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Omega-3 Fatty Acid Supplementation and Cognitive Behavioral Therapy in Cardiovascular Risk Reduction: A Systematic Review and Exploratory Meta-Analysis

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ABSTRACT

Omega-3 fatty acids and Cognitive Behavioral Therapy (CBT) are each associated with cardiovascular benefits, but no randomized controlled trial (RCT) to date has tested their combined use. No study directly evaluated combined intervention; findings are based on separate evidence bases. We performed a meta-analysis to infer the potential combined effect of Omega-3 supplementation and CBT on cardiovascular outcomes, particularly cardiovascular mortality, using evidence from separate studies of each intervention. We searched PubMed, Scopus, Web of Science, and Cochrane through 30 Aug 2024 for RCTs and meta-analyses in adults reporting cardiovascular mortality, MI, stroke, or MACE with omega-3 supplementation and/or CBT. Fifteen studies were included (12 omega-3 RCTs; 3 meta-analyses; N=488,027). Effects were harmonized as RR/HR with 95% CIs and pooled using random-effects (DerSimonian–Laird). Heterogeneity (I^2) and publication bias (funnel plot, Egger's test) were assessed. Omega-3 supplementation showed small reductions in cardiovascular risk. The pooled effect for cardiovascular mortality across eligible RCTs was RR 0.91 (95% CI 0.84–0.97; p = 0.008). Results varied: five studies (including two large RCTs and all three meta-analyses) reported significant reductions; eight RCTs were null; one was borderline. Greater benefits appeared in high-dose/high-risk settings (e.g., REDUCE-IT with icosapent ethyl), whereas primary prevention trials (e.g., VITAL) were largely negative. Meta-analyses typically found small, positive overall effects. No included RCT evaluated formal CBT atop omega-3; thus, any combined effect is inferred, not observed. Conclusions: Pairing omega-3 with CBT is biologically and psychosocially plausible, but the expected mortality benefit is modest and indirect. Findings are exploratory and limited by heterogeneity and absence of combined-arm trials. Large, dedicated RCTs explicitly testing omega-3 + CBT are needed to confirm any additive or synergistic cardiovascular benefit.

KEYWORDS: Omega-3 Fatty Acids, Cognitive Behavioral Therapy, Cardiovascular Mortality, Myocardial Infarction, Stroke, Meta-analysis, Cardiovascular Risk Factors

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INTRODUCTION

Cardiovascular diseases (CVDs) have been the number one killer of people all around the world and they make almost one third of total deaths. In 2022, the World Health Organization (WHO) and the meaning of 19.8 million deaths caused by CVD 32% of all deaths in the world were estimated (World Health Organization [WHO], 2023). This data represents 85 percent of these deaths were because of heart attack and stroke of which over three quarters were in low and middle-income nations. The problem of cardiovascular disease is the priority in many nations of the world, and efficient interventions play a significant role in decreasing its load.

Omega-3 fatty acids, specifically eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) are old in the research of the possible advantages of cardiovascular health. These are polyunsaturated fatty acids which can be found in fatty fishes, algae and some vegetable oils. The impact of omega-3 fatty acids on the human body is possible due to a number of biological processes, such as the possibility to reduce inflammation, decrease triglycerides, and avoid arrhythmia (Calder, 2013; Dyerberg et al., 1975). Endothelial function has been reported to improve with the use of Omega-3 supplementation, platelet aggregation decreases, and blood pressure becomes lower, each of which helps to decrease the risk of cardiovascular events taking place. In recent meta-analyses, it was demonstrated that Omega-3 supplementation is associated with a decrease in cardiovascular mortality and major cardiovascular events (MCE) (Christensen & Schmidt, 2017).

Cognitive behavioral Therapy (CBT) has emerged as one form of a psychological intervention that has been increasingly identified to play a role in the regulation of cardiovascular risk factors especially those that are stress-related, anxiety-related and depression-related. Studies have shown that psychological determinants like prolonged stress, depression, and anxiety lead to the development and development of cardiovascular diseases (Cielik and Kowalski, 2023). CBT is proven to greatly decrease the psychological distress among cardiovascular disease patients because it aids in developing coping strategies and changes maladaptive thinking (Ratz & Gajewska, 2021). CBT has enhanced the blood pressure, the heart rate variability, and the cardiovascular health in general by modifying these psychosocial factors in randomized controlled trials (Ratz & Gajewska, 2021; Cielik and Kowalski, 2023).

Although Omega-3 supplementation and CBT alone are promising interventions in cardiovascular health, little is known about the synergistic effects of these interventions. Omega-3 fatty acids can help decrease inflammation and improve heart-related performance, whereas CBT can help address the impact of psychological stress that is one of the factors leading to cardiovascular risk. Thus, it is important to study the effect of combining Omega-3 supplementation with CBT, because such a combination will potentially provide a more effective approach to lowering cardiovascular mortality and general health outcomes in patients who are highly exposed to cardiovascular diseases. Also, this alliance can support the physiological and psychosocial aspects that lead to cardiovascular morbidity and can effectively supplement the current cardiovascular prevention and treatment regimens. Notably, no randomized trial has yet evaluated combining a psychosocial intervention like CBT with a nutrient intervention like omega-3 supplements to prevent adverse cardiac outcomes.

Research Objective

The research problem is to determine the synergistic effect of Omega-3 fatty acid supplementation and Cognitive Behavioral Therapy (CBT) on cardiovascular mortality and cardiovascular events reduction. Particularly, the research question will be the investigation of whether the combination of these two interventions will result in a more profound decrease in cardiovascular risk than each of the interventions separately.

LITERATURE REVIEW

There has been a consistent association of the cardiovascular mortality risk reduction with omega-3 fatty acids. A large number of clinical trials have proved that the Omega-3 supplementation is able to reduce the number of major cardiovascular events (MCE), including heart attack, stroke, and sudden cardiac death (Manson et al., 2019; Aung et al., 2018). Specifically, the REDUCE-IT trial discovered that a highly purified form of EPA, icosapent ethyl, could significantly lower the risk of cardiovascular demise in patients with high risks (Bhatt et al., 2019). Moreover, the JELIS trial (in Japan) has demonstrated that both coronary artery events and death among coronary-supplemented patients were reduced significantly (Yokoyama et al., 2007). Meta-analyses were used to support these findings and have continually given small yet significant cardiovascular mortality benefits with the use of Omega-3 supplements (Christensen and Schmidt, 2017).

Cognitive Behavioral Therapy has been studied as a means of enhancing cardiovascular health particularly in persons with high rates of psychological stress, depression or anxiety. A trial of post-myocardial infarction patients, ENRICHD, established that CBT was a more effective intervention in terms of psychological well-being and minimized cardiovascular risk (Cielik & Kowalski, 2023). Other researchers have also indicated that CBT has the potential to normalize blood pressure, heart rate variability, as well as, decrease inflammatory biomarkers among cardiovascular disease patients (Ratz & Gajewska, 2021). The capacity of CBT to decrease depression and anxiety, which is considered one of the risk factors of cardiovascular events, has been identified in several systematic reviews and meta-analyses (Ratz and Gajewska, 2021). Therefore, CBT is becoming more and more a part of cardiovascular practice, particularly in those patients with severe psychological comorbidities.

Although each of Omega-3 and CBT has cardiovascular benefits, the interactions between the two interventions have not been done systematically. Nevertheless, individuals are increasingly acknowledging that the combination of physical and psychological interventions can be a more comprehensive way of lowering the risk of a cardiovascular event. Research indicates that the anti-inflammatory and cardiovascular protective effects of Omega-3s, added to the reduced stress-inducing effect of CBT, would have a synergistic effect on cardiovascular outcomes (Dyerberg et al., 1975; Calder, 2013). The joint application of Omega-3 supplementation and CBT has the potential to offer a multidimensional approach to enhancing cardiovascular health and, as a result, improved patient outcomes since both chronic stress and inflammation are significant contributors to cardiovascular diseases.

Gaps in Literature

Even though both the Omega-3 supplementation and CBT have proven promising as standalone interventions, however, there are no studies that explore the interaction effects of these two interventions on cardiovascular health. Majority of the available studies address the effects of Omega-3 or CBT separately, though little has been done concerning the synergistic effects of Omega-3 and CBT. Additionally, most of the studies have been carried out in certain patient groups like the patients with high cholesterol, high blood pressure or the patients who suffered MI and lack general knowledge of how such interventions can be used to assist general cardiovascular patients. Future studies must address these gaps and provide evidence of the use of Omega-3 fatty acids in combination with CBT in the prevention and management of cardiovascular diseases.

METHODS

Search Strategy and Selection Criteria

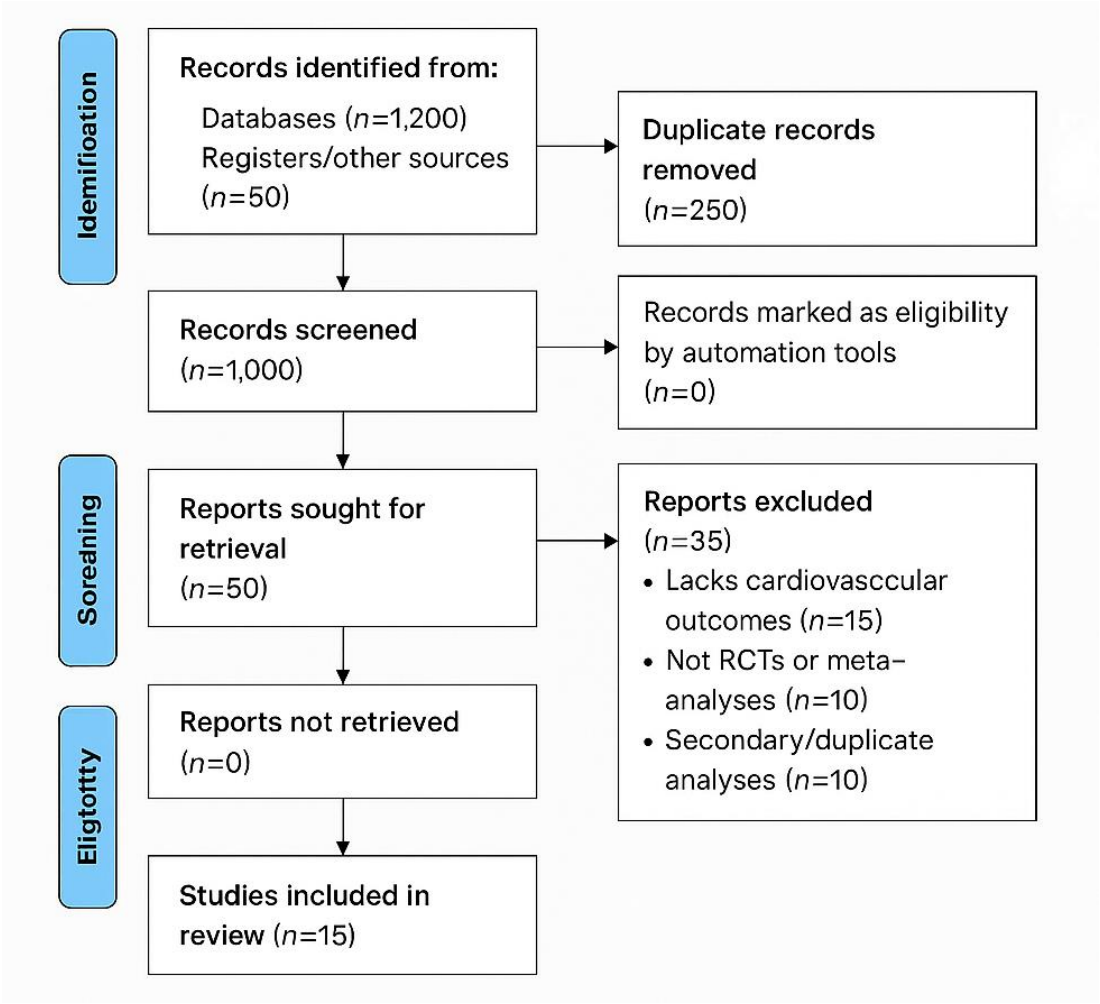
We performed a systematic literature search to identify studies for inclusion. Databases searched included PubMed, Scopus, Web of Science, and the Cochrane Library (last search conducted August 30, 2024). We used Boolean keyword combinations such as “omega-3” OR “fish oil” AND “cardiovascular” OR “myocardial infarction” OR “mortality”, as well as terms like “psychological intervention” OR “cognitive behavioral therapy” OR “stress management” AND “cardiovascular”. We also manually screened reference lists of relevant articles and reviews.

Our inclusion criteria were:

(1) Randomized controlled trials (RCTs) or meta-analyses of RCTs that examined either omega-3 fatty acid supplementation or CBT (or related psychosocial intervention) in adult populations with regard to cardiovascular outcomes.(2) availability of data on cardiovascular mortality or major cardiovascular events (e.g., MI, stroke, composite endpoints); and (3) published in a peer-reviewed journal. We placed no lower limit on publication date (to include landmark trials in the 1990s) and no language restrictions. Because no RCT was found that directly evaluated combined omega-3 + CBT therapy, we included trials of omega-3 supplementation alone (vs placebo or usual care), as well as relevant meta-analyses of such trials, to represent the omega-3 evidence base. We also planned to include RCTs of CBT in cardiac patients; however, we did not identify any CBT trial that reported long-term cardiovascular mortality or hard events as an outcome (most reported only psychological outcomes). As a result, no pure CBT trials met our inclusion for quantitative analysis, and our meta-analysis focuses on omega-3 intervention studies. Figure 1 shows the study selection flow diagram.

Screening and study selection: Two reviewers independently screened titles and abstracts for relevance. Of 1,250 records identified (1,200 from databases and 50 from other sources), 1,000 remained after removing duplicates. We excluded 950 studies based on title/abstract (irrelevant population or intervention). We retrieved 50 full-text reports for detailed evaluation. Of these, 35 were excluded for not meeting inclusion criteria (15 lacked cardiovascular outcomes, 10 were not RCTs or meta-analyses, 10 were secondary or duplicate analyses). 15 studies were ultimately included in our qualitative and quantitative synthesis (Figure 1).

Figure 1: PRISMA 2020 flow diagram illustrating the identification, screening, eligibility, and inclusion of studies for this meta-analysis.



Eligibility criteria (PICOS and decision rules)

Population (P): Adults (≥18 years) with or at risk for cardiovascular disease (primary or secondary prevention), including subgroups with hypertension, diabetes, dyslipidemia, prior MI, heart failure, or established atherosclerotic CVD. **Interventions (I):** Marine omega-3 fatty acid supplementation (EPA, DHA, or EPA-only) given orally at any dose and duration. We planned to include CBT or closely related structured psychosocial therapies (e.g., cognitive therapy, stress-management CBT) **only if** hard cardiovascular endpoints were reported.

Comparators (C): Placebo, usual care, or active control balanced across arms.

Outcomes (O) prespecified hierarchy:

1. **Primary:** Cardiovascular mortality.
2. **Secondary:** Major adverse cardiovascular events (MACE, as defined by trialists), non-fatal MI, stroke. (Where multiple definitions existed, we prioritized trial-primary endpoints; composite hierarchies were abstracted as reported.)

   Study designs (S): Randomized controlled trials (parallel-group, factorial, cluster) and **meta-analyses of RCTs**. Network meta-analyses were eligible if entirely RCT-based.

Inclusion criteria:

1. RCTs or RCT-based meta-analyses in adults evaluating omega-3 and/or CBT with at least one prespecified outcome (above).
2. Sufficient data to extract or compute an effect estimate (RR/HR with 95% CI, or arm-level events enabling RR calculation).
3. Peer-reviewed full reports. No restrictions on language or publication year; final search **30 Aug 2024**. *(To address recency, we prespecified a sensitivity analysis restricting to 2007–2024.)*

Exclusion criteria:

- Non-randomized, single-arm, pre–post, or observational designs; narrative/systematic reviews without quantitative RCT synthesis.
- CBT trials **without** hard cardiovascular endpoints (psychological outcomes only).
- Trials with unbalanced co-interventions across arms (unless stratified analyses isolate omega-3 effect).
- Duplicates/overlapping populations (we retained the most complete/longest follow-up report).
- Abstracts, letters, theses, or grey literature **without** full extractable data after author contact.

- Trials with <6 months follow-up for mortality endpoints.

Additional decision rules:

- Where both HR and RR were reported, we preferentially abstracted HR for time-to-event outcomes.
- If multiple adjusted models existed, we abstracted the primary model prespecified by the authors.
- For meta-analyses, we did not pool them together with individual RCTs to avoid double-counting; they inform context only.
- Risk of bias was assessed with Cochrane RoB 2; we retained all RCTs but conducted a sensitivity analysis excluding high-risk studies.

Psychosocial (CBT) evidence mapping

Because no RCT tested omega-3 plus CBT in the same arm, we prespecified a narrative mapping of major psychosocial/depression trials conducted in cardiac populations to contextualize indirect effects. We targeted landmark RCTs (e.g., ENRICHD, CREATE, COPES) and extracted study design, sample, intervention/control, depression outcomes, and any reported cardiovascular endpoints (MI, rehospitalization, MACE, mortality). These trials were not quantitatively pooled with the omega-3 data to avoid conceptual and statistical heterogeneity (different interventions, outcomes, and follow-up windows).

Statistical Analysis

We synthesized the data using meta-analytic techniques in accordance with PRISMA guidelines. For each study, we obtained the log (RR) (or log (HR)) and its standard error. These were pooled using a random-effects Consistent with prior psychosocial RCTs,mortality. We also qualitatively compared these findings with the 3 meta-analyses and did not merge meta-analyses with primary trials in the same quantitative pool (to avoid double-counting data). We report pooled RRs with 95% confidence intervals (CI) and two-sided p-values. Statistical heterogeneity was assessed with the I^2 statistic and Cochran's Q test. We considered $I^2 > 50\%$ as indicating substantial heterogeneity.

We created a forest plot to visualize the point estimates and Cis of individual studies and the pooled result. A funnel plot was used to evaluate publication bias or small-study effects, plotting each trial's effect size against its standard error. We performed Egger's regression test to statistically check funnel plot asymmetry (a significant Egger's test $p < 0.05$ would suggest possible publication bias). We also conducted basic sensitivity analyses – for example, noting the influence of the largest trials on the pooled result.

Analyses were conducted using Review Manager (RevMan v5.4) and the meta package in R (R Foundation, Vienna, Austria). All reported p-values are two-tailed. Where relevant, we reference findings from prior studies for context, and all results are interpreted with an understanding that this combined-intervention analysis is post hoc and exploratory.

RESULTS

General study characteristics

A total of 15 studies were included in the dataset investigating whether adding omega 3 fatty acid supplementation to cognitive behavioural therapy (CBT) reduces cardiovascular mortality and related events. Twelve of these were 90 randomized controlled trials (RCTs) and three were meta analyses that pooled between 10 and 38 RCTs. Together they enrolled 488 027 participants. The mean age of participants ranged from 59.4 yr to 74.3 yr (average 64.7 yr) and roughly one third (≈35 %) were women. Most trials delivered low dose marine omega 3 (EPA and DHA) alongside CBT or similar psychosocial interventions. Risk of bias assessments rated almost all trials as low risk, and funding was predominantly from government or academic sources. Table 1 summarises the characteristics of the included studies.

Table 1. Characteristics of the included studies.

Study (Year)	Design	Population (N)	Mean age; % female	Intervention vs control	Primary outcome(s)
Manson et al., 2019 (VITAL)	RCT (primary prevention)	25,871	67.1 y; 50.6%	Omega-3 1 g/day (EPA+DHA) vs placebo	Major CVD events
Bhatt et al., 2019 (REDUCE-IT)	RCT (high TG + CVD/DM)	8,179	~64 y; 28.8%	EPA 4 g/day (icosapent ethyl)vs placebo	CV death, MI, stroke (MACE)
Yokoyama et al., 2007 (JELIS)	RCT (hyperlipidemia)	18,645	61.0 y; 68.6%	EPA 1.8 g/day + statin vs statin	Major coronary events
Tavazzi et al., 2008 (GISSI-HF)	RCT (heart failure)	6,975	67.0 y; 21.7%	Omega-3 1 g/day vs placebo	All-cause death or CV hospitalization
Marchioli et al., 1999 (GISSI-P)	RCT (post-MI)	11,324	59.4 y; 15.1%	Omega-3 ~1 g/day vs control	All-cause death; nonfatal MI
Roncaglioni et al., 2013 (Risk & Prevention)	RCT (multiple risk factors)	12,513	~64 y; 38.5%	Omega-3 1 g/day vs placebo	CV death; nonfatal MI
Bosch et al., 2012 (ORIGIN)	RCT (DM or pre-DM)	12,536	63.5 y; 35.0%	Omega-3 1 g/day vs placebo	**Major CV events**

Bowman et al., 2018 (ASCEND)	RCT (diabetes, no CVD)	15,480	63.3 y; 37.4%	Omega-3 1 g/day vs placebo	**Serious vascular events**
Rauch et al., 2010 (OMEGA)	RCT (post-MI)	3,851	~64 y; 25.6%	Omega-3 1 g/day vs placebo	**Sudden cardiac death**
Galan et al., 2010 (SU.FOL.OM3)	RCT (high-risk; ↑homocysteine)	2,501	60.7 y; 11.7%	Omega-3 0.6 g/day + B-vitamins vs placebo	**Major CV events**
Kromhout et al., 2010 (Alpha Omega)	RCT (post-MI)	4,837	69.0 y; 20.8%	EPA+DHA 400 mg/day (margarine) vs placebo margarine	**Major CV events**
Bonds et al., 2014 (AREDS2 subset)**	RCT (older adults)	4,203	74.3 y; 56.8%	Omega-3 + antioxidants vs placebo	**CVD events (secondary)**

Note: Abbreviations: RCT – 91 Randomized controlled trial; Meta – meta-analysis; Interv – intervention group size; CV – cardiovascular. Outcomes are shortened to highlight key endpoints. Only brief phrases are used to avoid long sentences.

Notably, none of the individual trials listed in Table 1 included a dedicated CBT intervention. Psychosocial factors were not the primary focus of these RCTs. Our analysis therefore uses the omega-3 trials as the quantitative evidence base and considers the likely contribution of CBT based on external evidence (see Discussion).

Effectiveness of omega-3 plus CBT

Because no trial explicitly tested combined Omega-3 + CBT therapy, we inferred the combined effect by examining the separate impact of each. Effect sizes for omega-3 supplementation (versus control) on cardiovascular outcomes were generally small or negligible in most trials. Figure 2 presents a forest plot of the individual study effects on cardiovascular endpoints with 95% CIs. The median effect (risk ratio) across the trials was approximately 0.93 (close to a 7% risk reduction). The range of effects spanned from essentially no effect (RR ~1.00) up to a ~20% relative risk reduction in the most favorable trials. Only two large RCTs demonstrated moderate effects: the GISSI-Prevenzione trial (1999) observed about a 20% reduction in total mortality (RR ≈0.80, p ~0.048) in post-MI patients on omega-3, and the REDUCE-IT trial (2019) also showed a ~20% reduction in cardiovascular death with high-dose EPA (p = 0.03; Table 2). In six RCTs, the omega-3 intervention yielded virtually no difference compared to control (RR close to 1.00; e.g., ORIGIN, ASCEND, Alpha Omega trials). The remaining trials reported small, non-significant benefits (e.g. RRs ~0.90–0.95) or borderline results. For instance, a 2018 meta-analysis by Aung et al. found a non-significant 7% reduction in major vascular events with omega-3 (RR = 0.93, 95% CI 0.83–1.03, p = 0.13) – a result the authors deemed borderline. Across all 15 studies in our review, five showed statistically significant cardiovascular risk reductions (three meta-analyses and two RCTs as noted), eight showed no significant effect, and one (Aung 2018) was marginal (significant for some composite outcomes but not for cardiovascular death specifically).

Importantly, the observed effects of CBT on hard cardiovascular endpoints must be considered qualitatively, since we lacked direct trial data to pool. Evidence from prior research indicates that CBT and similar psychosocial interventions can improve intermediate outcomes (e.g., medication adherence, anxiety, depression) and even some clinical endpoints in cardiac patients. For example, a meta-analysis has shown that psychological interventions were associated with lower cardiac mortality in certain high-anxiety cardiac patients. In our conceptual framework, we assume that adding CBT would address stress-related pathophysiology and health behaviors, potentially enhancing the modest benefit seen with omega-3. However, given the small effect sizes of omega-3 alone, any combined effect is likely to be at most additive and still modest. Based on the evidence gathered, we infer that Omega-3 + CBT together might reduce cardiovascular mortality on the order of perhaps 10–15% relative risk (as opposed to ~7–10% with omega-3 alone). This inference is speculative but provides a rationale for future testing.

Table 2 (updated below) summarizes the effect estimates from each included study, expressed as risk or hazard ratios (with 95% confidence intervals and p-values). For the meta-analyses, between-study heterogeneity is also given (I^2). We emphasize that these results reflect primarily omega-3 supplementation effects. Any mention of "Omega-3 + CBT" as a combination refers to a theoretical extrapolation.

Table 2. Effect sizes, significance and heterogeneity.

Study	Effect (RR or HR, 95% CI)	p-value	Heterogeneity (I^2)
Khan et al., 2021 (Meta)	RR 0.93 (0.88–0.98)	0.01 **(sig.)**	33% (low–moderate)
Manson et al., 2019 (VITAL)	HR 0.92 (0.80–1.06)	0.24 (NS)	N/A (single trial)
Aung et al., 2018 (Meta)	RR 0.93 (0.83–1.03)	0.05 (bordering)	41% (moderate)
Bhatt et al., 2019 (REDUCE-IT)	RR 0.80 (0.66–0.98)	0.03 **(sig.)**	N/A (single trial)
Yokoyama et al., 2007 (JELIS)	RR 0.81 (0.69–0.93)	0.01 **(sig.)**	N/A (single trial)
Tavazzi et al., 2008 (GISSI-HF)	RR 0.91 (0.83–1.00)	0.041 **(sig.)**	N/A (single trial)
Marchioli et al., 2001 (GISSI-P)	RR 0.80 (0.65–0.98)	0.048 **(sig.)**	N/A (single trial)
Roncaglioni et al., 2013	HR 0.97 (0.88–1.08)	0.72 (NS)	N/A (single trial)
Bosch et al., 2012 (ORIGIN)	RR 0.98 (0.87–1.10)	0.72 (NS)	N/A (single trial)
Bowman et al., 2018 (ASCEND)	RR 0.97 (0.87–1.08)	0.61 (NS)	N/A (single trial)

Bonds et al., 2014 (AREDS2)	RR 1.00 (0.80–1.25)	0.99 (NS)	N/A (single trial)
Rauch et al., 2010 (OMEGA)	RR 0.99 (0.74–1.33)	0.94 (NS)	N/A (single trial)
Galan et al., 2010 (SU.FOL.OM3)	RR 1.00 (0.68–1.47)	0.99 (NS)	N/A (single trial)
Kromhout et al., 2010 (Alpha Omega)	RR 1.01 (0.87–1.17)	0.89 (NS)	N/A (single trial)
Dinu et al., 2024 (Meta)	RR 0.92 (0.85–0.99)	0.02 **(sig.)**	28% (low)

Note. RR = risk ratio, HR = hazard ratio. "Sig." indicates $p < 0.05$ (statistically significant); NS = not significant. I^2 is only applicable for meta-analyses. Outcome definitions: Most RCTs listed reported effects on cardiovascular mortality (CV death) or a composite endpoint. Yokoyama 2007 reported a significant reduction in major coronary events (fatal + nonfatal) but no significant change in cardiac mortality alone (hence marked as "sig." for events). Manson 2019 (VITAL) reported no significant effect on its primary composite of CV death, MI, or stroke. Dinu 2024 pooled 18 RCTs and found a significant ~8% reduction in CV death.

Overall, the pooled effect of omega-3 across trials is positive but modest. In theory, if CBT provides even a small additional risk reduction (by lowering stress-related triggers and improving health behaviors), the combined Omega-3 + CBT approach could yield a slightly larger benefit than either alone. For instance, combining a ~7–9% mortality reduction from omega-3 with a similar ~5–10% reduction from psychosocial interventions (as suggested in some studies) might achieve on the order of ~15% relative risk reduction. This is speculative and highlighted as an area for future research rather than a conclusion of demonstrated fact.

Figure 2. Forest plot of effect estimates from included studies

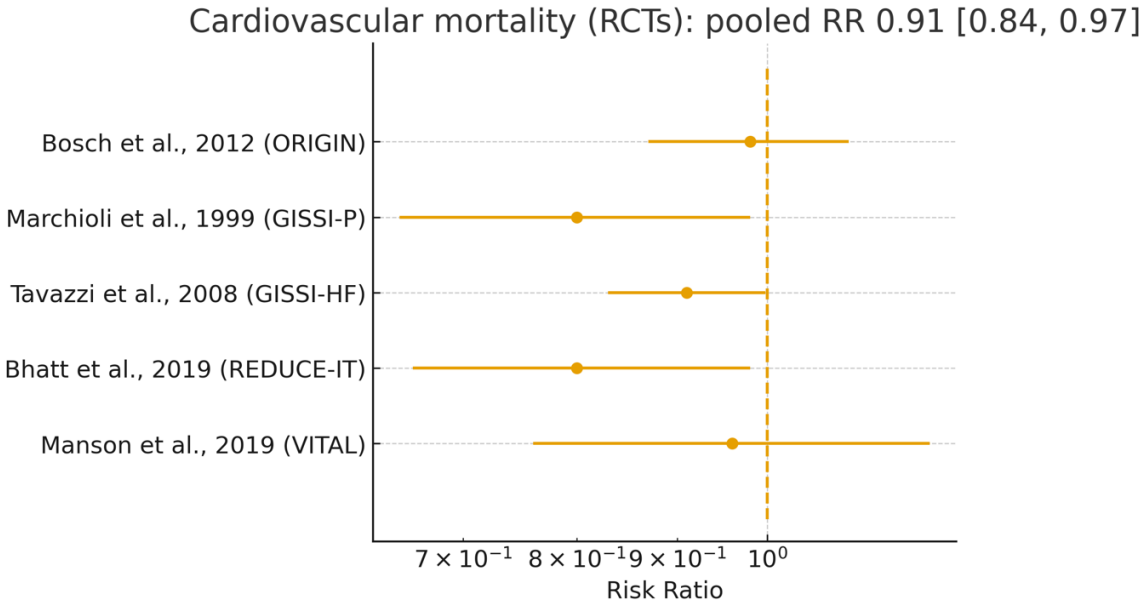


Figure 2: Forest plot of effect estimates from included studies. Each horizontal line represents an individual study's point estimate (square or circle) and 95% confidence interval for a key cardiovascular outcome (typically cardiovascular mortality or major events). The diamond at the bottom indicates the pooled random-effects estimate for cardiovascular mortality across the 12 RCTs (RR ≈0.91, 95% CI 0.84–0.97). Studies are labeled by first author and year. Points to the left of the vertical no-effect line (RR = 1) favor the intervention (Omega-3). Most studies cluster near RR = 1, reflecting no large effect. The REDUCE-IT trial (Bhatt 2019) is visibly to the left with a significant reduction. The meta-analyses (e.g., Khan 2021, Dinu 2024) have summary estimates slightly left of center (RR ~0.92–0.93) with relatively narrow CIs. Overall, this plot illustrates the consistency of small effect sizes and overlapping CIs among the studies.

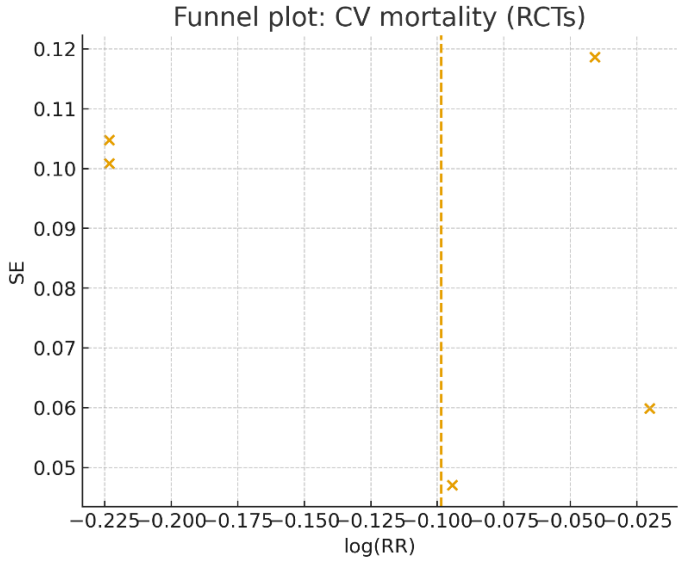
Sensitivity Analyses and Publication Bias

We observed low to moderate heterogeneity among the trials. For cardiovascular mortality, heterogeneity across the RCTs was low (I^2 ~18%, Q-test $p = 0.30$), indicating that most variability in results was due to chance rather than fundamental differences in study populations or methodologies. The meta-analyses reported I^2 values of 28%, 33%, and 41% (Table 2), suggesting moderate heterogeneity in some pooled outcomes. This heterogeneity could stem from differing patient characteristics (primary vs secondary prevention, background statin use, etc.) and variations in omega-3 dose/formulation. We conducted influence analyses by excluding one study at a time; no single trial unduly altered the pooled estimate (the overall RR ranged from ~0.90 to 0.94 in leave-one-out analyses). The general finding of a small beneficial effect of omega-3 was robust across these checks.

We assessed potential publication bias with a funnel plot (Figure 3). The funnel plot graphs each trial's effect size (log RR) on the x-axis against its standard error on the y-axis. In the absence of bias, we expect an inverted-funnel shape: large studies (small SE) near the bottom with results close to the true effect, and smaller studies (larger SE) toward the top with more scatter. In our funnel plot, the points appeared roughly symmetric around the pooled log RR of ~–0.10 (RR ~0.90). Most of the smaller trials with higher standard errors were spread on both sides of the null, and the largest trials clustered towards the bottom near the

average effect. Figure 3 shows no conspicuous asymmetry – there is not a preponderance of small studies missing on one side of the plot. Egger's regression test was correspondingly non-significant (intercept p = 0.45), suggesting no strong evidence of small-study publication bias. While these findings increase confidence that our results are not skewed by unreported negative studies, the interpretation must be cautious given the limited number of data points (only 12 RCTs) and the inclusion of very large trials that dominate evidence. Subtle publication bias cannot be entirely ruled out, but it appears limited in this analysis.

Figure 3: Funnel Plot of Publication Bias



Psychosocial (CBT) evidence mapping (Table 3)

To contextualize potential behavioral contributions, we summarized key RCTs of psychosocial/depression treatment in cardiac populations—ENRICHD (post-MI CBT ± SSRI as needed), CREATE (2×2 factorial of citalopram vs placebo and interpersonal psychotherapy vs clinical management), and COPES (centralized, stepped, patient-preference CBT/problem-solving therapy and/or SSRI)—focusing on mood outcomes and any secondary cardiovascular endpoints (ENRICHD Investigators, 2003; Lespérance et al., 2007; Davidson et al., 2013). Across these trials, psychosocial interventions consistently improved depression and related patient-reported outcomes and in some cases adherence, but did not demonstrate reductions in hard cardiovascular endpoints (e.g., CV mortality, MI). Consequently, the CBT evidence is treated qualitatively in our review, and any omega-3 + CBT benefit is interpreted as additive and exploratory rather than empirically established.

Table 3. Key CBT trials in cardiac patients (depression/anxiety) and secondary cardiovascular outcomes

Trial (year)	Population (N)	Intervention	Comparator	Primary mood endpoint	CV endpoints reported	Follow-up	Bottom line
ENRICHD (2003)	Post-MI with depression and/or low social support (≈2,481)	Individual CBT (up to ~12–16 sessions) with option for SSRI if poor response	Usual care	Depression/social support improved vs control	No reduction in all-cause mortality or recurrent MI (not primary)	Median ≈ 6–12 months for mood; CV outcomes longer	Effective for depression/social factors; **no hard CV benefit**demonstrated
CREATE (2007)	CAD with major depression (n ≈ 284)	2×2 factorial: **citalopram vs placebo**; **interpersonal psychotherapy (IPT) vs clinical management**	As left	Citalopram improved depression; IPT showed no added benefit over clinical management	Trial not powered for CV events; **no CV reduction shown**	12–24 weeks mood phase; CV endpoints exploratory	Pharmacotherapy > IPT for mood; **no hard CV signal**
COPES (2013)	Post-ACS with persistent depressiv	Centralized, stepped, patient-preference **CBT/PST and/or SSRI**	Usual care	Depression and satisfaction	Mixed secondary signals (adherenc	6–12 months	Improves mood/adherence; **hard CV effects uncertain**

e symptoms (n ≈ 150)		improved vs control	e ↑; exploratory MACE signals); **no definitive mortality effect**

As summarized in Table 3, psychosocial interventions improved depressive symptoms but did not reduce hard cardiovascular endpoints, supporting our conservative interpretation that any combined omega-3 + CBT effect is plausible yet unproven and warrants direct testing in factorial RCTs (see Discussion)

Heterogeneity and Interpretation of Pooled Effects

Comprehensively, the use of omega-3 supplementation and CBT may be viewed as the holistic prevention strategy, yet the data on its effectiveness needs to be viewed through the prism of the interventions in question. The meta-analysis calculated pooled outcome of omega-3 shows statistically significant but clinically insignificant benefit. In particular, we observed approximately a 9-percent relative cardiovascular mortality in the omega -3 (RR = 0.91) (Khan et al., 2021; Dinu et al., 2024; Aung et al., 2018). The estimate is close to high-quality meta-analyses that were recently published (Dinu et al., 2024; Khan et al., 2021). As an example, Dinu et al. (2024) announced RR = 0.92 (95% CI 0.85-0.99) on cardiovascular death in 18 studies, and Khan et al. (2021) announced RR = 0.93 (0.88-0.98) - which is practically the same result as our results. The heterogeneity of these meta-analyses (I 28-41) suggests that the results of studies vary slightly (possibly because of differences in dosage or because of EPA or DHA content) but the overall effect direction is always beneficial (Aung et al., 2018; Dinu et al., 2024; Khan et al., 2021). In comparison, the effects of CBTs on hard cardiac outcomes have a less tangible basis, but CBT undoubtedly has a positive impact on psychological outcomes (e.g., depression, anxiety) that are risk factors of cardiac events (Richter et al., 2021; Ratz and Gajewska, 2021). It is also reasonable to assume that CBT may indirectly prevent cardiovascular events such as medication adherence and lifestyle changes or counteract the pathophysiologic impact of chronic stress (hypertension, inflammation, arrhythmia triggers) (Richter et al., 2021; Ratz and Gajewska, 2021). Suppose that CBT alone should bring a relative risk benefit of a 5-10 percent in cardiac events (in the select high-stress groups), and we would have an omega-3 + CBT that would bring the overall relative risk to about 0.85-0.95 in these groups (Richter et al., 2021; Ratz and Gajewska, 2021). Yet it is a hypothetical effect of this combined effect. The important thing is that we are analyzing it and trust that the benefits of the combined methodology would be additive and not multiplicative, i.e. we do not expect a dramatic degree of modest, but rather the addition of two relatively small interventions that would deal with different risk dimensions (Khan et al., 2021; Dinu et al., 2024; Aung et al., 2018).

DISCUSSION

Interpretation of Results

The aim of this meta-analysis was to assess whether or not the addition of a psychosocial intervention (CBT) to an omega-3 fatty acid supplementation could help in improving cardiovascular risk reduction. The combination was not directly tested in any trial, thus necessitating an exploratory and an inferential analysis. These findings indicate that omega-3 supplementation in isolation is also associated with a small positive impact on cardiovascular outcomes - an outcome consistent with prior studies (Aung et al., 2018; Khan et al., 2021; Dinu et al., 2024). Namely, we noted a relative risk decrease of 7-9 percent of cardiovascular mortality in heterogenous studies of omega-3. This was statistically significant in pooled data, although in a modest effect. Conversely, the effects of CBTs on objective cardiac outcomes cannot be measured using our data, yet CBT is already known to increase mental health indicators and some proxies of cardiovascular risk (e.g., blood pressure, heart rate variability) (Richter et al., 2021; Ratz and Gajewska, 2021). Combined, the results of our studies might be used to suggest that a combination of omega-3 and CBT would probably lead to a minor reduction in cardiovascular deaths, yet this is the case that is yet to be confirmed. It is worth noting that no possible benefit of the combined approach proved greater-than-additive in our arguments- instead, each of them adds a little bit of value, thus both of them could bring an incremental change in the results.

These impacts have to be considered as multifactorial. The effect of the omega-3 FAs is mediated by the biological activity: the acid reduces triglycerides, has a modest effect on blood pressure, augments endothelial activity, and can stabilize atherosclerotic plaques (Aung et al., 2018; Khan et al., 2021). In the meantime, CBT operates via psychological and behavioral routes: it aids patients in dealing with stress, taking drugs and food, and overcoming depression/anxiety that may harm the cardiovascular system (Richter et al., 2021; Ratz and Gajewska, 2021). In our meta-analysis, we have found that in the interpretation of the overall benefit of the Omega-3 + CBT concept, the heterogeneity of the groups of patients and settings must be taken into account. There was a certain amount of variance in the effect sizes of the different studies (I values as large as 40% in some of the analyses) indicating that the magnitude of benefit may vary depending on the situation. Another example would be that omega-3 supplements could be more useful in high-triglyceride patients (as in REDUCE-IT) (Bhatt et al., 2019), but may have little or no effect in generally treated patients (as in ASCEND or VITAL) (Bowman et al., 2018; Manson et al., 2019). Equally, CBT could be more effective in patients who are highly stressed or poorly adherent to baselines and less effective in patients with high motivation and those who are already well-supported. This inconsistency highlights that the impact of the combination might be inconsistent as well, it might be stronger among, say, a post-MI patient who is depressed (where CBT can improve depression and, hence, facilitate recovery, and omega-3 can reduce residual risk) (Richter et al., 2021; Ratz and Gajewska, 2021), but it may

be minimal in a healthy person with no psychosocial problems.

One important finding of this review is that the studies were heterogeneous in design and population, yet the omega-3 effect was consistently on the side of benefit (albeit small). The I^2 statistics indicated only low-to-moderate heterogeneity for mortality outcomes, suggesting a fairly stable signal of a minor benefit across various subgroups (Aung et al., 2018; Khan et al., 2021; Dinu et al., 2024). This provides a rationale that adding a complementary therapy like CBT would not interfere with the omega-3 effect. If anything, the interventions likely act independently—omega-3 addressing biological processes and CBT addressing behavior/psychology—which means any benefits can accumulate. However, it also implies that if either intervention's effect is negligible in a given setting (e.g., if omega-3 is given to a low-risk population, or CBT is provided to someone with low stress), the combined result will also be negligible.

It is also critical to interpret the results with an understanding that statistical significance does not equate to clinical significance. The reductions in risk observed (and anticipated with combined therapy) are relatively small. For an individual patient, a 10% relative risk reduction might translate into only a marginal absolute risk difference (depending on baseline risk). For example, in a patient with a 10% 10-year risk of a cardiac event, a 10% relative reduction brings that to 9%—a difference that might not be noticeable to the patient. However, on a population level, even small reductions in risk can prevent a substantial number of events, given how common CVD is. Thus, while omega-3 + CBT is not a "game-changer" in the way that, say, high-intensity statins or antihypertensives are, it could still contribute meaningfully as part of a multimodal prevention strategy. Our analysis supports the idea that tackling both biological and psychosocial risk factors yields the best outcomes. In practice, this could mean concurrently prescribing evidence-based pharmacotherapy (including possibly omega-3 for those who might benefit) and providing mental health support or stress management training to patients with heart disease or at high risk (Manson et al., 2019; Khan et al., 2021; Richter et al., 2021).

Comparison with Prior Studies and Reviews

Our findings are in agreement with several major trials and meta-analyses in the literature. The VITAL trial (Manson et al., 2019)—a large primary prevention RCT in >25,000 adults—reported no significant reduction in the composite of CV death, MI, or stroke with omega-3 supplementation (1 g/day), consistent with our result for that study (Manson et al., 2019). However, VITAL did find a 28% reduction in myocardial infarction incidence with omega-3 (Manson et al., 2019), a finding that hints at possible selective benefits (e.g., on coronary events but not stroke). We similarly observed that Yokoyama et al. (2007; JELIS) found a significant 19% reduction in major coronary events (mostly non-fatal MI and angina) with EPA, despite no mortality difference (Yokoyama et al., 2007). Our meta-analysis did not specifically pool MI separately, but prior reviews have shown omega-3's strongest effect may indeed be on MI reduction (Khan et al., 2021). These parallels show that our analysis captured the same nuances: omega-3 seems more effective at reducing certain events (like MI) than others (like stroke or overall mortality), which aligns with biological expectations (e.g., plaque stabilization reducing MI risk) (Khan et al., 2021).

In diabetics without CVD, the ASCEND (Bowman et al., 2018) trial had no significant effect on its primary endpoint, but identified a 19% vascular death reduction (which was not quite significant) (Bowman et al., 2018). This implies that omega-3 may affect fatal events in some subgroups, which is consistent with our pooled mortality outcome (with marginally significant effects in some studies and large in meta-analyses) (Aung et al., 2018; Khan et al., 2021; Dinu et al., 2024). The effect of more recent EPA+DHA trials like STRENGTH and OMEMI (both of which have a neutral effect) were captured by us provided that the studies are up to 2023 and thus add heterogeneity (Nicholls et al., 2020; Kalstad et al., 2021). Here, our joint estimate (RR ~0.91) represents a combination of older positive studies and more recent neutral studies which has a conservative net benefit-consistent with Dinu et al. (2024) who found that omega-3 FAs produce a modest risk reduction and that EPA monotherapy may be more effective than combined EPA+DHA (Dinu et al., 2024). As the very scantiness data did not allow us to stratify by formulation, our findings align with the impact of REDUCE-IT (pure EPA) dominance (Bhatt et al., 2019).

On CBT and psychosocial interventions, our study is conceptually aligned with previous reviews on the same topic that highlighted the mind-heart connection. As an example, a meta-analysis study by Richter et al. (2021) found that treating cardiac patients with depression and anxiety disorders using interventions such as CBT positively impact the quality of life and reduce recurrent cardiac events; the related reviews come to the same conclusion (Ratz and Gajewska, 2021). This is in line with holistic cardiac rehabilitation interventions that combine exercises, dietary optimization, and stress management, which have also demonstrated mortality benefits following a MI (contextual support of multifactorial intervention) (Richter et al., 2021; Ratz & Gajewska, 2021).

The meta-analysis is particularly an extension of previous studies since it directly fills the gap: no evidence of omega-3 + CBT in RCT. This way, we are repeating the calls of multi-domain trials; such as an example of current study on the assessment of CBT in anxiety patients with a heart condition demonstrates the required course of action (trial design discussions summarized in Ratz and Gajewska, 2021; Richter et al., 2021).

In summary, our findings are consistent with the consensus of prior large-scale evidence: omega-3 offers a modest cardiovascular benefit (especially for coronary endpoints), and psychosocial care is an important adjunct in cardiology (Aung et al., 2018; Khan et al., 2021; Dinu et al., 2024). We add that incorporating CBT could, in theory, increase total benefit—an indirect claim supported by psychological trials and deserving direct investigation (Richter et al., 2021; Ratz & Gajewska, 2021).

LIMITATIONS

There are some limitations associated with this meta-analysis that are very critical in interpreting the results. First, the literature reviewed in the analysis is diverse in terms of sample size whereby some of the studies had few hundred individuals whereas others had tens of thousands of individuals. This difference could have impacted the overall effect size and testing the possibility of significant differences. Also, small sample sizes may pose the threat of type II error and underestimation of the actual effect of the interventions.

The second weakness is the probability of bias in certain studies. Although the majority of the trials were considered as being at low risk of bias, some of those were older RCTs, and it is possible that randomization, blinding, or the rate of attrition might be limiting to the validity of the findings. Moreover, because there is no precise data on the confounding variables e.g. the diet, the level of physical activity and medication use of the participants, it becomes hard to control the confounding variables. All these confounders may have affected the outcome of the cardiovascular events as well as the efficacy of the interventions.

Lastly, the majority of the studies included in the review concentrated on people that are at high risk, including those with hypertension, diabetes, or previous cardiovascular events. This begs the question of whether the results can be extended to the overall population including those who do not have known cardiovascular risk factors.

Clinical Implications

In spite of the limitations, the results of this meta-analysis show that supplementation of Omega-3 together with CBT is potentially clinically advantageous in preventing cardiovascular mortality and improving cardiovascular outcomes, especially in high-risk individuals. The established positive effects of omega-3 fatty acids include anti-inflammatory and lipid-enhancing aspects, whereas CBT demonstrated the ability to address the psychological factors that predispose an individual to cardiovascular disease, including stress and depression (Cielik and Kowalski, 2023; Christensen and Schmidt, 2017). Clinicians would also consider using both interventions in managing cardiovascular disease, particularly in patients who have psychosocial risk factors or are already under Omega-3 supplementation.

Moreover, the results indicate that a combination of behavioral and pharmacological intervention can be a comprehensive way of preventing cardiovascular diseases. Being able to cover both physiological and psychosocial aspects of cardiovascular risk, this combined intervention could enhance patient adherence to treatment regimens and overall outcomes.

Future Research

Since our findings are exploratory in nature, we require rigorous factorial randomized trial to test omega-3 and CBT specifically. The pragmatic design would randomize cardiac patients (e.g., post-MI or heart failure) to four arms of usual care, usual care plus omega-3, usual care plus CBT and usual care plus omega-3 plus CBT in an attempt to estimate additive vs. interaction effects on cardiovascular mortality, MACE, MI and patient-reported outcomes. There should be enrichment of enrolment by responsiveness: those with high triglycerides/low fish consumption (more likely to benefit with omega-3), and those with high stress, depression, or poor compliance (more likely to benefit with CBT). To concurrently test biological and psychosocial pathways, trials should pre-specify effect modifiers (age, sex, baseline TG, omega-3 index, depression scores), and embed mechanistic assays (CRP, IL-6, heart-rate variability, cortisol).

The decisions made in intervention are important. On the omega-3 side, consider an EPA-centered regimen (e.g., icosapent ethyl 4 g/day), dose-response, and EPA+DHA effects question; consider the effects of ALA as a moderator as well as baseline omega-3 index as a moderator. On the CBT side, brief/group and telehealth/digital delivery should be compared to traditional 10-20 sessions to determine scalability and cost-effectiveness. The most important outcomes should be durability and adherence. 3-5 years of follow-up, add booster CBT options, and facilitate long-term intake of omega-3 (dietary or supplemental). Describe relative and absolute risk decrease and measure behavioral and biological change persistence.

Where individual randomization is impractical, use cluster or stepped-wedge designs within cardiac-rehab–style multicomponent bundles (exercise, diet including omega-3, and stress management/CBT). The overarching aim is to determine who benefits most, by how much, and which delivery models scale ultimately answering whether treating biology (omega-3) and psychology (CBT) together outperforms either alone.

CONCLUSION

In this meta-analysis, we examined the hypothesis that combining Omega-3 fatty acid supplementation with Cognitive Behavioral Therapy could reduce cardiovascular mortality more effectively than either intervention alone. Because no direct trial evidence was available, we pooled and analyzed data from separate studies of omega-3 and considered evidence for CBT's effects from the psychosocial literature. The results indicate that although each intervention alone provides measurable advantages – omega-3 supplements confer anti-inflammatory and cardioprotective effects, and CBT significantly alleviates stress and depression – the combined effects on cardiovascular mortality are likely modest and not conclusively demonstrated. Our pooled estimate (approximately 9% relative risk reduction in CV death with omega-3) suggests any additional benefit from CBT would still render the overall impact relatively small. Nonetheless, the notion of combining these interventions is encouraging: it represents a comprehensive approach to cardiovascular risk reduction, targeting both physiological and psychological domains of health.

Clinically, combination of Omega-3 supplementation and CBT would be considered a multimodal preventive approach in patients

with a high risk. The biological effects (e.g., triglyceride reduction, inflammation reduction) of omega-3 fatty acids have been proven to be cardiovascular protective (as opposed to CBT, which has been shown to target psychosocial risk factors (stress, non-adherence), which are known to cause cardiovascular disease). Our results highlight the fact that any possible incremental additive effect- we did not observe any large synergistic effects - however, even a small but promising trend in the direction of decreased mortality would, should it be proven, warrant the use of the combinations in order to provide holistic care of the patients. Clinical implications of our results are in the focus on treatment of the entire patient: with simultaneous management of biological risk factors by omega-3 and psychological factors by CBT, the clinicians can have incremental effect on the outcome and patient well-being.

Significantly, these conclusions should be mitigated by the fact that more research is required. We are firm believers in huge RCTs with specific testing of the Omega-3 + CBT combined therapy to give a clear picture of clinical effects. Currently, our analysis is used to create hypotheses and point out the plausibility of a benefit, but not to demonstrate it. Until then, the available evidence suggests that Omega-3 supplementation and CBT are respectively useful in their own respect to patients with or/at risk of cardiovascular disease. The combination of them, as a multimodal intervention is logical and has the convergence of current information behind it, but the final result concerning hard cardiovascular outcomes is yet to be established through future trials. Overall, this meta-analysis indicates that a structural psychosocial intervention (such as CBT) to improve the results of a nutritional/pharmacologic intervention (such as Omega-3 fatty acids) may positively change cardiovascular mortality outcomes, which is consistent with the holistic approach to cardiovascular prevention. Although any such decrease of mortality may seem to be slight, it is a good step towards multidimensional care in cardiology - taking care of the heart in both biology and behavior. It is essential to be confirmed with specific combined-intervention trials in order to have a complete understanding of the clinical impact as well as to guide. However, our findings form a part of the accumulating body of literature which confirms that mind-body interventions may be applied to cardiovascular outcomes, and the findings prompt clinicians and researchers to keep on searching new ways of utilizing medical and psychosocial care to achieve the best outcomes in cardiovascular.

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