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# Marine Omega-3 Fatty Acids and Prevention of Vascular Disease and Cancer

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## Abstract

**Background—**Whether omega-3 fatty acid supplementation reduces risk of cardiovascular disease or cancer remains unclear.

**Methods—**The VITamin D and OmegA-3Trial (VITAL) was a randomized, placebo-controlled, 2X2 factorial trial of vitamin D3 (2000IU/day) and marine omega-3 fatty acids (1 g/day) in the primary prevention of cardiovascular disease and cancer among 25,871 U.S. men aged ≥50 and women aged ≥55, including 5,106 African Americans. Primary endpoints were major cardiovascular events (myocardial infarction, stroke, and cardiovascular mortality) and total invasive cancer. Secondary outcomes included individual components of the cardiovascular composite, the composite plus coronary revascularization, site-specific cancers, and cancer mortality. This paper reports the results of omega-3 and placebo.

**Results—**During a median 5.3 years, rates of the primary outcomes did not differ between the omega-3 and placebo groups -- 805 participants had a major cardiovascular event, hazard ratio [HR]= 0.92; 95% confidence interval [CI], 0.80–1.06, p= 0.24. Invasive cancer was diagnosed in 1,617 participants, HR 1.03 (0.93-1.13, p=0.56). In the analysis of key secondary endpoints, hazard ratios and 95% CIs comparing omega-3 to placebo were: expanded cardiovascular events, HR 0.93 (0.82-1.04); total myocardial infarction HR 0.72 (0.59-0.90); total stroke, HR 1.04 (0.83-1.31); cardiovascular mortality HR 0.96 (0.76-1.21); and cancer deaths (n=341, HR 0.97 (0.79-1.20). For all-cause mortality (n=978), the HR was 1.02 (0.90-1.15). No excess risks of bleeding or other serious adverse events were observed.

**Conclusions—**Omega-3 fatty acid supplementation did not reduce major cardiovascular events or cancer incidence.

Marine-derived long-chain omega-3 ( also called n-3) fatty acids have shown promise for the primary prevention of cardiovascular disease in animal studies, small randomized trials designed with intermediate cardiovascular endpoints, and observational epidemiologic investigations.[1] However, mid-sized to large trials testing the effect of n-3 fatty acid supplements on clinical cardiovascular outcomes in secondary prevention or high-risk settings have shown inconsistent results.[1, 2] Large trials of n-3 supplements for primary prevention of cardiovascular disease in a general population selected only on age and *not* on vascular risk factors such as diabetes or dyslipidemia are lacking. Data on n-3 fatty acids and cancer risk have also been inconsistent.[3] Given the popularity of fish oil as a strategy to reduce chronic disease,[4] clarifying the relation between supplemental n-3 fatty acids and risks of cardiovascular disease and cancer and obtaining more definitive data on the benefit-risk balance of these supplements is a high priority. The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL) was conducted to address these knowledge gaps in a diverse U.S. cohort.

## METHODS

### Study Design

This randomized, double-blind, placebo-controlled, 2×2 factorial trial tested the benefits and risks of vitamin $D_3$ (2000 IU/day) and n-3 fatty acids (1 g/day fish-oil capsule containing 840 mg of n-3 fatty acids including eicosapentaenoic acid [EPA, 460 mg] + docosahexaenoic acid [DHA, 380 mg]) in the primary prevention of cardiovascular disease and cancer among 25,871 men aged ≥50 and women aged ≥55, including 5,106 African Americans. The results are presented in two papers, with details of the full design in the accompanying paper containing the vitamin $D_3$ data, the Supplementary Appendix, and also published earlier.[5, 6] The protocol is posted at NEJM.org. The n-3 fatty acid dose chosen was that recommended by the American Heart Association for cardioprotection[7] and demonstrated as beneficial in a secondary prevention population.[8] The recruitment flow diagram is presented in Figure S1 in the Supplementary Appendix. Randomization to n-3 fatty acids, vitamin D, both active agents, or both placebos was completed in March 2014. Study medication ceased as planned on December 31, 2017, yielding a median intervention period of 5.3 years (range 3.8-6.1 years).

Baseline questionnaires collected data on clinical and lifestyle risk factors and included a dietary questionnaire that ascertained self-reported intake of fish and other foods. Annual questionnaires assessed adherence to and potential side effects of randomized treatments, incident major illnesses, and risk factor updates. Baseline blood samples were collected from all willing participants (n=16,956 of 25,871 [66%]) and were assayed for plasma omega-3 index (EPA+DHA as a percent of total fatty acids[9]) by Quest Diagnostics using liquid chromatography-tandem mass spectrometry.

### Study Endpoints

Primary endpoints were major cardiovascular events (composite of myocardial infarction, stroke, and cardiovascular mortality) and total invasive cancer. Secondary cardiovascular endpoints were major cardiovascular events plus coronary revascularization [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)] and individual

components of the primary endpoint. Secondary cancer endpoints were incident colorectal, breast, and prostate cancers, and total cancer mortality. Medical records of those reaching endpoints were reviewed by an Endpoints Committee of physicians blinded to treatment assignment. Myocardial infarction and stroke were confirmed using established criteria.[10, 11] Cancer was confirmed with histologic or cytologic data.[12] Additional details regarding endpoint confirmation can be found in the preceding paper and the Supplementary Appendix.

### Statistical Analysis

Treatment-effect analyses were based on the intention-to-treat principle, as described in the companion paper on vitamin D. Primary analyses were based on Cox proportional hazards models controlling for age, sex, and randomization to vitamin D.

Possible variations in treatment effect by age, sex, baseline cardiovascular risk factors, baseline dietary fish intake and plasma omega-3 index, and concurrent randomization to vitamin D were specified *a priori*. Because vitamin D was also studied, treatment effects in racial/ethnic groups were of interest. Aspirin and statin use were additional stratification variables. There was no control for multiple hypothesis testing, with no formal adjustment to the p-values or confidence intervals. Thus, results for exploratory outcomes and subgroups should be interpreted with caution. Additional details regarding the analyses are in the Supplementary Appendix.

## RESULTS

Baseline characteristics of study participants are in Table 1 (with further details in Table S1 of the Supplementary Appendix). Of the 25,871 participants, 51% were women and the mean age was 67.1 years. The cohort was racially diverse, including 20% African Americans. Randomization balanced characteristics between groups. The questionnaire response rate averaged 93.1%, and self-reported treatment adherence rates (percent taking ≥2/3 of the study capsules) in the active and placebo groups averaged 81.6% and 81.5%, respectively, over 5-year follow-up (Table S2, Supplementary Appendix). The prevalence of outside use of fish-oil supplements was below 3.5% in both groups throughout follow-up. Among the 15,535 participants with analyzable baseline blood samples (60%), the mean plasma omega-3 index was 2.67% (SD, 0.9%) in both groups. Among the 1,583 participants who also provided an analyzable one-year blood sample, the mean omega-3 index rose to 4.13% (54.7% increase) in the active group and changed <2% in the placebo group.

### Cardiovascular Disease

During follow-up, there were 805 major cardiovascular events, including 386 in the n-3 and 419 in the placebo group (comparing omega-3 with placebo, HR=0.92; 95% confidence interval, 0.80-1.06; p=0.24) (Table 2). Results of analyses of prespecified secondary cardiovascular outcomes were as follows: total myocardial infarction (HR=0.72 [0.59-0.90]; cardiovascular mortality (HR=0.96 [0.76-1.21]); total stroke (HR=1.04 [0.83-1.31]); and expanded cardiovascular composite (HR=0.93 [0.82-1.04]). Additional vascular outcomes included coronary artery bypass graft (HR=0.99 [0.73-1.33]), percutaneous coronary

intervention (HR=0.78 [0.63-0.95]); fatal myocardial infarction (HR=0.50 [0.26-0.97]); and total coronary heart disease (HR=0.83 [0.71-0.97]) (see Table 2, which also shows results for stroke subtypes and stroke death).

Cumulative incidence rates of major cardiovascular events are shown in Figure 1. For major cardiovascular events, the curves did not differ significantly between groups. After excluding the first 2 years of follow-up, the HR for major cardiovascular events was 0.89 (0.76-1.05), and the reduction in myocardial infarction persisted (Table 2).

Subgroup analyses showed a possible reduction in the primary cardiovascular outcome with omega-3 supplementation among those with low fish consumption (Figure 2). Additional subgroup analyses are presented in the Supplementary Appendix, Tables S3-S4 and Figure S2, with a focus on exploring differences according to race/ethnicity, diabetes status, number of traditional cardiovascular risk factors, dietary fish intake, and other variables for the primary endpoint of major cardiovascular events and the secondary endpoint of total myocardial infarction. For myocardial infarction, these are presented as explanatory analyses to assess whether the risk reduction was similar across subgroups. The suggestion of greater risk reductions for myocardial infarction among African Americans and those with lower fish intake, comparing the omega-3 group with the placebo group, is discussed in the Supplementary Appendix. For the other secondary cardiovascular endpoints of stroke, cardiovascular mortality, and the expanded composite of major cardiovascular events plus coronary revascularization, no appreciable effect modification was found (data not shown).

## Cancer and All-Cause Mortality

During follow-up, 1,617 participants developed invasive cancer, with similar rates in the n-3 and placebo groups (820 vs. 797 cancers; HR=1.03 [0.93-1.13]; p=0.56) (Table 2). No significant differences between randomized groups were observed for breast, prostate, or colorectal cancer; cancer mortality (RR=0.97 [0.79-1.20]); or all-cause mortality (HR=1.02 [0.90-1.15]).

Cumulative incidence curves for cancer and all-cause mortality did not differ significantly between treatment groups at any year of follow-up (Fig. 2). Tests for proportionality over time suggested violation for cancer (p=0.075). In analyses excluding the first two years of follow-up, the HRs were 1.13 (1.00-1.28) for cancer incidence and 0.93([0.0.73-1.19) for cancer mortality in the n-3 group (Table 2).

In subgroup analyses, sex may have modified the results for cancer incidence (p-interaction=0.024) (Table S5). Fish intake at baseline may have modified the intervention's effects on all-cause mortality, (p-interaction=0.017; Supplementary Appendix, Table S6). There were no other significant interactions for cancer endpoints or all-cause mortality.

## Adverse Events

The intervention was not associated with significant differences in gastrointestinal symptoms, major bleeding episodes, or other serious side effects, compared to placebo (Supplementary Appendix, Table S7).

## DISCUSSION

In this 5.3-year primary prevention trial, n-3 supplementation (1 g/day) as compared to placebo did not lead to a significant reduction in the primary endpoints of major cardiovascular events (a composite of myocardial infarction, stroke and cardiovascular mortality) or invasive cancer. Analyses of the components of the primary composite cardiovascular endpoint suggested a reduction in myocardial infarction and no change in cardiovascular mortality or stroke. Exploratory analyses excluding the first two years of follow-up suggested a nonsignificant increase in cancer incidence, but no increase in cancer mortality.

Meta-analyses of n-3 supplementation trials in adults with or at high risk for cardiovascular disease have concluded that supplementation has no, or at most a weak, preventive effect on cardiovascular outcomes, including major vascular events, major coronary events, myocardial infarction, stroke, and revascularization.[13–15] The recently completed ASCEND trial,[16] which tested n-3 supplementation (1 g/day) in U.K. adults with diabetes, also reported generally null results. Thus, the possible reduction in the secondary outcomes of myocardial infarction and PCI in our trial, which tested n-3 fatty acids for primary prevention in a usual-risk population, raises the question of potential differences in results between primary and secondary prevention settings. Notably, neither our trial nor the secondary prevention trials indicate benefit of n-3 supplementation on stroke or composite cardiovascular endpoints. Our finding of a possible reduction with n-3 supplementation for the primary cardiovascular outcome among those with low fish consumption -- a characteristic that has rarely been examined as an effect modifier in previous trials—is hypothesis-generating and requires further study.

Two early large (n≥10,000) open-label trials[8, 17] testing doses of 1 g/day or higher found significant coronary protection, but all but one[18] of the subsequent placebo-controlled trials[16, 18–23] (some with smaller sample sizes[18–21] and lower doses[19, 21]) did not. The finding of a possible reduction in our trial may be partly attributable to these design differences. Also, the prevalence of use of cardiovascular medications, including statins, β-blockers, and anticoagulants, was higher in recent trials, perhaps reducing the opportunity to detect incremental benefit. Although a recent meta-analysis[14] of n-3 trials found no variation in results by statin use, dilution of a potential n-3 effect by other medications cannot be ruled out. Such a dilution would likely be greater in secondary prevention settings, in which medication use is more prevalent. In addition, participants in secondary prevention trials generally have more advanced atherosclerosis, which may require more powerful interventions than n-3 fatty acids or higher n-3 doses to avert clinical events. Indeed, a greater n-3 benefit on major vascular events was observed among participants without prior stroke in a recent meta-analysis[14] and in those without prior vascular disease in a trial among patients with macular degeneration.[24] Differences in fish consumption across study populations may have also influenced findings. Finally, there were few black participants in the secondary prevention trials, and our trial suggest a greater coronary benefit of supplemental n-3 fatty acids in this racial group.

The finding in a subgroup analyses of the secondary outcome of MI suggesting possible greater cardiovascular benefits of n-3 supplementation for African Americans than for non-Hispanic whites, was unexpected, especially given that both racial/ethnic groups had similar baseline EPA+DHA blood levels and fish intake, and may be a chance finding that requires corroboration in future trials. Recent observational studies find racial variation in associations of both marine- and plant-derived n-3 biomarkers with incident coronary disease.[25] Gene variants influence metabolism and bioavailability of n-3 fatty acids, as demonstrated in Greenland Inuits,[26] and may influence coronary risk.[27] Other racial/ethnic differences in clinical, dietary, or environmental factors may also account for this finding.[28] Finally, African Americans have a higher prevalence of comorbidities such as diabetes and hypertension. However, treatment-associated HRs for myocardial infarction remained reduced across cardiovascular-risk strata in African Americans, with greater risk reductions than in non-Hispanic whites (Table S3).

That supplemental n-3 fatty acids confer coronary protection is biologically plausible. Data from laboratory and animal studies, as well as small trials of intermediate cardiovascular endpoints in humans, support mechanisms including anti-thrombotic, hypotriglyceridemic, blood pressure lowering, and anti-inflammatory effects; impeded growth of atherosclerotic plaques; slowing of heart rate; reduced susceptibility to cardiac arrhythmias; and promotion of nitric-oxide induced endothelial relaxation whereby n-3 fatty acids may reduce risk.[1, 5] Experimental studies support relevant molecular and gene-regulatory effects.[1] The dose-response curve for most effects plateaus at 1 g/day or lower.[29] Observational studies suggest significant inverse associations between fish intake or n-3 fatty acid biomarkers and coronary outcomes—findings compatible with these mechanisms.[25, 30–32]

With regard to cancer, our findings are consistent with results of secondary cardiovascular disease prevention trials, which have mostly reported neutral effects or slight (but nonsignificant) elevations in cancer incidence with n-3 fatty acids.[8, 16, 17, 22, 23, 33, 34] A 2014 meta-analysis of 10 n-3 fatty acid trials found a nonsignificant 10% increase in cancer risk (p=0.12).[35] A 2018 meta-analysis of n-3 trials of cardiovascular disease[14] also reported no significant association between supplementation and incident cancer but did not provide an effect estimate. Our finding of a more favorable effect on incident cancer in women contrasts with results of the SU.FOL.OM3 n-3 trial[33] of an increased cancer risk in women but not men. Three trials have reported on cancer mortality, with two finding a neutral effect[16, 18] and one a borderline significant reduction.[34] The absence of a significant n-3 treatment effect on all-cause mortality in the present trial is consistent with results of meta-analyses of earlier trials[13, 15] and ASCEND.[16]

The strengths of our trial include a large general population sample with racial/ethnic and geographic diversity; high follow-up rates and pill-taking adherence; high blood-collection rates; validated biomarkers of adherence; dietary assessments; and rigorously adjudicated endpoints. Ancillary studies examining diabetes, atrial fibrillation, cognition, autoimmune disorders, and other outcomes will inform the overall benefit-risk balance of n-3 supplementation.

Our study also has certain limitations. Median treatment duration was 5.3 years. The trial's single n-3 dose did not permit exploration of dose-response relationships. However, the dose used has been recommended by the American Heart Association for cardioprotection in persons with prior coronary disease[7, 36] and is at least twice the dose recommended for cardiovascular protection in healthy populations (1-2 servings of fish per week).[30, 36] Results of ongoing trials[37, 38] testing higher doses in high-risk populations will be informative but may not apply to primary prevention. Some of our subgroup analyses are based on small numbers of events.

In summary, omega-3 fatty acid supplementation did not reduce the primary outcomes of major cardiovascular events (myocardial infarction, stroke, and cardiovascular mortality) and total invasive cancer.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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VITAL Investigators, Staff, and Study Participants

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VITAL was approved by the Institutional Review Board of Partners Healthcare/Brigham and Women's Hospital, and the study agents have received Investigational New Drug Approval from the U.S. Food and Drug Administration.

VITAL is registered at clinicaltrials.gov (NCT01169259). The VITAL website is www.vitalstudy.org.

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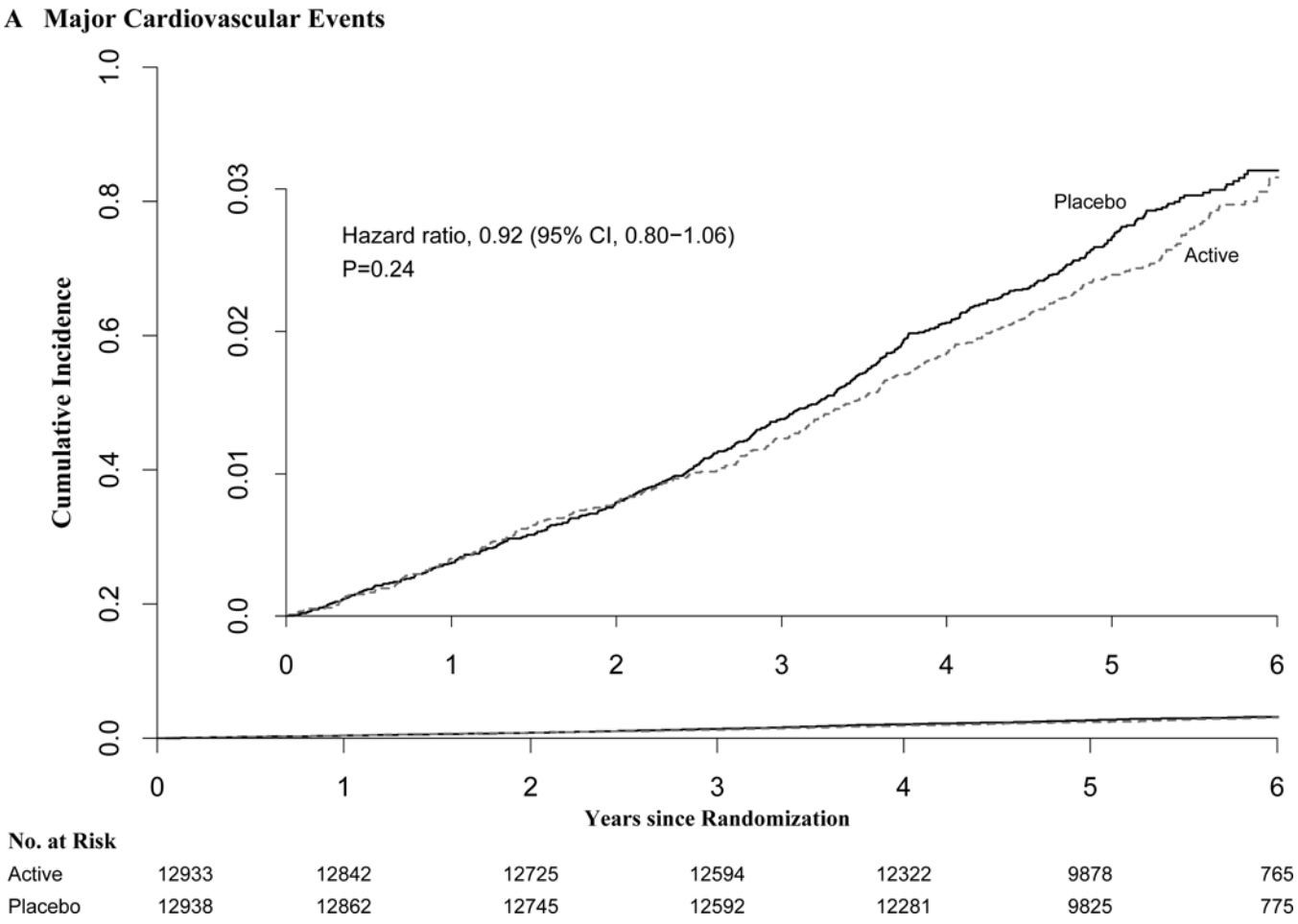


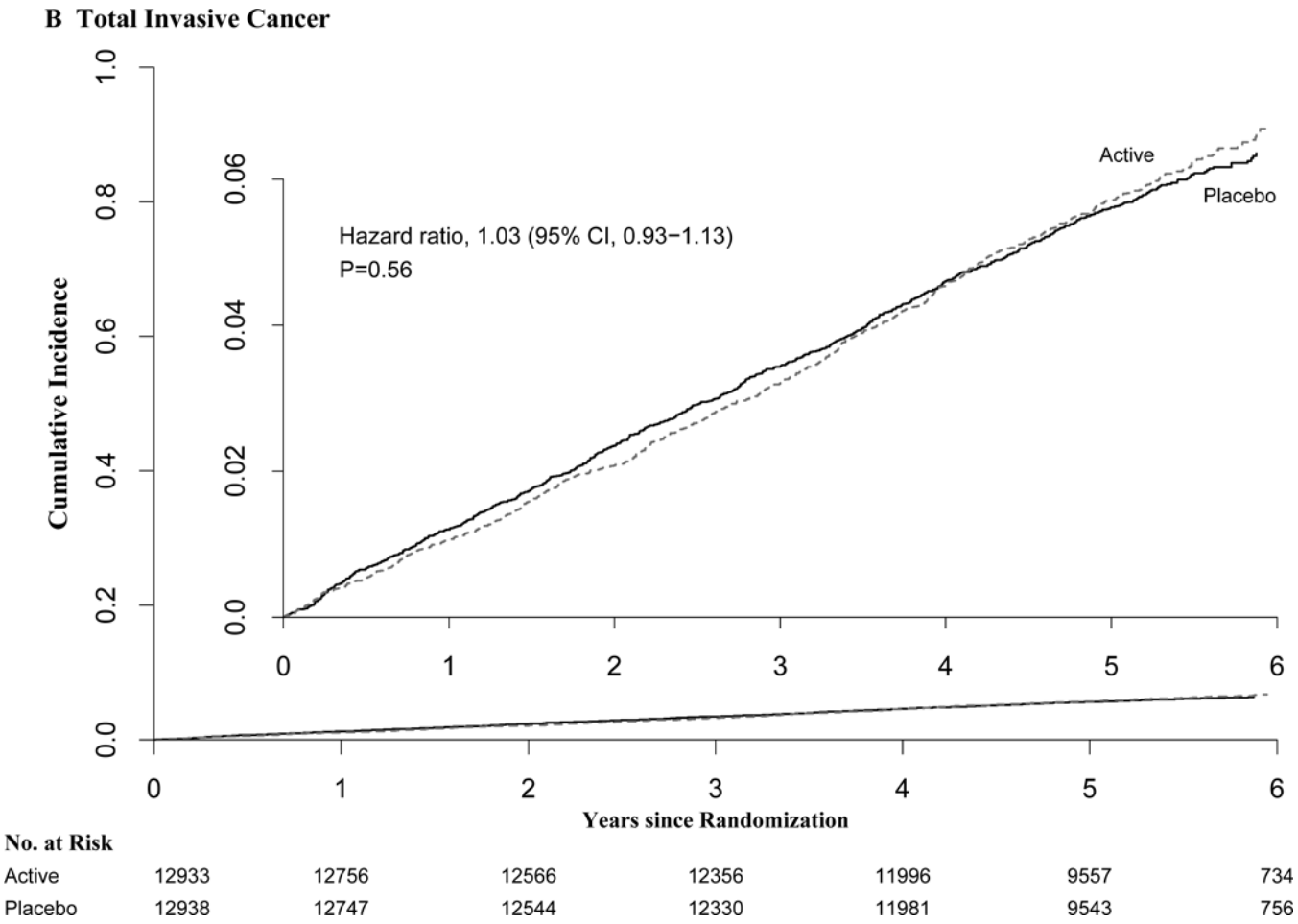
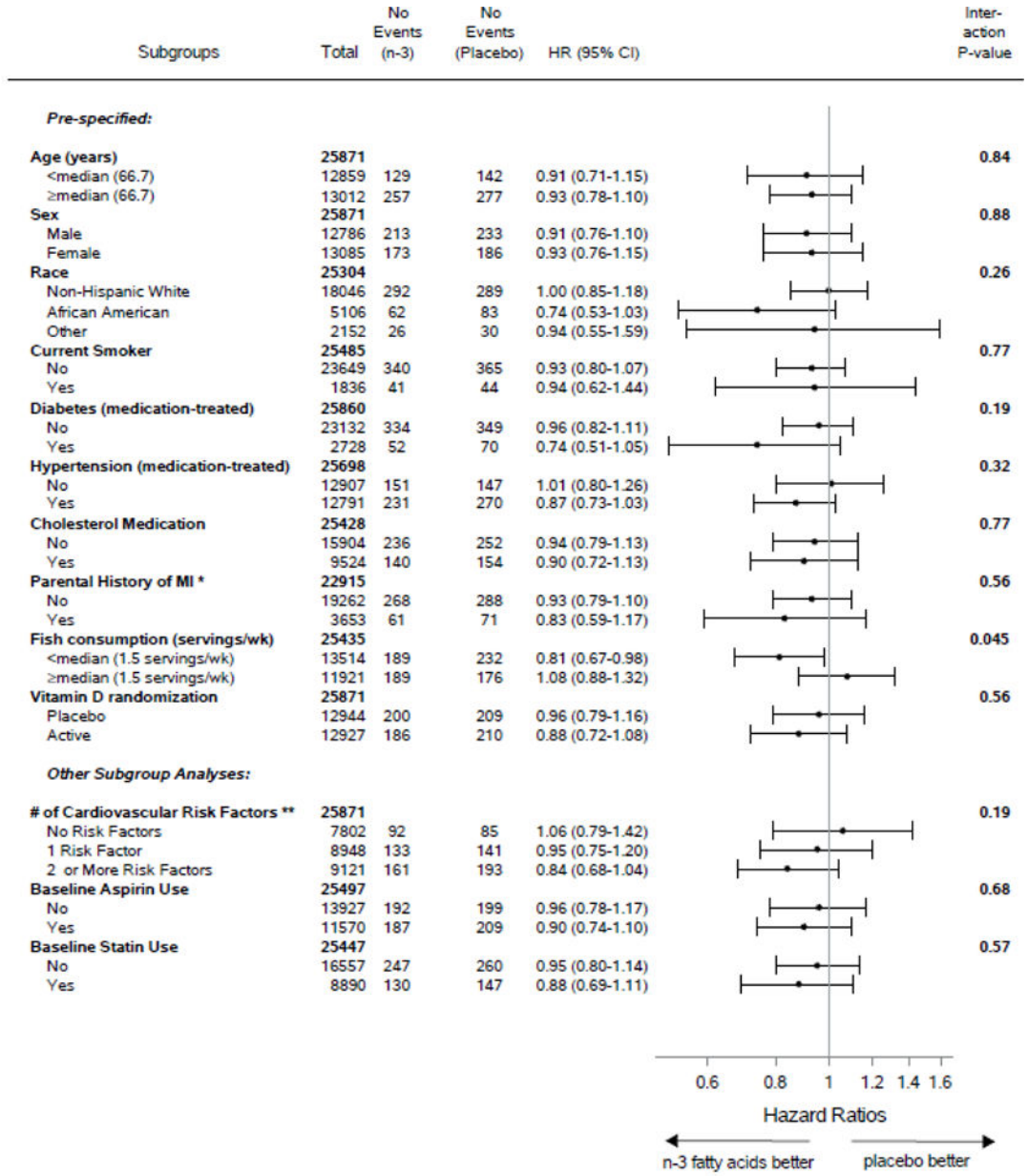



**Figure 1.**

Cumulative Incidence Rates of A) Major Cardiovascular Events, B) Total Invasive Cancer, by Year of Follow-up. From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses).




HR = hazard ratio; CI = confidence interval; MI = myocardial infarction

* Premature MI in a parent (before age 60 in father and before 65 in mother)

** Number of traditional cardiovascular disease risk factors (smoking, diabetes, hypertension high cholesterol, parental history of premature MI)

**Figure 2:**

Hazard Ratios of Major Cardiovascular Events by Subgroups, comparing Omega-3 Fatty Acids (n-3) and Placebo Groups. From Cox regressions models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). Analyses have not been adjusted for multiple comparisons.

**Table 1.**

Baseline Characteristics of the 25,871 VITAL Participants, According to Randomized Assignment to Marine Omega-3 Fatty Acids.[a]

| Baseline Characteristic | All Participants | Treatment Group | |
|---|---|---|---|
| | | Omega-3s | Placebo |
| N | 25,871 | 12,933 | 12,938 |
| Sex, % female | 13085 (50.6) | 6547 (50.6) | 6538 (50.5) |
| Mean age ± SD, years | 67.1 ± 7.1 | 67.2 ± 7.1 | 67.1 ± 7.1 |
| Race/ethnicity, % | | | |
| Non-Hispanic White | 18046 (71.3) | 9044 (71.5) | 9002 (71.2) |
| African American | 5106 (20.2) | 2549 (20.1) | 2557 (20.2) |
| Hispanic (not African American) | 1013 (4.0) | 491 (3.9) | 522 (4.1) |
| Asian/Pacific Islander | 388 (1.5) | 200 (1.6) | 188 (1.5) |
| American Indian/Alaskan Native | 228 (0.9) | 120 (0.9) | 108 (0.9) |
| Other/unknown | 523 (2.1) | 249 (2.0) | 274 (2.2) |
| Mean body mass index ± SD, kg/m$^2$ | 28.1 (5.7) | 28.1 ± 5.7 | 28.1 ± 5.8 |
| Current smoking, % | 1836 ( 7.2) | 920 ( 7.2) | 916 ( 7.2) |
| Hypertension, treated with medication, %, | 12791 (49.8) | 6338 (49.3) | 6453 (50.2) |
| Cholesterol-lowering medication (current use), % | 9524 (37.5) | 4788 (37.7) | 4736 (37.2) |
| Diabetes, % | 3549 (13.7) | 1799 (13.9) | 1750 (13.5) |

[a]Abbreviations: SD = standard deviation. There were no significant differences in the baseline characteristics between the groups.

**Table 2.**

Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Primary, Secondary, and Other Outcomes by Randomized Assignment to Omega-3 (n-3) Fatty Acids in Intention-to-Treat Analyses

| | No. of Events | | | |
|---|---|---|---|---|
| **Outcome** | **n-3 (N = 12,933)** | **Placebo (N = 12,938)** | **HR** | **95% CI** |
| **Cardiovascular disease**, 1° and 2° Outcomes | | | | |
| Major cardiovascular events[a,b] | 386 | 419 | 0.92 | 0.80-1.06 |
| Expanded cardiovascular events[c] | 527 | 567 | 0.93 | 0.82-1.04 |
| Total myocardial infarction | 145 | 200 | 0.72 | 0.59-0.90 |
| Total stroke | 148 | 142 | 1.04 | 0.83-1.31 |
| Cardiovascular mortality | 142 | 148 | 0.96 | 0.76-1.21 |
| **Other vascular outcomes**[d] | | | | |
| Coronary artery bypass graft (CABG) | 85 | 86 | 0.99 | 0.73-1.33 |
| Percutaneous coronary intervention (PCI) | 162 | 208 | 0.78 | 0.63-0.95 |
| Total coronary heart disease[e] | 308 | 370 | 0.83 | 0.71-0.97 |
| Ischemic stroke | 111 | 116 | 0.96 | 0.74-1.24 |
| Hemorrhagic stroke | 25 | 19 | 1.32 | 0.72-2.39 |
| Coronary heart disease death | 37 | 49 | 0.76 | 0.49-1.16 |
| Fatal myocardial infarction | 13 | 26 | 0.50 | 0.26-0.97 |
| Stroke death | 22 | 20 | 1.10 | 0.60-2.01 |
| **Total invasive cancer**[a] | 820 | 797 | 1.03 | 0.93-1.13 |
| Breast | 117 | 129 | 0.90 | 0.70-1.16 |
| Prostate | 219 | 192 | 1.15 | 0.94-1.39 |
| Colorectal | 54 | 44 | 1.23 | 0.83-1.83 |
| Cancer death | 168 | 173 | 0.97 | 0.79-1.20 |
| **All-cause mortality** | 493 | 485 | 1.02 | 0.90-1.15 |
| **Excluding the first two years of follow-up:** | | | | |
| **Major cardiovascular events** | 269 | 301 | 0.89 | 0.76-1.05 |
| Total myocardial infarction | 94 | 131 | 0.72 | 0.55-0.93 |
| **Total invasive cancer** | 536 | 476 | 1.13 | 1.00-1.28 |
| Cancer death | 126 | 135 | 0.93 | 0.73-1.19 |
| **All-cause mortality** | 371 | 381 | 0.97 | 0.84-1.12 |

[a] Primary outcomes

[b] A composite of myocardial infarction, stroke, and cardiovascular mortality

[c] A composite of myocardial infarction, stroke, cardiovascular mortality, and coronary revascularization (CABG, PCI)

[d] Not prespecified as 1° or 2° outcomes.

[e] A composite of myocardial infarction, coronary revascularization (CABG, PCI), and coronary heart disease death.

From Cox regression models controlling for age, sex, and vitamin D randomization group. The 95% CIs have not been adjusted for multiple comparisons.