Supplemental Online Content

Nissen SE, Lincoff AM, Wolski K, et al. Association between achieved ω-3 fatty acid levels and major adverse cardiovascular outcomes in patients with high cardiovascular risk: a secondary analysis of the STRENGTH Trial. *JAMA Cardiol.* Published online May 16, 2021. doi:10.1001/jamacardio.2021.1157

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

eTable 1. Baseline characteristics for patients with and without omega-3 fatty acid levels available

	Patients with omega 3 fatty acid data N=10382	Patients without omega 3 fatty acid data N=2696
Age, mean (SD),– (years)	62.5 ± 8.9	62.4 ± 9.5
Female sex – no. (%)	3588 (34.6)	980 (36.4)
Body mass index, mean (SD) – (kg/m^2)	32.5 ± 5.6	31.1 ± 5.8
Ethnicity – no (%)		
White	9025 (86.9)	1698 (63.0)
Black	277 (2.7)	69 (2.6)
Asian	564 (5.4)	791 (29.3)
Other	340 (3.3)	53 (2.0)
Established CVD at baseline no. (%)		
Coronary disease – no (%)	4629 (44.6)	1406 (52.2)
Cerebrovascular disease – no (%)	780 (7.5)	268 (9.9)
Peripheral vascular disease – no (%)	385 (3.7)	99 (3.7)
Aortic disease – no (%)	380 (3.7)	78 (2.9)
Diabetes mellitus at baseline - no (%)	3724 (35.9)	806 (29.9)
History of hypertension	9141 (88.1)	2279 (84.5)
eGFR, mean (SD) (mL/min/1.73m^2)	77.2 ± 19.3	78.1 ± 20.4
Medication use		
High-intensity statin – no (%)	5485 (52.8)	1043 (38.7)
Other statin – no (%)	4897 (47.2)	1653 (61.3)
Antiplatelet agents – no (%)	7343 (70.7)	1980 (73.4)
RAAS blockers – no (%)	8540 (82.3)	2085 (77.3)
Beta-blockers – no (%)	6897 (66.4)	1798 (66.7)
Laboratory data		
Total cholesterol (mg/dL)	162 (139, 190)	154 (135, 180)
LDL cholesterol (mg/dL)	76 (57, 101)	70 (52, 92)
HDL cholesterol (mg/dL)	36 (31, 40)	35 (31, 40)
Triglycerides (mg/dL)	240 (192, 309)	238 (189, 305)
Non-HDL cholesterol (mg/dL)	126 (105, 154)	119 (100, 144)

Apolipoprotein B (mg/dL)	57 (44, 73)	53 (41, 69)
Apolipoprotein C-III (mg/dL)	17 (14, 21)	17 (14, 21)

CVD=cardiovascular disease. eGFR=estimated glomerular filtration rate. RASS = renin aldosterone angiotensin system. LDL=Low density lipoprotein cholesterol. HDL=high density lipoprotein cholesterol.

Conversion factors for System International (SI) units. For HDL and LDL, multiply by 0.0259, for triglycerides, multiply by 0.0113

eTable 2. Absolute changes biochemical measurements from baseline to 12 months by tertile of on-treatment plasma EPA level

	All Patients N=10382	Corn Oil N=5207	All EPA N=5157	Plasma EPA Tertile 1 N=1733	Plasma EPA Tertile 2 N=1727	Plasma EPA Tertile 3 N=1715
Laboratory data						
Total cholesterol (mg/dL)	-3 (-22, 16)	0 (-19, 19)	-6 (-25, 13)	-5 (-29, 17)	-8 (-26, 7)	-4 (-21, 15)
LDL cholesterol (mg/dL)	0 (-15, 15)	-1 (-16, 14)	0 (-15, 16)	-1 (-21, 17)	-1 (-15, 12)	3 (-10, 19)
HDL cholesterol (mg/dL)	1 (-2, 5)	1 (-2, 5)	2 (-2, 5)	2 (-2, 6)	2 (-1, 5)	1 (-2, 5)
Triglycerides (mg/dL)	-24 (-88, 37)	-2 (-64, 59)	-44 (-105, 12)	-31 (-97, 29)	-49 (-106, -1)	-47 (-108, 8)
Non-HDL cholesterol (mg/dL)	-5 (-24, 14)	-2 (-20, 16)	-8 (-27, 11)	-7 (-31, 14)	-10 (-28, 5)	-6 (-23, 13)
Apolipoprotein B (mg/dL)	-1.1 (-16, 13)	-1 (-15, 12)	-1.2 (-16, 13)	-2.9 (-18, 12)	-2.1 (-16, 11)	1.3 (-13, 16)
Apolipoprotein C-III (mg/dL)	0 (-4, 4)	1 (-3, 5)	-1 (-5, 2)	-1 (-4, 3)	-2 (-5, 1)	-1 (-5, 2)
hsCRP (mg/L)*	-0.2 (-1.4, 0.6)	-0.1 (-1.2, 0.8)	-0.3 (-1.7, 0.4)	-0.5 (-1.8, 0.4)	-0.3 (-1.7, 0.6)	-0.2 (-1.6, 0.4)
Plasma EPA (ug/mL)	8 (-3.7, 66)	-2 (-8.8, 4.2)	64 (21, 102)	8 (-2, 25)	67 (53, 81)	121 (101, 148)
RBC EPA (% of total)	0.2 (-0.1, 2.1)	-0.04 (-0.2, 0.05)	2.1 (0.8, 3.2)	0.3 (0.02, 1.2)	2.3 (1.7, 2.9)	3.4 (2.7, 4.1)
Plasma DHA (ug/mL)	6 (-10, 30)	-4 (-16, 8)	24 (4, 47)	5.5 (-10, 19)	29 (13, 43)	48 (24, 69)
RBC DHA (% of total)	0.3 (-0.3, 1.4)	-0.2 (-0.6, 0.3)	1.2 (0.3, 2.2)	0.6 (-0.1, 1.4)	1.6 (0.8, 2.4)	1.6 (0.6, 2.6)

LDL=Low density lipoprotein cholesterol. HDL=high density lipoprotein cholesterol. hsCRP=high sensitivity C-reactive protein. EPA=eicosapentaenoic acid. RBC=Red blood cell. DHA=docosahexaenoic acid *All follow-up measureswere at 12 months, except for hs-CRP, which was measured at 60 months (n = 1499 in corn oil placebo and n = 1467 in omega-3 carboxylic acid).

Conversion factors for System International (SI) units. For HDL and LDL, multiply by 0.0259, for triglycerides, multiply by 0.0113

eTable 3. Relationship Between Tertiles of Achieved Red Blood Cell EPA and DHA Levels and Cardiovascular Events*

Achieved Red Blood Cell EPA				
	Red Blood Cell EPA (%)ˆ	N with events (percent)	†Adjusted HR (95% CI)	P value
Corn oil	NA	573/5185 (11.05%)	reference	NA
Achieved Red Blood Cell EPA Tertiles	<2.02	182/1719 (10.59)	1.08 (0.91, 1.28)	0.38
	2.03-3.56	203/1717 (11.82)	1.08 (0.92, 1.27)	0.36
	3.57-8.31	184/1713 (10.74)	0.90 (0.76, 1.07)	0.22
Achieved Red Blood Cell DHA				
	Red Blood Cell DHA (%)ˆ	N with events (percent)	†Adjusted HR (95% CI)	P value
Corn Oil	NA	573/5185 (11.05)	reference	NA
Achieved Red Blood Cell DHA Tertiles	<6.05	198/1713 (11.56)	1.16 (0.94, 1.43)	0.17
	6.06-6.99	184/1712 (10.75)	1.16 (0.95, 1.41)	0.14
	7-11.45	187/1724 (10.85)	0.95 (0.76, 1.17)	0.61

*Cardiovascular Death, myocardial infarction, stroke, Hospitalization for unstable angina, revascularization
†Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, gender, diabetes, creatinine, non-HDL cholesterol, high sensitivity C-reactive protein, antiplatelets agents, ß Blockers, renin angiotensin inhibitors
ˆPercent of total Omega-3 fatty acids

eTable 4. Relationship Between Tertiles of Change in Red Blood Cell EPA and DHA Levels and Cardiovascular Events*

Change in Red Blood Cell EPA				
	Red Blood Cell EPA (%)ˆ	N with events (percent)	†Adjusted HR (95% CI)	P value
Corn oil	NA	574/5207 (11.02)	reference	NA
Tertiles of Change in Red Blood Cell EPA	< 1.33	181/1714 (10.56)	1.07 (0.90, 1.27)	0.44
	1.34-2.83	203/1708 (11.89)	1.09 (0.92, 1.27)	0.32
	2.83-7.24	184/1715 (10.73)	0.92 (0.78, 1.09)	0.32

Change in Red Blood Cell DHA				
	Red Blood Cell DHA (%)ˆ	N with events (percent)	†Adjusted HR (95% CI)	P value
Corn Oil	NA	573/5185 (11.05)	reference	NA
Tertiles of Change in Red Blood Cell DHA	< 0.63	188/1718 (10.94)	1.07 (0.90, 1.27)	0.48
	0.63-1.88	189/1713 (11.03)	1.03 (0.87, 1.21)	0.76
	1.89-8.6	192/1718 (11.18)	0.96 (0.81, 1.14)	0.67

*Cardiovascular Death, myocardial infarction, stroke, Hospitalization for unstable angina, revascularization
†Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, gender, diabetes, creatinine, non-HDL cholesterol, high sensitivity C-reactive protein, antiplatelets agents, ß Blockers, renin angiotensin inhibitors
EPA=eicosapentaenoic acid. DHA=docosahexaenoic acid.
ˆPercent of total Omega-3 fatty acids

eTable 5. Relationship Between Tertiles of Change in Plasma EPA and DHA Levels and Cardiovascular Events* in the Primary Prevention Population*

	Achieved Plasma EPA			
	Plasma EPA (µg/mL)	N with events (percent)	Adjusted HR (95% CI)	Adjusted P value
Corn oil	NA	139/2367 (5.87)	reference	NA
Achieved EPA Tertiles	2.2-62.4	47/821 (5.72)	1.11 (0.79, 1.55)	0.55
	62.5-116.3	60/791 (7.59)	1.30 (0.96, 1.77)	0.09
	116.4-474.9	54/785 (6.88)	1.21 (0.88, 1.67)	0.23
	Achieved Plasma DHA Levels			
	Plasma EPA (µg/mL)	N with events (percent)	Adjusted HR (95% CI)	Adjusted P value
Corn Oil	NA	139/2367 (5.87)	reference	NA
Achieved DHA Tertiles	16-78.2	50/795 (6.29)	1.21 (0.87, 1.67)	0.26
	78.3-105.1	54/804 (6.72)	1.15 (0.84, 1.58)	0.38
	105.2-409.7	57/798 (7.14)	1.26 (0.92, 1.72)	0.15

*Cardiovascular Death, myocardial infarction, stroke, Hospitalization for unstable angina, revascularization
†Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, gender, diabetes, creatinine, non-HDL cholesterol, high sensitivity C-reactive protein, antiplatelets agents, ß Blockers, renin angiotensin inhibitors
EPA=eicosapentaenoic acid. DHA=docosahexaenoic acid.

eTable 6. Relationship Between Tertiles of Achieved Plasma EPA and DHA Levels and Cardiovascular Events* in the Secondary Prevention Population

		Achieved Plasma EPA		
	Plasma EPA (μg/mL)	N with events (percent)	†Adjusted HR (95% CI)	Adjusted P value
Corn oil	NA	435/2840 (15.32)	reference	NA
Achieved EPA Tertiles	2.2-62.4	126/912 (13.82)	0.97 (0.79, 1.18)	0.74
	62.5-116.3	148/936 (15.81)	1.03 (0.85, 1.24)	0.76
	116.4-474.9	140/930 (15.05)	0.91 (0.75, 1.11)	0.36
		Achieved Plasma DHA Levels		
	Plasma EPA (μg/mL)	N with events (percent)	†Adjusted HR (95% CI)	Adjusted P value
Corn Oil	NA	435/2840 (15.32)	reference	NA
Achieved DHA Tertiles	16-78.2	138/940 (14.68)	0.98 (0.81, 1.19)	0.87
	78.3-105.1	137/918 (14.92)	0.99 (0.81, 1.19)	0.88
	105.2-409.7	139/920 (15.11)	0.95 (0.78, 1.15)	0.59

*Cardiovascular Death, myocardial infarction, stroke, Hospitalization for unstable angina, revascularization
†Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, gender, diabetes, creatinine, non-HDL cholesterol, high sensitivity C-reactive protein, antiplatelets agents, ß Blockers, renin angiotensin inhibitors
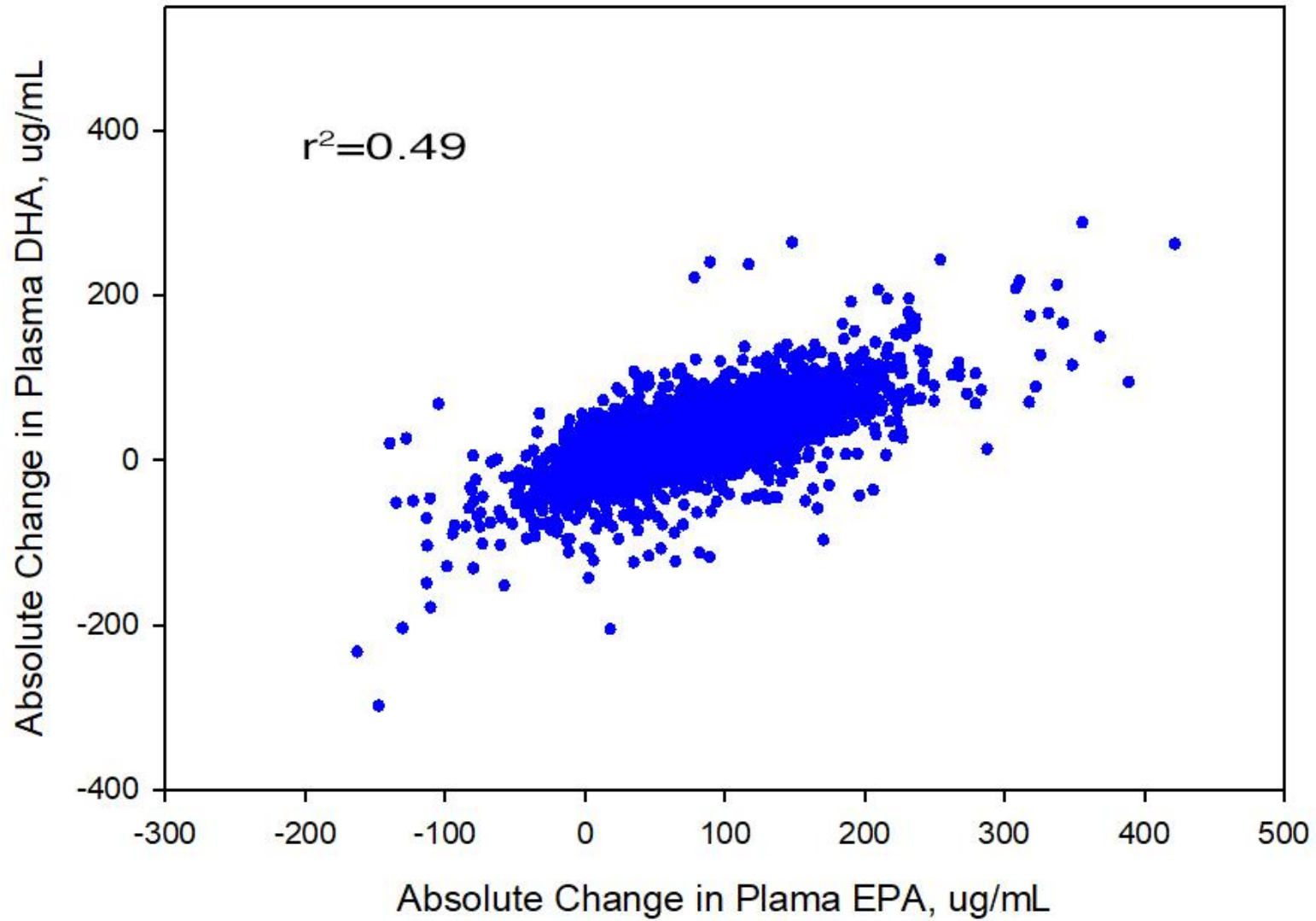EPA=eicosapentaenoic acid. DHA=docosahexaenoic acid.

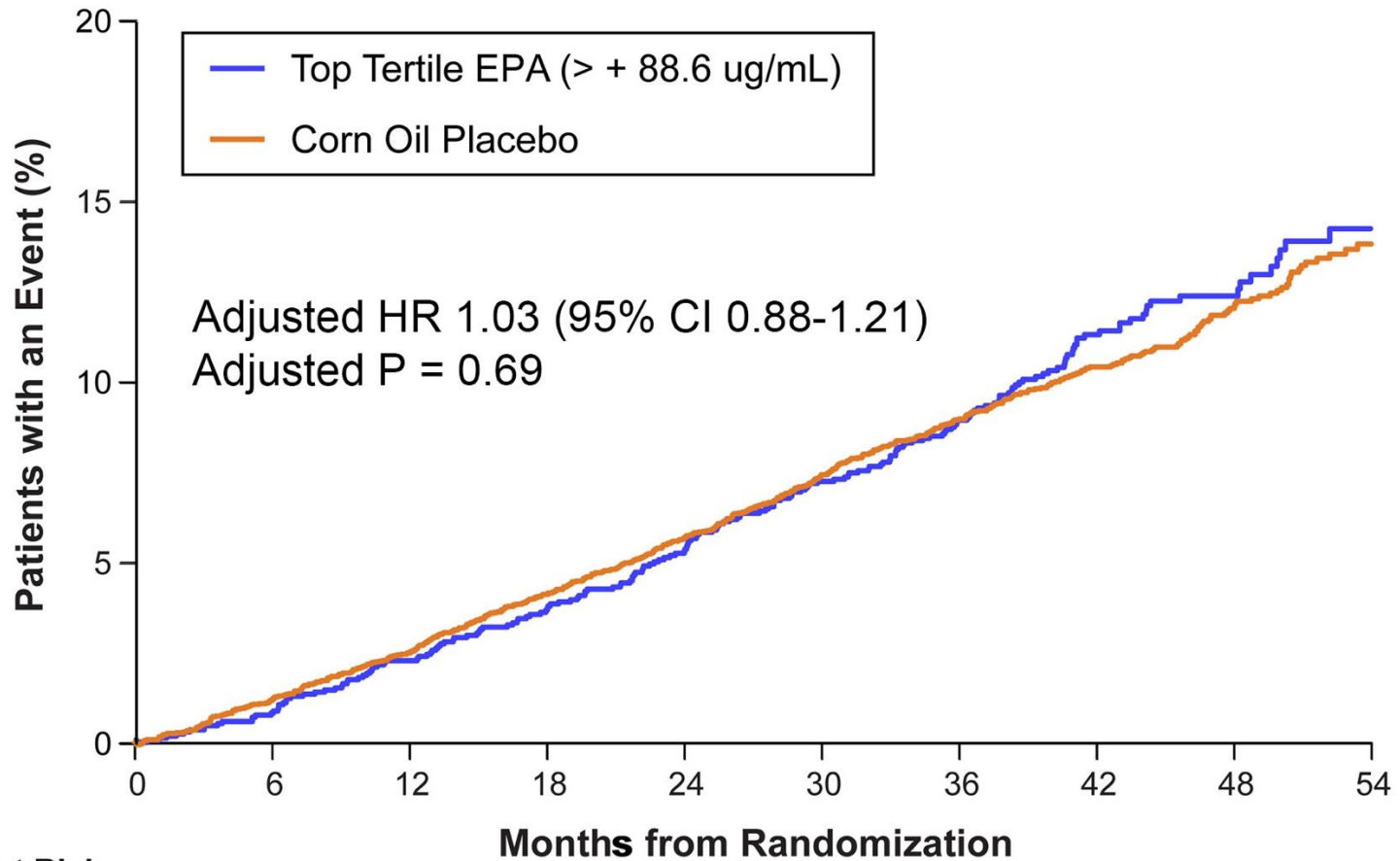**eFigure 1. Relationship between Plasma EPA and DHA Levels 12 Months after Randomization**
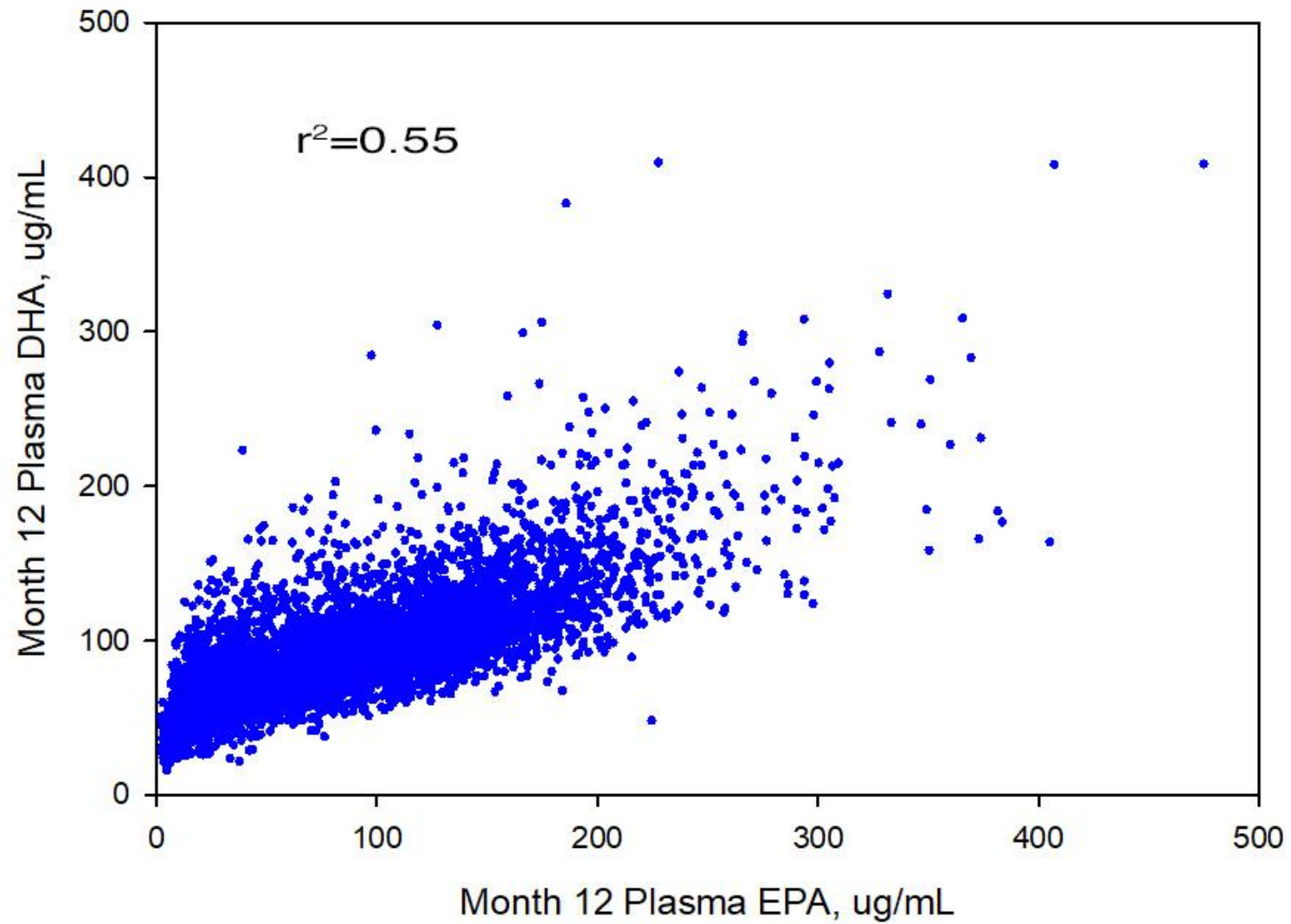
EPA=eicosapentaenoic acid. DHA=docosahexaenoic acid

eFigure 2. Relationship between Change in Plasma EPA and DHA Levels 12 Months after Randomization

EPA=eicosapentaenoic acid. DHA=docosahexaenoic acid

eFigure 3. Time to Event First Incidence of Any Component of the Primary Composite Endpoint for Patients in the Top Tertile of Change in EPA Level*
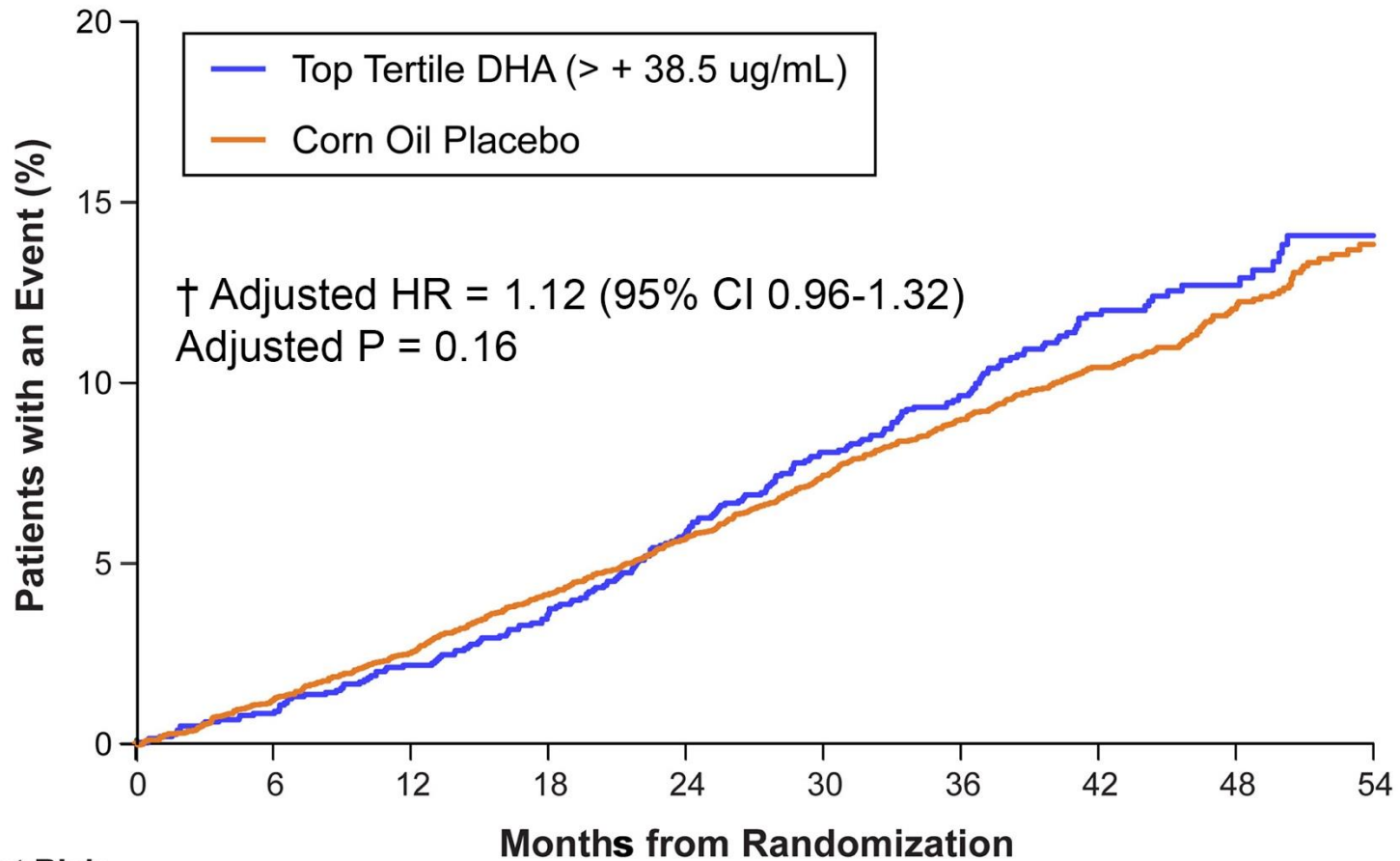

Adjusted HR 1.03 (95% CI 0.88-1.21)
Adjusted P = 0.69

Top Tertile EPA (> + 88.6 ug/mL)
Corn Oil Placebo

Patients with an Event (%)

Months from Randomization

Number at Risk

Corn Oil	5207	5063	4839	4093	1314	476
Top Tertile EPA	1724	1681	1618	1390	455	160

*The primary composite end point consisted of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.
Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, gender, diabetes, creatinine, non-HDL cholesterol, high sensitivity C-reactive protein, antiplatelets agents, ß Blockers, renin angiotensin inhibitors
EPA=eicosapentaenoic acid.

eFigure 4. Time to Event First Incidence of Any Component of the Primary Composite Endpoint for Patients in the Top Tertile of Change in DHA Level

The primary composite end point consisted of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.

†Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, gender, diabetes, creatinine, non-HDL cholesterol, high sensitivity C-reactive protein, antiplatelets agents, ß Blockers, renin angiotensin inhibitors

DHA=docosahexaenoic acid