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Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, double blind, placebo controlled trials

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Abstract

Background: Although omega-3 fatty acids have well documented properties which would reduce the cardiovascular (CV) disease risk, the evidence from randomized controlled trials (RCTs) remains inconclusive. We performed a meta-analysis of the available RCTs for investigating the CV preventive effect of administrating at least 1 gram/day, and for at least 1 year, omega-3 fatty acid supplements to patients with existing CV disease.

Methods: RCTs published up to March 2013 were searched from PubMed, EMBASE, and the Cochrane Library. Two of us independently reviewed and selected eligible trials.

Results: Of 360 articles retrieved, 11 randomized, double-blind, placebo controlled trials fulfilling inclusion criteria, overall involving 15,348 patients with a history of CV disease, were considered in the final analyses. No statistically significant association was observed for all-cause mortality (RR, 0.89; 95% CI, 0.78 to 1.02) and stroke (RR, 1.31; 95% CI, 0.90 to 1.90). Conversely, statistically significant protective effects were observed for cardiac death (RR, 0.68; 95% CI, 0.56 to 0.83), sudden death (RR, 0.67; 95% CI, 0.52 to 0.87), and myocardial infarction (RR, 0.75; 95% CI, 0.63 to 0.88).

Conclusion: Overall, our results supply evidence that long-term effect of high dose omega-3 fatty acid supplementation may be beneficial for the onset of cardiac death, sudden death and myocardial infarction among patients with a history of cardiovascular disease.

Keywords: Cardiovascular disease; Meta-analysis; Omega-3 fatty acid; Secondary prevention; Supplementation

1. Introduction

Since the 1970s, omega-3 polyunsaturated fatty acids have received a great deal of attention due to possible protective effect on the onset of cardiovascular (CV) disease [1]. In response to anecdotal reports of a low prevalence of coronary heart disease among Greenland Eskimos, Bang and Dyerberg undertook six expeditions to Greenland starting in the late 1960s. They observed that consumption of a large amount of fish or marine mammals rich in omega-3 fatty acid contributes to a low incidence of CV disease among Greenland Eskimos [2,3]. During the following decades, several investigations suggested that omega-3 fatty acid has anti-inflammatory, anti-atherogenic, and anti-arrhythmic effects [4–7], which are considered plausible mechanisms for reducing the CV disease risk [8].

Large-scale epidemiologic studies have suggested that people at risk for coronary heart disease benefit from

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consuming omega-3 fatty acid [9–18]. A protective effect against CV disease from fish or fish oil consumption has been reported from systematic reviews and meta-analyses of observational investigations [19,20].

A number of randomized clinical trials (RCTs) have also been designed specifically to provide a controlled evaluation of the effects of treatment with omega-3 fatty acid on CV risk, but conflicting findings have been found on this issue [8,21–30]. Inconsistency among systematic reviews and meta-analyses of RCTs might be explained by a number of factors [16,20–22]. First, some meta-analyses included RCTs which did not use placebo as control arm [8]. Second, by including RCTs with different omega-3 fatty acid doses and sources, heterogeneous effects are likely generated [31]. Third, the change in tissue lipid composition as well as the beneficial anti-inflammatory and anti-atherogenic properties of omega-3 fatty acid may take time to manifest. Thus, studies including patients followed for less than a year may be unable to detect a clinical benefit [21]. Finally, inconsistency between systematic reviews and meta-analyses may also derive from differences in the patients' inclusion criteria of the primary RCTs, being some of them performed on high-risk (such as heart failure) patients [32], while others mainly investigated primary prevention [33].

In the present study we performed a large-scale synthesis of the available randomized, double-blind, placebo controlled trials for investigating the CV preventive effect of omega-3 fatty acid administration to patients with existing CV disease (i.e. in the setting of secondary prevention of CV outcomes), through supplements (no dietary counselling) with doses sufficiently high, and for time windows sufficiently long, to manifest their preventive action.

2. Methods

This systematic review and meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [34].

2.1. Search strategy

We carried out a MEDLINE, EMBASE, and COCHRANE search for RCTs published up to March 2013 which investigated the association between use of omega-3 and risk of CV disease. The following keywords and/or corresponding MeSH terms were used: ('fatty acid, omega-3' OR 'eicosapentaenoic acid' OR 'docosahexaenoic acid' OR 'fish oils' OR 'fatty acid, omega-6') AND ('cardiovascular diseases' OR 'myocardial infarction' OR 'sudden cardiac death' OR 'stroke'). In addition, the references listed from reviews and meta-analyses published on this issue were hand-checked to identify additional relevant publications [8,21–30].

2.2. Selection criteria

We included studies that met the following criteria: (1) the design was a randomized, double-blind, placebo controlled trial; (2) adult patients with a history of CV disease were investigated in the study; (3) the patients had used omega-3 fatty acid supplements at least 1 gram/day dosage and for at least 1 year; (4) investigated outcomes such as all-cause mortality, cardiac death, sudden death, myocardial infarction and/or stroke; (5) the studies reported quantitative estimates of the exposure-outcome association (odds ratio, rate ratio, or hazard ratio and their corresponding 95% CI or *p*-value) or sufficient data to calculate it. If data were published more than once, the most recent and complete publication was included in the analysis. Two of us (MC and DS) independently evaluated the eligibility of all studies according to the selection criteria. Discrepancies between readers were resolved in conference.

2.3. Data collection

The following data were collected from each included article: first author, publication year, country, number of participants and their main characteristics (e.g. gender, age, type of previous cardiovascular event), study duration, omega-3 dosage, investigated outcomes, number of events, number of participants, magnitude of the exposure–outcome association (expressed as risk ratio: RR) and corresponding 95% confidence interval (CI). Quality assessment of the included trials was evaluated using the Jadad scale [35], according which a score ranging from zero (very poor) to 13 points (rigorous) was calculated.

2.4. Statistical analysis

The summary RR for the association between omega-3 fatty acid supplement versus placebo and the risk of the considered outcomes was the measure of interest. Analyses were performed separately for each outcome. Between-study heterogeneity was tested using the Cochrane's Q test, and measured with the I^2 statistics (the proportion of between-study variability caused by heterogeneity) [36]. We pooled the original estimates by using both the Mantel & Haenszel method (fixed-effects model) and the DerSimonian & Laird method (random-effects model) [37]. When a significant heterogeneity was found, the results from the random-effects model were presented. An influence analysis was also conducted by omitting one study at a time, in order to identify to what extent the results were influenced by a single study. Publication bias was evaluated through funnel plot visual analysis and with the Egger's test [38].

All tests were considered significant statistically for *p*-values less than 0.05. The analyses and the correspondent graphical visualization of forest and funnel plots were respectively conducted by using RevMan Version 5.1

(Nordic Cochrane Center) and STATA Software Program Version 9 (STATA, College Station, TX).

3. Results

Figure 1 shows how we identified relevant trials from literature search. Based on title and abstract, 255, 243, and 132 papers were respectively retrieved from PUBMED, EMBASE and COCHRANE databases. From the resulting 360 articles which were reported at least once, 349 papers were excluded because of several reasons. Thus, 11 randomized, placebo-controlled trials fulfilling inclusion criteria were considered in the final analyses [32,33,39–47].

Table 1 shows that these studies included 15,348 patients, of whom 7,694 received omega-3 and the remaining 7,654 placebo. Overall 825 patients experienced death for any cause, 395 cardiac deaths, 249 sudden deaths, 640 myocardial infarctions, and 116 strokes. All studies were of high methodological quality, the Jadad score ranging from 8 [42] to 13 points [41,46,47].

As shown in Fig. 2, there was not statistical evidence that omega-3 fatty-acid supplementation reduced the risk of all-cause mortality and stroke, being the summary RR (and 95% CI) 0.89 (0.78 to 1.02), and 1.31 (0.90 to 1.90), respectively. Conversely, statistical significant protective effects were observed for cardiac death (0.68; 0.56 to 0.83), sudden death (0.67; 0.52 to 0.87), and myocardial infarction (0.75; 0.63 to 0.88). Between-study heterogeneity was not significant and numerically irrelevant, with the exception of sudden death for which I^2 statistics showed 42% variation across the studies due to heterogeneity. Influence analysis showed that the protective effects of omega-3 on the risk of cardiac death, sudden death, and myocardial infarction became not statistically significant by excluding the study by Marchioli et al. [32], being the summary RRs 0.77 (0.52 to 1.14), 0.95 (0.62 to 1.45), and 0.73 (0.53 to 1.01), respectively. There was no evidence for publication bias neither from funnel plots, nor from the Egger's test, ranging the *p*-values from 0.08 (cardiac death) to 0.96 (all-cause mortality).

4. Discussion

Our study incorporating the available published evidence from RCTs on the effect of omega-3 fatty acid administration to high risk patients did not show statistically significant reduction in all-cause mortality and risk of stroke. Conversely, favourable effects were observed on other CV outcomes. Indeed, with respect to patients who received placebo, those to whom omega-3 fatty acids were administered had risk reductions of cardiac death (−32%), sudden death (−33%), and myocardial infarction (−25%). Assurances over the robustness of our findings derive from at least two observations: there was no evidence of between-study heterogeneity, neither of selective inclusion of studies reporting higher protective effects. Nevertheless, our findings were influenced by the more relevant study on this issue [32], omitting it more modest benefit was observed.

Systematic reviews and meta-analyses on this issue [8,21–30] have addressed different key questions with respect to ours. We chose to include randomized, double-blind, placebo controlled trials investigating the effect of omega-3 fatty acid administration to patients with existing CV disease (the group most likely to benefit from their use), through administration of sufficiently high doses, and

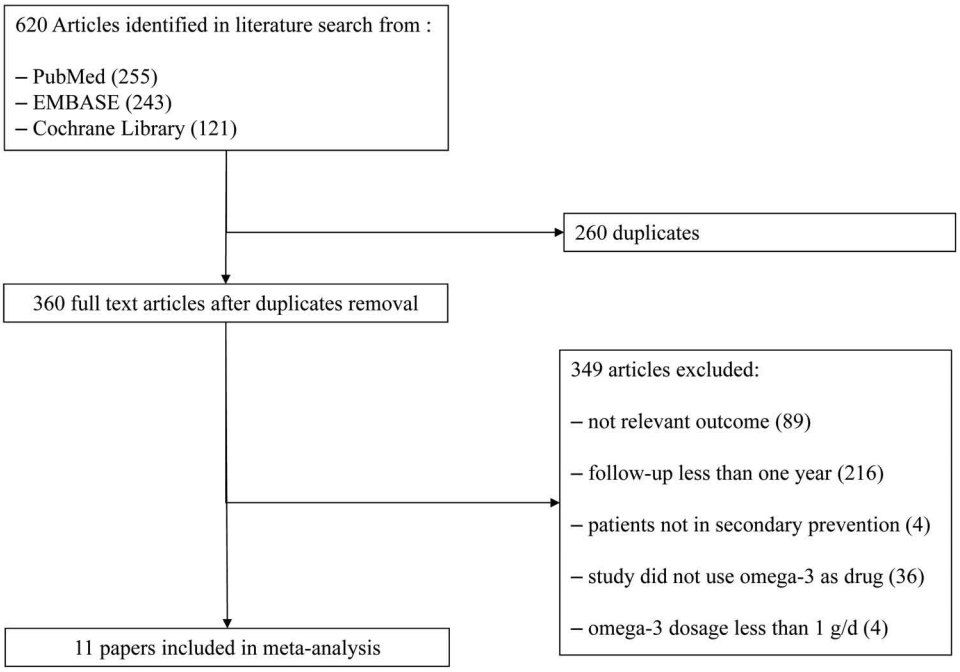

Fig. 1. Flow-chart for the selection of elegible randomized, double-blind, placebo-controlled trials.

Table 1
Selected characteristics of 11 randomized, double blind, placebo controlled trials included in the meta-analysis

Source, year [ref]	Country	Gender	Age, Median (range), y	Previous CV event	Control	Omega-3 dosage, g/day	Treatment duration, y	Outcome	No. of events		No. of participants		RR (95% CI)	Quality score
									Omega-3	Control	Omega-3	Control		
Sacks et al, 1995 [39]	USA	MW	62 (30–75)	CHD	Placebo (olive oil)	6	2.3	All cause mortality	0	1	31	28	0.30 (0.01 to 7.11)	11
								Cardiac death	0	1	31	28	0.30 (0.01 to 7.11)	
								MI (non fatal)	1	2	31	28	0.45 (0.04 to 4.71)	
								Stroke (non fatal)	1	0	31	28	2.71 (0.12 to 64.00)	
Singh et al, 1997 [40]	India	MW	49 (NR)	MI	Placebo	1.80	1	Cardiac death	14	26	122	118	0.52 (0.22 to 1.21)	11
								Sudden death	2	8	122	118	0.24 (0.03 to 2.00)	
								MI (non fatal)	16	30	122	118	0.51 (0.23 to 1.28)	
Marchioli et al, 1999 [32]	Italy	MW	59 (NR)	MI	Control	1	3.5	All cause mortality	236	293	2,836	2,828	0.80 (0.67 to 0.94)	9
								Cardiac death	108	165	2,836	2,828	0.65 (0.51 to 0.82)	
								Sudden death	55	99	2,836	2,828	0.55 (0.40 to 0.76)	
								MI (fatal/non fatal)	196	259	2,836	2,828	0.75 (0.62 to 0.90)	
								Stroke (fatal/non fatal)	54	41	2,836	2,828	1.30 (0.87 to 1.96)	
Von Schascky et al, 1999 [41]	Germany	MW	58 (18–75)	PTCA	Placebo (nonmarine fatty acids)	3.3 (3 months) 1.7 (21 months)	2	All cause mortality	1	2	112	111	0.50 (0.05 to 5.39)	13
								Cardiac death	0	1	112	111	0.33 (0.01 to 8.02)	
								MI (fatal/non fatal)	1	4	112	111	0.25 (0.03 to 2.18)	
								Stroke (non fatal)	1	3	112	111	0.33 (0.03 to 3.13)	
Nilsen et al, 2001 [42]	Norway	MW	64 (29–88)	MI	Placebo (corn oil)	3.4	1.5	All cause mortality	11	11	150	150	1.02 (0.44 to 2.36)	8
								Cardiac death	8	8	150	150	1.02 (0.38 to 2.71)	
								MI (non fatal)	21	15	150	150	1.43 (0.74 to 2.78)	

Table 1 (*continued*)

Source, year [ref]	Country	Gender	Age, Median (range), y	Previous CV event	Control	Omega-3 dosage, g/day	Treatment duration, y	Outcome	No. of events		No. of participants		RR (95% CI)	Quality score
									Omega-3	Control	Omega-3	Control		
Leaf et al, 2005 [43]	USA	MW	65 (NR)	ICD	Placebo (olive oil)	2.6	1	All cause mortality	13	12	200	202	1.09 (0.51 to 2.34)	12
								Cardiac death	9	9	200	202	1.01 (0.41 to 2.49)	
Raitt et al, 2005 [44]	USA	MW	63 (NR)	ICD	Placebo (olive oil)	1.8	2	All cause mortality	4	10	100	100	0.40 (0.13 to 1.23)	12
								Cardiac death	2	5	100	100	0.40 (0.08 to 2.01)	
								Sudden death	2	0	100	100	5.00 (0.24 to 102.85)	
								MI (NR)	1	3	100	100	0.33 (0.04 to 3.15)	
Svensson et al, 2006 [45]	Denmark	MW	67 (NR)	CVD	Placebo (olive oil)	1.7	2	All cause mortality	34	30	103	103	1.12 (0.69 to 1.83)	12
								MI (NR)	4	13	103	103	0.30 (0.10 to 0.92)	
								Stroke (NR)	7	3	103	103	2.23 (0.58 to 8.64)	
Yokoyama et al, 2007 [33]	Japan	MW	61 (NR)	CHD	Placebo (Prava, Simva)	1.8	5	Cardiac death	18	21	1,832	1,832	0.87 (0.46 to 1.64)	10
								MI (fatal/non fatal)	31	42	1,832	1,832	0.75 (0.47 to 1.19)	
Rauch et al, 2010 [46]	Germany	MW	64 (NR)	MI	Placebo (olive oil)	1	1	All cause mortality	88	70	1,919	1,885	1.25 (0.90 to 1.72)	13
								Sudden death	28	29	1,919	1,885	0.95 (0.56 to 1.60)	
Macchia et al, 2013 [47]	Argentina	MW	66 (NR)	AF	Placebo (olive oil)	1	1	All cause mortality	4	5	289	297	0.80 (0.21 to 3.00)	13
								MI (non fatal)	1	1	289	297	1.10 (0.07 to 17.90)	
								Stroke (non fatal)	3	3	289	297	1.16 (0.23 to 5.78)	

CHD, Coronary Heart Disease; MI, Myocardial Infarction; PTCA, Percutaneous Transluminal Coronary Angioplasty; ICD, Implantable Cardioverter Defibrillator; CVD, Cardiovascular Disease; AF, Atrial Fibrillation; M, Men; W, Women; Prava, Pravastatin; Simva, Simvastatin.

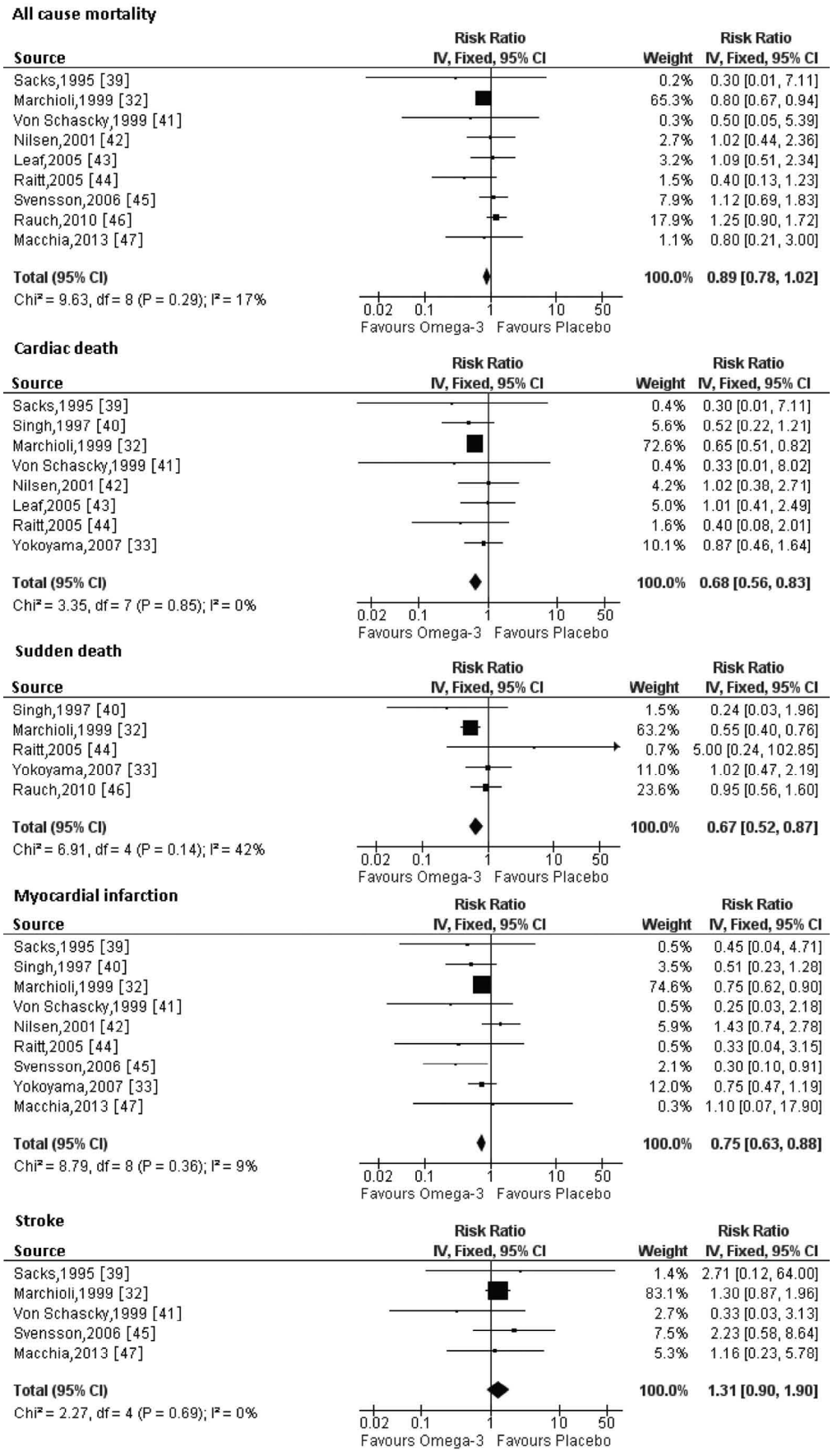

Fig. 2. Meta-analysis of omega-3 fatty acid supplements for different outcomes.

for time windows sufficiently long to manifest their CV preventive action. Our stringent inclusion criteria likely explain the inconsistency of our findings with respect to those reported by two recent meta-analyses published on this topic [8,28] that have lead to a wide range of reactions in the scientific community.

It has been suggested that omega-3 fatty acids may have several beneficial CV effects, such as anti-arrhythmic properties, anti-atherothrombotic influences, plaque stabilization, vasodilatation, and lipid level reduction [4–7,48]. Our results showing that omega-3 fatty acid supplement administered with dosage >1 g/day for at least one year to high risk patients prevents the onset of cardiac death, sudden death and myocardial infarction, support therefore their biological properties. On the other hand, the lack of an effect of omega-3 fatty acid supplements observed by some trials [17,47,49,50] and meta-analyses [21,23,24] could be the result of other cardioprotective drug treatments, such as statin use [17]. This might explain the main protective effect of omega-3 supplementation observed from the GISSI-Prevenzione trial [32], in which only 5% of patients had received statins at baseline. It has been suggested that additional use of omega-3 fatty acid supplements in patients receiving statins might not be beneficial in preventing CV outcomes [8]. However, it may be more difficult to demonstrate an association of omega-3 fatty acid treatment in patients with a history of statin therapy use. In addition, the effect on sudden death of omega 3 appears to be not spared by statin treatment. Because of these considerations the relationship between cardiovascular disease events and omega-3 PUFA supplementation controlling for statin use needs to be explored and clarified as the patients on no statin or low doses of statins are frequently encountered in clinical practice because of either poor adherence to therapy or intolerance to omega-3 treatment [51]. Of note, omega-3 treatment is essentially devoid of any adverse effect.

Our study has limitations. First, we initially had planned to conduct subgroup analyses, for example according to the type of funding source, as well as to selected baseline characteristics of the included patients (e.g. treatment with other cardioprotective agents). There was not, however, a sufficient number of trials to perform this analysis. Second, our findings are limited to Western populations because of a paucity of data for Eastern populations. Third, we only used published information on exposure (e.g. compliance of the dispensed omega-3 supplementation) and outcomes (e.g. nonfatal or fatal myocardial infarction). Therefore, we are unable to exclude exposure and/or outcome misclassifications, if any.

In summary, our results provide further evidence on the positive effect of omega-3 fatty acid supplementation administered with dosage >1 g/day for at least one year in preventing cardiac death, sudden death and myocardial infarction among patients with a history of cardiovascular disease. Experimental 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, co-treatments with other cardioprotective drug agents.

Conflict of interest

ALC declares the following conflict of interest: acting as speaker for Sigma-Tau industries.

The other authors declare no conflict of interest.

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