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Omega-3 fatty acids supplementation on major cardiovascular outcomes: an umbrella review of meta-analyses of observational studies and randomized controlled trials

H. CHOI[1], J.Y. KIM[1], K.H. LEE[2,3], J.S. KIM[4], J.Y. LEE[4], E.K. CHOI[5], H.J. SEONG[6], G. KIM[7], H. PARK[8], E. JUNG[8,9], S.H. HONG[6,10], A. KRONBICHLER[11], M. EISENHUT[12], A. KOYANAGI[13,14], L. JACOB[13,15], D.K. YON[16], S.W. LEE[17], M.S. KIM[18,19], K. KOSTEV[20], J.I. SHIN[2,3], J.W. YANG[4], L. SMITH[21]

[1]Department of Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[3]Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[5]College of Nursing and Mo-Im Kim Nursing Research Institute, Yonsei University, Seoul, Republic of Korea
[6]Yonsei University College of Medicine, Seoul, Republic of Korea
[7]Keimyung University College of Nursing, Daegu, Republic of Korea
[8]Department of Nursing, Yonsei University Graduate School, Seoul, Republic of Korea
[9]Korea Armed Forces Nursing Academy, Daejeon, Republic of Korea
[10]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[11]Department of Internal Medicine IV, Medical University Innsbruck, Innsbruck, Austria
[12]Department of Pediatrics, Luton and Dunstable University Hospital NHS Foundation Trust, Luton, UK
[13]Parc Sanitari Sant Joan de Déu/CIBERSAM, Universitat de Barcelona, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain
[14]ICREA, Pg, Lluis Companys 23, Barcelona, Spain
[15]Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
[16]Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, South Korea
[17]Department of Data Science, Sejong University College of Software Convergence, Seoul, South Korea
[18]Korea University, College of Medicine, Seoul, Republic of Korea
[19]Genomics and Digital Health, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea
[20]University Clinic of Marburg, Marburg, Germany
[21]The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge CB1 1PT, UK

Hyeok Choi, Jong Yeob Kim, Keum Hwa Lee, and Jae Seok Kim contributed equally to this work

Abstract. – OBJECTIVE: Omega-3 fatty acids are commonly used as a lipid-lowering agent or dietary supplement for the purpose of prevention of cardiovascular diseases. However, even large-scale clinical trials have not shown significant results demonstrating clear clinical benefits in cardiovascular diseases. Thus, this umbrella review aims to summarize and evaluate the evidence of clinical effects of omega-3 fatty acids supplementation on cardiovascular outcomes through comprehensive analyses of previous randomized controlled trials (RCTs) or observational cohort studies.

MATERIALS AND METHODS: We conducted relevant publication search in PubMed, Embase, and Cochrane Database of Systematic Reviews. We retrieved and analyzed 3,298 articles published until August 28th, 2019.

RESULTS: We identified 29 relevant articles and analyzed 83 meta-analyses of RCTs or cohort studies therefrom. As a result, we identified 12 cardiovascular outcomes that are related to

Corresponding Authors: Jae Il Shin, MD, Ph.D; e-mail: shinji@yuhs.ac
Jae Won Yang, M.D, Ph.D; e-mail: kidney74@yonsei.ac.kr

omega-3 fatty acids supplementation. Among them, total mortality from major cardiovascular causes (RR 0.92, 95% CI 0.86 to 0.98) had significant inverse associations, and moreover, statistical significances were maintained even in subgroup analysis of large scale RCTs including more than 1,000 patients (RR 0.94, 95% CI 0.88 to 0.99).

CONCLUSIONS: Our umbrella review study shows that omega-3 fatty acids supplementation have a clinical benefit in reducing mortality from cardiovascular causes. However, many studies still have shown conflicting results, and therefore, further studies will be needed to verify the clinical benefit of omega-3 supplementation.

Key Words:
Omega-3 fatty acids, Cardiovascular outcome, Mortality, Meta-analysis, Systematic review.

Introduction

In the general population and among healthcare professionals, it is widely recognized that omega-3 fatty acids exhibit properties that can potentially prevent cardiovascular diseases[1]. However, controversy still exists due to discrepancies between available evidences[2]. Significant results in clinical trials and observational studies of small patient groups have been reported[3-5], but the true association remains unclear, as large clinical trials have often reported non-significant results[6-8]. Furthermore, the recently published Vitamin D and Omega-3 (VITAL) trial, a large-sized randomized controlled trial (RCT) that recruited 25,871 patients, concluded that marine omega-3 fatty acids supplementation has no effects in preventing cardiovascular diseases[9].

Therefore, although systematic reviews and meta-analyses have attempted to synthesize the results from numerous clinical trials and observational studies investigating the effect of omega-3 supplementation on cardiovascular outcomes, they reached no definite conclusion. Several recent systematic reviews have performed quantitative syntheses of the vast amount of available evidences. Among them, a recent systemic review indicated the beneficial effect of omega-3 supplementation on cardiovascular diseases[10], while the other review showed the positive effect of omega-3 fatty acids but only a small effect with moderate- and low-certainty evidence[11].

The aim of this umbrella review was, therefore, to examine the effect of omega-3 fatty acids supplementation on cardiovascular diseases avoiding research biases, and thereby overcoming the shortcomings of previous studies.

Materials and Methods

We performed an umbrella review assessing the effects of omega-fatty acids supplementation on cardiovascular outcomes according to a pre-registered protocol in PROSPERO (registration number: CRD42018115797). We reported the results according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[12].

Literature Search Strategy and Eligibility Criteria

We searched PubMed, Embase, and Cochrane Database of Systematic Reviews (CDSR) from their inception to August 28th, 2019 to identify meta-analyses that investigated the association between omega-3 supplementation and cardiovascular outcomes. We performed a publication search using the following keywords: omega-3 fatty acids, n-3 fatty acids, w-3 fatty acids, α-linolenic acid, ALA, eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA, polyunsaturated fatty acids, PUFA, long chain polyunsaturated fatty acids, LCPUFA, fish oil, and meta.

Only English articles were eligible. We first screened titles, followed by the abstract, and then the full text of potentially eligible articles. We only included systematic reviews containing meta-analyses that investigated the effect of omega-3 fatty acids supplementation on cardiovascular disease. On the other hand, we did not include studies on the relationship between fish consumption and cardiovascular outcome, because fish contains various nutrients other than omega-3 fatty acids. For example, a RCT that examined the difference in effects of between fresh fish consumption and omega-3 fatty acids supplementation concluded that fish consumption was associated with positive cardiovascular outcomes, but omega-3 fatty acids supplementation was not[13]. In addition, we excluded meta-analyses that studied dietary interventions such as Mediterranean diet education and food frequency questionnaire results.

Inclusion of meta-analysis was independent of the study design of the component study (i.e. either RCTs or observational studies). There was no restriction of the study population. If an article included more than one eligible meta-analysis, we included these separately.

Data Extraction

From each eligible article, we extracted the name of the first author and the date of publication. From each eligible meta-analysis, we extracted the outcome of interest, the number of cardiovascular outcome events and total participants, individual study estimates and corresponding 95% confidence interval (CI), metrics used for analyses such as odds ratio (OR), risk ratio (RR), and hazard ratio (HR), and individual study designs as RCT or observational study. We also extracted the summary effect estimates and meta-analysis model of the original meta-analyses to check whether the original results were consistent with the results of our re-analysis. From the meta-analyses of observational studies, we extracted the maximally adjusted study estimate available.

Statistical Analysis

We estimated the summary effects, corresponding 95% CIs and *p*-values using both fixed- and random-effects models[14]. We also estimated between-study heterogeneity as the I^2 metric[15,16]. I^2 statistic above 50% and 75% are usually judged to represent large and very large heterogeneity, respectively[17]. To assess the reliability of analyses, we adopted a series of statistical tests and bias assessment methods. We estimated the 95% prediction interval, which is the range for the true effect of the intervention for 95% of similar studies in the future[18]. In addition, we assessed the small study effect with the regression asymmetry test proposed by Egger et al[19] because small studies may overestimate the effect size. We claimed a small study effect with a p-value < 0.1. Presence of small study effects indicates reporting bias such as publication bias, poor methodological quality of individual studies, or genuine heterogeneity[20]. We also defined the study with the smallest standard error as the largest study, and assumed that the largest study reflects the true effect size. The expected number of significant studies was obtained by multiplying the power of the largest study with the number of all studies in the meta-analysis[21]. We assessed the presence of excess significance bias which was determined if the observed number of studies reporting nominally statistically significant result were greater than the expected number of studies reporting a significant result[22,23].

For meta-analyses of RCTs, we performed subgroup analyses according to the total number of participants (above 1,000 or below 1,000) and compared their results. For outcomes presented in both meta-analyses of RCTs and meta-analysis of observational studies, we compared the summary effects of the two study designs.

In addition, we applied credibility ceilings to the meta-analyses of observational studies. We assumed that due to inherent methods used in observational studies, any observational study could not give more than 100-c% (c = credibility ceiling) probability of an effect being in a particular direction and not in the other[24,25]. We obtained the I^2 index and the random-effects summary estimate of meta-analyses of observational studies under various credibility ceilings ranging from 5% to 20%.

All statistical tests and reported *p*-values are two-sided. The software used for analysis was Comprehensive Meta-analysis ver.3.3.070 (Borenstein, NH, USA), R Studio ver. 1.1.456., and R package "metafor" and "pwr"[26-28].

Results

Selection of Eligible Meta-Analyses

We identified 1,771 articles from a PubMed, 1,977 articles from a Embase, and 349 articles from a CDSR search (Figure 1). We excluded 799 duplicate articles. From 3,298 unique articles reviewed by title screening, we excluded 1,460 articles not related to omega-3 fatty acids supplementation. From 1,838 articles reviewed by abstract screening, we excluded 1,385 articles, of which 126 articles were conference abstracts, 399 articles did not contain respective interventions, 71 articles did not contain meta-analyses, and 789 articles did not contain cardiovascular outcomes. After the full-text screening of 453 articles, 29 articles were finally judged to be eligible for inclusion in our analysis.

From the 29 eligible articles, 83 eligible meta-analyses were identified, from which data were extracted. From 76 meta-analyses of RCTs, 31 (41%) were statistically significant ($p < 0.05$). Nine-teen (25%) had large heterogeneity ($50\% < I^2 < 75\%$) and 1 (1%) had very large heterogeneity ($I^2 > 75\%$). Seventeen (22%) had significant bias of small study effect. Eight (11%) had prediction intervals excluding the null. Of 7 meta-analyses of observational cohort studies, 4 (57%) were statistically significant ($p < 0.05$). One (14%) had large heterogeneity ($50\% < I^2 < 75\%$) and 2 (29%) had very large heterogeneity ($I^2 > 75\%$). One (14%) had significant bias of small study effect. All 7 (100%) lost significance under 10% credibility

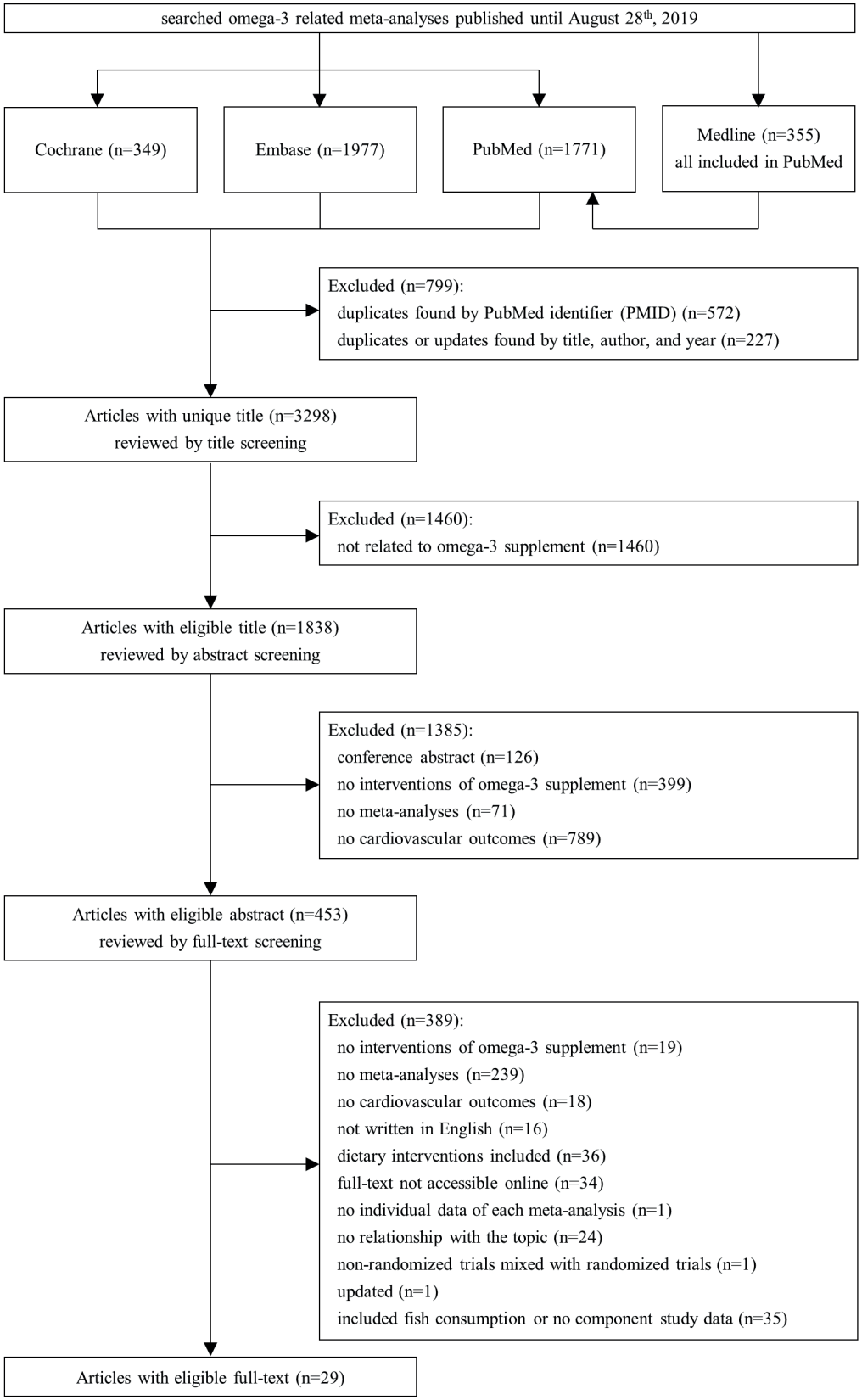

Figure 1. Flow chart of literature search.

ceiling. One (14%) had prediction interval excluding the null.

Determination of Cardiovascular Outcomes

We identified 11 cardiovascular outcomes from the literatures, which included cardiovascular, cardiac, and coronary events, cardiovascular, cardiac, and coronary deaths, arrhythmia or sudden death, myocardial infarction, stroke or transient ischemic attack, post-operative atrial fibrillation, and recurrent atrial fibrillation. Although these outcomes were similar to each other, we followed the definition and terminology of the eligible articles as they were. In addition, we created a composite outcome, total mortality from major cardiovascular causes by merging component studies reporting any of the following: cardiovascular, cardiac, coronary, or sudden deaths. Eventually, we were able to analyze 12 outcomes in the meta-analyses of RCTs and 6 outcomes in observational cohort studies.

Total Mortality from Major Cardiovascular Causes in Meta-Analyses of RCTs

Meta-analyses from 5 articles were merged for total mortality from major cardiovascular causes. In total, 26 RCTs including 82,696 participants having more than 3,250 (> 3.9%) events were included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.92, 95% Cl 0.86 to 0.98, $p = 0.014$) in reducing overall mortality of major cardiovascular causes. There was a low heterogeneity between component studies ($I^2 = 4\%$), and small study effect bias was observed. The 95% prediction interval did not exclude the null (0.83 to 1.02) (Table I). There was no excess significance bias .

Cardiovascular Death in Meta-Analyses of RCTs

Meta-analyses from 3 articles were merged for cardiovascular death. In total, 22 RCTs including 76,407 participants with more than 3,192 (> 4.2%) events were included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.93, 95% CI 0.88 to 0.98, $p = 0.012$). There was low heterogeneity between component studies ($I^2 = 0\%$). There was small study effect bias. The 95% prediction interval did exclude the null (0.87 to 0.99) (Table I). There was no excess significance bias.

Cardiac Death in Meta-Analyses of RCTs

Three articles derived from meta-analyses were merged for cardiac death. In total, 20 RCTs with more than 79,410 participants reported 3,618 (4.6%) events. The effect of omega-3 fatty acids supplementation was statistically significant (RR 0.90, 95% CI 0.82 to 1.00, $p = 0.040$). Low heterogeneity between component studies ($I^2 = 20\%$) was found in our analysis. There was small study effect bias. The 95% prediction interval did not exclude the null (0.74 to 1.10) (Table I). There was no excess significance bias.

Post-operative Atrial Fibrillation in Meta-Analyses of RCTs

Meta-analyses from 3 articles were merged for post-operative atrial fibrillation. In total, 21 RCTs with 4,201 participants were included, and a total of 1,247 (29.7%) events were recorded. The overall effect of omega-3 fatty acids supplementation was statistically significant (OR 0.65, 95% CI 0.51 to 0.82, $p < 0.001$). There was relatively large heterogeneity between component studies ($I^2 = 53\%$). There was small study effect bias. The 95% prediction interval did not exclude the null (0.29 to 1.45) (Table I). Excess significance bias was found.

Other Outcomes in Meta-Analyses of RCTs

Meta-analyses of the other 8 outcomes did not reveal significant associations, including cardiovascular events, cardiac events, coronary events, coronary deaths, arrhythmia or sudden deaths, myocardial infarction, stroke or transient ischemic attack, and recurrent atrial fibrillation (Table I). There was relatively large heterogeneity between component studies for recurrent atrial fibrillation ($I^2 = 74\%$), and not for the other 7 outcomes.

Total Mortality from Major Cardiovascular Causes in Meta-analyses of Cohort Studies

There was only one article reporting total mortality from major cardiovascular causes. A total of 558,826 participants derived from 15 cohorts was included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.76, 95% CI 0.65 to 0.90, $p = 0.0013$). There was relatively large heterogeneity between component studies ($I^2 = 60\%$). There was no small study effect bias. The 95% prediction interval did not exclude the null (0.45 to 1.28) (Table II). A loss of significance under 10% credibility ceiling was found.

Coronary Events in Meta-Analyses of Cohort Studies

Again, only one article was reported for coronary events. A total of 344,722 participants from

Table I. Meta-analyses of randomized controlled trials of omega-3 fatty acids on major cardiovascular outcomes.

Cardiovascular outcome	Population	Events/total participants	Number of study estimates	Effect metrics	Random effects summary estimate (95% CI)	Random effects *p* value	I^2 (%)	95% prediction interval	Evaluation of biases*
Total mortality of major cardiovascular cause[35-39]	**Overall**	**>3,250 / 82,696**	**26**	**RR**	**0.92 (0.86 to 0.98)**	**0.014**	**4**	**0.83 to 1.02**	**Small study effects**
Cardiovascular event[41-45]	Overall	17,033 / >72,179	39	RR	0.97 (0.92 to 1.03)	0.330	45	0.80 to 1.18	None
Cardiac event[46]	With coronary heart disease	2,852 / 25,134	10	OR	0.92 (0.79 to 1.06)	0.250	49	0.63 to 1.33	None
Coronary event[45]	Overall	6,093 / 77,917	10	RR	0.95 (0.89 to 1.03)	0.210	0	0.88 to 1.04	None
Cardiovascular death[35,38,39]	**Overall**	**>3,192 / 76,407**	**22**	**RR**	**0.93 (0.88 to 0.98)**	**0.012**	**0**	**0.87 to 0.99**	**Small study effects**
Cardiac death[36,37,47]	**Overall**	**3,618 / 79,410**	**20**	**RR**	**0.90 (0.82 to 1.00)**	**0.040**	**20**	**0.74 to 1.10**	**Small study effects**
Coronary death[45]	Overall	2,695 / 77,917	10	RR	0.93 (0.84 to 1.03)	0.150	0	0.82 to 1.05	None
Arrhythmia or sudden death[46,48,49]	Overall	1,415 / 43,987	12	OR	0.85 (0.71 to 1.02)	0.086	32	0.57 to 1.28	None
Myocardial infarction[38,45,47]	Overall	2,846 / 86,411	20	RR	0.90 (0.80 to 1.00)	0.056	13	0.72 to 1.12	None
Stroke or transient ischemic attack[41,47]	Overall	259 / 32,026	11	RR	1.20 (0.94 to 1.53)	0.150	0	0.90 to 1.59	None
Post-operative atrial fibrillation[50-52]	**Underwent cardiac surgery**	**1,247 / 4,201**	**21**	**OR**	**0.65 (0.51 to 0.82)**	**< 0.001**	**53**	**0.29 to 1.45**	**Large heterogeneity; small study effects; excess significance bias**
Recurrent atrial fibrillation[53]	With previous atrial fibrillation	894 / 1,990	8	OR	0.81 (0.52 to 1.25)	0.340	74	0.21 to 3.14	Large heterogeneity

All statistical tests are two-sided. **Bold** Summary effect was statistically significant. *Presence of large heterogeneity, small study effects, or excess significance bias. **Abbreviations:** CI, confidence interval; NR, not reported; OR, odds ratio; RR, risk ratio.

14 cohorts was included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.89, 95% CI 0.84 to 0.96, $p = 0.001$). A low heterogeneity between component studies ($I^2 = 3\%$) was found. There was no small study effect bias. The 95% prediction interval excluded the null (0.82 to 0.98) (Table II). There was a loss of significance under 10% credibility ceiling.

Coronary Deaths in Meta-Analyses of Cohort Studies

There was only one article reporting coronary deaths. A total of 357,621 participants from 10 cohorts was included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.85, 95% CI 0.73 to 1.00, $p = 0.047$). There was no large heterogeneity between component studies ($I^2 = 49\%$), nor small study effect bias. The 95% prediction interval did not exclude the null (0.57 to 1.29) (Table II). There was a loss of significance under 10% credibility ceiling.

Arrhythmia or Sudden Deaths in Meta-Analyses of Cohort Studies

There was only one article reporting on arrhythmia or sudden deaths. In total, 201,205 participants of 5 cohorts were included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.53, 95% CI 0.41 to 0.67, $p < 0.001$). There was no heterogeneity between component studies ($I^2 = 0\%$). There was no small study effect bias. The 95% prediction interval excluded the null (0.36 to 0.78) (Table II). A loss of significance under 10% credibility ceiling was found.

Other Outcomes in Meta-Analyses of Cohort Studies

Both other outcomes, cardiovascular events and myocardial infarction, were not statistically significant (Table II). There was very large heterogeneity between component studies of cardiovascular events ($I^2 = 77\%$), and relatively large heterogeneity between component studies of myocardial infarction ($I^2 = 72\%$).

Comparison of Meta-Analyses Between RCTs and Cohort Studies

Twelve outcomes have been reviewed from the meta-analyses of RCTs, and 6 outcomes have been reviewed from the meta-analyses of cohort studies. From the 6 overlapping outcomes, only 1 outcome of a meta-analysis of RCTs and 4 outcomes of meta-analyses of cohort studies showed statistical significance ($p < 0.05$ for random-effect model) (Table III). For the outcome of total mortality of major cardiovascular causes, the meta-analysis of RCTs and cohort studies both showed statistical significance. For the outcomes of coronary events, coronary deaths, and arrhythmia or sudden deaths, only meta-analyses of cohort studies showed statistical significance while meta-analyses of RCTs did not. For the outcomes of cardiovascular event and myocardial infarction, both meta-analyses of RCTs and cohort studies did not show statistical significance (Figure 2).

Comparison of Meta-Analyses Between RCTs with More Than 1,000 Participants and Less than 1,000 Participants

While the effect sizes reported from the largest cohort studies were similar compared to the meta-analyses of cohort studies, the discrepancy was present between the effect size reported from the largest RCTs and the meta-analyses of RCTs, which underlines the need for subgroup analysis according to the number of total participants (> 1,000 *vs.* < 1,000) (Table III and Figure 2).

Out of all 12 major cardiovascular outcomes, total mortality from major cardiovascular causes, cardiovascular death, cardiac death, and postoperative atrial fibrillation showed statistical significance in meta-analyses of RCTs with less than 1,000 participants, whereas only 2 outcomes were still supported by statistically significance even in meta-analyses of RCTs of total participants larger than 1,000. These 2 outcomes were total mortality from major cardiovascular causes (RR = 0.94, 95% CI 0.88 to 0.99) and cardiovascular deaths (RR = 0.94, 95% CI 0.89 to 1.00) (Table III).

Notably, there was a tendency for the meta-analyses of RCTs with less than 1,000 participants to report a dramatically larger effect size (RR = 0.58 for total mortality of major cardiovascular causes, RR = 0.61 for cardiovascular death, RR = 0.60 for cardiac death) compared to those with more than 1,000 participants (RR = 0.94 for total mortality from major cardiovascular causes, RR = 0.94 for cardiovascular death, RR = 0.93 for cardiac death) (Table III). These 2 outcomes had small study effects as well.

Nonetheless, when subgroup analysis was conducted with RCTs of more than 1,000 patients, statistical significance for total mortality from major cardiovascular causes was maintained ($p = 0.033$) with low heterogeneity ($I^2 = 0\%$), and there was no small study effect. As for cardio-

Table II. Meta-analyses of cohort studies of omega-3 fatty acids on major cardiovascular outcomes.

Cardiovascular outcome	Population	Events/total population	Number of study estimates	Effect metrics	Random effects summary estimate (95% CI)	Random effects *p* value	I^2 (%)	95% prediction interval	Evaluation of biases*
Total mortality from major cardiovascular causes[54]	**Non-hospitalized adults of at least 18 years old**	**NR/558,826**	**15**	**RR**	**0.76 (0.65 to 0.90)**	**< 0.001**	**60**	**0.45 to 1.28**	**Large heterogeneity**
Cardiovascular event[41]	Overall	1842/68,954	6	RR	0.97 (0.78 to 1.21)	0.800	77	0.49 to 1.94	Large heterogeneity
Coronary event[55]	**Overall**	**NR/344,722**	**14**	**RR**	**0.89 (0.84 to 0.96)**	**0.001**	**3**	**0.82 to 0.98**	**Loss of significance under 10% credibility ceiling**
Coronary death[54]	**Non-hospitalized adults of at least 18 years old**	**NR/357,621**	**10**	**RR**	**0.85 (0.73 to 1.00)**	**0.047**	**49**	**0.57 to 1.29**	**Loss of significance under 10% credibility ceiling**
Arrhythmia or sudden death[54]	**Non-hospitalized adults of at least 18 years old**	**NR / 201,205**	**5**	**RR**	**0.53 (0.41 to 0.67)**	**< 0.001**	**0**	**0.36 to 0.78**	**Loss of significance under 10% credibility ceiling**
Myocardial infarction[54]	Non-hospitalized adults of at least 18 years old	NR/274,083	7	RR	0.91 (0.74 to 1.11)	0.340	72	0.48 to 1.70	Large heterogeneity

All statistical tests are two-sided. **Bold** Summary effect was statistically significant. *Large heterogeneity, small study effects, excess significance bias, or loss of heterogeneity under 10% credibility ceiling. **Abbreviations:** CI, confidence interval; NR, not reported; OR, odds ratio; RR, risk ratio.

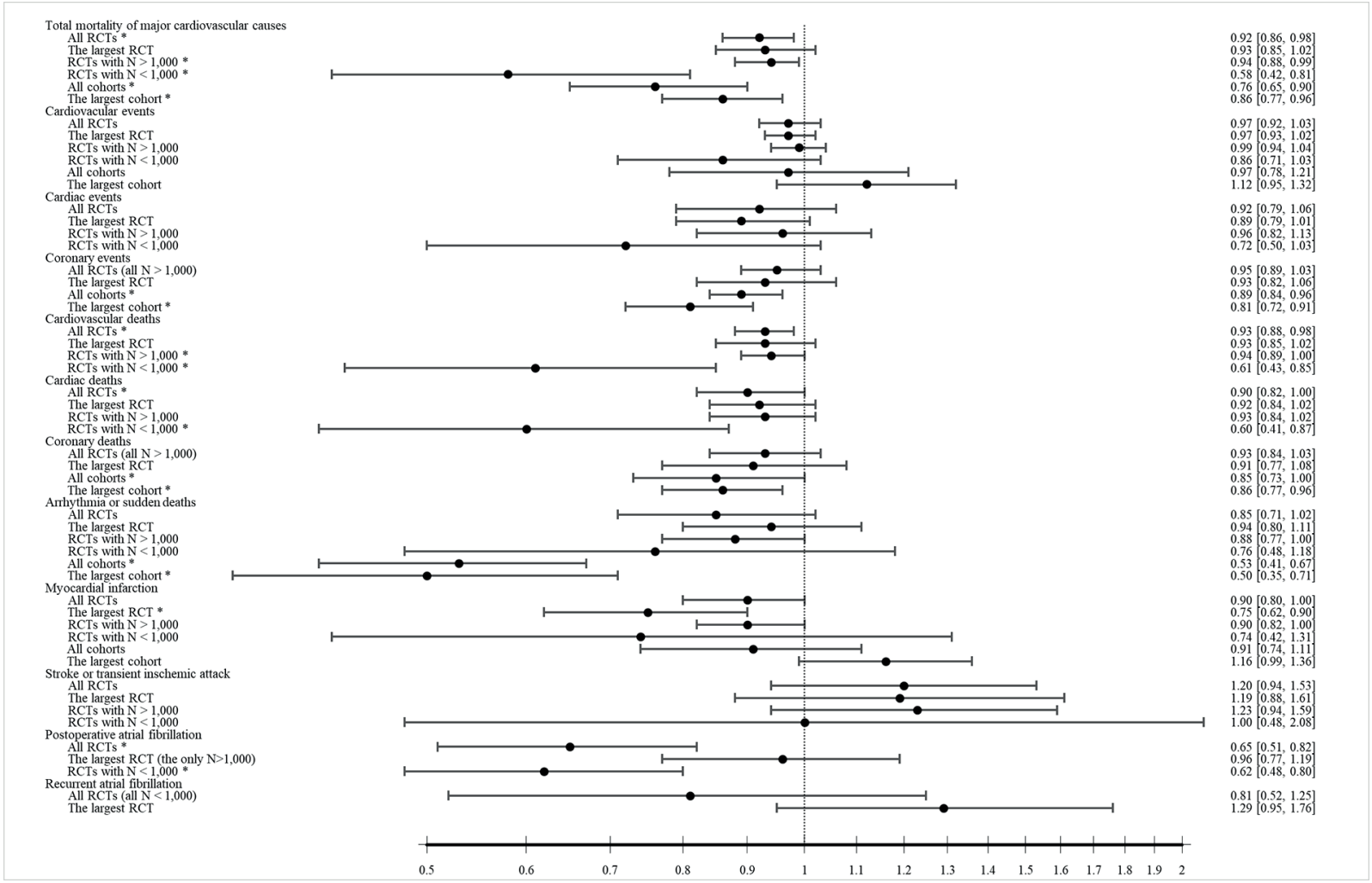

Figure 2. Forest plot of meta-analyses of randomized controlled trials and cohort studies for all the categories of major cardiovascular outcomes.

Table III. Comparison and Subgroup analyses of randomized controlled trials and cohort studies.

	Randomized controlled trials					Cohort studies		
Cardiovascular outcome	**Metric**	**Meta-analysis of RCTs**	**The largest RCT**	**Meta-analysis of RCTs with participants > 1,000**	**Meta-analysis of RCTs with participants < 1,000**	**Metric**	**Meta-analysis of cohort studies**	**The largest cohort study**
Total mortality from major cardiovascular causes	RR	**0.92 (0.86 to 0.98)***	0.93 (0.85 to 1.02)	**0.94 (0.88 to 0.99)***	**0.58 (0.42 to 0.81)***	RR	**0.76 (0.65 to 0.90)***	**0.86 (0.77 to 0.96)***
Cardiovascular event	RR	0.97 (0.92 to 1.03)	0.97 (0.93 to 1.02)	0.99 (0.94 to 1.04)	0.86 (0.71 to 1.03)	RR	0.97 (0.78 to 1.21)	1.12 (0.95 to 1.32)
Cardiac event	OR	0.92 (0.79 to 1.06)	0.89 (0.79 to 1.01)	0.96 (0.82 to 1.13)	0.72 (0.50 to 1.03)	NA	NA	NA
Coronary event	RR	0.95 (0.89 to 1.03)	0.93 (0.82 to 1.06)	0.95 (0.89 to 1.03)	NA	RR	**0.89 (0.84 to 0.96)***	**0.81 (0.72 to 0.91)***
Cardiovascular death	RR	**0.93 (0.88 to 0.98)***	0.93 (0.85 to 1.02)	**0.94 (0.89 to 1.00)***	**0.61 (0.43 to 0.85)***	NA	NA	NA
Cardiac death	RR	0.90 (0.82 to 1.00)	0.92 (0.84 to 1.02)	0.93 (0.84 to 1.02)	**0.60 (0.41 to 0.87)***	NA	NA	NA
Coronary death	RR	0.93 (0.84 to 1.03)	0.91 (0.77 to 1.08)	0.93 (0.84 to 1.03)	NA	RR	**0.85 (0.73 to 1.00)***	**0.86 (0.77 to 0.96)***
Arrhythmia or sudden death	OR	0.85 (0.71 to 1.02)	0.94 (0.80 to 1.11)	0.88 (0.77 to 1.00)	0.76 (0.48 to 1.18)	RR	**0.53 (0.41 to 0.67)***	**0.50 (0.35 to 0.71)***
Myocardial infarction	RR	**0.90 (0.80 to 1.00)***	0.75 (0.62 to 0.90)*	0.90 (0.82 to 1.00)	0.74 (0.42 to 1.31)	RR	0.91 (0.74 to 1.11)	1.16 (0.99 to 1.36)
Stroke or transient ischemic attack	RR	1.20 (0.94 to 1.53)	1.19 (0.88 to 1.61)	1.23 (0.94 to 1.59)	1.00 (0.48 to 2.08)	NA	NA	NA
Postoperative atrial fibrillation	OR	**0.65 (0.51 to 0.82)***	0.96 (0.77 to 1.19)	NA	**0.62 (0.48 to 0.80)***	NA	NA	NA
Recurrent atrial fibrillation	OR	0.81 (0.52 to 1.25)	1.29 (0.95 to 1.76)	NA	0.81 (0.52 to 1.25)	NA	NA	NA

All statistical tests are two-sided. Underline means overlapping outcomes. *Summary effect was statistically significant ($p < 0.05$). Abbreviations: NA, not available; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

vascular deaths, statistical significance was also maintained ($p = 0.043$) with low heterogeneity ($I^2 = 0\%$), and there was no small study effect.

Discussion

Even though a clear clinical benefit has not been established, it has been assumed that omega-3 fatty acids supplementation might have some beneficial effect on cardiovascular outcomes[29]. However, previous large clinical trials demonstrated no evidence of the effect of omega-3 fatty acids supplementation on various cardiovascular outcomes. The OMEGA trial, a randomized, placebo-controlled, double-blind, multicenter trial included 3,851 participants with one year of follow-up and concluded that omega-3 fatty acids supplementation did not reduce sudden cardiac deaths and cardiovascular events[6]. The ORIGIN trial concluded that omega-3 fatty acids supplementation did not reduce cardiovascular events in patients with dysglycemia[7]. The Risk and Prevention Study trial concluded that omega-3 fatty acids supplementation did not reduce cardiovascular mortality[8]. Even the VITAL trial, the most recently conducted clinical trial of omega-3 fatty acids, showed that omega-3 fatty acids supplementation did not reduce the incidence of major cardiovascular events[9].

There have been 3 umbrella reviews comparing the effects of various nutrients including omega-3 and cardiovascular outcome to date[30-32], but to the best of our knowledge, an umbrella review focusing only omega-3 effects on cardiovascular outcomes has not been conducted. In particular, in this current review study, we aimed to identify true associations between omega-3 fatty acids and cardiovascular outcome more strictly by excluding biases and performing subgroup analyses. Furthermore, we comprehensively analyzed previous literature by including RCTs as well as observational cohort studies.

In our study, total mortality from major cardiovascular causes showed statistical significance from meta-analyses of cohort studies despite large heterogeneity. In addition, the meta-analyses of RCTs also showed that total mortality from major cardiovascular causes was reduced by omega-3 fatty acids supplementation with statistical significance. Furthermore, when we performed subgroup-analyses to verify the reliability of evidence more strictly, statistical significance was maintained even in the case of RCTs with more than 1,000 participants. From the meta-analyses of RCTs with more than 1,000 participants, the bias of small study effects was not detected, showing that the significant effects were persistent among the large-sized RCTs without any significant bias that had to be considered during the review.

Interestingly, in our umbrella review, most cardiovascular outcomes other than mortality did not show significant associations with omega-3 fatty acids supplementation. Rather, only mortality from cardiovascular causes had an inverse relationship with omega-3 fatty acids supplementation. The result is somewhat intriguing because mortality was reduced by omega-3 fatty acids supplementation, while less severe cardiac events were not affected. Although we are not sure of the exact reason for such a paradoxical result, we can consider the possibility that it may be due to the differences in clarity of clinical presentation and probability of diagnosis of each outcome. For example, severe diseases such as myocardial infarction are usually well-diagnosed with clear clinical manifestations, whereas less severe diseases such as ischemic heart disease and transient ischemic attack often have sub-clinical presentation and may not have been properly diagnosed due to silent symptoms. On the other hand, death is an uncontroversial clinical outcome and the diagnosis is definitive. In this case, mortality may be a more reliable outcome and may reflect more accurately the clinical effect of a medical intervention. We believe that our study may have had paradoxical results for this same reason, and that the significant reduction in mortality by omega-3 supplementation is reliable even in the absence of clinical significance for other relevant outcomes.

Strengths and Limitations

This umbrella review is distinct from the prior umbrella review, since we examined the effect of only omega-3 fatty acids on various cardiovascular outcomes of specific causes. A recent comprehensive meta-analysis[11] studied the effect of omega-3 fatty acids on cardiovascular outcomes, which included individual studies assessing dietary interventions such as advising to increase oily fish consumption, while we focused on the effects of omega-3 fatty acids supplement only. The meta-analysis[11] concluded that alpha-linolenic acid, a type of omega-3 fatty acids, reduces coronary heart disease mortality, prevalence of arrhythmia, and cardiovascular disease events. However, this might not necessarily mean that these beneficial effects are the results of omega-3

fatty acids intake, because fish intake is nutritionally different from omega-3 fatty acids intake alone. There is evidence from a RCT[12] that fish intake of 500g per week has beneficial effects on cardiovascular outcomes, while omega-3 fatty acids supplementation dose not. Indeed, during the literature research, we identified several articles[33,34] which concluded that omega-3 fatty acids intake was beneficial in preventing cardiovascular disease but included component studies of dietary interventions in their meta-analyses, which may not act as sufficient evidence for the effect of the omega-3 fatty acids alone on cardiovascular outcome.

This umbrella review has advantages over previous meta-analyses because it includes quantitative analyses of all non-overlapping component studies derived from meta-analyses showing different conclusions. Several previous articles concluded that omega-3 fatty acids supplementation has a beneficial effect on cardiovascular outcomes, based on the statistically significant results of their meta-analyses. Among the eligible meta-analyses in our review, evidence of RCTs studying the association with omega-3 fatty acids supplementation and total mortality from major cardiovascular events were studied by a total of five articles, with two of them concluding significant associations[35,36] and three of them concluding non-significant associations[37-39]. Our meta-analysis included all non-overlapping component studies from the meta-analyses of these 5 articles and showed that the association was statistically significant, even when the analysis was restricted to RCTs with more than 1,000 patients. In addition, the association of omega-3 fatty acids supplementation and cardiovascular events was studied by a total of 6 articles. One of these studies concluded a statistically significant association[40], while 5 of them found non-significant associations[41-45]. In our meta-analysis that included all non-overlapping component studies from the meta-analyses of these 6 articles, we found that the association was not statistically significant, implying that there was no significant positive effect of omega-3 fatty acids supplementation on the overall number of cardiovascular events.

There are several limitations which need to be taken into account. First, we systematically searched and identified results of meta-analyses, which means that recent clinical trials might have been overlooked. However, for the outcomes of total mortality of cardiac causes, cardiovascular events, coronary events, cardiovascular deaths, coronary deaths, and myocardial infarctions, we identified and included meta-analyses published in 2018, so it is likely that this review includes recent clinical trials for these outcomes. Additionally, we also have conducted meta-analyses including the latest trial[9] reported on January 3rd, 2019. This RCT reported five major cardiovascular outcomes, total mortality from cardiovascular causes, cardiovascular events, cardiovascular deaths, myocardial infarctions, stroke or transient ischemic attack. The results of meta-analyses were not different from the previous meta-analyses we had. Second, we did not evaluate the quality of individual component studies, which is the responsibility of the authors of the original meta-analyses and was beyond the scope of our review. Third, because we did not list and consider the amount of fish consumption, we could not deny the possibility that the random effect of fish consumption could be greater and obscured the effect of omega-3 fatty acids, which could be a strong reason why various outcomes were not statistically significant.

Conclusions

Our umbrella review indicates that omega-3 fatty acids supplementation reduces overall mortality from cardiovascular causes. Even though a few large RCTs showed no evidence of clinical effect of omega-3 on cardiovascular outcomes, our comprehensive review study still provides a clue of clinical utility of omega-3 fatty acids supplementation. Considering that there have been conflicting results in many existing studies, in future clinical trials, it is necessary to identify the true clinical evidence concerning omega-3 fatty acids supplementation through efforts to reduce various research biases.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Mozaffarian D, Wu JHY. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011; 58: 2047-2067.

2) Rizos EC, Elisaf MS. Does with omega-3 PUFAs add to the prevention of cardiovascular disease? Curr Cardiol Rep 2017; 19: 47.
3) Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D; Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acids intake. Circulation 2005; 112: 2762-2768.
4) Svensson M, Schmidt EB, Jorgensen KA, Christensen JH. OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. Clin J Am Soc Nephrol 2006; 1: 780-786.
5) Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y, JELIS Investigators. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circ J 2009; 73: 1283-1290.
6) Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Castillo UD, Sack R, Worth H, Katus H, Spitzer W, Sabin G, Senges J, OMEGA Study Group. Omega, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation 2010; 122: 2152-2159.
7) The ORIGIN Trial Investigators. N–3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012; 367: 309-318.
8) Risk and Prevention Study Collaborative Group. N-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med 2013; 368: 1800-1808.
9) Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, D'Agostino D, Friedenberg G, Ridge C, Bubes V, Giovannucci EL, Willett WC, Buring JE, VITAL Research Group. Marine n–3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med 2019; 380: 23-32.
10) 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: e013543.
11) Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KH, AlAbdulghafoor FK, Summerbell CD, Worthington HV, Song F, Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2020; 3: CD003177.
12) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62: e1-34.
13) Zibaeenezhad MJ, Ghavipisheh M, Attar A, Aslani A. Comparison of the effect of omega-3 supplements and fresh fish on lipid profile: a randomized, open-labeled trial. Nutr Diabetes 2017; 7: 1.
14) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
15) Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10: 101-129.
16) Ioannidis JPA, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007; 335: 914-916.
17) Belbasis L, Bellou V, Evangelou E, Ioannidis JPA, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. Lancet Neurol 2015; 14: 263-273.
18) Higgins JPT, Thompson SG, Spiegelhalter DJ, A re-evaluation of random-effects meta-analysis. J Roy Stat Soc Ser A (Stat Soc) 2009: 172: 137-159.
19) Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
20) Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002.
21) Ioannidis JPA. Clarifications on the application and interpretation of the test for excess significance and its extensions. J Math Psychol 2013; 57: 184-187.
22) Ioannidis JPA, Trikalinos TA. An exploratory test for an excess of significant findings. Clinical Trials 2007; 4: 245-253.
23) Ioannidis JPA. Excess significance bias in the literature on brain volume abnormalities. Arch Gen Psychiatry 2011; 68: 773-780.
24) Salanti G, Ioannidis JPA. Synthesis of observational studies should consider credibility ceilings. J Clin Epidemiol 2009; 62: 115-122.
25) Papatheodorou SI, Tsilidis KK, Evangelou E, Ioannidis JPA. Application of credibility ceilings probes the robustness of meta-analyses of biomarkers and cancer risk. J Clin Epidemiol 2015; 68: 163-174.
26) RStudio Team. RStudio: Integrated Development for R. RStudio, Inc., Boston, MA. http://www.rstudio.com/. Published 2015. Accessed.
27) Viechtbauer W. Conducting meta-analyses in R with the meta for package. J Stat Softw 2010; 36.
28) Champely S, Ekstrom C, Dalgaard P, Gill J, Weibelzahl S, Anandkumar A, Ford C, Volcic R, Rosario HD. Package 'pwr': Basic Functions for Power Analysis. https://cran.r-project.org/package=pwr. Published 2018. Accessed.
29) Cao Y, Lu L, Liang J, Liu M, Li X, Sun R, Zheng Y, Zhang P. Omega-3 fatty acids and primary and secondary prevention of cardiovascular disease. Cell Biochem Biophys 2015; 72: 77-81.
30) Ruiz EM, de Labry AO, Epstein D. Primary prevention of cardiovascular disease: an umbrella review. An Sist Sanit Navar 2018; 41: 355-369.
31) Khan SU, Khan MU, Riaz H, Valavoor S, Zhao D, Vaughan L, Okunrintemi V, Riaz IB, Khan MS, Kaluski E, Murad MH, Blaha MJ, Guallar E, Michos ED. Effects of nutritional supplements and

dietary interventions on cardiovascular outcomes: an umbrella review and evidence map. Ann Intern Med 2019; 171: 190-198.
32) Chareonrungrueangchai K, Wongkawinwoot K, Anothaisintawee T, Reutrakul S. Dietary factors and risks of cardiovascular diseases: an umbrella review. Nutrients 2020; 12: E1088.
33) Yzebe D, Lievre M. Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. Fundam Clin Pharmacol 2004; 18: 581-592.
34) Cheng P, Huang W, Bai S, Wu Y, Yu J, Zhu X, Qi Z, Shao W, Xie P. BMI affects the relationship between long chain n-3 polyunsaturated fatty acids intake and stroke risk: a meta-analysis. Sci Rep 2015; 5: 14161.
35) Sethi A, Bajaj A, Khosla S, Arora RR. Statin use mitigate the benefit of omega-3 fatty acids - a meta-regression of randomized trials. Am J Ther 2016; 23: e737-748.
36) 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: 1152-1160.
37) Chen Q, Cheng LQ, Xiao TH, Zhang YX, Zhu M, Zhang R, Li K, Wang Y, Li Y. Effects of omega-3 fatty acids for sudden cardiac death prevention in patients with cardiovascular disease: a contemporary meta-analysis of randomized, controlled trials. Cardiovasc Drugs Ther 2011; 25: 259-265.
38) Lim AK, Manley KJ, Roberts MA, Fraenkel MB. Fish oil for kidney transplant recipients. Cochrane Database Syst Rev 2016; CD005282.
39) Leshno M, Goldbourt U, Pinchuk I, Lichtenberg D. The cardiovascular benefits of indiscriminate of omega-3 fatty acids; meta-analysis and decision-making approach. Int J Food Sci Nutr 2018; 69: 549-556.
40) He L, Li MS, Lin M, Zhao TY, Gao P. Effect of fish oil supplement in maintenance hemodialysis patients: a systematic review and meta-analysis of published randomized controlled trials. Eur J Clin Pharmacol 2016; 72: 129-139.
41) Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, Worthington HV, Durrington PN, Higgins JP, Capps NE, Riemersma RA, Ebrahim SB, Davey Smith G. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ 2006; 332: 752-760.
42) Kwak SM, Myung SK, Lee YJ, Seo HG. Efficacy of omega-3 fatty acids supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med 2012; 172: 686-694.
43) Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012; 5: 808-818.
44) Zheng T, Zhao J, Wang Y, Liu W, Wang Z, Shang Y, Zhang W, Zhang Y, Zhong M. The limited effect of omega-3 polyunsaturated fatty acids on cardiovascular risk in patients with impaired glucose metabolism: a meta-analysis. Clin Biochem 2014; 47: 369-377.
45) Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, Chew Y, Bosch J, Collins R, Lewington S, Armitage J, Clarke R; Omega-3 Treatment Trialists' Collaboration. Associations of omega-3 fatty acids supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77917 individuals. JAMA Cardiol 2018; 3: 225-234.
46) Wen YT, Dai JH, Gao Q. Effects of omega-3 fatty acids on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2014; 24: 470-475.
47) Casula M, Soranna D, Catapano AL, Corrao G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: a meta-analysis of randomized, placebo controlled trials. Atheroscler Suppl 2013; 14: 243-251.
48) Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. BMJ 2008; 337: a2931.
49) Khoueiry G, Abi Rafeh N, Sullivan E, Saiful F, Jaffery Z, Kenigsberg DN, Krishnan SC, Khanal S, Bekheit S, Kowalski M. Do omega-3 polyunsaturated fatty acids reduce risk of sudden cardiac death and ventricular arrhythmias? A meta-analysis of randomized trials. Heart Lung 2013; 42: 251-256.
50) Guo XY, Yan XL, Chen YW, Tang RB, Du X, Dong JZ, Ma CS. Omega-3 fatty acids for postoperative atrial fibrillation: alone or in combination with antioxidant vitamins? Heart Lung Circ 2014; 23: 743-750.
51) Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: an updated systematic review and meta-analysis. Clin Nutr 2017; 36: 737-746.
52) Ali- Hasan- Al- Saegh S, Mirhosseini SJ, Tahernejad M, Mahdavi P, Shahidzadeh A, Karimi-Bondarabadi AA, Dehghan AM, Rahimizadeh E, Haddad F, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Shahidzadeh A, Ghanei A, Lotfaliani M, Zeriouh M, Weymann A, Popov AF, Sabashnikov A. Impact of antioxidants on cardio-renal protection in cardiac surgery: an updated and comprehensive meta-analysis and systematic review. Cardiovasc Ther 2016; 34: 360-370.
53) Cheng X, Chen S, Hu Q, Yin Y, Liu Z. Fish oil increase the risk of recurrent atrial fibrillation: result from a meta-analysis. Int J Cardiol 2013; 168: 4538-4541.
54) Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, Bylsma LC. A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. Mayo Clin Proc 2017; 92: 15-29.
55) Wei J, Hou R, Xi Y, Kowalski A, Wang T, Yu Z, Hu Y, Chandrasekar EK, Sun H, Ali MK. The association and dose-response relationship between dietary intake of alpha-linolenic acid and risk of CHD: a systematic review and meta-analysis of cohort studies. Br J Nutr 2018; 119: 83-89.