Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY APPENDIX: DETAILED METHODS, TABLES, AND FIGURES

METHODS (details of study methods, omega-3 component)

Study Design

VITAL was a randomized, double-blind, placebo-controlled, 2x2 factorial trial of the benefits and risks of vitamin D_3 (cholecalciferol, 2000 IU/d) and marine omega-3 fatty acids (1 g/d fish oil capsule [Omacor], containing 840 mg of n-3 FAs 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. Study details are described elsewhere.[1,2] The omega-3 fatty acid dose was chosen because it was recommended by the American Heart Association for cardioprotection[3] and demonstrated to be beneficial and to have minimal side effects in a secondary prevention population.[4] The placebo capsule contained olive oil. Participants were recruited throughout the U.S., balanced by sex, and with a goal to enroll at least 5,000 African Americans. Eligible participants had no history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, transient ischemic attack, or coronary revascularization at enrollment and were required to forgo use of fish-oil supplements and to complete a 3-month placebo run-in phase. Safety exclusions included renal failure or dialysis, cirrhosis, fish allergy, anticoagulant use, or other serious conditions that would preclude participation. 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 took place from November 2011 to March 2014 and was computer generated within sex, race (African American vs. not) and 5-year age groups in blocks of eight. All participants provided written informed consent. Study pill-taking ended as planned on December 31, 2017, yielding a median treatment period of 5.3 years (range 3.8-6.1 years). The trial was approved by the institutional review board of Partners Health Care-Brigham and Women's Hospital, Boston, and was monitored by an external Data and Safety Monitoring Board.

Baseline questionnaires collected data on risk factors for cardiovascular disease, cancer, and other conditions, and included a food frequency questionnaire that ascertained intake of fish and other foods.

Participants received follow-up questionnaires at 6 months and 1 year after randomization and annually thereafter to assess compliance with randomized treatments, use of nonstudy fish-oil supplements, development of major illnesses, updates on risk factors, and potential side effects of the interventions. Study capsules were mailed to participants with the questionnaires.

Baseline blood samples were collected during the run-in period from all willing individuals, including 16,956 randomized participants. Assays for plasma omega-3 index (EPA+DHA as a percent of total fatty acids[5]) were performed on samples 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 expanded cardiovascular events (major cardiovascular events plus coronary revascularization [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)]) and individual components of major cardiovascular events. Additional cardiovascular events were total coronary heart disease (a composite of myocardial infarction, coronary revascularization, and coronary heart disease death), fatal myocardial infarction, fatal stroke, and stroke subtypes. Secondary cancer endpoints were incident colorectal, breast, and prostate cancers, and total cancer mortality. Participants reporting a relevant endpoint were asked to sign a release for medical records, which were then reviewed by an Endpoints Committee of physicians blinded to treatment assignment to confirm or disconfirm reports. Myocardial infarction and stroke were confirmed using established criteria.[6,7] Coronary revascularization was confirmed by medical record review. Cardiovascular deaths were confirmed by convincing evidence of a cardiovascular event from available sources, including death certificates, hospital records, autopsy reports, and, for non-hospital deaths, observer accounts. Cancer was confirmed with histologic or cytologic data.[8] Analyses include confirmed endpoints only.

For deaths reported by family members, the next-of-kin was asked for permission to obtain medical records and a copy of the death certificate. Alternatively, the latter was obtained from the state vital records bureau. The Endpoints Committee reviewed records to assign cause of death. If records were unavailable (or participants lost to follow-up), the National Death Index (NDI) Plus was searched to obtain an International Classification of Disease-coded cause of death based on death-certificate information. Deaths were defined using all sources.

Statistical Analysis

Treatment-effect analyses compared randomized interventions and were based on the intention-to-treat principle (all randomized participants were analyzed). The trial was designed to have >85% power to detect observed hazard ratios (HR) of 0.80 and 0.85 for the primary cardiovascular and cancer endpoints, respectively.[1] Initial analyses compared baseline characteristics of the study population by randomized treatment assignment using t-tests or chi-square tests as appropriate. Primary analyses compared the main effects of n-3 fatty acids on cardiovascular disease and cancer using Cox proportional hazards models controlling for age, sex, and randomization to vitamin D. Person-time was counted from randomization to the endpoint, to death, or to end of the trial on December 31, 2017. Cumulative incidence plots and interactions with time examined whether treatment effects varied over time. Prespecified analyses excluding events occurring during the first year and first two years of follow-up explored latent treatment effects. Compliance effects were estimated by censoring follow-up when participants stopped taking study capsules and/or began taking outside fish-oil supplements.

Possible variations in treatment effect by age, sex, concurrent randomization to vitamin D, baseline cardiovascular risk factors, and baseline fish intake and plasma omega-3 (EPA+DHA) index were specified *a priori*. Because vitamin D was also studied, treatment effects in racial/ethnic groups were of interest. We additionally collected information on aspirin and statin use as stratification variables. There was no control for multiple hypothesis testing, with no formal adjustment to the P values or confidence intervals. Thus, results for

secondary and exploratory outcomes, and for subgroups, should be interpreted with caution. Finally, potential side effects, including gastrointestinal symptoms and bleeding risks, in the randomized groups were compared.

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Table S1. Baseline Characteristics of the 25,871 Participants, According to Randomized Assignment to Marine Omega-3 Fatty Acids[a]

Baseline Characteristic	All Participants	Omega-3 Fatty Acids	
		Active	Placebo
N	25,871	12,933	12,938
Sex, % female	13,085 (50.6)	6,547 (50.6)	6,538 (50.5)
Mean age ± SD, years	67.1 ± 7.1	67.2 ± 7.1	67.1 ± 7.1
Age group, years, %			
50-54	977 (3.8)	488 (3.8)	489 (3.8)
55-64	8,871 (34.3)	4,431 (34.3)	4,440 (34.3)
65-74	12,705 (49.1)	6,352 (49.1)	6,353 (49.1)
≥75	3,318 (12.8)	1,662 (12.9)	1,656 (12.8)
Race/ethnicity, %			
Non-Hispanic White	18,046/25,304 (71.3)	9,044/12,653 (71.5)	9,002/12,651 (71.2)
African American	5,106/25,304 (20.2)	2,549/12,653 (20.1)	2,557/12,651 (20.2)
Hispanic (not African American)	1,013/25,304 (4.0)	491/12,653 (3.9)	522/12,651 (4.1)
Asian/Pacific Islander	388/25,304 (1.5)	200/12,653 (1.6)	188/12,651 (1.5)
Native American or Alaskan Native	228/25,304 (0.9)	120/12,653 (0.9)	108/12,651 (0.9)
Other	523/25,304 (2.1)	249/12,653 (2.0)	274/12,651 (2.2)
Mean body mass index ± SD, kg/m^2	28.1 ± 5.7	28.1 ± 5.7	28.1 ± 5.8
Hypertension, treated with medication, %,	12,791/25,698 (49.8)	6,338/12,853 (49.3)	6,453/12,845 (50.2)
Cholesterol-lowering medication (current use), %	9,524/25,428 (37.5)	4,788/12,707 (37.7)	4,736/12,721 (37.2)
Diabetes, %	3,549/25,828 (13.7)	1,799/12,912 (13.9)	1,750/12,916 (13.5)
Current smoking, %	1,836/2,5485 (7.2)	920/12,739 (7.2)	916/12,746 (7.2)
Any alcohol use, %[b]	17,443/25,437 (68.6)	8,759/12,728 (68.8)	8,684/12,709 (68.3)
Current regular aspirin use, %b	11,570/25,497 (45.4)	5,771/12,745 (45.3)	5,799/12,752 (45.5)
Current postmenopausal	1,483/12,811 (11.6)	735/6,400 (11.5)	748/6,411 (11.7)

hormone use, % (women only)			
Current use of multivitamins, %	11,406/25,439 (44.8)	5,661/12,726 (44.5)	5,745/12,713 (45.2)
Intake of foods related to omega-3 fatty acids, mean ± SD			
Dark-meat fish, servings/week	1.05 ± 1.84	1.05 ± 1.93	1.04 ± 1.76
Other fish and seafood, servings/week	1.11 ± 2.32	1.11 ± 2.36	1.11 ± 2.29
Plasma EPA, %, median [IQR][c]	0.50 [0.40-0.70]	0.50 [0.40-0.70]	0.50 [0.40-0.70]
Plasma DHA, %, median [IQR][c]	1.90 [1.50-2.40]	1.90 [1.50-2.40]	1.90 [1.50-2.40]

[a]Abbreviations: SD = standard deviation; BMI = body mass index; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; IQR = interquartile range.
[b]At least monthly.
[c]N = 15,527 with measured values for EPA and 15,534 for DHA.
For body mass index, data were missing for 2.4% of the participants. For dietary factors, data were missing for 1.7% to 2.7% of participants.
There were no significant differences in the baseline characteristics between the groups.

Table S2. Participant-Reported Adherence with the Omega-3 and Placebo Study Capsules (percent of capsules taken) at Time Points over 5 Years.

A. Among those answering the compliance question by questionnaire:

		Omega-3		Placebo	
Time	N	Mean	(SD)	Mean	(SD)
6 Months	24108	92.4	(16.8)	92.5	(16.4)
1 Year	24211	89.7	(21.0)	90.2	(20.1)
2 Years	23432	87.0	(25.5)	87.6	(24.7)
3 Years	22630	86.3	(26.9)	86.4	(26.4)
4 Years	21217	86.4	(26.7)	86.5	(26.4)
5 Years	13962	85.7	(27.9)	86.2	(27.0)

B. Including nonrespondents to questionnaires and assuming noncompliance among all nonrespondents:

		Omega-3		Placebo	
Time	N	Mean	(SD)	Mean	(SD)
6 Months	25830	87.8	(25.9)	87.8	(25.8)
1 Year	25751	86.3	(26.9)	86.6	(26.4)
2 Years	25576	82.7	(31.2)	82.9	(31.1)
3 Years	25373	81.2	(33.0)	81.2	(32.8)
4 Years	24616	79.0	(35.2)	79.4	(34.7)
5 Years	16920	75.8	(37.9)	75.7	(37.9)

Additional Details on Subgroup Analyses

In subgroup analyses, baseline dietary fish intake modified the n-3 intervention effect on major cardiovascular events (Fig. 2) and total myocardial infarction (Supplementary Appendix Fig. S3), with nominally significant reductions of 19% and 40%, respectively, in participants with below-median intake (<1.5 servings per week) but no reductions in those with higher intake (nominal p-interaction<0.05 for both). The HR for myocardial infarction among those who ate fish less than once per month was 0.43 (0.21-0.91). For major cardiovascular events, no other significant interactions were observed. For myocardial infarction, however, race/ethnicity also modified the treatment effect, with a 77% reduction among African Americans (HR=0.23 [0.11-0.47]) and smaller reductions in other racial/ethnic groups (nominal p-interaction by race=0.001) (Fig. S3). African Americans also had reductions in coronary revascularization (HR=0.51 [0.28-0.92]) and total coronary heart disease (HR=0.47 [0.29-0.75]) with n-3 fatty acids. For myocardial infarction, treatment-associated reductions were also observed in participants with comorbidities and a larger number of traditional risk factors (nominal p-interaction=0.047) (Fig. S3). Treatment-associated benefits were more apparent in African Americans than in non-Hispanic whites across all cardiovascular risk factor strata, including among those with diabetes (HR=0.06 [0.01-0.49] in African Americans vs. HR=0.88 [0.43-1.80] in non-Hispanic whites, nominal p-interaction=0.018) (Supplementary Appendix, Table S3). For major cardiovascular events, treatment-associated reductions were greater in those with low baseline fish intake in both racial/ethnic groups (Table S4). For myocardial infarction, treatment-associated reductions among African Americans were observed irrespective of baseline fish intake, but non-Hispanic whites benefited from supplementation only if fish consumption was low (Table S4). The plasma omega-3 index did not significantly modify the intervention's effects. Analyses that censored for nonadherence did not materially change results (HR=0.91 [0.78-1.07] for major cardiovascular events and HR=0.74 [0.58-0.95] for myocardial infarction in the overall cohort).

Table S3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Major Cardiovascular Events and Total Myocardial Infarction According to Diabetes Status and Number of Cardiovascular Risk Factors at Baseline, Comparing Omega-3 Fatty Acids (n-3) and Placebo in Racial/Ethnic Groups

		Major Cardiovascular Events				Total Myocardial Infarction			
		No. of Events			Interaction P-value	No. of Events			Interaction P-value
Participants with Diabetes[a]	**Total**	**n-3**	**Placebo**	**HR (95%CI)**		**n-3**	**Placebo**	**HR (95%CI)**	
Race	**2387**				**0.17**				**0.018**
Non-Hispanic Whites	1449	33	32	1.04 (0.64-1.69)		14	16	0.88 (0.43-1.80)	
African Americans	938	17	27	0.60 (0.33-1.11)		1	15	0.06 (0.01-0.49)	
Total Number of CVD Risk Factors[b]									
Non-Hispanic Whites	**18046**				**0.88**				**0.82**
No Risk Factors	5896	70	70	0.97 (0.69-1.35)		34	35	0.95 (0.59-1.53)	
1 Risk Factor	6177	105	102	1.01 (0.77-1.33)		48	50	0.93 (0.63-1.39)	
2 or More Risk Factors	5973	117	117	1.01 (0.78-1.30)		44	50	0.89 (0.59-1.33)	
African Americans	**5106**				**0.94**				**0.17**
No Risk Factors	1054	7	11	0.62 (0.24-1.59)		2	3	0.65 (0.11-3.89)	
1 Risk Factor	1857	20	25	0.83 (0.46-1.50)		3	11	0.28 (0.08-0.99)	
2 or More Risk Factors	2195	35	47	0.72 (0.47-1.12)		4	25	0.16 (0.05-0.45)	

[a]Reported diabetes treated with medication.
[b]Number of traditional cardiovascular disease risk factors (smoking, diabetes, hypertension, high cholesterol, parental history of premature myocardial infarction).
From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses).
Analyses have not been adjusted for multiple comparisons.

Table S4. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Major Outcomes According to Baseline Fish Intake and Race/Ethnicity, Comparing Omega-3 Fatty Acids (n-3) and Placebo Groups

		Major Cardiovascular Events				Total Myocardial Infarction			
		No. of Events				No. of Events			
Total Fish Consumption (servings/week)	**Total N**	**n-3**	**Placebo**	**HR (95%CI)**	**Interaction P-value**	**n-3**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
Total Cohort	**25435**				**0.045**				**0.048**
<median (1.5 servings/wk)	13514	189	232	0.81 (0.67-0.98)		74	121	0.60 (0.45-0.81)	
≥median (1.5 servings/wk)	11921	189	176	1.08 (0.88-1.32)		67	72	0.94 (0.67-1.31)	
Non-Hispanic Whites	17851				0.043				0.016
<median (1.5 servings/wk)	9618	146	168	0.86 (0.69-1.07)		64	88	0.71 (0.51-0.98)	
≥median (1.5 servings/wk)	8233	141	116	1.21 (0.95-1.55)		59	45	1.32 (0.90-1.95)	
African Americans	4939				0.23				0.92
<median (1.5 servings/wk)	2461	26	42	0.61 (0.37-0.99)		5	21	0.23 (0.09-0.62)	
≥median (1.5 servings/wk)	2478	33	36	0.92 (0.57-1.48)		3	14	0.21 (0.06-0.74)	

		Total Invasive Cancer				Total Mortality			
		No. of Events				No. of Events			
Total Fish Consumption (servings/week)	**Total N**	**n-3**	**Placebo**	**HR (95%CI)**	**Interaction P-value**	**n-3**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
Total Cohort	**25435**				**0.094**				**0.017**
<median (1.5 servings/wk)	13514	421	435	0.96 (0.84-1.09)		237	271	0.87 (0.73-1.04)	
≥median (1.5 servings/wk)	11921	386	346	1.13 (0.98-1.31)		240	202	1.19 (0.99-1.44)	
Non-Hispanic Whites	17851				0.095				0.031
<median (1.5 servings/wk)	9618	331	347	0.94 (0.80-1.09)		175	187	0.93 (0.76-1.14)	
≥median (1.5 servings/wk)	8233	299	266	1.13 (0.96-1.34)		167	127	1.30 (1.04-1.64)	
African Americans	4939				0.55				0.104
<median (1.5 servings/wk)	2461	55	58	0.94 (0.65-1.36)		37	57	0.64 (0.42-0.96)	
≥median (1.5 servings/wk)	2478	53	48	1.10 (0.75-1.63)		53	52	1.02 (0.70-1.50)	

From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). Analyses have not been adjusted for multiple comparisons.

Table S5. Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Total Invasive Cancer Comparing Active Omega-3 Fatty Acids (n-3) and Placebo Groups, According to Baseline Characteristics

		Total Invasive Cancer			
		No. of Events			
Subgroup Category	**Total**	**n-3**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
Pre-specified					
Age	**25871**				**0.50**
<median (66.7 years)	12859	323	301	1.07 (0.92-1.25)	
≥median (66.7 years)	13012	497	496	1.00 (0.89-1.14)	
Sex	**25871**				**0.024**
Male	12786	498	442	1.13 (1.00-1.29)	
Female	13085	322	355	0.90 (0.78-1.05)	
Race	**25304**				**0.86**
Non-Hispanic White	18046	637	621	1.02 (0.91-1.13)	
African American	5106	113	111	1.02 (0.79-1.33)	
Other	2152	54	51	1.13 (0.77-1.66)	
Current Smoker	**25485**				**0.79**
No	23649	740	705	1.05 (0.95-1.16)	
Yes	1836	73	75	1.01 (0.73-1.39)	
Total Fish Intake	**25435**				**0.09**
<median (1.5 servings/wk)	13514	421	435	0.96 (0.84-1.09)	
≥median (1.5 servings/wk)	11921	386	346	1.13 (0.98-1.31)	
Vitamin D randomization	**25871**				**0.56**
Placebo group	12944	412	412	1.00 (0.87-1.15)	
Active group	12927	408	385	1.06 (0.92-1.22)	
Other Subgroup Analyses					
Baseline Aspirin Use	**25497**				**0.50**
No	13927	432	424	1.01 (0.88-1.16)	
Yes	11570	378	352	1.08 (0.94-1.25)	
Baseline Statin Use	**25447**				**0.63**
No	16557	494	483	1.03 (0.91-1.17)	
Yes	8890	318	293	1.08 (0.92-1.27)	

From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). Analyses have not been adjusted for multiple comparisons.

Table S6. Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Total Mortality Comparing Active Omega-3 Fatty Acids (n-3) and Placebo Groups, According to Baseline Characteristics

		Total Mortality			
		No. of Events			
Subgroup Category	**Total**	**n-3**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
Pre-specified					
Age	**25871**				**0.93**
<median (66.7 years)	12859	163	158	1.03 (0.83-1.28)	
≥median (66.7 years)	13012	330	327	1.01 (0.87-1.18)	
Sex	**25871**				**0.15**
Male	12786	283	256	1.11 (0.93-1.31)	
Female	13085	210	229	0.92 (0.76-1.11)	
Race	**25304**				**0.26**
Non-Hispanic White	18046	351	320	1.09 (0.93-1.26)	
African American	5106	97	114	0.84 (0.64-1.11)	
Other	2152	37	38	1.08 (0.69-1.70)	
Current Smoker	**25485**				**0.093**
No	23649	400	406	0.98 (0.85-1.13)	
Yes	1836	84	69	1.28 (0.93-1.76)	
Diabetes (medication-treated)	**25860**				**0.29**
No	23132	413	394	1.05 (0.91-1.20)	
Yes	2728	80	91	0.87 (0.65-1.18)	
Hypertension (medication-treated)	**25698**				**0.55**
No	12907	190	175	1.06 (0.87-1.30)	
Yes	12791	293	304	0.98 (0.84-1.15)	
High Cholesterol (medication-treated)	**25428**				**0.69**
No	15904	304	293	1.05 (0.89-1.23)	
Yes	9524	173	174	0.99 (0.80-1.22)	
Parental History of Myocardial Infarction[a]	**22915**				**0.53**
No	19262	337	327	1.03 (0.89-1.20)	
Yes	3653	76	80	0.92 (0.67-1.26)	
Total Fish Intake	**25435**				**0.017**
<median (1.5 servings/wk)	13514	237	271	0.87 (0.73-1.04)	
≥median (1.5 servings/wk)	11921	240	202	1.19 (0.99-1.44)	
Vitamin D randomization	**25871**				**0.65**
Placebo group	12944	252	241	1.05 (0.88-1.25)	
Active group	12927	241	244	0.99 (0.83-1.18)	
Other Subgroup Analyses					
# of Cardiovascular Risk Factors[b]	**25871**				**0.55**
No risk factors	7802	114	92	1.21 (0.92-1.59)	
1 risk factor	8948	162	181	0.90 (0.73-1.11)	
2 or more risk factors	9121	217	212	1.03 (0.86-1.25)	
Baseline Aspirin Use	**25497**				**0.58**
No	13927	255	253	1.00 (0.84-1.19)	
Yes	11570	228	215	1.07 (0.89-1.29)	
Baseline Statin Use	**25447**				**0.66**
No	16557	316	304	1.05 (0.89-1.22)	
Yes	8890	161	163	0.98 (0.79-1.22)	

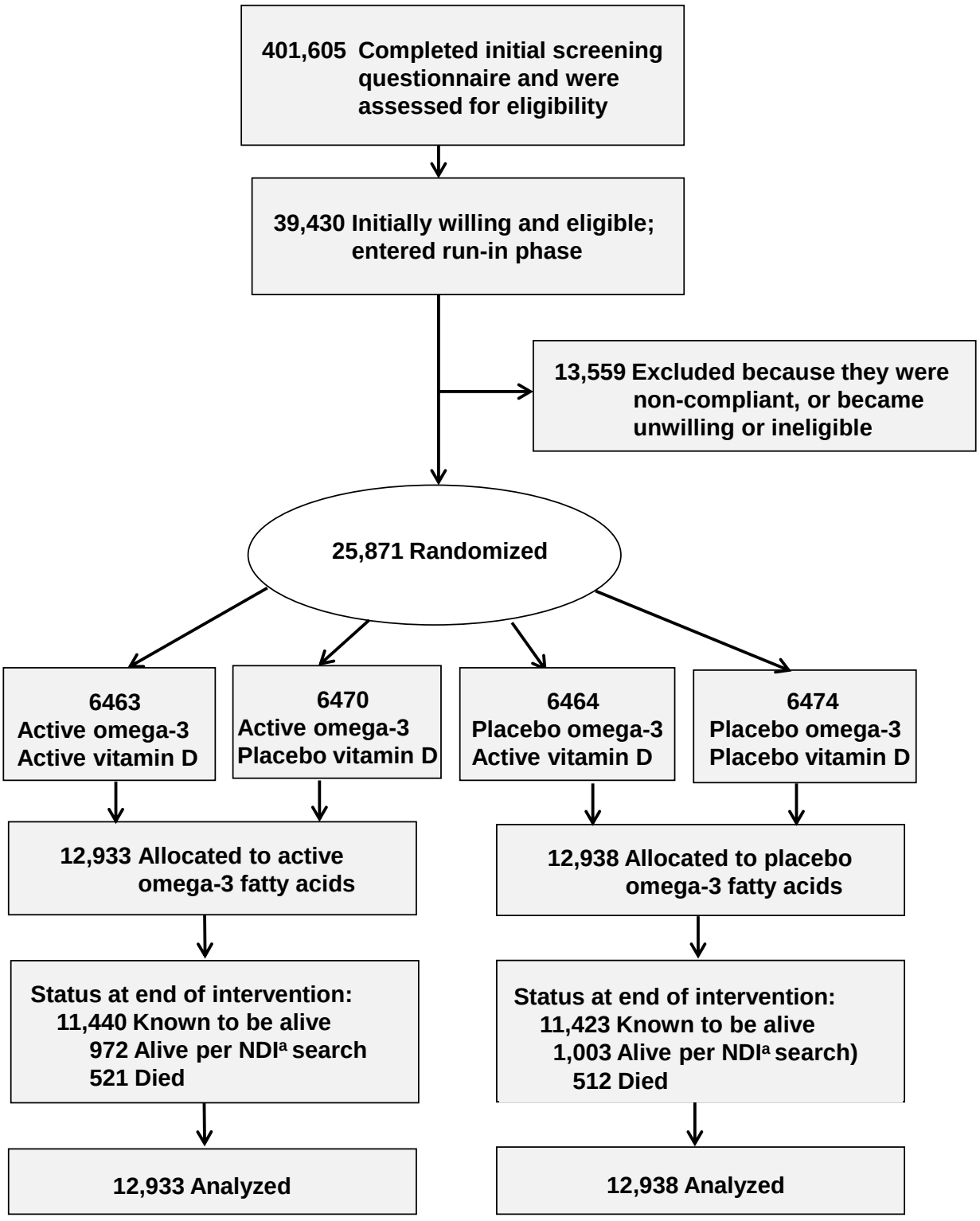
[a]Premature myocardial infarction in a parent (before age 60 in father and before age 65 in mother).
[b]Number of traditional cardiovascular disease risk factors (smoking, diabetes, hypertension, high cholesterol, parental history of premature myocardial infarction).
From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). Analyses have not been adjusted for multiple comparisons.

Table S7. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Safety and Adverse Events by Randomized Assignment to Omega-3 Fatty Acids (n-3) compared to Placebo

	No. of Events				
Outcome	**n-3 (N = 12,933)**	**Placebo (N = 12,938)**	**HR**	**95% CI**	**P-value**
Monitored safety conditions					
Gastrointestinal bleeding	370	374	0.99	0.86-1.14	0.89
Blood in urine	919	874	1.06	0.96-1.16	0.25
Easy bruising	3443	3399	1.02	0.97-1.07	0.48
Frequent nosebleeds	465	491	0.95	0.83-1.07	0.40
Kidney failure or dialysis	85	88	0.97	0.72-1.30	0.82
Other symptoms and side effects					
Stomach upset or pain	4887	4843	1.01	0.97-1.05	0.72
Nausea	3558	3550	1.00	0.96-1.05	0.94
Constipation	5184	5111	1.01	0.97-1.05	0.51
Diarrhea	5599	5580	1.00	0.97-1.04	0.77
Skin rash	3331	3367	0.99	0.94-1.03	0.58
Bad taste in mouth	2240	2245	1.00	0.95-1.06	0.92
Increased burping	2217	2158	1.03	0.97-1.10	0.29

From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). Analyses have not been adjusted for multiple comparisons.

Figure S1. Flow Diagram of Enrollment in the Omega-3 Fatty Acid Component of the Trial



[a]National Death Index

Figure S2. Cumulative Incidence Rates of A) Expanded Cardiovascular Events, B) Total Myocardial Infarction, C) Total Stroke, and D) Cardiovascular Mortality, By Year of Follow-up. From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). The insets show the data on an enlarged y axis.

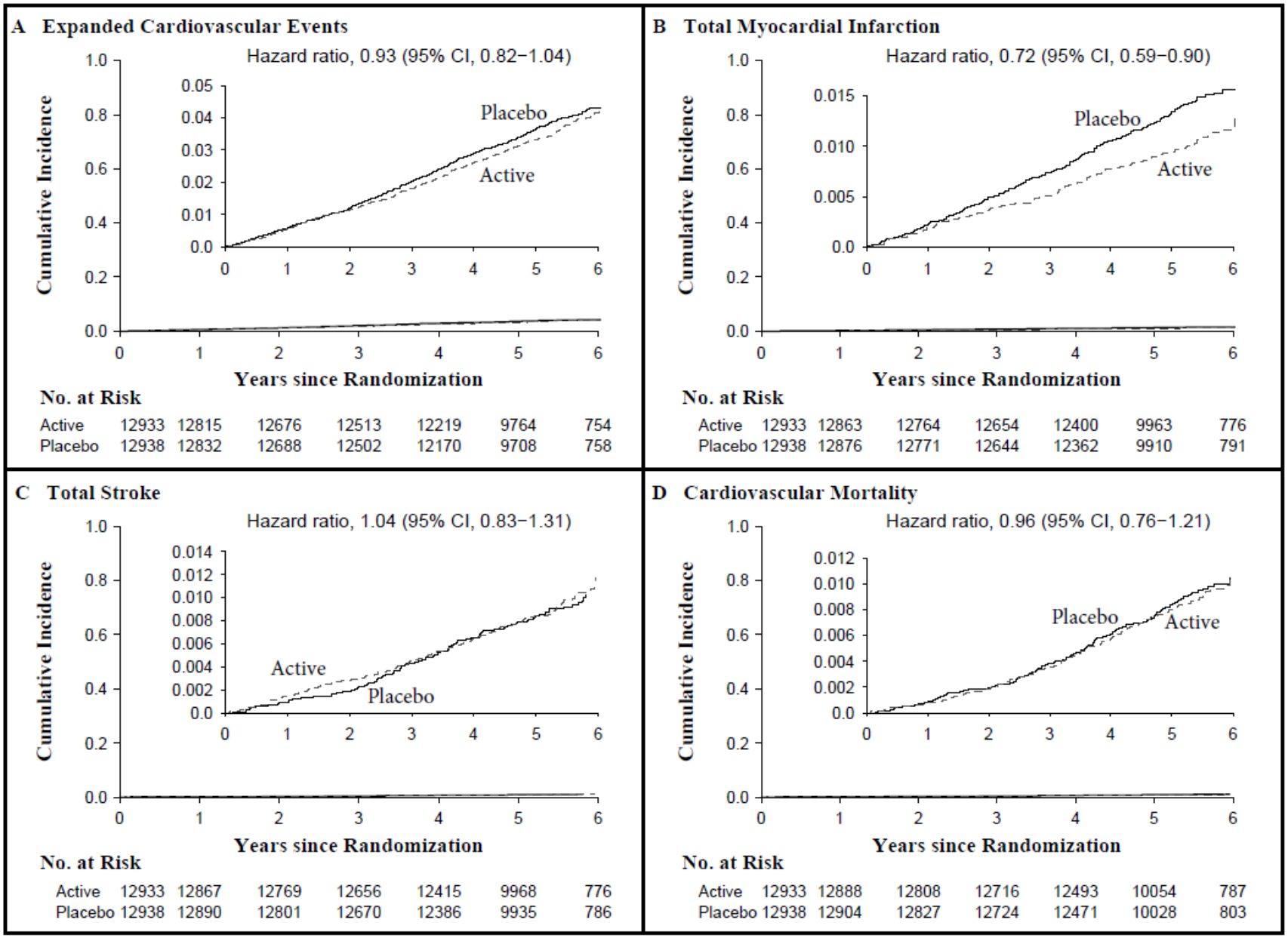
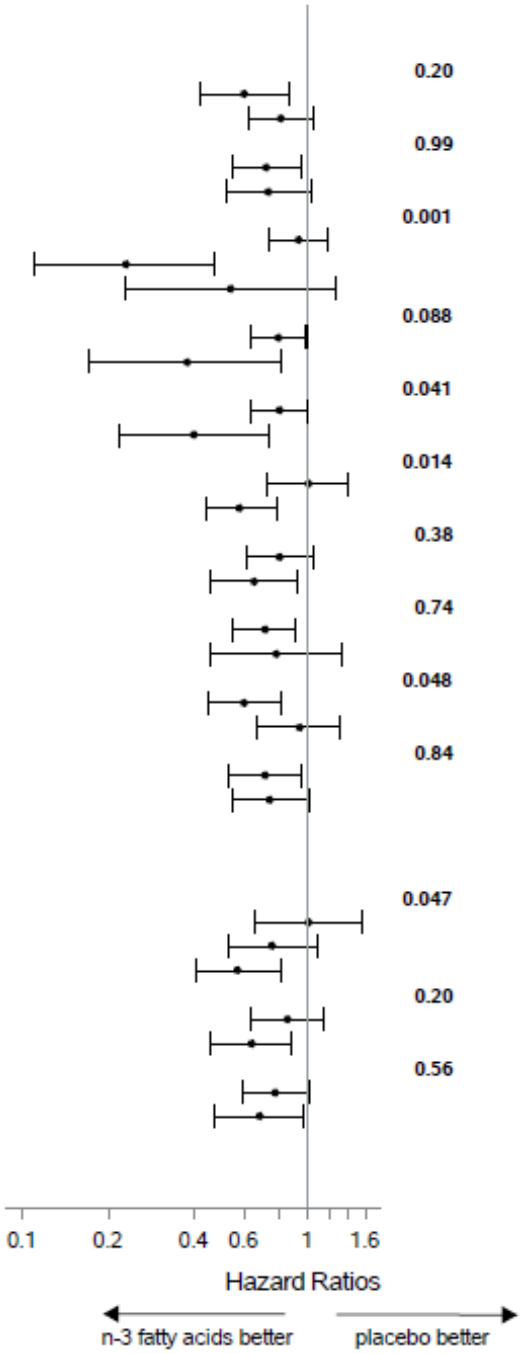


Figure S3. Hazard Ratios of Total Myocardial Infarction by Subgroups, Comparing Omega-3 Fatty Acids (n-3) and Placebo Groups. From Cox Regression Models Controlling for Age, Sex, and Vitamin D Randomization group (intention-to-treat analyses). Analyses were not adjusted for multiple comparisons.

Subgroups	Total	No Events (n-3)	No Events (Placebo)	HR (95% CI)	Inter-action P-value
Pre-specified:					
Age (years)	**25871**				**0.20**
<median (66.7)	12859	49	81	0.60 (0.42-0.86)	
≥median (66.7)	13012	96	119	0.81 (0.62-1.06)	
Sex	**25871**				**0.99**
Male	12786	89	123	0.72 (0.55-0.95)	
Female	13085	56	77	0.73 (0.52-1.03)	
Race	**25304**				**0.001**
Non-Hispanic White	18046	126	135	0.93 (0.73-1.18)	
African American	5106	9	39	0.23 (0.11-0.47)	
Other	2152	8	16	0.54 (0.23-1.26)	
Current Smoker	**25485**				**0.088**
No	23649	136	172	0.79 (0.63-0.99)	
Yes	1836	9	24	0.38 (0.17-0.81)	
Diabetes (medication-treated)	**25860**				**0.041**
No	23132	130	163	0.80 (0.63-1.00)	
Yes	2728	15	37	0.40 (0.22-0.74)	
Hypertension (medication-treated)	**25698**				**0.014**
No	12907	71	69	1.01 (0.72-1.40)	
Yes	12791	74	129	0.58 (0.44-0.78)	
Cholesterol Medication	**25428**				**0.38**
No	15904	94	118	0.80 (0.61-1.05)	
Yes	9524	50	76	0.65 (0.46-0.93)	
Parental History of MI *	**22915**				**0.74**
No	19262	101	143	0.71 (0.55-0.91)	
Yes	3653	25	31	0.78 (0.46-1.32)	
Fish consumption (servings/wk)	**25435**				**0.048**
<median (1.5 servings/wk)	13514	74	121	0.60 (0.45-0.81)	
≥median (1.5 servings/wk)	11921	67	72	0.94 (0.67-1.31)	
Vitamin D randomization	**25871**				**0.84**
Placebo	12944	73	103	0.71 (0.53-0.96)	
Active	12927	72	97	0.74 (0.55-1.01)	
Other Subgroup Analyses:					
# of Cardiovascular Risk Factors **	**25871**				**0.047**
No Risk Factors	7802	41	40	1.01 (0.65-1.56)	
1 Risk Factor	8948	53	70	0.75 (0.53-1.08)	
2 or More Risk Factors	9121	51	90	0.57 (0.41-0.81)	
Baseline Aspirin Use	**25497**				**0.20**
No	13927	82	96	0.85 (0.63-1.14)	
Yes	11570	62	98	0.64 (0.46-0.88)	
Baseline Statin Use	**25447**				**0.56**
No	16557	95	123	0.77 (0.59-1.01)	
Yes	8890	49	72	0.68 (0.47-0.97)	



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)