	Non-industry
Raitt et al,[33] 2005 (US)[c]	63 (NR)	1.8	0.76	0.54	Placebo (olive oil)	2	ICD	100/100	All-cause mortality, cardiac death, sudden death, MI	Mixed
Brouwer et al (SOFA),[35] 2006 (multiple)[d]	61 (NR)	0.96	0.46	0.34	Placebo (sunflower oil)	1	ICD	273/273	All-cause mortality, cardiac death, MI	Non-industry
Svensson et al,[32] 2006 (Denmark)	67 (NR)	1.7	0.77	0.64	Placebo (olive oil)	2	Secondary/ hemodialysis	103/103	All-cause mortality, MI, stroke	Mixed
Yokoyama et al (JELIS),[3] 2007 (Japan)[e]	61 (40-75)	1.8	1.8	0	Standard care	4.6	Primary/ secondary	7503/7478 (1823/1841)[e]	All-cause mortality, cardiac death, sudden death, MI, stroke	Industry
Tavazzi et al (GISSI-HF),[2] 2008 (Italy)	67 (NR)	1	0.4	0.48	Placebo	3.9	Primary/ secondary	3494/3481	All-cause mortality, cardiac death, sudden death, MI, stroke	Mixed
Garbagnati et al,[38] 2009 (Italy)	65 (NR)	0.5	0.25	0.25	Placebo	1	Secondary	20/18	All-cause mortality	Mixed
Galan et al (SU.FOL.OM3),[29] 2010 (France)	61 (54-69)	0.6	0.4	0.2	Placebo	4.7	Secondary	1253/1248	All-cause mortality, MI, stroke	Mixed
Kromhout et al,[4] 2010 (Netherlands)	69 (60-80)	0.4	0.23	0.15	Placebo (margarine)	3.4	Secondary	2404/2433	All-cause mortality, cardiac death	Mixed
Rauch et al,[36] 2010 (Germany)	64 (NR)	1	0.46	0.38	Placebo (olive oil)	1	Secondary	1925/1893	All-cause mortality, sudden death	Industry
Einvik et al,[37] 2010 (Norway)	70 (64-76)	2.4	1.18	0.84	Placebo (corn oil)	3	Primary/ secondary	282/281	All-cause mortality, sudden death	Mixed
Bosch et al (ORIGIN),[5] 2012 (multiple)	64	1	0.47	0.38	Placebo (olive oil)	6.2	Primary/ secondary	6281/6255	All-cause mortality, cardiac death, MI, stroke	Industry

Abbreviations: D, diet; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICD, implantable cardioverter defibrillator; NR, not reported; Primary, primary prevention; S, supplement; Secondary, secondary prevention.

[a] All studies administered omega-3 polyunsaturated fatty acid supplements except Burr et al[31] (1989) and Burr et al[30] (2003).

[b] Mixed refers to both industry and nonindustry.

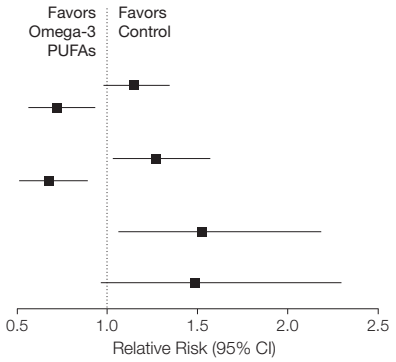
[c] 96% European ancestry.

[d] Poland, Germany, Switzerland, United Kingdom, Czech Republic, Austria, Belgium, Netherlands.

[e] Primary and secondary prevention populations reported separately.

Figure 2. Efficacy of Omega-3 Polyunsaturated Fatty Acids Administration Through Dietary Counseling

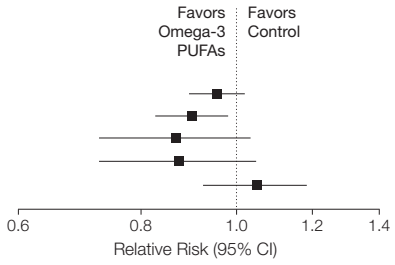
	No. of Events		No. of Participants		
	Omega-3 PUFAs	Control	Omega-3 PUFAs	Control	RR (95% CI)
All-cause mortality					
Burr et al,[30] 2003	283	242	1571	1543	1.15 (0.98-1.34)
Burr et al,[31] 1989	94	130	1015	1018	0.73 (0.56-0.93)
Cardiac death					
Burr et al,[30] 2003	180	139	1571	1543	1.27 (1.03-1.57)
Burr et al,[31] 1989	78	116	1015	1018	0.67 (0.51-0.89)
Sudden death					
Burr et al,[30] 2003	73	47	1571	1543	1.53 (1.06-2.19)
Nonfatal MI					
Burr et al,[31] 1989	49	33	1015	1018	1.49 (0.97-2.30)



Error bars indicate 95% CIs; MI, myocardial infarction; PUFAs, polyunsaturated fatty acids; RR, relative risk.

Figure 3. Efficacy of Omega-3 Polyunsaturated Fatty Acid Supplements Across Different Outcomes

	No.			
	Studies	Events	Participants	RR (95% CI)
Outcome				
All-cause mortality	17	6295	63 279	0.96 (0.91-1.02)
Cardiac death	13	3480	56 407	0.91 (0.85-0.98)
Sudden death	7	1030	41 751	0.87 (0.75-1.01)
Myocardial infarction	13	1755	53 875	0.89 (0.76-1.04)
Stroke	9	1490	52 589	1.05 (0.93-1.18)



Error bars indicate 95% CIs; PUFAs, polyunsaturated fatty acids; RR, relative risk.

I^2=12%; RD, −0.004; 95% CI, −0.01 to 0.02; P=.19; I^2=38%) (FIGURE 4). In a cumulative meta-analysis for all-cause mortality (FIGURE 5), the originally proposed significant omega-3 PUFA effect was refuted by the accumulated evidence by 2007 and remained unchanged since, lingering around a small effect and borderline statistical significance, although 49 899 more patients have been randomized. There was no evidence for an association between treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (TABLE 3). Although visual inspection of the funnel plot including all studies showed asymmetry, the Begg-Mazumbar test was not statistically significant and the trim-and-fill approach gave an identical imputed estimate indicating a low risk of publication bias (eFigure 2A).

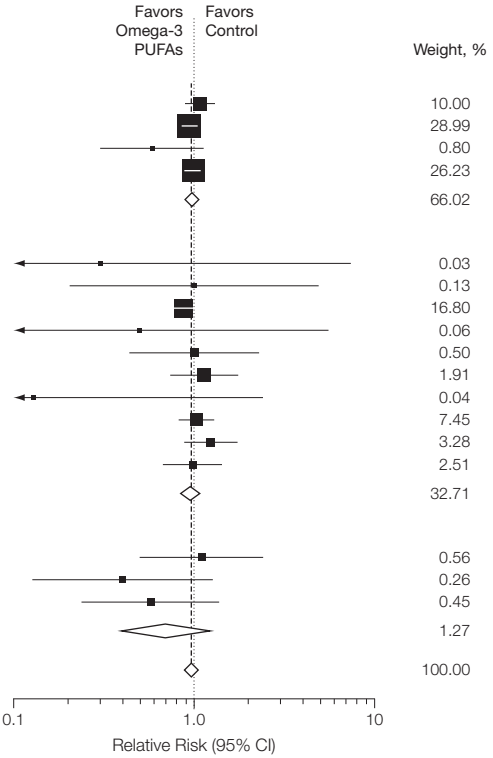
From 13 studies analyzed, there were 3480 cardiac deaths among 56 407 participants. Evidence synthesis for cardiac death did not show a statistically significant association for omega-3 PUFA supplements after correction for multiple comparisons (RR, 0.91; 95% CI, 0.85 to 0.98; P=.01; I^2=6%) and a nonsignificant absolute risk reduction (RD, −0.01; 95% CI, −0.02 to 0.00; P=.09; I^2=78%) (eFigure 1A). There was no evidence for an association between the observed treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (Table 3, eFigure 1A). Although visual inspection of the funnel plot including all studies showed asymmetry, the Begg-Mazumbar test was not statistically significant and the trim-and-fill approach gave an identical imputed estimate indicating a low risk of publication bias (eFigure 2B).

For the outcome of sudden death, 7 studies provided data for 41 751 participants and 1030 events. Omega-3 supplementation was not statistically significantly associated with reduced rates of sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; P=.06; I^2=8%; RD, −0.003; 95% CI −0.012 to 0.006; P=.49; I^2=91%). There was no evidence for an association between treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (Table 3, eFigure 1B). The Begg-Mazumbar test was not statistically significant, and visual inspection of the funnel plot including all studies showed symmetry, indicating a low risk of publication bias (eFigure 2C). With the trim-and-fill approach, the imputed estimate was identical to that in the main analysis, indicating that results are unlikely to be explained by publication bias.

Thirteen studies were included for the outcome MI, involving 53 875

Figure 4. Meta-analysis of Omega-3 Supplements for All-Cause Mortality

	No. of Events		No. of Participants			
	Omega-3 PUFAs	Control	Omega-3 PUFAs	Control	RR (95% CI)	Weight, %
Mixed prevention						
Yokoyama et al,[3] 2007	286	265	9326	9319	1.08 (0.91-1.27)	10.00
Tavazzi et al,[2] 2008	955	1014	3494	3481	0.94 (0.87-1.01)	28.99
Einvik et al,[37] 2010	14	24	282	281	0.58 (0.31-1.10)	0.80
ORIGIN,[5] 2012	951	964	6281	6255	0.98 (0.90-1.07)	26.23
Subtotal: I^2=38.9%, P=.18	2206	2267	19383	19336	0.97 (0.90-1.05)	66.02
Secondary prevention						
Sacks et al,[27] 1995	0	1	31	28	0.30 (0.01-7.13)	0.03
Leng et al,[26] 1998	3	3	60	60	1.00 (0.21-4.76)	0.13
Marchioli et al,[1] 1999	472	545	5666	5658	0.86 (0.77-0.97)	16.80
von Schacky et al,[25] 1999	1	2	112	111	0.50 (0.05-5.39)	0.06
Nilsen et al,[24] 2001	11	11	150	150	1.00 (0.45-2.24)	0.50
Svensson et al,[32] 2006	34	30	103	103	1.13 (0.75-1.70)	1.91
Garbagnati et al,[38] 2009	0	3	20	18	0.13 (0.01-2.34)	0.04
Kromhout et al,[4] 2010	186	184	2404	2433	1.02 (0.84-1.24)	7.45
Rauch et al,[36] 2010	88	70	1919	1885	1.23 (0.91-1.68)	3.28
Galan et al,[29] 2010	58	59	1253	1248	0.98 (0.69-1.39)	2.51
Subtotal: I^2=1.5%, P=.43	853	908	11718	11694	0.95 (0.86-1.04)	32.71
ICD						
Leaf et al,[34] 2005	13	12	200	202	1.09 (0.51-2.34)	0.56
Raitt et al,[33] 2005	4	10	100	100	0.40 (0.13-1.23)	0.26
Brouwer et al,[35] 2006	8	14	273	273	0.57 (0.24-1.34)	0.45
Subtotal: I^2=19.9%, P=.29	25	36	573	575	0.69 (0.39-1.23)	1.27
Overall: I^2=11.7%, P=.32	3084	3211	31674	31605	0.96 (0.91-1.02)	100.00



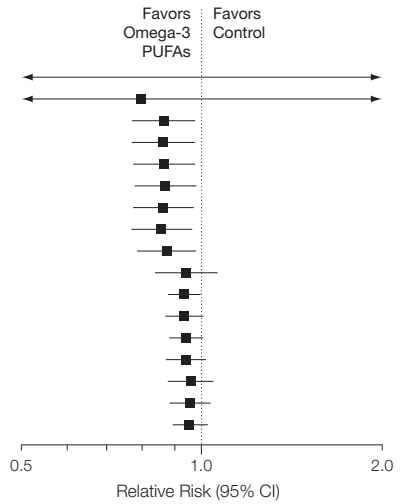
Error bars indicate 95% CIs of the relative risk (RR) estimates. The size of the squares correspond to the study weight in the random-effects meta-analysis. Diamonds represent the meta-analysis summary effect estimate. ICD indicates implantable cardioverter-defibrillator; PUFAs, polyunsaturated fatty acids.

participants and 1755 events. Overall, omega-3 PUFA supplementation was not significantly associated with a reduced risk of MI (RR, 0.89; 95% CI, 0.76 to 1.04; P=.14; I^2=35%; RD, −0.002; 95% CI, −0.007 to 0.002; P=.23; I^2=35%). There was no evidence for an association between treatment effect and the presence of blinding, the omega-3 PUFA dose, the prevention setting, or the presence of ICD (Table 3, eFigure 1C). Visual inspection of the funnel plot including all studies showed asymmetry, and the Begg-Mazumbar test for publication bias was statistically significant (P=.01), although the trim-and-fill approach gave an identical imputed estimate (eFigure 2D).

Nine studies were included in the analysis of stroke; there were 1490 events among 52 589 participants. The available evidence for stroke points to an opposite but not statistically significant effect (RR, 1.05; 95% CI, 0.93 to 1.18; P=.47; I^2=14%; RD, 0.001; 95% CI, −0.002 to 0.004; P=.46; I^2=15%) (eFigure 1D). All available studies included non-ICD patients treated with omega-3 supplements. There was no evidence for an

Figure 5. Cumulative Meta-analysis of the Omega-3 Supplements for All-Cause Mortality

	Cumulative Sample Size	RR (95% CI)
Sacks et al,[27] 1995	59	0.30 (0.01-7.13)
Leng et al,[26] 1998	179	0.79 (0.20-3.20)
Marchioli et al,[1] 1999	11503	0.86 (0.77-0.97)
von Schacky et al,[25] 1999	11726	0.86 (0.77-0.97)
Nilsen et al,[24] 2001	12326	0.87 (0.77-0.97)
Leaf et al,[34] 2005	12728	0.87 (0.78-0.98)
Raitt et al,[33] 2005	12928	0.86 (0.77-0.97)
Brouwer et al,[35] 2006	13474	0.86 (0.77-0.96)
Svensson et al,[32] 2006	13680	0.87 (0.78-0.97)
Yokoyama et al,[3] 2007	32325	0.94 (0.84-1.06)
Tavazzi et al,[2] 2008	39300	0.94 (0.88-0.99)
Garbagnati et al,[38] 2009	39338	0.94 (0.87-1.00)
Kromhout et al,[4] 2010	44175	0.94 (0.89-1.00)
Einvik et al,[37] 2010	44738	0.94 (0.88-1.01)
Rauch et al,[36] 2010	48542	0.96 (0.88-1.04)
Galan et al,[29] 2010	50743	0.96 (0.89-1.03)
ORIGIN,[5] 2012	63279	0.96 (0.91-1.02)



Error bars indicate the 95% CI of the cumulative meta-analysis estimates as randomized patients accumulate through time. PUFAs indicates polyunsaturated fatty acids; RR, relative risk.

association between treatment effect and the presence of blinding, the omega-3 PUFA dose, or the prevention setting (Table 3), and the available data did not allow for a separate analysis for hemorrhagic and nonhemorrhagic stroke. The Begg-Mazumbar test was not statistically significant, and visual inspection of the funnel plot including all studies showed symmetry, indicating a low risk of publication bias (eFigure 2E). With the trim-and-fill approach, the imputed estimate (RR, 1.03; 95% CI, 0.93 to 1.15, $P=.56$) was similar to that in the main analysis, indicating that results are unlikely to be explained by publication bias.

COMMENT

Our study incorporating the available published randomized evidence shows that omega-3 PUFAs are not universally statistically significantly associated with major cardiovascular outcomes across patient populations at increased cardiovascular risk. Omega-3 supplementation was not significantly associated with all-cause mortality, cardiac death, sudden death, MI, or stroke. The observed effect was not associated with study-specific or population-specific characteristics, and the majority of the large studies in the field agree with the results of our work.

Systematic reviews and meta-analyses published on the same topic[11-16] posed variably different key questions, thus assessing different subgroups of studies. In our study, we chose to include all the available published randomized evidence addressing the cardiovascular benefit of the omega-3 supplementation regardless of methodological study characteristics, the prevention setting, or the supplementation mode, opting for the totality of the evidence and thus a valid interpretation of the results. Despite the variation in the research questions assessed, the results of the previously published meta-analyses are in accordance with our findings regarding the evolution of the omega-3 supplementation effect over time and its replication validity. The first quantitative synthesis in the field[39] showed a strong, significant effect across all major cardiovascular outcomes. As more randomized evidence accumulated, the effect became weaker and nonsignificant and lost its universal aspect[11-16] (eTable 2, Figure 4). The magnitude and nonsignificance of the observed effect has remained stable over the last 5 years, although the available cumulative sample size increased considerably and no clear improvement in the methodological quality of the assessed studies occurred during this period of time.

In our meta-analysis, there were 9 studies with available sample sizes of more than 1000 participants, the 2 open-label diet-based studies and 7 supplement studies. The DART1,[31] the first large study in the field, was diet-based; showed an impressive effect; and was validated by the large, open-label, pre–statin-era GISSI trial[1] among predominantly male patients with recent acute MI, which claimed a significant clinical benefit for omega-3 PUFAs and drove considerable atten-

Table 3. Subgroup Analyses for the Omega-3 PUFA Supplements Effect Across the Assessed Randomized Trials

Outcome	Subgroup	No. of Studies	RR (95% CI)	*P* Value	I^2 Value, %
All-cause mortality					
Prevention	Secondary	10	0.95 (0.86-1.04)	.51	2
	ICD	3	0.69 (0.39-1.23)		20
	Mixed	4	0.97 (0.90-0.05)		39
Blinding	Open-label	2	0.96 (0.78-1.19)	.69	78
	Blinding	15	0.97 (0.92-1.02)		0
Omega-3 dose		17		.75[a]	
Cardiac death					
Prevention[b]	Secondary	8	0.81 (0.70-0.93)	.07	0
	ICD	3	0.65 (0.35-1.18)		0
	Mixed	3	0.95 (0.89-1.02)		0
Blinding	Open-label	2	0.80 (0.68-0.93)	.08	0
	Blinding	11	0.94 (0.88-1.00)		0
Omega-3 dose		13		.54[a]	
Sudden death					
Prevention[b]	Secondary	4	0.78 (0.61-1.01)	.22	12
	ICD	1	5.00 (0.2-102.9)		
	Mixed	3	0.94 (0.81-1.09)		0
Blinding	Open-label	2	0.77 (0.62-0.96)	.21	0
	Blinding	5	0.91 (0.70-1.17)		29
Omega-3 dose		7		.78[a]	
Myocardial infarction					
Prevention[b]	Secondary	9	0.82 (0.63-1.08)	.40	42
	ICD	2	0.33 (0.07-1.64)		0
	Mixed	3	0.95 (0.77-1.17)		47
Blinding	Open-label	2	0.91 (0.76-1.10)	.97	15
	Blinding	11	0.86 (0.67-1.01)		43
Omega-3 dose		13		.84[a]	
Stroke					
Prevention	Secondary	6	1.17 (0.90-1.53)	.33	7
	Mixed	3	1.01 (0.89-1.14)		20
Blinding	Open-label	2	1.09 (0.92-1.30)	.64	0
	Blinding	7	1.04 (0.86-1.26)		23
Omega-3 dose		9		.79[a]	

Abbreviations: ICD, implantable cardioverter-defibrillator; PUFA, polyunsaturated fatty acid; RR, relative risk.
[a] *P* value for the meta-regression.
[b] Primary and secondary prevention populations reported separately for the JELIS study.[3]

tion to the field. Nevertheless, the originally proposed effect was not replicated in subsequently published large trials.[2-5,29,30,36] The open-label diet-based DART2[30] trial performed by the same research team as DART1 failed to replicate the DART1 and GISSI findings and gave an effect estimate of opposite direction that was statistically significantly different from the DART1 trial. The Japanese, open-label, high-baseline-intake, mainly primary prevention JELIS trial,[3] predominantly in women, failed to replicate the GISSI trial for the outcomes assessed (sudden and cardiac death) even in the secondary prevention subgroup analysis. The GISSI-HF,[2] a double-blind, statin-era study performed on high-risk (heart failure) patients with a staggering control event rate of almost 30% for all-cause mortality, also failed to replicate the magnitude of the GISSI effect but yielded marginal statistical significance in adjusted analyses. Moreover, the recent double-blind Alpha-Omega Trial[4] on secondary prevention with comparable control event rates to the GISSI trial but with patients with a longer history of clinical CVD showed that low-dose omega-3 supplementation was not significantly associated with a reduced rate of major cardiovascular events among patients who had an MI and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy. Similarly, the double-blind OMEGA trial[36] and the SU.FO.OM3 trial[29] concluded that omega-3 fatty acids do not seem to add to the guideline-adjusted treatment of secondary prevention CVD patients at a low rate of sudden cardiac death. Finally, the recently published ORIGIN trial[5] performed in 12 536 patients found that omega-3 did not prevent death or any cardiovascular outcomes in high-risk patients for cardiovascular events who had (or were at high risk for) diabetes and were receiving all antihypertensive, antithrombotic, antidiabetic, and lipid-modifying medications proposed by the current guidelines.

The observed effect variation poses a challenge to the interpretation of the evidence synthesis results, and one approach toward explaining it would be through the postulated underlying pathophysiology, namely the omega-3 effect on triglycerides, arrhythmias, and hypertension. Overall, the proposed protective role of omega-3 PUFAs by lowering triglyceride levels is not supported by our study, because our findings do not support an advantage of higher (triglyceride-lowering) doses compared with lower doses of omega-3; this could be attributed to the limited strength of the primary association between triglycerides and CVD[40,41] or varying baseline triglyceride levels. Life-threatening ventricular arrhythmias are the most common cause of sudden cardiac death in the early stages after MI.[42,43]

Our meta-analysis did not find any significant protective association with sudden death in the various groups of patients examined, thus rejecting a distinct antiarrhythmic mediated omega-3 PUFA effect, although the accumulated evidence would still be underpowered to detect a small underlying effect. Hypertension is another important risk factor for CVD,[42] and several studies have indicated that high doses of omega-3 PUFAs are associated with a modest reduction in systemic blood pressure (0.66 mm Hg systolic and 0.35 mm Hg diastolic blood pressure reduction per 1 g of omega-3 PUFAs).[44] Interestingly, our meta-analysis did not show a protective effect on stroke (the CVD outcome most profoundly influenced by hypertension).

Our study has certain limitations. Our findings come from published evidence including and not limited to large RCTs. Publication and language bias is a major concern when dealing with efficacy trials,[45] but the assessed studies were published from 1989 to 2012, pertained to a cumulative sample size of more than 68 500 randomized patients, and included several large studies; furthermore, to enhance comprehensiveness, our searches were extended to the Cochrane Controlled Trials Registry, which is built from multiple large databases.[45] We would thus expect that the incorporation of unpublished evidence would not substantially alter the status of the evidence, a notion supported by the observed consistency of the effect when small studies (<1000 participants) were excluded from the analysis. Moreover, although randomized evidence is protected from selection bias, performance and detection bias could be operating in the field. An approach toward dealing with such a situation would be to exclude open-label studies. Unfortunately, 2 of the open-label trials are also by far the largest in the field, and should we choose to exclude them,[1,3] we would be excluding almost half of the accumulated randomized evidence. The subsequent effect estimate cannot be validly attributed to the substantial reduction in sample size or the possible correction for performance bias.

Another consideration pertains to the differential influence of co-interventions (ie, background treatment strategies) that could be considerable in quantifying the underlying therapeutic effect of any given intervention. Yet omega-3 PUFAs have been tested under various baseline risk settings and background treatment strategies (including and not limited to statin therapy) without showing an association toward a differential effect based on co-interventions. Finally, although omega-3 PUFAs are usually administered as an EPA/DHA combination, a component-specific effect has been previously proposed.[46] Among the assessed studies, only the relatively small study by Leng et al[26] and the large, high-baseline-intake Japanese JELIS study[3] used EPA-only interventions. Thus, a subgroup analysis investigating the role of the separate

components in the observed study variability would be considerably underpowered and particularly vulnerable to a biased interpretation. Moreover, regarding adherence, we acknowledge that varying compliance rates could create effect variation; yet the fact that most studies were of reported high compliance (>80%) and the considerable variation in noncompliance definitions make a compliance-based subgroup analysis less informative for the available published reports.

Finally, the varying event rates and baseline risk estimates in the assessed trials could explain some of the effect variation. Even among the large studies investigating high-risk populations (GISSI, GISSI-HF, Alpha-Omega, ORIGIN), which could attain maximum precision for the therapeutic effect quantification, inconsistency prevails. If the observed summary effects were consistent in the direction of the association or the results of the large studies, we could claim that the observed heterogeneity represents an overinflation of the true underlying clinical heterogeneity. Nevertheless, we confirmed the previously extensively discussed major divergence of the observed effect in the field, even though we chose to assess only randomized, well-designed, less-bias-prone clinical trials.

In conclusion, omega-3 PUFAs are not statistically significantly associated with major cardiovascular outcomes across various patient populations. Our findings do not justify the use of omega-3 as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3 PUFA administration.[7] Randomized evidence will continue to accumulate in the field, yet an individual patient data meta-analysis would be more appropriate to refine possible associations related to, among others, dose, adherence, baseline intake, and CVD risk group.[15]

Author Contributions: Dr Rizos had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Rizos and Dr Ntzani contributed equally to the work.
Study concept and design: Rizos, Ntzani, Bika, Kostapanos, Elisaf.
Acquisition of data: Rizos, Bika, Kostapanos.
Analysis and interpretation of data: Rizos, Ntzani, Elisaf.
Drafting of the manuscript: Rizos, Ntzani, Elisaf.
Critical revision of the manuscript for important intellectual content: Rizos, Ntzani, Bika, Kostapanos, Elisaf.
Study supervision: Rizos, Ntzani, Elisaf.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Elisaf reported having given talks, attended conferences, and participated in trials sponsored by industry not associated with those that manufacture or market omega-3 supplements.
Online-Only Material: The eTables, eFigures, and eMethods are available at http://www.jama.com.

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