Supplemental Table 1. Selected studies linking total mortality with n-3 PUFAs (from dietary records, supplementation use, randomized trials or circulating biomarkers).

	N	Patient Type	Years Follow-up	Results
Dietary Data				
Bell(1)	70,495	Vitamins and Lifestyle Study, USA	5	Reduced total (and cancer) mortality associated with higher LC n-3PUFA intake
Yamagishi(2)	57,972	Healthy Japanese	12.7	Trend (p=0.1) for lower mortality with higher LC n-PUFA intakes (1.0 to 2.3 g/d)
Yuan(3)	18,224	Healthy Chinese men	12	Fish intake inversely associated with mortality
Folsom(4)	41,836	Iowa Women's Study	14	No associations with mortality across n-3 FA intake of 20 to 470 mg/d
Engeset(5)	480,535	European Prospective Investigation into Cancer and Nutrition (EPIC)	11-18	No associations between fish intake and total mortality
Sala-Vila(6)	7202	PREDIMED Cohort	5.9	Patients meeting intake recommendation for ALA had reduced total mortality, with greatest reduction in those meeting recommendations for ALA and EPA+DHA
Fish Oil Use – Non-randomized trials				
Poole(7)	12,178	Immediately Post-MI Prescribed FOS or not	2.6	Prescription of FOS associated with reduced total mortality
Patel(8)	3827	Hyperlipidemic patients prescribed statins with or without ezetimibe	3	Only predictors of reduced mortality were higher HDL-C and reported use of fish oil supplements
Macchia(9)	11,532	Post MI patients taking statins with or without fish oil	4	Significant reduction in mortality in those on combination therapy
Fish Oil Use – Randomized trials				
Rizos(10)	63,279	Meta-analysis of 17 trials with fish oils	2.65 (mean)	No reduction in total mortality with fish oil use [HR = 0.96 (95% CI, 0.91-1.02)]
Casula(11)	15,384	Meta-analysis of 11 secondary prevention trials giving at least 1 g n-3 FA for at least 1 year	2.0 (mean)	No reduction in total mortality with fish oil use [HR = 0.89 (95% CI, 0.78-1.02)] but significant reductions in cardiac and sudden death and myocardial infarction
Biomarker				
Wu(12) Plasma phospholipids (PL)	2792	Generally healthy elderly (mean age 74 at baseline)	11.5	Higher plasma PL LA associated with lower risk for total (and CVD) mortality. Higher levels of total n-6 and n-3 associated with the lowest total mortality risk
Warensjo(13) Plasma cholesteryl esters (CE)	279 cases 279 controls	Population-based cohort	12.5	Only PUFA associated with total mortality was LA (inversely)
Laaksonen(14) Plasma	1551	Population-based cohort of men	15	Serum LA associated with lower total mortality; data for EPA/DHA not reported
Mozaffarian(15) Plasma PL	2692	Generally healthy elderly (mean age 74 at baseline)	11.5	Higher plasma PL LC n-3 PUFA associated with lower total and CVD mortality
Lindberg(16) Plasma PL	254	Elderly admitted for acute illness	3	Higher plasma PL EPA (not DHA) associated with reduced mortality (Q1 v Q234)
Harris(17) Red Blood Cells (RBC)	1114	Immediately Post-MI	2	Higher EPA associated with lower mortality
Pottala(18) Whole Blood	956	History of CVD	5.6	Reduced mortality associated with higher blood EPA+DHA
Chien(19) Plasma	1833	Healthy Taiwanese	9.6	Plasma EPA inversely associated with total mortality
Marklund(20) Plasma CE	4232	Generally healthy cohort (mean age 60)	14.9	EPA and DHA (and LA) inversely associated with total mortality

Eide(21) Plasma PL	1990	Renal transplant recipients in Norway	6.8	Higher marine n-3 PUFA associated with lower total and CVD mortality
Kleber(22) RBC	3259	Suspected CAD	10	Higher marine n-3 PUFA associated with lower total mortality
Current Study RBC	6501	Generally healthy post-menopausal women (mean age 70)	14.9	Higher Omega-3 Index, EPA and DHA associated with reduced total mortality; EPA also associated with reduced CVD mortality

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Supplementaal Table 2. Participant's baseline characteristics by survival status at last contact and causes of death during 14.9-years median follow up (IQR (12.9-15.9)

	Alive	Dead		Cause of death			
			P value[1]	Cancer	CVD	Others	P value[1]
	4650	1851		462	617	772	
Age at baseline [years]: mean (SD)	69.6 (3.6)	71.5 (4.0)	<0.0001	70.7 (4.0)	72.0 (4.1)	71.7 (3.9)	<0.0001
HT randomization arms: n (%)			0.41				0.06
E-alone intervention	909 (19.6)	367 (19.8)		80 (17.3)	133 (21.6)	154 (20.0)	
E-alone control	892 (19.2)	383 (20.7)		93 (20.1)	147 (23.8)	143 (18.5)	
E+P intervention	1408 (30.3)	559 (30.2)		150 (32.5)	177 (28.7)	232 (30.1)	
E+P control	1441 (31.0)	542 (29.3)		139 (30.1)	160 (25.9)	243 (31.5)	
Race: n (%)			0.0001				0.1
Asian or Pacific Islander	90 (1.9)	27 (2.0)		8 (1.7)	11 (1.8)	8 (1.0)	
Black or African American	328 (7.1)	106 (5.7)		32 (6.9)	43 (7.0)	31 (1.6)	
Hispanic or Latino	120 (2.6)	20 (1.1)		4 (0.9)	4 (0.7)	12 (1.6)	
Non-Hispanic White	4025 (87)	1672 (90.3)		411 (89.0)	552 (89.5)	709 (91.8)	
Other	87 (1.9)	26 (1.4)		7 (1.5)	7 (1.1)	12 (1.6)	
Highest Education: n (%)			0.2				0.2
High School or Less	1373 (29.5)	548 (29.6)		137 (30.0)	176 (28.5)	235 (30.4)	
Some College/Tech School	1848 (39.7)	780 (42.1)		204 (44.2)	277 (44.9)	299 (38.7)	
Bachelor's Degree	832 (17.9)	308 (16.6)		73 (15.8)	89 (14.4)	146 (18.9)	
Master's Degree or Higher	597 (12.8)	215 (11.6)		48 (10.4)	75 (12.2)	92 (12.5)	
Body Mass Index [kg/m^2]: n (%)			0.9				0.1
< 25	1356 (29.2)	559 (30.2)		140 (30.3)	171 (27.7)	248 (32.1)	
[25 – 30)	1730 (37.2)	672 (36.3)		154 (33.3)	231 (37.4)	287 (37.2)	
[30 – 35)	1009 (21.7)	401 (21.7)		112 (24.2)	139 (22.5)	150 (19.4)	
[35 – 40)	392 (8.4)	159 (8.6)		47 (10.2)	53 (8.6)	59 (7.6)	
≥ 40	163 (3.5)	60 (3.2)		9 (2.0)	23 (3.7)	28 (3.6)	
Waist circumference [cm]: mean (SD)	88.0 (13.2)	89.4 (13.5)	0.0002	89.8 (13.5)	90.0 (13.4)	88.7 (13.6)	0.2
Physical activity [METs/wk]: mean (SD)	11.9 (13.5)	10.0 (12.9)	<0.0001	10.2 (12.0)	9.5 (12.0)	10.2 (14.0)	0.5
Alcohol >7 drinks/wk: n (%)	542 (11.7)	244 (13.2)	0.09	74 (16.0)	69 (11.2)	101 (13.1)	0.07
Smoking pack-years: n (%)			<0.0001				0.006
Never smoking	2645 (56.9)	868 (46.9)		180 (39.0)	306 (49.6)	382 (49.5)	
<10	773 (16.6)	273 (14.8)		66 (14.3)	102 (16.5)	105 (13.6)	
[10 – 20)	406 (8.7)	133 (7.2)		35 (7.6)	44 (7.1)	54 (7.0)	
[20 - 30)	288 (6.2)	151 (8.2)		49 (10.6)	41 (6.7)	61 (7.9)	
[30 – 40)	179 (3.9)	82 (4.4)		24 (5.2)	25 (4.1)	33 (4.3)	
≥ 40	359 (7.7)	344 (18.6)		108 (23.4)	99(16.1)	137 (17.8)	
Family history of cancer: n (%)	3004 (64.6)	1169 (63.2)	0.3	313 (67.8)	231 (62.6)	302 (60.9)	0.05
Family history of CVD: n (%)	3222 (69.3)	1302 (70.3)	0.4	315 (68.2)	452 (73.3)	535 (69.3)	0.1
Region of USA			0.2				0.2
Northeast	1265 (27.2)	534 (28.9)		140 (30.3)	172 (27.9)	22 (28.8)	
South	971 (20.9)	379 (20.5)		75 (16.2)	135 (21.9)	169 (21.9)	
Midwest	1154 (24.8)	420 (22.7)		107 (23.2)	131 (21.2)	182 (23.6)	
West	1260 (27.1)	518 (28.0)		140 (30.3)	179 (29.0)	199 (25.8)	
Aspirin use: n (%)	1213 (26.1)	508 (27.4)	0.3	133 (28.8)	183 (29.7)	192 (24.9)	0.1
Taking pills for cholesterol: n (%)	811 (17.4)	346 (18.7)	0.2	76 (16.5)	142 (23.0)	128 (16.6)	0.0034
Hypertension: n (%)	2142 (46.1)	1071 (57.9)	<0.0001	226 (48.9)	410 (66.5)	435 (56.4)	<0.0001
Diabetes: n (%)	228 (4.9)	192 (10.4)	<0.0001	30 (6.5)	89 (14.4)	73 (9.5)	<0.0001
Cardiovascular disease: n (%)	677 (14.6)	446 (24.1)	<0.0001	90 (19.5)	194 (31.4)	162 (21.0)	<0.0001
History of Cancer: n (%)	147 (3.2)	87 (4.7)	0.0034	25 (5.4)	29 (4.7)	33 (4.3)	0.7

[1] A Chi-squared test was used to evaluate differences for categorical variables, and a t-test or one-way ANOVA was used for continuous variables.

Supplemental Table 3. Sensitivity Analyses for Associations of RBC PUFA and Total Mortality: Multivariable-adjusted hazard ratios (99% CI) per 1-SD in the fully-adjusted model[a]

	Excluding death in first two years	*Excluding CVD/cancer at baseline*	*Stratified by ASA use at baseline[b]*	
	(n=6436)	(n=5144)	No (n=4780)	Yes (n=1721)
Omega-3 index (EPA+DHA)	**0.91 (0.85, 0.98)**	**0.91 (0.84, 0.99)**	**0.9 (0.83, 0.99)**	0.96 (0.83, 1.1)
Eicosapentaenoic (EPA)	**0.89 (0.82, 0.96)**	**0.88 (0.8, 0.97)**	**0.88 (0.8, 0.95)**	0.92 (0.79, 1.06)
Docosahexaenoic (DHA)	**0.93 (0.86, 1)**	0.93 (0.85, 1.01)	0.92 (0.84, 1.01)	0.97 (0.84, 1.11)
Linoleic Acid (LA)	0.99 (0.92, 1.06)	1.01 (0.93, 1.1)	1 (0.92, 1.08)	0.99 (0.87, 1.12)
PUFA Factor Score[c]	**0.77 (0.65, 0.91)**	**0.78 (0.63, 0.96)**	**0.75 (0.61, 0.91)**	0.85 (0.64, 1.13)
Alpha linolenic (ALA)	0.97 (0.9, 1.05)	1 (0.91, 1.09)	0.97 (0.88, 1.07)	1 (0.86, 1.15)
Docosapentaenoic n-3 (DPAn-3)	0.93 (0.86, 1.01)	0.93 (0.85, 1.02)	0.92 (0.84, 1)	0.96 (0.84, 1.11)
Arachidonic (ARA)	1 (0.92, 1.09)	1.01 (0.91, 1.12)	0.99 (0.89, 1.1)	1.02 (0.85, 1.22)
ARA/EPA ratio	**1.12 (1.03, 1.22)**	**1.13 (1.03, 1.25)**	**1.13 (1.03, 1.24)**	1.09 (0.93, 1.28)
N-6/N-3 ratio	**1.1 (1.02, 1.2)**	**1.12 (1.02, 1.22)**	**1.12 (1.01, 1.24)**	1.06 (0.92, 1.22)

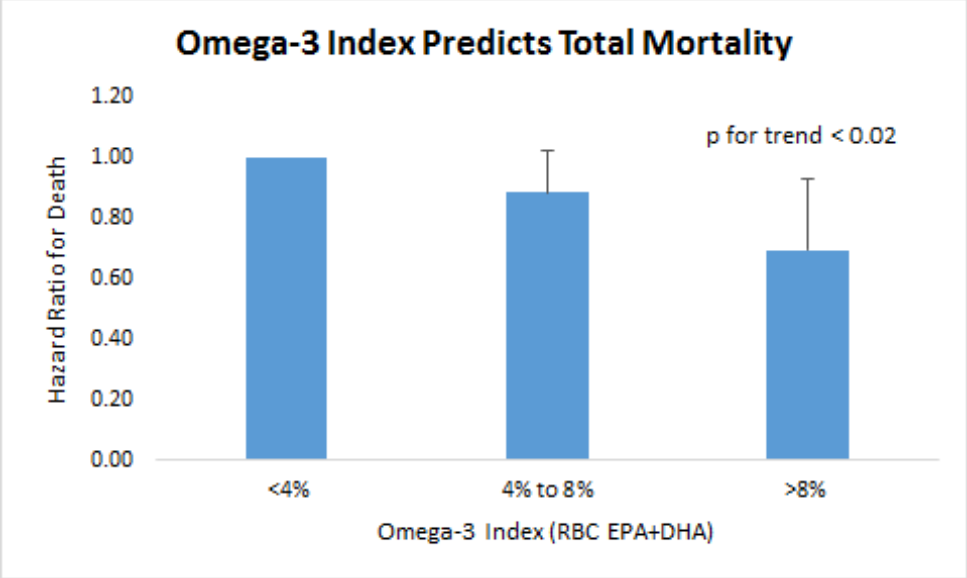
[a] Model components shown in Table 3. [b] Interactions all p>0.08. [c] See Table 2.

Supplemental Table 4. Multivariable-adjusted hazard ratios (99% CI) per 1-SD increase in red blood cell polyunsaturated fatty acids for CVD, cancer and other mortality over 14.9 (median) years follow up from the fully adjusted model[a].

	CVD Death (n=617)	*Cancer Death (n=462)*	*Other Death (n=772)*
Omega-3 index (EPA+DHA)	0.97 (0.85, 1.12)	0.92 (0.79, 1.07)	0.89 (0.78, 1.01)
Eicosapentaenoic (EPA)	**0.88 (0.77, 1.00)**	0.91 (0.78, 1.07)	0.87 (0.76, 1.01)
Docosahexaenoic (DHA)	1 (0.87, 1.14)	0.93 (0.79, 1.09)	0.9 (0.79, 1.02)
Linoleic Acid (LA)	0.96 (0.86, 1.08)	0.94 (0.83, 1.07)	1.05 (0.93, 1.17)
PUFA Factor Score	0.76 (0.57, 1.01)	0.81 (0.57, 1.16)	0.76 (0.55, 1.04)
Alpha linolenic (ALA)	0.97 (0.84, 1.12)	0.98 (0.85, 1.12)	0.98 (0.86, 1.13)
Docosapentaenoic n-3 (DPAn-3)	0.92 (0.8, 1.05)	0.93 (0.81, 1.07)	0.94 (0.82, 1.07)
Arachidonic (ARA)	1 (0.85, 1.18)	1.03 (0.89, 1.18)	0.98 (0.84, 1.14)
ARA/EPA ratio	1.13 (0.99, 1.29)	1.1 (0.93, 1.3)	1.13 (0.97, 1.31)
N-6/N-3 ratio	1.05 (0.9, 1.23)	1.1 (0.93, 1.3)	1.13 (0.97, 1.31)

[a] Model 3 described in legend for Table 2. Values in **bold** are significant ($p<0.01$).

Supplemental Figure 1. Risk for death from any cause was significantly lower at an Omega-3 Index >8% vs <4% (HR, 0.69; 95% CI 0.52 to 0.93, p=0.017), and the trend across the 3 categories (<4%, 4-8% and >8%) was significant (p=0.019).



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