

1 Erythrocyte n-6 fatty acids and risk for cardiovascular outcomes and total mortality in the
2 Framingham Heart Study

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26

27 **Abbreviations:** ADA, adrenic acid; AA, arachidonic acid; CVD, cardiovascular disease; DGLA,
28 dihomogamma linolenic acid; DHA, docosahexaenoic acid; DPA n-6, docosapentaenoic acid;
29 EDA, eicosadienoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; GLA, gamma-linolenic
30 acid; HR, hazard ratio; LA, linoleic acid; Omega-3 Index, erythrocyte EPA+DHA; PUFA,
31 polyunsaturated FA; RBC, red blood cell; SD, standard deviation

32

33 **ABSTRACT**

34 **Background:** The prognostic value of erythrocyte levels of the n-6 fatty acids (FAs) for total
35 mortality and cardiovascular disease (CVD) outcomes remains an open question.

36 **Methods:** We examined CV outcomes and death in 2500 individuals in the Framingham Heart
37 Study Offspring cohort without prevalent CVD (mean age 66 years, 57% women) as a function
38 of baseline levels of different length n-6 FAs (18 carbon, 20 carbon and 22 carbon) in the
39 erythrocyte membranes. Clinical outcomes were monitored for up to 9.5 years (median follow
40 up, 7.26 years). Cox proportional hazards models were adjusted for a variety of demographic
41 characteristics, clinical status and RBC n-6 and long chain n-3 FA content.

42 **Results:** There were 245 CV events, 119 CHD events, 105 ischemic strokes, 58 CVD deaths,
43 and 350 deaths from all causes. Few associations between either mortality or CVD outcomes
44 were observed for the n-6 FAs, with those that were observed becoming non-significant after
45 adjusting for n-3 FA levels.

46 **Conclusions:** Higher circulating levels of the marine n-3 FA levels are associated with reduced
47 risk for incident CVD and ischemic stroke and for death from CHD and all-causes, however in
48 the same sample, little evidence exists for association with n-6 FAs. Further work is needed to
49 identify a full profile of FAs associated with cardiovascular risk and mortality.

50 **Keywords:** epidemiology; prospective cohort study; n-6 fatty acids; n-3 fatty acids; linoleic acid;
51 arachidonic acid.

52 INTRODUCTION

53 The roles of n-3 and/or n-6 polyunsaturated fatty acids (PUFAs) in health and disease are
54 controversial. Whereas most studies have reported that higher circulating levels of the long-chain
55 n-3 PUFAs (i.e., eicosapentaenoic and docosahexaenoic acids, EPA and DHA) are protective
56 against cardiovascular disease (CVD) and premature death¹, the story is not as clear for the n-6
57 PUFAs. In a previous report from the Framingham Offspring cohort, we examined relations
58 between RBC n-3 FAs, specifically EPA and DHA (the sum of which is called the Omega-3
59 Index²) and risk for CVD and total mortality³. In this follow-up analyses, we focus on the n-6 FA
60 family and their relations with these outcomes.

61

62 METHODS

63 The Framingham Heart Study is a longitudinal community-based cohort study that was initiated
64 in 1948. The selection criteria for the Framingham Offspring Cohort and the Framingham Omni
65 Cohort have previously been described^{4,5} (<http://nhlbi.nih.gov/about/framingham>). Briefly, adult
66 children of the Original cohort were recruited in 1971 into the Framingham Offspring Cohort.
67 We evaluated Framingham Offspring participants ($n = 3021$) who attended their eighth
68 examination cycle (2005-2008). Participants were excluded in hierarchical order if they were
69 missing RBC fatty acid measurements or clinical covariates ($n = 122$), or having prevalent
70 cardiovascular disease (e.g., nonfatal CHD or stroke; $n=350$), leaving $n=2500$ for this analysis.
71 The study protocol was approved by the Institutional Review Board of the Boston University
72 Medical Center. Informed consent was provided by all participants.

73

74 Covariates and Mortality Outcomes:

75 We considered seventeen primary baseline demographic and cardiovascular risk covariates: sex,
76 age, body mass index (BMI), marital status, education level, employment status, health insurance
77 status, regular aspirin user, prevalent hypertensive status, use of cholesterol medication,
78 prevalent diabetes, alcohol consumption, smoking status, metabolic equivalent (METs), Total to
79 HDL cholesterol ratio, systolic blood pressure and C-reactive protein. Seven endpoints were
80 examined: four mortality related outcomes (any mortality, CVD mortality (CHD death or sudden
81 cardiac death), cancer mortality or death from non-CVD or cancer causes) and three cardio-
82 vascular related outcomes (total stroke (any fatal or non-fatal ischemic stroke), total CHD (fatal

83 or non-fatal MI, CHD death or sudden cardiac death), and total CVD (any stroke, CHD or CHD
84 mortality)). We focused our analyses on seven RBC FAs from the n-6 family: 18:2n6 (linoleic
85 acid, LA), 18:3n6 (gamma-linolenic acid, GLA), 20:2n6 (eicosadienoic acid, EDA), 20:3n6
86 (dihomo-gamma linolenic acid, DGLA), 20:4n6 (arachidonic acid, AA), 22:4n6 (adrenic acid,
87 ADA) and 22:5n6 (docosapentaenoic acid, DPA n-6). In some analyses, we adjusted for the
88 Omega-3 Index (EPA+DHA).

89

90 **RBC Fatty Acid Analysis**

91 Blood was drawn after a 10-12 hour fast into an EDTA tube, and RBCs were separated from
92 plasma by centrifugation. The RBC fraction was frozen at -80°C immediately after collection.
93 RBC fatty acid composition was determined as described previously⁶. Briefly, RBCs were
94 incubated at 100°C with boron trifluoride-methanol and hexane to generate fatty acid methyl
95 esters that were then analyzed by gas chromatography with flame ionization detection. The
96 coefficients of variation for the seven n-6 FAs measured were <3% for 18:2n6, 20:3n6, 20:4n6,
97 and 22:4n6; 7% for 22:5n6; 11% for 20:2n6 and 21% for 18:3n6.

98

99 **Statistical analysis**

100 Description of sample characteristics was conducted using standard statistical metrics (e.g.,
101 means, SDs, correlations). Hazard ratios were estimated using the survival package in R⁷.
102 Primary analyses predicted incident clinical outcomes [date of event (CVD or death) or date of
103 censoring] by groups of n-6 FAs (the 18 carbon, the 20 carbon, and the 22 carbon moieties), with
104 follow-up analyses adjusting for a variety of demographic covariates, and finally for the Omega-
105 3 Index. Secondary analyses explored the relationship between event risk and n-6 FA levels by
106 quintiles, individual omega-6 FA levels, and the sum of all omega-6 FAs. All analyses used two-
107 sided tests at the 0.05 significance level.

108

109 **RESULTS**

110 *Cohort description*

111 The Framingham Offspring study consists of 2500 individuals for whom FAs, clinical outcomes
112 and demographic covariates were available who also did not have prevalent CVD at baseline. At
113 baseline, the average age was 66 and the sample contained slightly more females (57%) than

114 males (43%). The sample was fairly well educated (over 2/3 of the sample had at least some
115 college education), with approximately half of the sample employed and the majority of the
116 remainder having retired. Most (88%) of the sample had insurance at baseline and the
117 distribution of cardiometabolic traits followed expected distributions, with approximately 40% of
118 the sample using aspirin regularly, and similar numbers with prevalent hypertension, and for
119 high cholesterol. Rates of prevalent diabetes was lower (13%). The majority of the sample
120 periodically consumed alcohol, and the vast majority (over 90%) were nonsmokers. Table 1
121 provides a complete overview of the demographic profile of the sample. Supplemental Table 1
122 illustrates the correlation between and among the major n-3 and n-6 fatty acids in this sample.
123 While correlations are generally higher within the n-3 or n-6 fatty acids than between, this is not
124 always the case (e.g., moderate negative correlations between both 20:2n6, 20:3n6 and 20:4n6
125 levels). Supplemental Table 2 illustrates the number of events present in the sample with 350 of
126 the participants having died from any cause during the course of the study, but only 58 of those
127 deaths were attributable to CVD. The max time to follow-up was approximately 9 years.

128

129 *Omega-6 fatty acids and mortality and cardiovascular disease risk*

130 Across all three classes of n-6 FAs (18-carbon, 20-carbon and 22-carbon) little evidence of
131 association with cardiovascular outcomes or mortality was observed. In unadjusted analyses, the
132 18-carbon n-6's showed associated with reduced risk of CVD and other (non-CVD, non-cancer)
133 mortality, however, these associations became non-significant after adjusting for demographic
134 variables (Table 3a). No associations were detected before or after evaluating twenty-carbon n-6s
135 (Table 3b). While twenty-two carbon n-6's showed some evidence of positive association with
136 Total CVD, CHD and stroke risk after adjusting for demographic covariates, all of these
137 associations became non-significant after also adjusting for the Omega-3 Index (Table 3c).
138 Notably, the Omega-3 Index remained significant in many of the models for CVD event risk and
139 CVD, non-cancer/non-CVD and all-cause mortality (Tables 3a-3c; Figure 1).

140

141 *Additional fatty acid analyses*

142 Supplemental tables S3a-S3g illustrate parallel analyses for each of the seven individual n-6 FAs.
143 In short, these analyses follow what was observed for the classes of FAs. Namely, few
144 associations were observed between the individual FAs and either cardiovascular events or

145 mortality and what few associations were observed in unadjusted models tended to become non-
146 significant in models that adjusted for demographic covariates. One exception was the positive
147 association between ESA (C20:2n6) and all-cause mortality, a relationship which remained even
148 after adjusting for the Omega-3 Index (Table S3c). Other exceptions were the positive
149 associations between DTA (C22:4n6) and stroke, and the positive associations between DPA
150 (C22:5n6) and all-cause mortality and non-CVD/non-cancer mortality, though these associations
151 all became non-significant after adjusting for the Omega-3 Index (Table S2f-S2g). An analysis
152 on the sum of all seven omega-6 FAs identified no significant associations after adjusting for the
153 Omega-3 Index.

154

155 **DISCUSSION**

156 In this study of participants in the Framingham Offspring study, the n-6 PUFAs were generally
157 unrelated with vital status, especially in fully adjusted models accounting for subject
158 characteristics and the Omega-3 Index. The only exception was for EDA which was directly
159 related with risk all-cause mortality. The Omega-3 Index was inversely associated with most of
160 the outcomes examined here even after adjustment for the n-6 FAs, whether in the full aggregate,
161 the carbon-chain groups, or the individual n-6 FAs.

162

163 EDA levels were found to be adversely associated with cognitive function in the Boston Puerto
164 Rican Health Study⁸ and with risk for acute coronary syndromes in a case-control study from
165 Kansas City⁹. These two findings – along with those of the present study – would suggest that
166 EDA participates in some untoward manner in pathophysiology of these conditions. On the other
167 hand, serum EDA levels were recently reported to be reduced in patients with inflammatory
168 bowel disease¹⁰, and in a large prospective study of plasma phospholipid FAs and risk for type 2
169 diabetes, EDA was inversely associated with incident disease¹¹. These findings support a
170 favorable role for this FA. EDA is an elongation product of LA (C18 to C20, both with 2 double
171 bonds), and on the biosynthetic path to DGLA and AA. These latter two n-6 FAs serve as
172 substrates for the production of a wide variety of active metabolites called oxylipins¹², but
173 whether the beneficial/harmful effects of EDA (if they indeed exist) are mediated by oxylipin
174 metabolism is unknown. Complicating these inconsistent observations is the fact that levels of

175 EDA in these subjects were very low, averaging only about 0.25% of total RBC FAs.

176 Consequently, the ultimate meaning and impact of EDA in biology is unclear.

177

178 As regards the major n-6 FAs, previous studies have reported that higher intakes of LA and
179 higher circulating levels of AA are associated with CV benefit^{1, 13}. In addition, LA blood levels
180 are inversely associated with risk for type 2 diabetes mellitus¹⁴. Nevertheless, some warn that
181 current intakes (and thus blood levels) of the n-6 PUFAs, especially these two major FAs in the
182 n-6 family, are dangerous^{15, 16}. The proposed mechanism of harm is via increased inflammation,
183 driven by the conversion of AA into pro-inflammatory/pro-thrombotic eicosanoids such as
184 prostaglandin E2, thromboxane A2, and leukotriene B4¹⁷. Accordingly, ratios like n-6:n-3¹⁸ or
185 AA:EPA¹⁹ have been promoted as better summary metrics of PUFA status than either family
186 alone. This perspective has, however, been criticized on both theoretical²⁰⁻²³ and evidential²⁴⁻²⁶
187 bases.

188

189 Delgado et al. recently reported the relations between red blood cell (RBC) n-6 FA levels and
190 risk for death from all causes²⁷. Using data from 3259 patients undergoing diagnostic coronary
191 artery catheterization and followed for 10 years, these investigators found that RBC levels of n-6
192 FAs were inversely related with risk for death. However, a more granular examination revealed
193 widely varying associations with n-6 FAs depending on chain length. The 18-carbon species (LA
194 and GLA) were inversely associated with death, those with 20 carbons (AA and DGLA) were
195 largely unrelated with risk, and those with 22 carbons (ADA and DPAn-6) were directly related
196 with risk. A case-control study using RBC FA profiles from acute coronary syndrome patients
197 found that a suite of 10 RBC FAs was able to predict case status better than the classical risk
198 factors included in the Framingham Risk Score⁹. In that study, LA, AA and GLA were predictors
199 of lower risk for coronary disease, whereas EDA (as noted above) was associated with higher
200 risk. In yet another study, RBC both EPA and DPAn-6 added independent predictive power to a
201 standard algorithm used to predict risk for death in post myocardial infarction patients²⁸. All of
202 these studies suggest that not n-6 FAs are all created equal, and that to speak of them as a
203 monolithic class of FAs with similar biochemical functions and physiological roles is probably
204 incorrect. In this study, we further illustrated a widely varying correlation structure between n-3
205 FAs and n-6 FAs, as well as within the n-6 FAs further supporting the argument that not all n-6's

206 are created equal. Further work is needed to better understand the role of the full profile of fatty
207 acids on disease risk.

208

209 Strengths and Limitations

210 Strengths of this study include the large sample size and number of events, the unambiguous
211 nature of the primary endpoint, the inclusion of community dwellers (instead of a patient
212 population), and the use of an objective biomarker of PUFA exposure with low biological
213 variability²⁹. The previous detection of clear inverse relations between the Omega-3 Index and
214 outcomes in this same cohort suggests that our failure to see associations with the n-6 FAs was
215 not due to a lack of power, but a lack of effect. The assessment of PUFA exposure at only one-
216 time point cannot capture PUFA status changes throughout follow-up. Finally, the inability to
217 rule out the possibility of residual or unmeasured confounding also precludes inferences about
218 causality³¹.

219

220 In conclusion, we found no meaningful relationship between RBC levels of n-6 PUFAs and risk
221 for CVD or total mortality. Importantly, after adjustment for covariates, there was no increase in
222 risk for adverse outcomes with higher n-6 PUFA levels, with the possible exception of EDA.
223 These findings, in the context of the totality of available evidence on this subject, provide no
224 support for a harmful role of n-6 PUFAs in these important clinical outcomes.

225

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227 Author Contributions

228 Conceptualization, William Harris; Formal analysis, Nathan Tintle; Funding acquisition, William Harris and
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234

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Table 1. Demographic overview (n=2500)

	Died (n=350)	Still living (n=2150)	Total
Variable	% (n) or Mean (SD)	% (n) or Mean (SD)	% (n) or Mean (SD)
Sex			
Male	52.9% (185)	41.5% (893)	43.1% (1078)
Female	47.1% (165)	58.5% (1257)	56.9% (1422)
Age	72.9 (8.6)	64.4 (8.2)	65.56 (8.76)
BMI	27.9 (5.9)	28.3 (5.4)	28.2 (5.4)
Marital Status			
Single/Never Married	4.3% (15)	6.7% (144)	6.4% (159)
Married	63.7% (223)	70.7% (1519)	69.7% (1742)
Separated/Divorced	12.0% (42)	12.7% (273)	12.6% (315)
Widowed	18.3% (64)	9.4% (203)	10.7% (267)
Education			
Some HS or less	6.0% (21)	2.4% (51)	2.9% (72)
HS graduate	33.7% (118)	24.8% (533)	26.0% (651)
Some college or vocational	22.9% (78)	21.9% (471)	22.0% (549)
College graduate	36.6% (128)	50.5% (1086)	48.6% (1214)
Employment			
Employed	31.1% (109)	56.3% (1210)	52.8% (1319)
Disabled/unemployed	3.1% (11)	2.5% (53)	2.6% (64)
Retired	64.3% (225)	40.8% (877)	44.1% (1102)
Health insurance status			
No insurance	2.3% (8)	1.9% (40)	1.9% (48)
Insurance, but no prescription	11.4% (40)	8.4% (181)	8.8% (221)
Full insurance	84.0% (294)	88.7% (1906)	88.0% (2200)
Regular aspirin use	49.7% (174)	38.6% (830)	40.2% (1004)
Prevalent hypertension	57.1% (200)	42.2% (908)	44.3% (1108)

Cholesterol medication	41.4% (145)	36.9% (794)	37.6% (939)
Prevalent diabetes	22.3% (78)	11.6% (249)	13.1% (327)
Alcohol consumption			
None	34.0% (119)	23.2% (499)	24.7% (618)
<1 drink p/day	36.0% (126)	50.7% (1089)	48.6% (1215)
1-2 drinks p/day	22.6% (79)	20.2% (434)	20.5% (513)
>2 drinks p/day	6.9% (24)	5.7% (123)	5.9% (147)
Smoking			
Not current smoker	89.1% (312)	90.5% (1946)	90.3% (2258)
Current	10.6% (37)	9.3% (200)	9.5% (237)
METS	4.7 (15.4)	3.3 (8.6)	3.5 (9.9)
Total to HDL cholesterol ratio	3.5 (1.1)	3.5 (1.0)	3.5 (1.1)
Systolic BP	133.6 (19.8)	128.2 (16.9)	129.0 (17.4)
C-reactive protein	4.9 (12.7)	3.0 (6.1)	3.3 (7.4)
Omega-3 Index	0.0544 (0.0167)	0.0555 (0.0169)	0.0554 (0.0168)

Table 2. Risk of events and mortality by n-6 fatty acid carbon chain length (n=2500)

Table 2a. Eighteen carbon n-6 fatty acids (18:2n6 + 18:3n6)

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Eighteen carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<9.8% (n=433)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9.8-10.7% (n=488)	1.07 (0.71, 1.61)	1.30 (0.72, 2.35)	1.28 (0.67, 2.43)	1.14 (0.45, 2.89)	0.96 (0.58, 1.58)	0.56 (0.31, 1.02)	0.92 (0.64, 1.31)
10.7-11.5% (n=522)	1.05 (0.71, 1.57)	1.08 (0.59, 1.98)	1.33 (0.72, 2.43)	0.86 (0.33, 2.19)	0.81 (0.48, 1.36)	0.51 (0.29, 0.92)*	0.77 (0.54, 1.11)
11.5-12.5% (n=522)	0.74 (0.48, 1.13)	0.80 (0.42, 1.52)	0.70 (0.35, 1.38)	1.74 (0.71, 4.25)	0.56 (0.32, 1.00)	0.86 (0.53, 1.39)	0.94 (0.67, 1.31)
>12.5% (n=535)	0.73 (0.48, 1.13)	1.01 (0.56, 1.81)	0.80 (0.39, 1.63)	0.57 (0.22, 1.53)	0.74 (0.43, 1.25)	0.52 (0.29, 0.93)*	0.74 (0.52, 1.06)
p-value for linear trend	0.032*	0.45	0.15	0.26	0.08	0.17	0.14
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Eighteen carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<9.8% (n=433)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9.8-10.7% (n=488)	1.28 (0.83, 1.95)	1.42 (0.76, 2.67)	1.46 (0.71, 3.00)	1.19 (0.48, 2.96)	1.09 (0.63, 1.88)	0.87 (0.47, 1.60)	1.21 (0.84, 1.73)
10.7-11.5% (n=522)	1.37 (0.90, 2.08)	1.38 (0.74, 2.56)	1.51 (0.77, 2.96)	1.12 (0.42, 2.97)	0.89 (0.49, 1.61)	0.83 (0.45, 1.56)	1.02 (0.69, 1.50)
11.5-12.5% (n=522)	0.78 (0.48, 1.27)	0.96 (0.46, 2.02)	0.72 (0.33, 1.61)	1.59 (0.67, 3.75)	0.65 (0.35, 1.20)	1.02 (0.58, 1.80)	0.99 (0.68, 1.44)
>12.5% (n=535)	1.16 (0.72, 1.89)	1.53 (0.75, 3.13)	1.12 (0.52, 2.40)	0.96 (0.33, 2.80)	0.88 (0.47, 1.65)	0.62 (0.29, 1.33)	1.02 (0.68, 1.53)
p-value for linear trend	0.68	0.59	0.49	0.68	0.30	0.42	0.69
	Hazard ratios (95% CIs)						
	Total Events			Mortality			

C. Eighteen carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<9.8% (n=433)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9.8-10.7% (n=488)	1.19 (0.78, 1.82)	1.32 (0.70, 2.49)	1.29 (0.62, 2.66)	1.08 (0.43, 2.73)	1.07 (0.62, 1.87)	0.74 (0.39, 1.41)	1.14 (0.79, 1.64)
10.7-11.5% (n=522)	1.28 (0.84, 1.95)	1.28 (0.69, 2.38)	1.34 (0.67, 2.65)	1.04 (0.38, 2.78)	0.87 (0.47, 1.61)	0.71 (0.38, 1.34)	0.95 (0.64, 1.41)
11.5-12.5% (n=522)	0.71 (0.44, 1.16)	0.86 (0.41, 1.79)	0.62 (0.28, 1.39)	1.49 (0.65, 3.44)	0.64 (0.34, 1.19)	0.83 (0.46, 1.50)	0.92 (0.63, 1.34)
>12.5% (n=535)	1.03 (0.63, 1.67)	1.32 (0.64, 2.73)	0.93 (0.43, 2.03)	0.78 (0.26, 2.34)	0.86 (0.45, 1.63)	0.52 (0.24, 1.11)	0.92 (0.61, 1.40)
p-value for linear trend	0.34	0.92	0.23	0.87	0.28	0.18	0.38
p-value for omega3	0.005**	0.034*	0.004**	0.10	0.70	0.004**	0.011

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table 2b. Twenty carbon n-6 fatty acids (20:2n6 + 20:3n6 + 20:4n6)

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Twenty carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<17.5% (n=508)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
17.5-18.4% (n=509)	1.03 (0.71, 1.50)	0.95 (0.53, 1.70)	0.96 (0.54, 1.70)	1.19 (0.54, 2.62)	0.80 (0.48, 1.32)	0.84 (0.49, 1.46)	0.89 (0.65, 1.22)
18.4-19.1% (n=502)	0.92 (0.61, 1.39)	0.95 (0.52, 1.71)	0.78 (0.41, 1.49)	0.83 (0.31, 2.20)	0.90 (0.53, 1.53)	1.59 (0.94, 2.67)	1.16 (0.83, 1.63)
19.1-19.9% (n=502)	0.88 (0.58, 1.33)	1.22 (0.71, 2.09)	0.63 (0.32, 1.24)	1.24 (0.55, 2.80)	0.87 (0.52, 1.46)	1.19 (0.67, 2.09)	1.02 (0.73, 1.42)
>19.9% (n=479)	1.03 (0.70, 1.52)	0.99 (0.55, 1.77)	1.04 (0.59, 1.82)	0.77 (0.37, 1.60)	0.92 (0.55, 1.53)	1.14 (0.65, 2.01)	0.95 (0.69, 1.33)
p-value for linear trend	0.82	0.71	0.68	0.54	0.83	0.32	0.90
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Twenty carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<17.5% (n=508)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
17.5-18.4% (n=509)	1.10 (0.74, 1.65)	0.96 (0.52, 1.75)	1.19 (0.62, 2.30)	1.58 (0.61, 4.11)	0.84 (0.49, 1.42)	0.86 (0.45, 1.67)	1.01 (0.71, 1.44)
18.4-19.1% (n=502)	0.96 (0.61, 1.51)	0.93 (0.49, 1.79)	1.09 (0.54, 2.21)	1.23 (0.38, 4.02)	0.98 (0.53, 1.81)	1.91 (1.08, 3.36)*	1.33 (0.92, 1.92)
19.1-19.9% (n=502)	1.04 (0.67, 1.61)	1.29 (0.71, 2.36)	0.88 (0.43, 1.80)	1.98 (0.75, 5.19)	1.02 (0.58, 1.78)	1.45 (0.77, 2.70)	1.27 (0.88, 1.81)
>19.9% (n=479)	1.21 (0.78, 1.88)	1.06 (0.56, 2.02)	1.48 (0.75, 2.92)	1.19 (0.44, 3.21)	1.21 (0.69, 2.13)	1.40 (0.75, 2.61)	1.19 (0.82, 1.73)
p-value for linear trend	0.52	0.52	0.53	0.55	0.42	0.11	0.16
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
C. Twenty carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total

<17.5% (n=508)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
17.5-18.4% (n=509)	0.97 (0.65, 1.46)	0.84 (0.46, 1.51)	0.96 (0.50, 1.86)	1.30 (0.47, 3.61)	0.84 (0.49, 1.44)	0.77 (0.40, 1.51)	0.94 (0.65, 1.36)
18.4-19.1% (n=502)	0.81 (0.51, 1.30)	0.77 (0.39, 1.51)	0.82 (0.39, 1.72)	0.99 (0.28, 3.55)	0.99 (0.52, 1.88)	1.62 (0.92, 2.86)	1.19 (0.81, 1.75)
19.1-19.9% (n=502)	0.85 (0.53, 1.34)	1.03 (0.55, 1.91)	0.61 (0.28, 1.33)	1.55 (0.56, 4.30)	1.03 (0.57, 1.86)	1.17 (0.60, 2.27)	1.12 (0.76, 1.65)
>19.9% (n=479)	0.97 (0.60, 1.56)	0.82 (0.41, 1.65)	1.03 (0.49, 2.15)	0.85 (0.27, 2.72)	1.23 (0.67, 2.26)	1.12 (0.58, 2.16)	1.04 (0.70, 1.56)
p-value for linear trend	0.72	0.87	0.91	0.89	0.42	0.44	0.58
p-value for omega3	0.011*	0.039*	0.009**	0.13	0.87	0.03*	0.04*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table 2c. Twenty-two carbon n-6 fatty acids (22:4n6+22:5n6)

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Twenty-two carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<3.6% (n=514)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3.6-4.3% (n=508)	1.37 (0.88, 2.12)	1.24 (0.63, 2.43)	1.25 (0.62, 2.53)	0.93 (0.42, 2.03)	0.86 (0.52, 1.42)	1.11 (0.64, 1.93)	0.96 (0.69, 1.31)
4.3-4.7% (n=500)	1.73 (1.14, 2.62)**	2.43 (1.34, 4.42)**	1.36 (0.71, 2.61)	0.81 (0.35, 1.83)	0.65 (0.38, 1.13)	0.96 (0.53, 1.73)	0.80 (0.57, 1.13)
4.7-5.3% (n=509)	1.46 (0.96, 2.22)	1.61 (0.86, 3.03)	1.58 (0.83, 2.98)	1.16 (0.54, 2.49)	0.78 (0.46, 1.31)	1.27 (0.72, 2.26)	1.04 (0.75, 1.45)
>5.3% (n=469)	1.73 (1.12, 2.68)*	2.25 (1.22, 4.16)**	1.48 (0.74, 2.98)	0.63 (0.24, 1.67)	1.18 (0.71, 1.95)	1.43 (0.82, 2.50)	1.10 (0.77, 1.56)
p-value for linear trend	0.02*	0.006**	0.18	0.57	0.74	0.17	0.48
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Twenty-two carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<3.6% (n=514)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3.6-4.3% (n=508)	1.20 (0.75, 1.93)	1.05 (0.50, 2.20)	1.39 (0.62, 3.13)	0.83 (0.28, 2.41)	0.94 (0.56, 1.60)	1.06 (0.60, 1.88)	1.01 (0.71, 1.44)
4.3-4.7% (n=500)	1.74 (1.13, 2.67)*	2.38 (1.26, 4.48)**	1.73 (0.85, 3.55)	0.65 (0.26, 1.62)	0.74 (0.41, 1.32)	0.85 (0.41, 1.76)	0.85 (0.58, 1.25)
4.7-5.3% (n=509)	1.36 (0.87, 2.13)	1.51 (0.76, 2.99)	1.89 (0.92, 3.87)	1.28 (0.62, 2.62)	0.74 (0.41, 1.31)	1.31 (0.68, 2.51)	1.11 (0.78, 1.59)
>5.3% (n=469)	1.66 (1.02, 2.69)*	1.91 (0.95, 3.83)	2.01 (0.92, 4.42)	0.60 (0.18, 2.01)	1.21 (0.71, 2.07)	1.53 (0.85, 2.74)	1.17 (0.81, 1.71)
p-value for linear trend	0.031*	0.04*	0.04*	0.80	0.91	0.10	0.32
	Hazard ratios (95% CIs)						
	Total Events			Mortality			

C. Twenty-two carbon	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<3.6% (n=514)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3.6-4.3% (n=508)	1.11 (0.69, 1.79)	0.99 (0.48, 2.05)	1.20 (0.53, 2.69)	0.62 (0.20, 1.95)	0.93 (0.54, 1.60)	0.89 (0.48, 1.63)	0.89 (0.62, 1.29)
4.3-4.7% (n=500)	1.52 (0.96, 2.39)	2.09 (1.07, 4.06)*	1.35 (0.65, 2.80)	0.42 (0.17, 1.06)	0.72 (0.38, 1.36)	0.67 (0.32, 1.42)	0.69 (0.45, 1.05)
4.7-5.3% (n=509)	1.14 (0.70, 1.86)	1.25 (0.60, 2.62)	1.37 (0.64, 2.97)	0.69 (0.27, 1.76)	0.71 (0.38, 1.34)	0.97 (0.48, 1.94)	0.87 (0.58, 1.30)
>5.3% (n=469)	1.33 (0.77, 2.28)	1.51 (0.69, 3.30)	1.38 (0.60, 3.18)	0.30 (0.07, 1.26)	1.15 (0.57, 2.33)	0.98 (0.48, 1.98)	0.85 (0.54, 1.34)
p-value for linear trend	0.42	0.34	0.44	0.14	0.97	0.88	0.57
p-value for omega3	0.09	0.22	0.049*	0.034*	0.92	0.03*	0.021*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

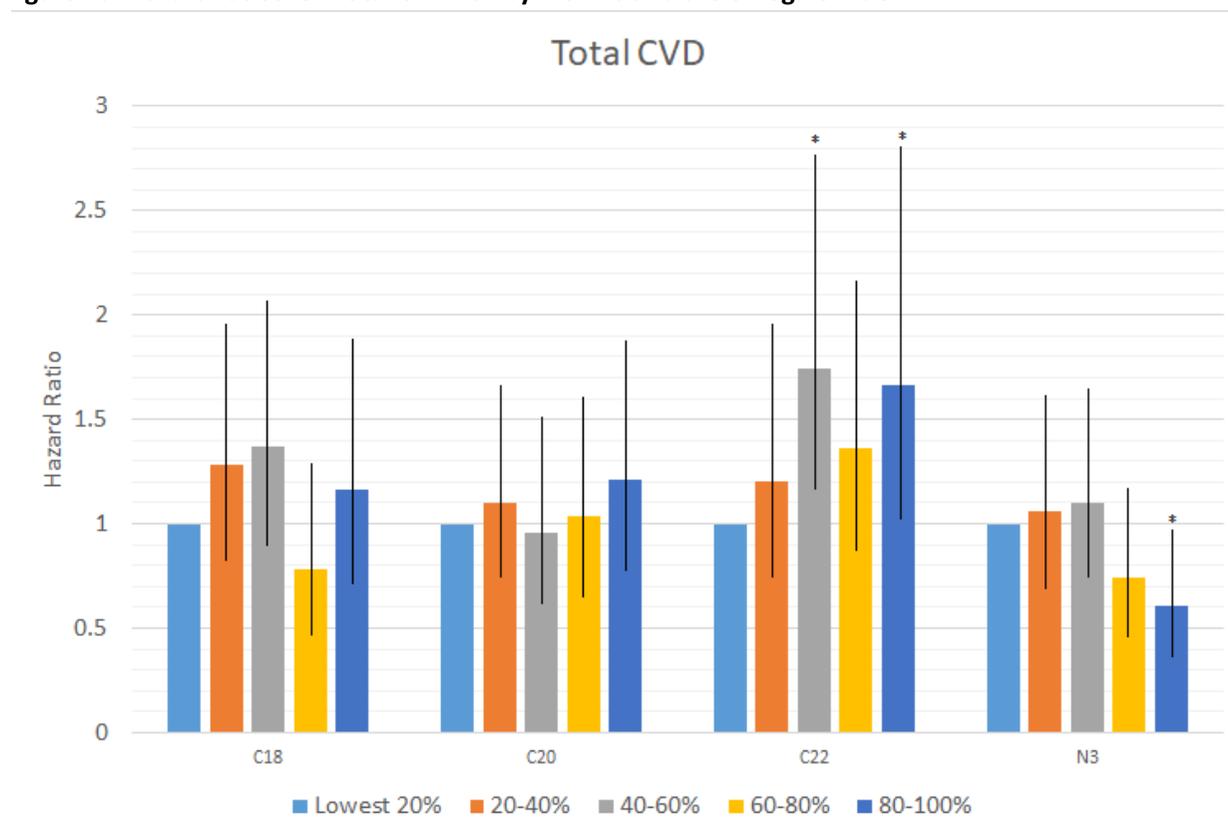
Figure 1a. Hazard ratios for Total CVD risk by n-6 FAs and the omega-3 index

Figure 1a illustrates the associations between n-6 or n-3 fatty acids and Total CVD risk. Bar heights are hazard ratios with 95% confidence intervals provided for each hazard ratio. Hazard ratios are provided for each quintile are all relative to the risk within the lowest quintile. Statistically significant HRs at the 0.05 level are denoted with asterisks. Hazard ratios depicted in this figure are from models adjusting for all demographic variables in Table 1, but do not adjust for the omega-3 index and/or other omega-6 FAs. There is no significant linear trend for the 18 carbon n-6 FAs ($p=0.68$) or the 20 carbon n-6 FAs ($p=0.52$), while the 22 carbon n-6 FAs ($p=0.031$) and the omega-3 index ($p=0.008$) both have significant linear trends across the 5 quintile groups (see Tables 2a-2c for additional details). Finally, we note that, as shown in Table 2c, both linear associations as well as all individual quintile group associations become non-significant ($p>0.05$) for both the omega-3 index and 22 carbon n-6 FAs when both are simultaneously entered into the statistical model.

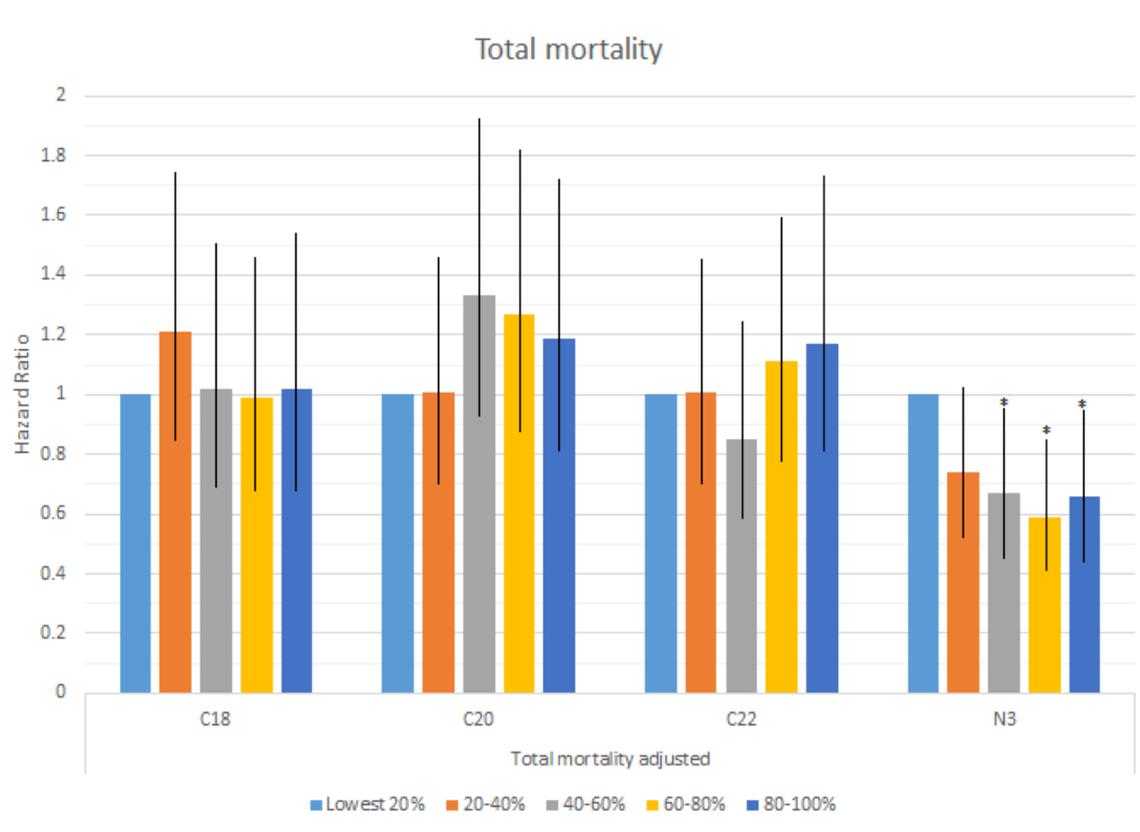
Figure 1b. Total mortality

Figure 1b illustrates the associations between n-6 or n-3 fatty acids and Total mortality. Bar heights are hazard ratios with 95% confidence intervals provided for each hazard ratio. Hazard ratios are provided for each quintile are all relative to the risk within the lowest quintile. Statistically significant HRs at the 0.05 level are denoted with asterisks. Hazard ratios depicted in this figure are from models adjusting for all demographic variables in Table 1, but do not adjust for the omega-3 index and/or other omega-6 FAs. There is no significant linear trend for the 18 carbon n-6 FAs ($p=0.69$), the 20 carbon n-6 FAs ($p=0.16$) and the 22 carbon n-6 FAs ($p=0.31$), while, the omega-3 index ($p=0.015$) has a significant linear trend across the 5 quintile groups. Finally, we note that, as shown in Table 2c, linear associations as well as all individual quintile group associations become non-significant ($p>0.05$) for all n-6 fatty acids when adjusting for the omega-3 index, while the omega-3 index remains significant ($p<0.05$) in all models.

Supplemental Tables

Table S1. Correlation between and among red blood cell n-3 and n-6 fatty acids

	18:3n3	20:5n3	22:5n3	22:6n3	18:2n6	18:3n6	20:2n6	20:3n6	20:4n6	22:4n6	22:5n6
18:3n3	1.00	0.11	0.03	-0.01	0.24	0.01	0.13	0.07	-0.23	-0.22	-0.17
20:5n3		1.00	0.64	0.65	-0.13	-0.02	-0.20	-0.20	-0.46	-0.65	-0.63
22:5n3			1.00	0.42	-0.32	-0.10	-0.17	-0.16	-0.21	-0.25	-0.40
22:6n3				1.00	-0.26	-0.07	-0.09	-0.21	-0.33	-0.58	-0.48
18:2n6					1.00	0.05	0.43	0.26	-0.47	-0.23	-0.17
18:3n6						1.00	0.02	0.02	-0.02	-0.03	-0.04
20:2n6							1.00	0.26	-0.22	0.05	-0.01
20:3n6								1.00	-0.32	-0.04	0.15
20:4n6									1.00	0.57	0.49
22:4n6										1.00	0.66
22:5n6											1.00

Table S2. Distribution of outcomes (n=2500)

	Number of people with events (cases)	Number of people without events (controls)	Median follow-up days ¹	Maximum follow-up days ¹
Total CVD	245	2255	2351	3833
Total CHD	119	2381	2342	3815
Ischemic stroke	105	2395	2342	3833
CVD mortality	58	2442	2673	3815
Death from any cause ²	350	2150	2686	3815

1. Across all 2500 participants and so computed as days to event or days to censoring

2. The causes of the 350 observed deaths, besides CVD, were 146 Cancer (42%), 128 Other (37%) and 18 Unknown (5%).

Table S3. Risk of events and mortality by individual n-6 fatty acids (n=2500)

Table S3a. Linoleic Acid – Unadjusted, Adjusted for demographics (Table 1 variables), and further adjusted for the Omega-3 Index (5-groups)

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Linoleic (18:2n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<9.7% (n=436)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9.7-10.6% (n=486)	1.12 (0.75, 1.70)	1.43 (0.79, 2.53)	1.30 (0.68, 2.46)	1.40 (0.55, 3.60)	0.92 (0.56, 1.52)	0.56 (0.31, 1.02)	0.92 (0.64, 1.31)
10.6-11.4% (n=519)	1.08 (0.72, 1.61)	1.19 (0.64, 2.20)	1.34 (0.73, 2.44)	0.86 (0.32, 2.28)	0.82 (0.49, 1.35)	0.49 (0.27, 0.88)*	0.76 (0.53, 1.09)
11.4-12.4% (n=522)	0.79 (0.52, 1.21)	0.84 (0.44, 1.62)	0.75 (0.38, 1.46)	2.07 (0.83, 5.16)	0.54 (0.30, 0.96)*	0.85 (0.53, 1.38)	0.94 (0.67, 1.31)
>12.4% (n=537)	0.72 (0.47, 1.11)	1.02 (0.55, 1.86)	0.76 (0.37, 1.56)	0.63 (0.23, 1.720)	0.72(0.43, 1.22)	0.51 (0.29, 0.91)*	0.74 (0.52, 1.05)
p-value for linear trend	0.029*	0.41	0.13	0.77	0.073	0.14	0.14
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Linoleic (18:2n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<9.7% (n=436)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9.7-10.6% (n=486)	1.37 (0.89, 2.09)	1.57 (0.83, 2.96)	1.51 (0.73, 3.12)	1.57 (0.62, 3.97)	1.05 (0.61, 1.82)	0.86 (0.47, 1.56)	1.22 (0.85, 1.76)
10.6-11.4% (n=519)	1.42 (0.93, 2.16)	1.53 (0.81, 2.89)	1.51 (0.77, 2.97)	1.13 (0.40, 3.17)	0.91 (0.51, 1.63)	0.78 (0.42, 1.48)	1.01 (0.68, 1.49)
11.4-12.4% (n=522)	0.87 (0.54, 1.41)	1.03 (0.49, 2.18)	0.80 (0.37, 1.75)	2.12 (0.88, 5.10)	0.63 (0.34, 1.16)	1.00 (0.58, 1.76)	1.01 (0.69, 1.46)
>12.4% (n=537)	1.16 (0.71, 1.91)	1.56 (0.75, 3.25)	1.09 (0.49, 2.39)	1.11 (0.37, 3.32)	0.86 (0.46, 1.62)	0.61 (0.29, 1.28)	1.02 (0.67, 1.54)
p-value for linear trend	0.73	0.60	0.52	0.43	0.29	0.37	0.70
	Hazard ratios (95% CIs)						
	Total Events			Mortality			

C. Linoleic (18:2n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<9.7% (n=436)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9.7-10.6% (n=486)	1.27 (0.83, 1.95)	1.46 (0.77, 2.75)	1.32 (0.64, 2.74)	1.43 (0.56, 3.66)	1.04 (0.59, 1.81)	0.72 (0.38, 1.36)	1.15 (0.80, 1.66)
10.6-11.4% (n=519)	1.31 (0.86, 2.01)	1.41 (0.75, 2.67)	1.33 (0.67, 2.65)	1.04 (0.37, 2.95)	0.89 (0.49, 1.63)	0.67 (0.35, 1.26)	0.94 (0.63, 1.40)
11.4-12.4% (n=522)	0.79 (0.49, 1.28)	0.92 (0.44, 1.95)	0.68 (0.31, 1.51)	1.97 (0.84, 4.62)	0.61 (0.32, 1.16)	0.82 (0.46, 1.45)	0.93 (0.64, 1.35)
>12.4% (n=537)	1.03 (0.62, 1.70)	1.35 (0.65, 2.84)	0.90 (0.40, 2.02)	0.91 (0.30, 2.79)	0.84 (0.44, 1.60)	0.50 (0.25, 1.07)	0.92 (0.61, 1.40)
p-value for linear trend	0.38	0.93	0.25	0.59	0.26	0.16	0.39
p-value for omega-3	<i>0.005**</i>	<i>0.033*</i>	<i>0.004**</i>	0.11	0.69	<i>0.004**</i>	<i>0.011*</i>

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3b. Gamma-linolenic Acid

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Gamma-linolenic (18:3n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.04% (n=500)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.04-0.06% (n=497)	0.79 (0.53, 1.18)	0.76 (0.41, 1.40)	0.72 (0.40, 1.32)	0.60 (0.26, 1.35)	0.87 (0.52, 1.46)	0.63 (0.35, 1.12)	0.68 (0.49, 0.96)*
0.06-0.07% (n=495)	0.96 (0.64, 1.46)	1.50 (0.87, 2.58)	0.49 (0.24, 1.00)	0.95 (0.42, 2.17)	0.79 (0.47, 1.34)	0.82 (0.48, 1.40)	0.79 (0.56, 1.11)
0.07-0.10% (n=504)	0.93 (0.63, 1.36)	0.91 (0.49, 1.67)	0.96 (0.57, 1.64)	0.66 (0.27, 1.59)	0.95 (0.56, 1.60)	0.59 (0.32, 1.10)	0.74 (0.52, 1.05)
>0.10% (n=504)	0.92 (0.62, 1.37)	1.04 (0.58, 1.86)	0.82 (0.44, 1.52)	1.22 (0.58, 2.57)	0.86 (0.50, 1.47)	0.97 (0.56, 1.10)	0.95 (0.69, 1.32)
p-value for linear trend	0.98	0.70	0.83	0.46	0.72	0.83	0.95
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Gamma-linolenic (18:3n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.04% (n=500)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.04-0.06% (n=497)	0.79 (0.51, 1.23)	0.66 (0.34, 1.32)	0.75 (0.38, 1.48)	1.15 (0.40, 3.24)	1.01 (0.57, 1.79)	0.67 (0.33, 1.34)	0.81 (0.55, 1.18)
0.06-0.07% (n=495)	1.04 (0.67, 1.60)	1.48 (0.82, 2.65)	0.60 (0.29, 1.28)	1.60 (0.59, 4.35)	0.96 (0.54, 1.70)	0.86 (0.47, 1.55)	0.94 (0.65, 1.35)
0.07-0.10% (n=504)	1.01 (0.66, 1.54)	0.88 (0.43, 1.80)	1.07 (0.57, 2.01)	0.93 (0.30, 2.93)	1.07 (0.58, 2.00)	0.42 (0.21, 0.81)**	0.79 (0.53, 1.16)
>0.10% (n=504)	0.89 (0.58, 1.35)	0.92 (0.49, 1.71)	0.81 (0.41, 1.61)	1.78 (0.73, 4.35)	1.02 (0.57, 1.83)	0.84 (0.45, 1.55)	1.07 (0.75, 1.53)
p-value for linear trend	0.97	0.85	0.91	0.27	0.87	0.32	0.74
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
C. Gamma-linolenic (18:3n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total

<0.04% (n=500)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.04-0.06% (n=497)	0.74 (0.48, 1.14)	0.62 (0.31, 1.22)	0.68 (0.35, 1.35)	1.02 (0.36, 2.89)	1.01 (0.56, 1.79)	0.58 (0.29, 1.16)	0.75 (0.51, 1.10)
0.06-0.07% (n=495)	0.99 (0.64, 1.52)	1.39 (0.78, 2.49)	0.58 (0.27, 1.21)	1.55 (0.57, 4.19)	0.96 (0.54, 1.70)	0.75 (0.41, 1.37)	0.90 (0.62, 1.29)
0.07-0.10% (n=504)	0.94 (0.62, 1.43)	0.83 (0.41, 1.70)	0.96 (0.51, 1.80)	0.82 (0.26, 2.54)	1.07 (0.57, 2.00)	0.37 (0.19, 0.73)**	0.73 (0.50, 1.08)
>0.10% (n=504)	0.80 (0.53, 1.22)	0.83 (0.45, 1.52)	0.71 (0.35, 1.42)	1.52 (0.63, 3.66)	1.02 (0.57, 1.82)	0.69 (0.37, 1.30)	0.97 (0.68, 1.38)
p-value for linear trend	0.73	0.93	0.66	0.39	0.89	0.16	0.93
p-value for omega-3	0.008**	0.03*	0.005**	0.12	0.89	0.004**	0.014*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3c. Eicosadienoic Acid

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Eicosadienoic (20:2n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.24% (n=482)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.24-0.26% (n=499)	0.91 (0.61, 1.36)	0.86 (0.48, 1.53)	1.03 (0.54, 1.97)	0.61 (0.24, 1.53)	1.31 (0.77, 2.23)	1.11 (0.65, 1.88)	1.14 (0.81, 1.62)
0.26-0.28% (n=502)	0.76 (0.49, 1.18)	0.56 (0.29, 1.08)	1.12 (0.57, 2.18)	0.50 (0.17, 1.44)	0.93 (0.53, 1.66)	0.95 (0.52, 1.70)	0.97 (0.67, 1.41)
0.28-0.31% (n=506)	1.07 (0.73, 1.56)	0.79 (0.44, 1.43)	1.32 (0.72, 2.43)	1.20 (0.52, 2.79)	1.23 (0.72, 2.11)	1.13 (0.67, 1.93)	1.32 (0.95, 1.85)
>0.31% (n=511)	1.07 (0.72, 1.60)	1.32 (0.80, 2.17)	1.02 (0.53, 1.97)	1.35 (0.52, 2.79)	1.32 (0.78, 2.23)	1.25 (0.73, 2.14)	1.37 (0.98, 1.92)
p-value for linear trend	0.72	0.34	0.67	0.19	0.37	0.44	0.035*
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Eicosadienoic (20:2n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.24% (n=482)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.24-0.26% (n=499)	0.91 (0.59, 1.40)	0.75 (0.40, 1.40)	1.12 (0.53, 2.35)	0.47 (0.17, 1.27)	1.57 (0.91, 2.72)	1.06 (0.55, 2.04)	1.24 (0.84, 1.83)
0.26-0.28% (n=502)	0.89 (0.56, 1.41)	0.67 (0.34, 1.34)	1.20 (0.58, 2.48)	0.43 (0.14, 1.31)	0.98 (0.50, 1.92)	1.12 (0.61, 2.02)	1.12 (0.76, 1.66)
0.28-0.31% (n=506)	1.10 (0.71, 1.71)	0.99 (0.51, 1.92)	1.25 (0.62, 2.50)	0.80 (0.28, 2.24)	1.28 (0.71, 2.31)	1.20 (0.68, 2.14)	1.28 (0.88, 1.85)
>0.31% (n=511)	1.26 (0.82, 1.92)	1.64 (0.92, 2.93)	1.16 (0.59, 2.28)	1.34 (0.56, 3.21)	1.46 (0.83, 2.56)	1.46 (0.82, 2.60)	1.52 (1.06, 2.17)*
p-value for linear trend	0.18	0.07	0.60	0.33	0.35	0.18	0.028*
	Hazard ratios (95% CIs)						
	Total Events			Mortality			

C. Eicosadienoic (20:2n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.24% (n=482)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.24-0.26% (n=499)	0.87 (0.56, 1.34)	0.72 (0.38, 1.34)	1.05 (0.49, 2.24)	0.44 (0.16, 1.23)	1.57 (0.90, 2.72)	0.98 (0.50, 1.92)	1.21 (0.82, 1.80)
0.26-0.28% (n=502)	0.85 (0.53, 1.35)	0.64 (0.32, 1.28)	1.12 (0.54, 2.33)	0.42 (0.13, 1.32)	0.98 (0.49, 1.94)	1.05 (0.57, 1.92)	1.09 (0.73, 1.61)
0.28-0.31% (n=506)	1.07 (0.69, 1.66)	0.97 (0.51, 1.87)	1.20 (0.61, 2.36)	0.85 (0.31, 2.36)	1.28 (0.70, 2.32)	1.09 (0.60, 1.99)	1.25 (0.85, 1.82)
>0.31% (n=511)	1.17 (0.76, 1.79)	1.52 (0.85, 2.70)	1.07 (0.54, 2.10)	1.25 (0.52, 3.00)	1.45 (0.82, 2.57)	1.34 (0.74, 2.41)	1.46 (1.02, 2.10)*
p-value for linear trend	0.27	0.10	0.74	0.34	0.36	0.31	0.045*
p-value for omega-3	0.013*	0.051	0.006**	0.10	0.93	0.013*	0.023*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3d. Eicosatrienoic Acid

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Eicosatrienoic (20:3n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<1.30% (n=489)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1.30-1.46% (n=477)	1.10 (0.73, 1.65)	1.08 (0.58, 1.99)	1.26 (0.68, 2.32)	0.78 (0.32, 1.92)	1.10 (0.63, 1.93)	1.05 (0.62, 1.79)	1.01 (0.71, 1.43)
1.46-1.63% (n=500)	1.23 (0.82, 1.83)	1.24 (0.68, 2.26)	1.24 (0.68, 2.29)	1.00 (0.44, 2.27)	1.36 (0.80, 2.31)	0.88 (0.50, 1.56)	1.14 (0.81, 1.60)
1.63-1.85% (n=504)	1.12 (0.74, 1.69)	0.94 (0.50, 1.77)	1.06 (0.55, 2.04)	1.18 (0.53, 2.61)	1.03 (0.61, 1.77)	1.00 (0.59, 1.72)	1.02 (0.73, 1.44)
>1.85% (n=530)	0.94 (0.62, 1.41)	1.39 (0.79, 2.45)	0.71 (0.37, 1.35)	0.89 (0.42, 1.88)	1.16 (0.67, 2.02)	0.94 (0.52, 1.69)	1.03 (0.73, 1.44)
p-value for linear trend	0.77	0.36	0.22	0.92	0.71	0.78	0.88
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Eicosatrienoic (20:3n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<1.30% (n=489)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1.30-1.46% (n=477)	1.22 (0.77, 1.91)	1.05 (0.54, 2.03)	1.52 (0.75, 3.08)	1.02 (0.32, 3.24)	1.12 (0.61, 2.06)	0.86 (0.47, 1.56)	1.05 (0.71, 1.56)
1.46-1.63% (n=500)	1.44 (0.93, 2.22)	1.19 (0.63, 2.25)	1.76 (0.90, 3.46)	1.40 (0.47, 4.20)	1.52 (0.84, 2.75)	1.00 (0.54, 1.82)	1.39 (0.96, 2.02)
1.63-1.85% (n=504)	1.31 (0.85, 2.04)	0.91 (0.46, 1.81)	1.65 (0.81, 3.33)	1.59 (0.57, 4.41)	1.07 (0.58, 1.98)	1.06 (0.60, 1.86)	1.21 (0.84, 1.76)
>1.85% (n=530)	1.05 (0.66, 1.67)	1.29 (0.69, 2.42)	0.90 (0.42, 1.94)	1.45 (0.49, 4.35)	1.37 (0.71, 2.66)	1.02 (0.56, 1.87)	1.37 (0.93, 2.01)
p-value for linear trend	0.72	0.58	0.78	0.32	0.43	0.69	0.083
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
C. Eicosatrienoic (20:3n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total

<1.30% (n=489)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1.30-1.46% (n=477)	1.18 (0.75, 1.85)	1.00 (0.52, 1.94)	1.47 (0.73, 2.98)	1.04 (0.34, 3.19)	1.12 (0.61, 2.07)	0.82 (0.45, 1.50)	1.04 (0.71, 1.54)
1.46-1.63% (n=500)	1.37 (0.89, 2.11)	1.12 (0.59, 2.13)	1.64 (0.84, 3.20)	1.32 (0.43, 4.00)	1.52 (0.83, 2.79)	0.92 (0.49, 1.71)	1.32 (0.90, 1.94)
1.63-1.85% (n=504)	1.25 (0.80, 1.93)	0.85 (0.43, 1.67)	1.53 (0.76, 3.09)	1.51 (0.55, 4.15)	1.07 (0.58, 1.99)	1.00 (0.57, 1.76)	1.18 (0.82, 1.71)
>1.85% (n=530)	0.95 (0.59, 1.51)	1.15 (0.62, 2.15)	0.75 (0.34, 1.65)	1.27 (0.44, 3.69)	1.38 (0.71, 2.68)	0.87 (0.46, 1.63)	1.27 (0.86, 1.88)
p-value for linear trend	0.89	0.85	0.57	0.46	0.43	0.94	0.18
p-value for omega-3	0.009**	0.032*	0.005**	0.12	0.96	0.009**	0.028*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3e. Arachidonic Acid

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Arachidonic (20:4n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<15.6% (n=507)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
15.6-16.5% (n=519)	1.17 (0.80, 1.71)	1.01 (0.57, 1.77)	1.13 (0.63, 2.03)	2.34 (1.10, 5.35)*	0.74 (0.45, 1.25)	1.13 (0.67, 1.92)	1.10 (0.80, 1.51)
16.5-17.3% (n=502)	0.93 (0.62, 1.39)	0.92 (0.52, 1.64)	0.77 (0.41, 1.47)	0.99 (0.39, 2.53)	0.82 (0.49, 1.36)	1.02 (0.57, 1.83)	0.92 (0.65, 1.30)
17.3-18.1% (n=497)	1.13 (0.75, 1.71)	1.23 (0.71, 2.13)	0.98 (0.52, 1.87)	1.68 (0.72, 3.93)	1.01 (0.61, 1.65)	1.28 (0.75, 2.20)	1.18 (0.86, 1.63)
>18.1% (n=475)	0.98 (0.66, 1.45)	0.87 (0.48, 1.57)	1.04 (0.58, 1.87)	0.84 (0.37, 1.88)	0.72 (0.43, 1.21)	1.25 (0.72, 2.17)	0.92 (0.66, 1.28)
p-value for linear trend	0.86	0.96	0.95	0.42	0.53	0.35	0.83
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Arachidonic (20:4n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<15.6% (n=507)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
15.6-16.5% (n=519)	1.29 (0.86, 1.94)	1.06 (0.58, 1.93)	1.44 (0.75, 2.79)	3.11 (1.31, 7.31)**	0.87 (0.51, 1.49)	1.34 (0.74, 2.38)	1.25 (0.89, 1.76)
16.5-17.3% (n=502)	0.94 (0.61, 1.42)	0.89 (0.48, 1.65)	0.97 (0.50, 1.87)	1.22 (0.30, 3.71)	0.80 (0.44, 1.47)	1.15 (0.60, 2.23)	1.04 (0.71, 1.52)
17.3-18.1% (n=497)	1.32 (0.86, 2.03)	1.37 (0.75, 2.51)	1.34 (0.67, 2.66)	2.45 (0.93, 6.46)	1.16 (0.68, 1.99)	1.50 (0.82, 2.74)	1.36 (0.95, 1.95)
>18.1% (n=475)	1.11 (0.71, 1.72)	0.93 (0.48, 1.77)	1.42 (0.73, 2.77)	1.08 (0.37, 3.19)	0.93 (0.53, 1.63)	1.51 (0.81, 2.80)	1.11 (0.76, 1.62)
p-value for linear trend	0.64	0.84	0.40	0.96	0.82	0.18	0.43
	Hazard ratios (95% CIs)						

C. Arachidonic (20:4n6)	Total Events			Mortality			
	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<15.6% (n=507)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
15.6-16.5% (n=519)	1.17 (0.77, 1.75)	0.96 (0.53, 1.72)	1.24 (0.64, 2.39)	2.69 (1.04, 6.99)*	0.86 (0.50, 1.50)	1.23 (0.68, 2.22)	1.18 (0.83, 1.67)
16.5-17.3% (n=502)	0.83 (0.54, 1.26)	0.76 (0.41, 1.40)	0.80 (0.41, 1.58)	1.05 (0.32, 2.48)	0.79 (0.42, 1.50)	0.99 (0.50, 1.95)	0.94 (0.63, 1.40)
17.3-18.1% (n=497)	1.12 (0.72, 1.75)	1.14 (0.62, 2.11)	1.03 (0.51, 2.09)	1.98 (0.66, 5.93)	1.15 (0.65, 2.02)	1.29 (0.69, 2.38)	1.21 (0.83, 1.78)
>18.1% (n=475)	0.93 (0.59, 1.47)	0.74 (0.38, 1.46)	1.09 (0.55, 2.19)	0.89 (0.28, 2.81)	0.92 (0.50, 1.68)	1.28 (0.68, 2.41)	0.99 (0.66, 1.47)
p-value for linear trend	0.69	0.62	0.97	0.54	0.85	0.46	0.95
p-value for omega-3	0.009**	0.03*	0.01*	0.09	0.94	0.02*	0.023*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3f. Docosatetraenoic Acid

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Docosatetraenoic (22:4n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<3.08% (n=515)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3.08-3.62% (n=510)	1.60 (1.04, 2.46)*	1.62 (0.85, 3.08)	1.47 (0.71, 3.03)	1.25 (0.56, 2.78)	0.80 (0.49, 1.31)	1.29 (0.75, 2.23)	1.02 (0.75, 1.40)
3.62-4.03% (n=502)	1.56 (1.02, 2.39)*	2.19 (1.19, 4.03)*	1.38 (0.70, 2.74)	0.93 (0.40, 2.13)	0.61 (0.36, 1.05)	0.97 (0.53, 1.78)	0.78 (0.55, 1.09)
4.03-4.47% (n=499)	1.57 (1.04, 2.37)*	1.58 (0.83, 3.00)	1.98 (1.04, 3.77)*	1.23 (0.57, 2.4)	0.63 (0.37, 1.07)	1.14 (0.61, 2.12)	0.95 (0.68, 1.32)
>4.47% (n=474)	1.68 (1.10, 2.58)*	2.19 (1.18, 4.07)*	1.62 (0.80, 3.26)	0.68 (0.26, 1.78)	1.15 (0.71, 1.86)	1.43 (0.82, 2.49)	1.11 (0.78, 1.56)
p-value for linear trend	0.036*	0.025*	0.10	0.54	0.98	0.37	0.78
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Docosatetraenoic (22:4n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<3.08% (n=515)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3.08-3.62% (n=510)	1.42 (0.89, 2.26)	1.39 (0.70, 2.78)	1.75 (0.76, 4.00)	1.04 (0.39, 2.79)	0.78 (0.37, 1.31)	1.15 (0.63, 2.09)	0.97 (0.68, 1.37)
3.62-4.03% (n=502)	1.52 (0.98, 2.35)	2.01 (1.05, 3.84)*	1.80 (0.85, 3.82)	0.89 (0.36, 2.21)	0.70 (0.40, 1.21)	0.88 (0.42, 1.84)	0.85 (0.58, 1.24)
4.03-4.47% (n=499)	1.54 (1.00, 2.37)	1.45 (0.72, 2.92)	2.51 (1.25, 5.04)**	1.51 (0.71, 3.23)	0.56 (0.30, 1.04)	1.27 (0.66, 2.44)	1.00 (0.70, 1.42)
>4.47% (n=474)	1.56 (0.97, 2.50)	1.81 (0.89, 3.69)	2.11 (0.97, 4.59)	0.76 (0.25, 2.32)	1.15 (0.6, 1.93)	1.43 (0.78, 2.61)	1.14 (0.79, 1.66)
p-value for linear trend	0.068	0.13	0.022*	0.92	0.91	0.22	0.49
	Hazard ratios (95% CIs)						
	Total Events			Mortality			

C. Docosatetraenoic (22:4n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<3.08% (n=515)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3.08-3.62% (n=510)	1.33 (0.84, 2.11)	1.30 (0.65, 2.59)	1.59 (0.70, 3.59)	0.94 (0.35, 2.55)	0.76 (0.45, 1.29)	0.99 (0.54, 1.82)	0.88 (0.62, 1.2)
3.62-4.03% (n=502)	1.30 (0.81, 2.07)	1.69 (0.84, 3.42)	1.44 (0.68, 3.07)	0.63 (0.24, 1.65)	0.66 (0.36, 1.20)	0.67 ((0.31, 1.45)	0.69 (0.46, 1.04)
4.03-4.47% (n=499)	1.26 (0.78, 2.03)	1.16 (0.55, 2.45)	1.92 (0.91, 4.06)	0.93 (0.36, 2.42)	0.52 (0.26, 1.02)	0.91 (0.46, 1.81)	0.77 (0.52, 1.15)
>4.47% (n=474)	1.24 (0.74, 2.08)	1.37 (0.61, 3.05)	1.58 (0.72, 3.48)	0.47 (0.13, 1.66)	1.05 (0.54, 2.06)	0.92 (0.47, 1.80)	0.84 (0.54, 1.29)
p-value for linear trend	0.64	0.71	0.27	0.29	0.81	0.77	0.39
p-value for omega-3	0.051	0.11	0.07	0.07	0.79	0.02*	0.012*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3g. Docosapentaenoic Acid

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Docosapentaenoic (22:5n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.51% (n=493)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.51-0.61% (n=504)	1.41 (0.93, 2.12)	1.21 (0.65, 2.27)	1.96 (1.01, 3.84)*	0.76 (0.35, 1.63)	0.69 (0.41, 1.16)	0.93 (0.49, 1.76)	0.79 (0.57, 1.11)
0.61-0.70% (n=520)	1.24 (0.81, 1.89)	1.28 (0.68, 2.41)	1.53 (0.78, 3.02)	0.59 (0.23, 1.53)	0.63 (0.37, 1.08)	1.57 (0.89, 2.77)	0.91 (0.65, 1.27)
0.70-0.80% (n=497)	1.41 (0.92, 2.16)	1.70 (0.95, 3.05)	1.26 (0.60, 3.02)	1.07 (0.47, 2.44)	0.72 (0.41, 1.22)	1.72 (0.97, 3.06)	1.08 (0.77, 1.51)
>0.80% (n=486)	1.44 (0.93, 2.22)	1.67 (0.92, 3.04)	1.64 (0.79, 3.40)	1.11 (0.50, 2.46)	1.01 (0.62, 1.65)	1.84 (1.03, 3.29)*	1.25 (0.89, 1.73)
p-value for linear trend	0.13	0.04*	0.61	0.55	0.93	0.006*	0.048*
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Docosapentaenoic (22:5n6)	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<0.51% (n=493)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.51-0.61% (n=504)	1.31 (0.84, 2.03)	0.95 (0.47, 1.90)	2.35 (1.10, 4.99)*	0.86 (0.35, 2.13)	0.77 (0.45, 1.33)	0.68 (0.35, 1.33)	0.81 (0.56, 1.17)
0.61-0.70% (n=520)	1.11 (0.70, 1.78)	1.15 (0.57, 2.34)	1.69 (0.79, 3.61)	0.45 (0.15, 1.32)	0.61 (0.34, 1.09)	1.26 (0.65, 2.46)	0.80 (0.55, 1.17)
0.70-0.80% (n=497)	1.46 (0.94, 2.27)	1.50 (0.79, 2.84)	1.85 (0.85, 4.01)	1.29 (0.54, 3.13)	0.78 (0.44, 1.39)	1.58 (0.87, 2.85)	1.12 (0.78, 1.62)
>0.80% (n=486)	1.39 (0.88, 2.20)	1.41 (0.73, 2.70)	2.01 (0.93, 4.35)	1.48 (0.61, 3.62)	1.04 (0.62, 1.76)	1.51 (0.83, 2.74)	1.28 (0.90, 1.80)
p-value for linear trend	0.13	0.30	0.23	0.25	0.89	0.02*	0.04*
	Hazard ratios (95% CIs)						

	Total Events			Mortality			
	CVD	CHD	Stroke	CVD	Cancer	Other	Total
C. Docosapentaenoic (22:5n6)							
<0.51% (n=493)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.51-0.61% (n=504)	1.16 (0.73, 1.83)	0.85 (0.42, 1.72)	1.93 (0.91, 4.11)	0.63 (0.23, 1.76)	0.75 (0.43, 1.31)	0.57 (0.29, 1.14)	0.73 (0.50, 1.06)
0.61-0.70% (n=520)	0.92 (0.56, 1.50)	0.93 (0.45, 1.93)	1.23 (0.55, 2.73)	0.27 (0.08, 0.88)*	0.58 (0.31, 1.08)	0.96 (0.47, 1.94)	0.67 (0.44, 1.00)
0.70-0.80% (n=497)	1.17 (0.72, 1.89)	1.17 (0.57, 2.40)	1.27 (0.56, 2.88)	0.83 (0.35, 2.05)	0.73 (0.38, 1.41)	1.20 (0.63, 2.32)	0.93 (0.63, 1.39)
>0.80% (n=486)	1.08 (0.64, 1.81)	1.06 (0.51, 2.20)	1.34 (0.57, 3.14)	0.89 (0.34, 2.33)	0.98 (0.54, 1.77)	1.09 (0.57, 2.11)	1.02 (0.69, 1.52)
p-value for linear trend	0.79	0.53	0.88	0.64	0.95	0.19	0.29
p-value for omega-3	0.03*	0.11	0.01*	0.15	0.92	0.07	0.09

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD

Table S3h. n6 index (sum of all 7 n6's)

	Hazard ratios (95% CIs)						
	Total Events			Mortality			
A. Omega-6 index	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<32.6% (n=473)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
32.6-34.1% (n=502)	1.01 (0.66, 1.54)	0.78 (0.39, 1.55)	1.03 (0.53, 2.00)	0.90 (0.38, 2.15)	0.79 (0.47, 1.33)	1.24 (0.74, 2.07)	1.08 (0.77, 1.51)
34.1-35.1% (n=510)	1.17 (0.79, 1.74)	1.52 (0.84, 2.75)	1.14 (0.62, 2.08)	1.25 (0.53, 2.94)	0.84 (0.52, 1.36)	1.06 (0.58, 1.94)	1.06 (0.75, 1.49)
35.1-36.2% (n=491)	1.51 (1.01, 2.24)*	1.60 (0.90, 2.86)	1.61 (0.88, 2.94)	1.11 (0.52, 2.36)	0.79 (0.53, 1.38)	0.94 (0.54, 1.65)	1.05 (0.75, 1.45)
>36.2% (n=524)	0.77 (0.49, 1.20)	1.33 (0.74, 2.40)	0.47 (0.21, 1.07)	0.57 (0.22, 1.49)	0.64 (0.38, 1.10)	1.05 (0.61, 1.83)	0.86 (0.61, 1.21)
p-value for linear trend	0.93	0.06	0.42	0.52	0.19	0.76	0.41
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
B. Omega-6 index	CVD	CHD	Stroke	CVD	Cancer	Other	Total
<32.6% (n=473)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
32.6-34.1% (n=502)	0.94 (0.60, 1.48)	0.66 (0.30, 1.43)	1.08 (0.51, 2.30)	1.19 (0.38, 2.94)	0.86 (0.50, 1.49)	1.23 (0.68, 2.21)	1.15 (0.79, 1.66)
34.1-35.1% (n=510)	1.28 (0.84, 1.95)	1.68 (0.88, 3.21)	1.38 (0.70, 2.73)	2.16 (0.92, 5.10)	1.02 (0.61, 1.71)	1.48 (0.79, 2.77)	1.44 (1.00, 2.06)
35.1-36.2% (n=491)	1.76 (1.17, 2.65)**	1.82 (0.99, 3.36)	2.31 (1.20, 4.47)*	1.81 (0.82, 3.96)	1.12 (0.65, 1.93)	0.96 (0.52, 1.77)	1.27 (0.89, 1.82)
>36.2% (n=524)	1.06 (0.65, 1.74)	1.69 (0.87, 3.26)	0.77 (0.32, 1.86)	1.05 (0.37, 2.97)	0.83 (0.44, 1.56)	1.72 (0.97, 3.07)	1.28 (0.87, 1.88)
p-value for linear trend	0.08	0.006*	0.31	0.28	0.88	0.24	0.14
	Hazard ratios (95% CIs)						
	Total Events			Mortality			
C. Omega-6 index	CVD	CHD	Stroke	CVD	Cancer	Other	Total

<32.6% (n=473)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
32.6-34.1% (n=502)	0.84 (0.52, 1.34)	0.63 (0.28, 1.40)	0.82 (0.36, 1.83)	1.01 (0.36, 2.78)	0.84 (0.48, 1.46)	0.95 (0.51, 1.78)	1.02 (0.70, 1.49)
34.1-35.1% (n=510)	1.03 (0.64, 1.66)	1.55 (0.79, 3.06)	0.85 (0.38, 1.91)	1.60 (0.59, 4.30)	0.97 (0.56, 1.66)	0.93 (0.45, 1.93)	1.17 (0.78, 1.76)
35.1-36.2% (n=491)	1.35 (0.84, 2.19)	1.64 (0.84, 3.22)	1.33 (0.58, 3.03)	1.26 (0.43, 3.66)	1.05 (0.55, 2.03)	0.54 (0.25, 1.18)	0.99 (0.64, 1.55)
>36.2% (n=524)	0.78 (0.42, 1.42)	1.48 (0.66, 3.35)	0.41 (0.14, 1.22)	0.73 (0.22, 2.46)	0.77 (0.36, 1.65)	0.91 (0.42, 1.94)	0.97 (0.60, 1.57)
p-value for linear trend	0.96	0.07	0.37	0.74	0.74	0.43	0.77
p-value for omega-3	0.041*	0.60	0.007**	0.14	0.73	0.01*	0.047*

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

*P<0.05; **P<0.01

All significant hazard ratios/P-values are shown in bold italics.

A. Unadjusted model, B. Adjusted for all variables in Table 1 except history of CVD, C. Adjusted for omega-3 index and all variables in Table 1 except history of CVD