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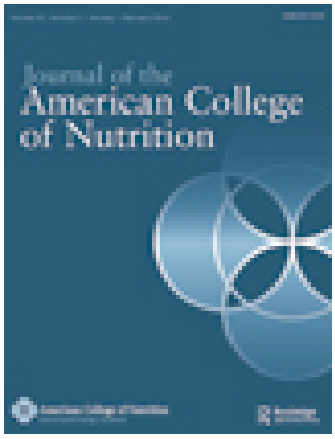

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A Meta-Analysis of Omega-3 Fatty Acids and Incidence of Atrial Fibrillation

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Review

A Meta-Analysis of Omega-3 Fatty Acids and Incidence of Atrial Fibrillation

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Key words: fibrillation, fatty acids, arrhythmia, inflammation

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Objectives: Atrial fibrillation (AF) is associated with higher health care costs. Although omega-3 (n-3) fatty acids have been associated with a decreased risk of coronary heart disease, their effects on the risk of AF are inconsistent. We therefore sought to review the relation between n-3 fatty acids and the risk of AF.

Methods: Using an extensive online search, we conducted a meta-analysis of new onset incident/recurrent AF following exposure to fish/fish oil or long-chain n-3 polyunsaturated fatty acids. A random-effect model was used and between-studies heterogeneity was estimated with I^2. The quality of studies was assessed using Jadad and United States Preventive Services Task Force (USPSTF) scoring systems. All analyses were performed with RevMan (version 5.0.20).

Results: Seven cohort studies and 11 randomized controlled trials (RCTs) were included in this meta-analysis. The pooled odds ratio (OR) was 0.79 (95% confidence interval [CI] = 0.56–1.12; $p = 0.19$) for RCTs and 0.83 (95% CI = 0.59–1.16; $p = 0.27$) for cohort studies. On sensitivity analysis, no statistically significant difference was noted when stratified by study design or quality of the studies (as graded by Jadad or USPSTF scoring systems).

Conclusion: This study does not suggest a major effect of fish/fish oil or n-3 fatty acids on the risk of AF.

INTRODUCTION

Atrial fibrillation (AF) is highly prevalent in clinical practice, affecting approximately 2.3 million people in the United States and 4.5 million people in the European Union [1,2]. The incidence of AF increases by about 0.1%–0.2% per year after the age of 40, and the prevalence of AF ranges from 2%–4% in people over 60 years of age to 8% in people over 80 years of age [3–5]. Prevalence for age-adjusted AF is reported to be higher in men than in women [4,5]. The age-adjusted risk of developing AF has also been noted to be 50% lower in blacks than in whites [2,6]. AF is associated with a 2–7 times higher incidence of ischemic stroke as compared with people without AF [7,8] and is associated with a higher incidence of mortality as compared with patients in normal sinus rhythm [9,10].

Fish consumption has been shown to be associated with lower blood pressure, reduced inflammation, improved left ventricular diastolic function, lower risk of cardiac arrhythmias, and sudden cardiac death [11–19]. The long-chain omega-3 (n-3) fatty acids present in fish and fish oil (i.e., eicosapentaenoic acid [EPA, 20:5 n-3] and docosahexaenoic acid [DHA, 22:6 n-3]) appear to be the major mediator of protective effects against cardiovascular disease [20]. Prior studies [21] have suggested a beneficial effect of upstream therapies including n-3 polyunsaturated fatty acids (PUFAs) in modifying the arrhythmia responsible for AF and thereby offering primary prevention. The evidence is, however, controversial in regard to the prevention of AF recurrence (i.e., secondary prevention) [22]. Various studies including prospective studies and randomized controlled trials (RCTs) have shown inconsistent results on the association between fish consumption and incidence of AF [23–40].

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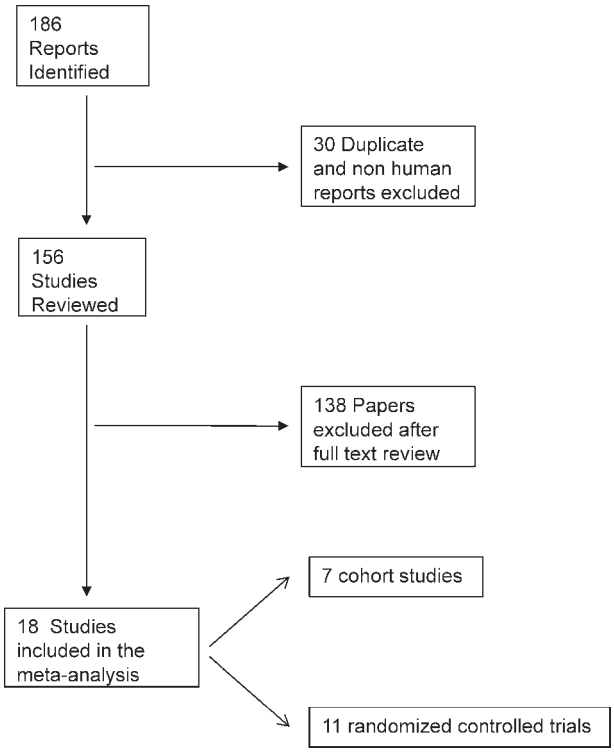

Fig. 1. Search strategy results.

Identification of simple yet effective strategies that can help prevent the development of AF can, therefore, be of great significance, not only to reduce the overall morbidity and mortality but also to decrease health care costs and social burden associated with AF. We therefore conducted this meta-analysis of RCTs and prospective cohort studies to assess the role of n-3 fatty acids on the incidence of AF in humans.

METHODS

Search Strategy

We conducted a search in MEDLINE (1948 to August 31, 2011), Embase (1988 to week 34 of 2011) and Cochrane databases (from inception till second quarter 2011) for studies that reported new onset incident/recurrent AF following exposure to n-3 PUFAs. We used the following key words for our search: *atrial fibrillation* and *fatty acids*. The search was performed for studies in the English language and was limited to human subjects. For the purpose of our analysis, both full-text articles and published abstracts were included. When an abstract from a meeting and a full article referred to the same report, only the full report was included in the analysis. In case of multiple reports from the same study, we used the most complete and/or most recently reported data. We also conducted a manual search for abstracts presented at the scientific sessions of the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and the Heart Rhythm Society over the past 5 years.

Inclusion and Exclusion Criteria

We included studies reporting on new onset incident/recurrent AF following exposure to n-3 PUFAs, which was defined as consuming fish, fish oils, or using n-3 PUFAs in the form of capsules/pills/infusion in any dose. Only studies comparing event rates between two or more groups with complete information available were included in this report. The quality of RCTs was graded 1–5 using Jadad scores, as reported in detail elsewhere [41]. Quality of other studies (i.e., population-based cohort studies) was graded as *good*, *fair*, or *poor* using criteria developed by the United States Preventive Services Task Force (USPSTF) [42]. Data for each trial was abstracted by an investigator (O.K.) and was confirmed by a second investigator (L.D.). A final score was reached after consensus if there was a disagreement between the reviewers.

Statistical Analysis

The meta-analysis was performed by computing unadjusted odds ratios (ORs) using a random-effects model. The OR for new onset incident/recurrent AF was calculated along with 95% confidence intervals (CIs). Between-studies heterogeneity was analyzed by means of I^2, which describes the percentage of the variability in effect estimate across studies that is due to heterogeneity rather than sampling error (chance); I^2 of more than 50% suggests heterogeneity. Publication bias was assessed graphically using a funnel plot. We also conducted sensitivity analysis stratified by study type (RCT vs cohort) and primary vs secondary AF in RCT; in addition, we evaluated the impact of exclusion of (1) cohort studies with fair/poor quality, (2) a study by Macchia et al. [28] with post-myocardial infarction (MI) patients or a paper by Heidt et al. [23] that used intravenous (IV) fish oil formulations, and (3) RCTs with a Jadad score ≤ 3 on the pooled OR. All analyses were performed with RevMan Analyses Version 5.0.20 (Nordic Cochrane Center, Ringshopitalet).

RESULTS

Overall, we found 186 reports on primary search and excluded 30 studies due to duplication or nonhuman subjects. From the remaining 156 reports, we included 18 reports after full-text review. Of these 18 studies, 11 were RCTs and 7 were population-based prospective cohort studies. Fig. 1 summarizes the results of the literature search along with excluded studies. Basic characteristics of these studies are shown in Table 1.

Seven of the 11 RCTs (Heidarsdottir et al. [27], Heidt et al. [23], Saravanan et al. [31], Kowey et al. [35], Nodari et al. [33],

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Table 1. Baseline Characteristics of Study Included in Meta-Analysis

Study	Total No. of Study Participants	Types of Intervention	Experimental Group vs Control Group
Calo et al. [25] (Jadad score = 3)	160	2 g/day n-3 PUFA (as two 850–882 mg capsules of EPA and DHA /day as ethyl esters in a ratio of 1.2:1) for 5 days pre-op and continued until discharge	79 vs 81
Margos et al. [37] (Jadad score = N/A)	40	Placebo vs PUFA	20 vs 20
Heidarsdottir et al. [27] (Jadad score = 5)	170	1240 mg EPA + 1000 mg DHA vs olive oil capsules started 5–7 days pre-op and continued until discharge or 2 wk post-op	83 vs 85
Heidt et al. [23] (Jadad score = 3)	102	Infusion of 100 mg fish oil per kg/d vs 100 mg soy oil per kg/d starting on admission and ending on intensive care unit (ICU) discharge	52 vs 50
Saravanan et al. [31] (Jadad score = 5)	108	2 g/d n-3 PUFA (providing 85%–88% EPA + DHA as ethyl esters in a ratio of 1.2:1) vs placebo (olive oil) for at least 5 days prior to surgery	52 vs 51
Kowey et al. [35] (Jadad score = 5)	663	n-3 PUFA 8 g/d (465 mg EPA + 375 mg DHA/g n-3 PUFA) vs placebo for the first 7 d followed by 4 g/d vs placebo through week 24	323 vs 322
Nodari et al. [33] (Jadad score = 5)	254	n-3 PUFA 1 g/d vs placebo	100 vs 99
Bianconi et al. [34] (Jadad score = 4)	204	n-3 PUFA 3 g/d until ECV followed by 2 g/d vs placebo for 6 mo	95 vs 92
Sandesara et al. [38] (Jadad score = N/A)	243	n-3 PUFA (EPA: DHA 1.24:1) vs corn oil 4 g/d before CABG, 2 g/d after CABG	120 vs 123
Erdogan et al. [39] (Jadad score = N/A)	108	PUFA (301.5 mg α-linoleic acid) vs placebo for 4 wk before to 1 y after cardioversion	54 vs 54
Ozaydın et al. [40] (Jadad score = 2)	47	Amiodarone vs amiodarone + 2 g n-3 PUFA	24 vs 23
Shen et al. [36] (USPSTF score = good)	4526 participants (i.e. 9640 examinations)	n-3 PUFA consumption based on FFQ	2429 vs 2319
Brouwer et al. [30] (USPSTF score = good)	5184	Fish consumption based on FFQ	1728 vs 1728
Mozaffarian et al. [24] (USPSTF score = fair)	4815	Fish consumption (tuna/other broiled or baked) based on FFQ	513 vs 930
Virtanen et al. [29] (USPSTF score = fair)	2174	Serum EPA/DHA/DPA levels	543 vs 543
Berry et al. [32] (USPSTF score = good)	44,720	Nonfried fish consumption based on FFQ	10,776 vs 13,002
Frost and Vestergaard [26] (USPSTF score = fair)	47,949	Fish consumption based on FFQ	9589 vs 9589
Macchia et al. [28] (USPSTF score = poor)	3242	Any prescription of n-3 PUFA 12 mo before or within 360 days after MI	208 vs 3034

AF = atrial fibrillation, CABG = coronary artery bypass grafting, DHA = docosahexaenoic acid, DPA = decosapentaenoic acid, EKG = electrocardiogram, EPA = eicosapentaenoic acid, ECV = electrical cardioversion, FFQ = Food Frequency Questionnaire, MI = myocardial infarction, N/A = not available, PUFA = polyunsaturated fatty acids, RCT = randomized controlled trial.

Sandesara et al. [38], and Bianconi et al. [34]) were double blind, one was triple blind (Erdogan et al. [39]), two were open label (Calo et al. [25] and Margos et al. [37]), and information on blinding was not available for one RCT (Ozaydın et al. [40]). Overall, these RCTs had a total of 2002 patients with 1000 (50%) in the intervention group and 1002 (50%) in the control group. Kowey et al. [35] had the greatest number of patients, whereas Margos et al. [37] had the least—663 (33%) and 40 (2%), respectively—among all included RCTs. Five of the 11 RCTs had a score greater than 3, 3 trials had a score of 3 or less, and 3 studies available as abstract only could not be assigned a score. Overall, there were 912 cases of incident AF in this subgroup, of which 443 cases (49%) were in the intervention group vs 469 cases (51%) in the control group. The pooled OR for incident AF was 0.79 (95% CI = 0.56–1.12; $p = 0.19$) comparing n-3 PUFA intervention with a placebo (Fig. 2).

Seven population-based prospective cohort studies were included in this meta-analysis (Berry et al. [32], Brouwer et al. [30], Frost and Vestergaard [26], Mozaffarian et al. [24],

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Table 1. Extended

Follow-Up Duration	Outcome Assessment	Study Type
Until discharge from hospital	EKG based, done daily until discharge	Open-label, RCT of CABG patients aged ≥18 y
6 mo	Holter monitoring at 1 mo and EKG based	Open-label, RCT of patients, in persistent AF to maintain normal sinus rhythm postcardioversion
Until discharge from hospital or 2 wk post-op, whichever came first	Continuous monitoring until discharge and EKG based	Double-blind RCT of CABG/valve repair surgery patients >40 y of age
Until transfer from ICU to a normal ward post-op	Continuous monitoring and EKG based	Double-blind RCT of CABG patients aged ≥18 y
5 d	Continuous monitoring and EKG based	Double-blind RCT of CABG patients aged ≥18 y
6 mo	Transtelephonic monitoring and EKG based	Double-blind RCT of patients ≥18 y for prevention of recurrent symptomatic AF
12 mo	Holter monitoring and EKG based	Double-blind RCT of patients to maintain normal sinus rhythm after conversion from persistent AF
6 mo	Transtelephonic monitoring and EKG based	Double-blind RCT of patients ≥18 y to prevent recurrent AF post-ECV among patients with chronic persistent AF
14 days	Continuous monitoring and EKG	Double-blind RCT of CABG patients 18–85 y
12 mo	Clinical examination with EKG at regular intervals and occurrence of symptoms	Triple-blind RCT of patients in persistent AF to maintain normal sinus rhythm postcardioversion
12 mo	EKG based	RCT of patients to maintain normal sinus rhythm post-ECV from persistent AF
4 y	EKG based	Prospective cohort study of men/women ≥45 y (Framingham Heart Study)
6.4 ± 1.6 y	EKG and record based	Prospective cohort study of men/women >55 y (Rotterdam Study)
12 y	EKG or record based	Prospective cohort study of men/women >65 y of age (Cardiovascular Health Study)
17.7 ± 5.6 y	Record based	Prospective cohort study of men 42–60 y of age hospitalized with the diagnosis of AF
6 y	EKG (at 3 and 6 years) based	Prospective cohort study of women 50–79 y (Women's Health Initiative)
5.7 y	Record based	Prospective cohort study of men/women 50–64 y
360 d	Record based	Prospective cohort study of MI patients with first AF-related hospitalization

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Macchia et al. [28], Virtanen et al. [29], and Shen et al. [36]). Given that the purpose of this meta-analysis was to see if there is any benefit of fish consumption on the primary/secondary AF prevention, we used the broiled/baked fish group (shown to lower the risk of several cardiovascular events) in the article by Mozaffarian et al. [24] to see how it impacts the overall analysis. Using the sandwich/fried fish did not significantly alter the results of the analysis (OR = 0.95, 95% CI = 0.72–1.26]). For our analysis, we included only those in the highest and lowest quartiles of fish consumption/serum level of the n-3 PUFA group from each of these cohort studies. Therefore, we had a total of 56,931 subjects with 26,203 (46%) in the highest quartile of fish consumption/serum level of the n-3 PUFA group and 30,728 (54%) subjects in the lowest quartile of fish consumption/serum level of n-3 PUFAs. Berry et al. [32] had the greatest number of patients, whereas Virtanen et al. [29] had the least—23,778 (42%) and 1086 (2%), respectively—among prospective cohort studies. Overall, there were 1672 cases of incident AF in this subgroup, with 636 cases (38%) in the highest quartile and 1036 cases (62%) in the lowest quartile group. The pooled OR was 0.83 (95% CI = 0.59–1.16; p = 0.27) (Fig. 3).

Sensitivity analysis (e.g., stratification by study type, quality, type of AF) did not alter the main conclusion (Table

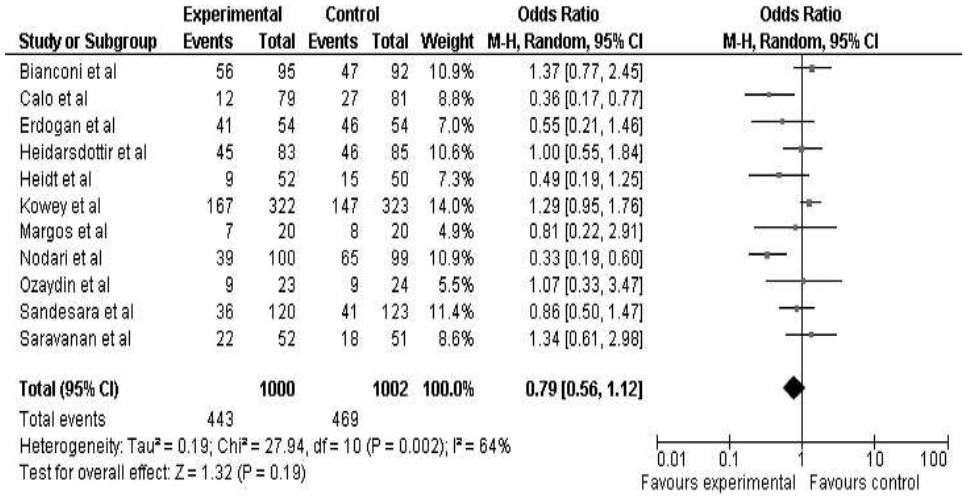

Fig. 2. Pooled odds ratio for new onset atrial fibrillation across randomized controlled trials between the patients exposed to n-3 polyunsaturated fatty acids vs those unexposed.

2). There was evidence of modest heterogeneity for RCTs $I^2 = 64\%$ (Fig. 2) and substantial heterogeneity for cohort studies ($I^2 = 87\%$, Fig 3). On exclusion of Macchia et al. [28], which included post-MI patients, there was still significant heterogeneity for cohort studies ($I^2 = 80\%$). The funnel plot analysis for RCTs and cohort studies did show modest asymmetrical distribution of OR estimates, suggesting potential publication bias (Figs. 4 and 5).

DISCUSSION

Based on the findings of this meta-analysis, intervention with n-3 PUFAs was not associated with a statistically significant effect on the risk of AF. In addition, nonexperimental studies did not provide evidence of an association between n-3 fatty acids/fish consumption and AF risk either.

Interest in the possible role of n-3 PUFAs on cardiac arrhythmias dates back to the first study conducted in 1985 on an isolated rabbit heart, demonstrating a lowered threshold for cardiac arrhythmias by alpha-linoleic acid [43]. The possible explanation for this effect potentially includes an increased duration of the phase 4 refractory period, hyperpolarization of the resting membrane potential, and an increase in the current needed to elicit an action potential, thereby protecting against cardiac arrhythmias [16,44,45]. Subsequently, several studies [17,19,46] have validated the protective effect of n-3 PUFAs on the incidence of ventricular arrhythmias in animal models.

However, findings on antiarrhythmic effects of n-3 PUFAs have been inconsistent in human studies. The n-3 PUFA supplementation was associated with a trend for a lower incidence of fatal ventricular arrhythmias in a RCT of post-MI patients (risk reduction of 28%, $p = 0.057$) [47]. However, for probable episodes of ventricular tachycardia or ventricular fibrillation in subjects consuming n-3 for a longer period of

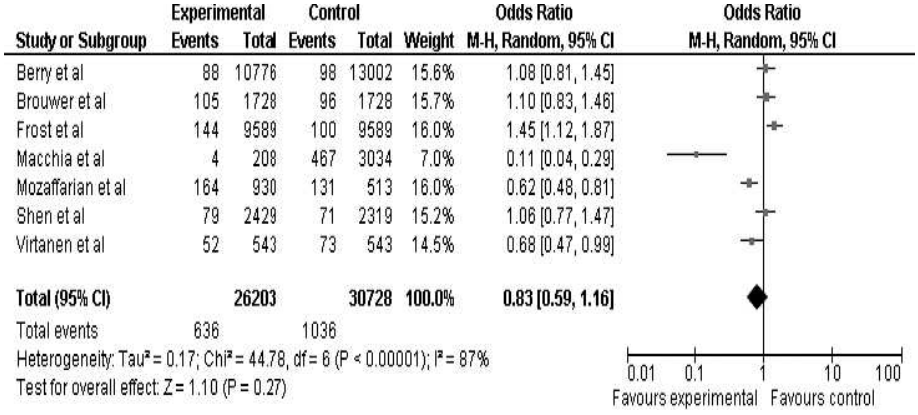

Fig. 3. Pooled odds ratio for new onset atrial fibrillation across the cohort studies between the patients in the highest quartile of n-3 polyunsaturated fatty acids/fish consumption vs those in the lowest quartile.

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Table 2. Sensitivity Analysis

Included Studies	OR (95% CI)	*p* Value
All included randomized controlled trials	0.79 (0.56–1.12)	0.844
vs all included cohort studies	0.83 (0.59–1.16)	
Excluding Macchia et al. [28] with post-MI patient from cohort studies	0.97 (0.74–1.27)	0.48
vs all included cohort studies	0.83 (0.59–1.16)	
Excluding cohort studies with fair/poor quality per USPSTF score	1.08 (0.91–1.29)	0.152
vs all included cohort studies	0.83 (0.59–1.16)	
Excluding Heidt et al. [23] using IV formulation from randomized controlled trials	0.82 (0.58–1.18)	0.886
vs all included randomized controlled trials	0.79 (0.56–1.12)	
Excluding randomized controlled trials with Jadad scores ≤ 3	0.89 (0.61–1.29)	0.656
vs all included randomized controlled trials	0.79 (0.56–1.12)	
Primary prevention randomized controlled trials	0.76 (0.49–1.17)	0.84
vs secondary prevention randomized controlled trials	0.82 (0.48–1.43)	

CI = confidence interval, IV = intravenous, MI = myocardial infarction, OR = odds ratio, USPSTF = United States Preventive Services Task Force.

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time (11 months), n-3 PUFAs appeared to be protective against arrhythmias (risk reduction of 31%–38%, *p* value ranging from 0.033–0.034) [47]. In another study, n-3 PUFAs were associated with increased heart rate variability in survivors of MI [48]. Increased heart rate variability has been shown to raise the ventricular fibrillation threshold and thereby protect against ventricular arrhythmias, whereas decreased heart rate variability has been associated with increased mortality in post-MI patients [49,50].

The n-3 PUFAs have also been demonstrated to significantly decrease heart rate by 2.1 beats per minute, thereby predicting a decreased risk of sudden cardiac death [51]. Similar results were observed in the GISSI-Prevenzione trial where supplementation with 1 g/d n-3 PUFA was associated with a significantly lowered risk of sudden cardiac and coronary deaths [52]. Other studies with fish oil supplementation, however, have failed to demonstrate a reduction in premature ventricular complexes/arrhythmias [53]. Recently, a meta-analysis of RCTs in patients with implantable converter defibrillators (ICD) did not show a statistically significant difference in ICD discharge in patients on fish oil supplementation vs placebo (relative risk = 0.93, 95% CI = 0.70–1.24) [54]. It is unclear whether inadequate dosage, duration of intervention, and/or statistical power precluded the observation of desirable effects of n-3.

The n-3 PUFAs have also been shown to have an anti-inflammatory effect that can potentially help in prevention of AF, especially in patients undergoing cardiac surgery. Recently, a study on dogs demonstrated lower levels of inflammatory mediators including C-reactive protein (CRP), interleukin-6, and tumor necrosis factor on the second postoperative day in the PUFA treatment group compared

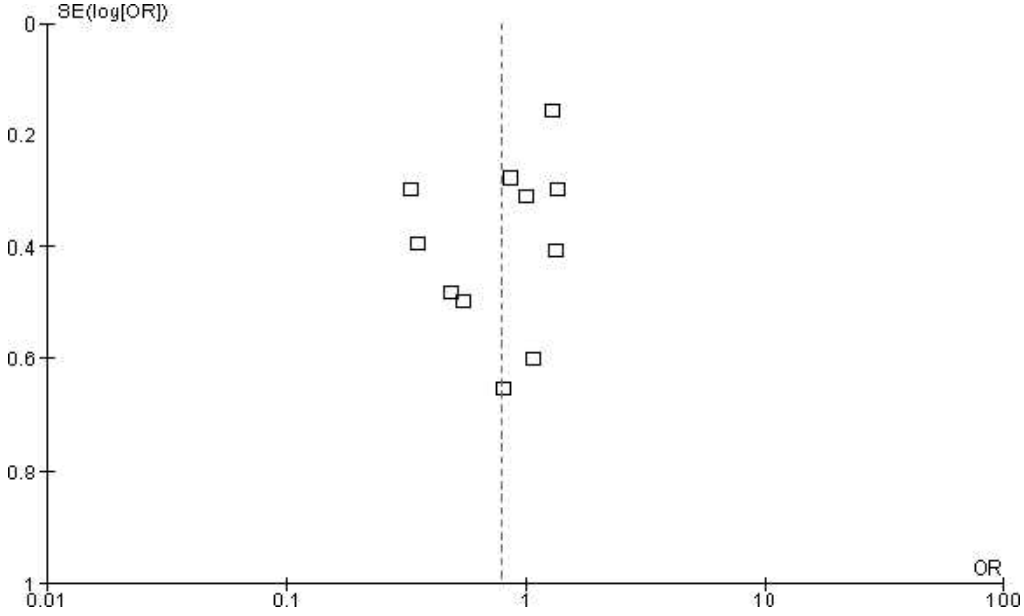

Fig. 4. Funnel plot for pooled analysis for randomized controlled trials. There is evidence of publication bias.

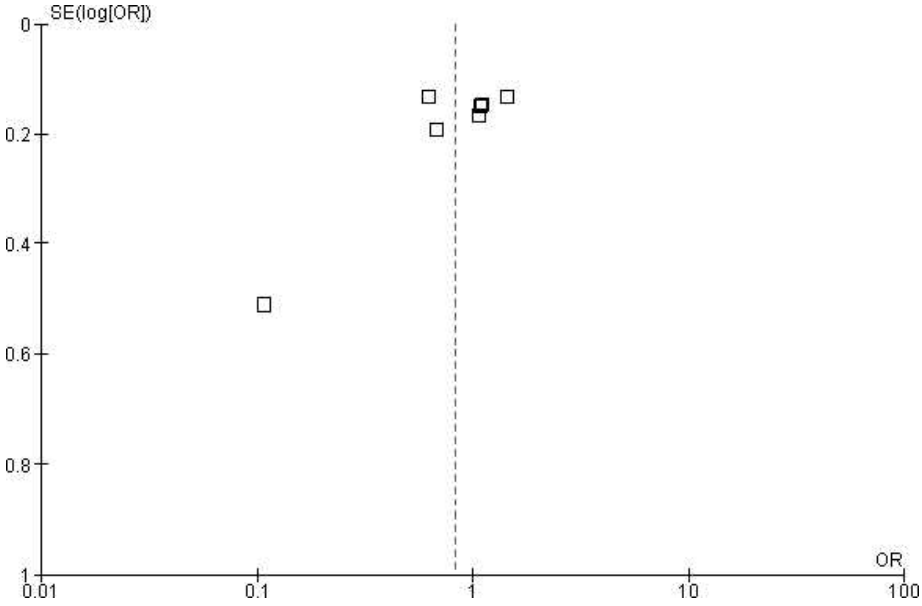

Fig. 5. Funnel plot for pooled analysis for cohort studies. There is evidence of publication bias.

with the control group [55]. Another study demonstrated increased production of adiponectin, an insulin sensitizer and anti-inflammatory protein secreted from adipose tissue, following culture of isolated human adipocytes with EPA and DHA [56]. However, the results in our meta-analysis did not demonstrate a statistically significant decrease in the incidence of AF following exposure to n-3 PUFAs under different clinical settings including patients undergoing cardiac surgery.

The lack of effectiveness in preventing new onset AF by PUFAs could potentially be explained by the fact that the results were an aggregate of the cumulative effect of EPA and DHA rather than each of them individually. As shown in various studies, DHA but not EPA was found to be effective in preventing cardiac arrhythmias in rats and had a beneficial effect on heart rate variability, blood pressure, and CRP as well as atherosclerosis progression [57–61]. Similar results were also shown on the subanalysis of the individual fatty acids by Virtanen et al. [29], where only serum DHA levels were associated with a lower incidence of AF (hazard ratio = 0.62; 95% CI = 0.42–0.92) comparing the highest to the lowest quartile of serum n-3 PUFAs.

Our systematic review has several strengths. All studies included were prospective in nature. The large sample size improved the statistical power to detect smaller effect size. Outcome in the current study was validly ascertained, thereby minimizing misclassification of outcome. Similarity in pooled estimate of effect between RCT and cohort studies suggests minimal unmeasured confounding in cohort studies.

On the other hand, our analysis has some possible limitations. There was heterogeneity in the study design and the number of participants across the different studies included in this meta-analysis. Variations in the dose of n-3 PUFAs among the exposed groups across the included studies as well as variations in the methods for assessing n-3 intake is a limitation of our analysis. Population-based studies using the Food Frequency Questionnaire (FFQ) to measure exposure to n-3 PUFA might have introduced exposure misclassification. However, because the FFQ was obtained prior to AF incidence, such misclassification is more likely to be nondifferential and would have biased the results toward the null. Almost half of the included RCTs in this meta-analysis were conducted on patients undergoing cardiac surgery who are predisposed to a specific transient form of AF. These findings, therefore, might not be applicable to the general population.

CONCLUSION

Overall, this meta-analysis shows no statistically significant reduction of incident AF with n-3 exposure. Given the heterogeneity across reviewed studies, we cannot exclude potential benefits of n-3 on AF risk.

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