

Omega-3 Index and Cardiovascular Health

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Outline

What the Omega-3 Index measures

What is a cardioprotective Omega-3 Index value?

How much EPA and DHA do you need to achieve a cardioprotective Omega-3 Index?

Omega-3 treatment and risk for cardiovascular disease

ASCEND, VITAL and REDUCE-IT

Safety of Omega-3

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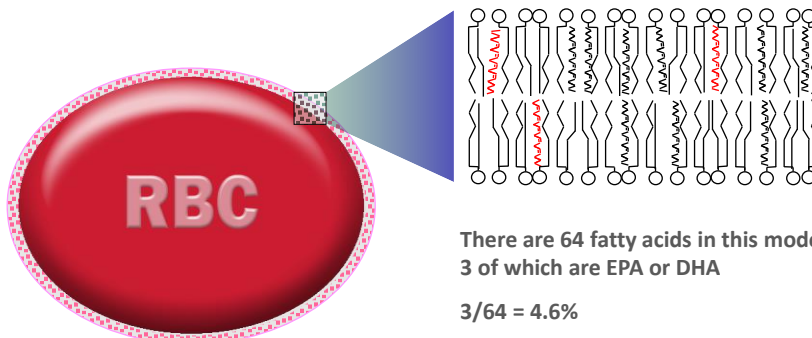


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Omega-3 Index

A measure of the amount of EPA+DHA in red blood cell membrane phospholipids expressed as the percent of total fatty acids



There are 64 fatty acids in this model membrane,
3 of which are EPA or DHA

$$3/64 = 4.6\%$$

Omega-3 Index = 4.6%

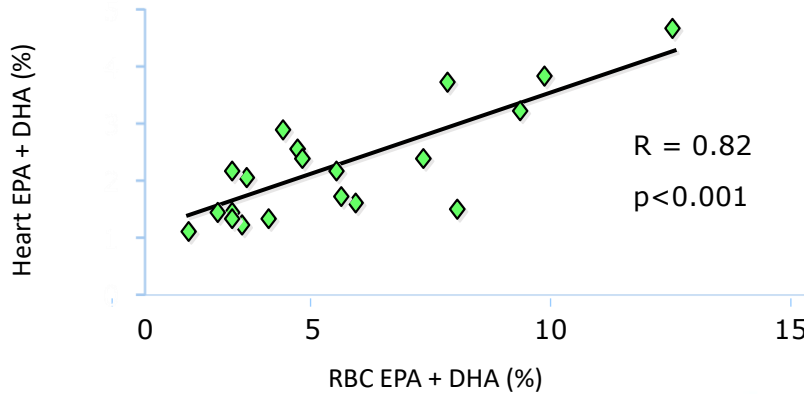
Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.



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Red Blood Cell EPA + DHA Levels are Highly Correlated with Human Myocardial Omega-3 (n=20)

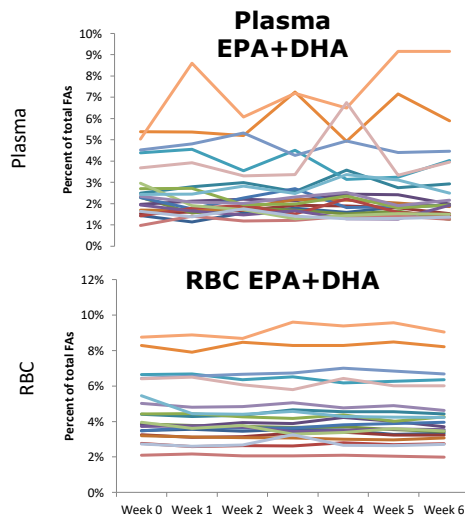


Harris WS et al. *Circulation* 2004;110:1645-1649.



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20 healthy volunteers tested weekly for 6 weeks

Total Coefficients of Variability (CVs)

EPA+DHA in...

- RBC = 4.1%
- Whole Blood = 6.7%
- Plasma = 16%
- Plasma PL = 15%

The Omega-3 Index Has Low Biological Variability

The Omega-3 Index is the "HbA1c" of Omega-3 Status

Perspective

Within person variability for hsCRP = 46%
(n=541, 2 exams 19 days apart)

Harris and Thomas. *Clin Biochem* 2010;12:338-340
Bower et al. *Arch Intern Med.* 2012;172:1519-1521



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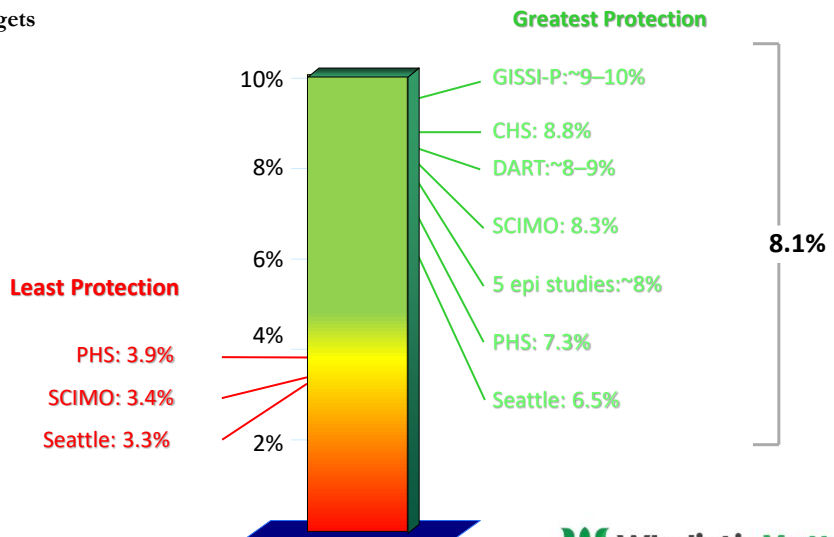


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RBC Fatty Acids & CVD Risk

Selecting Omega-3 Index Targets



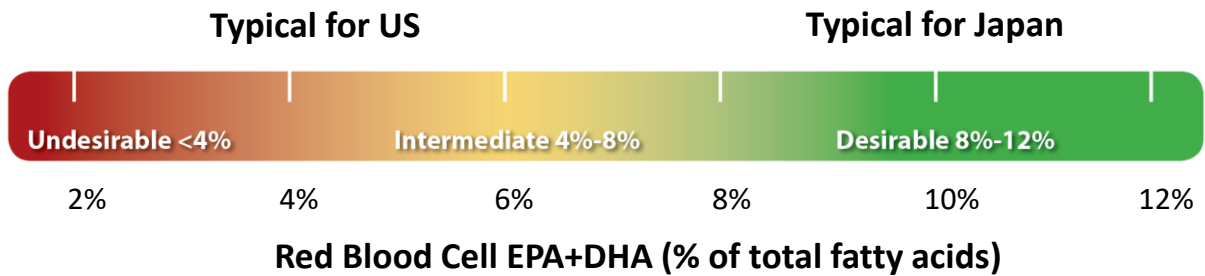
Harris WS and von Schacky. *Prev Med* 2004;39:212-220.

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Desirable Omega-3 Index is >8%



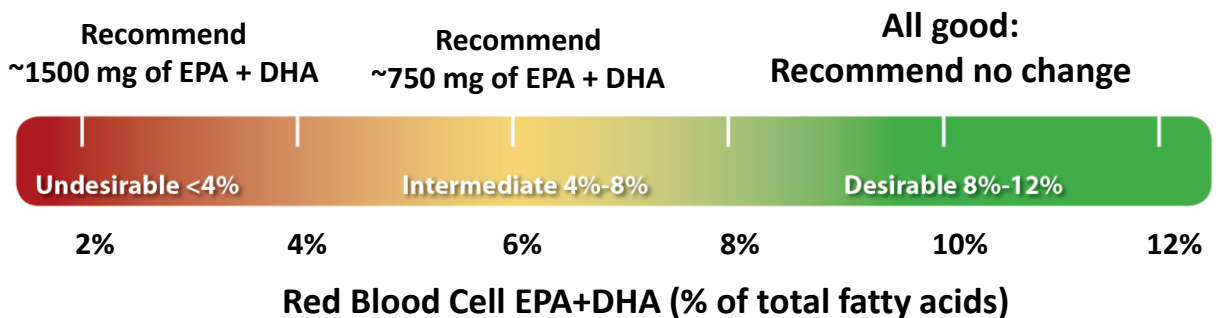
Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.



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What do you do with the Omega-3 Index?



Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.

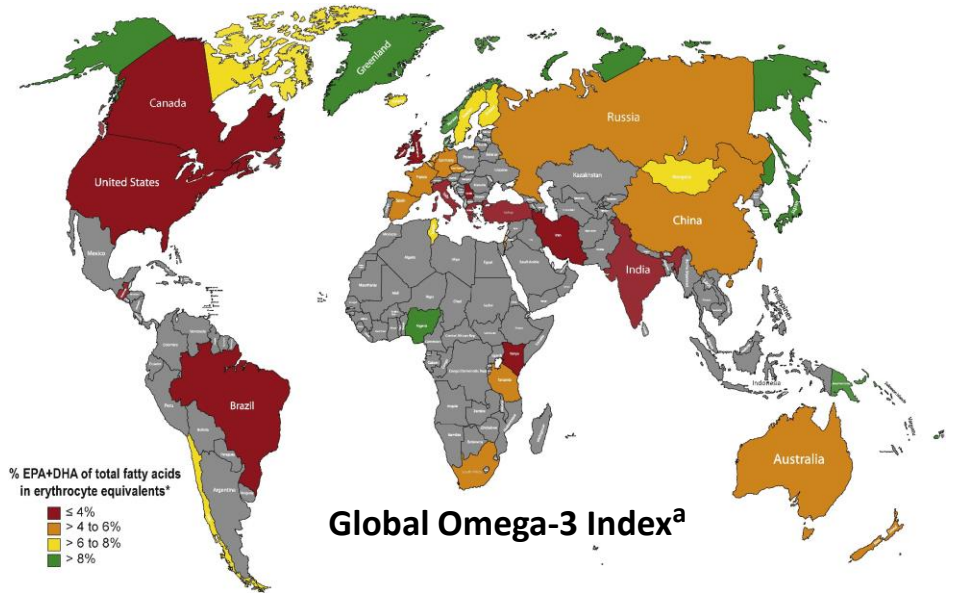


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Circulating EPA+DHA levels taken from:

- 24,129 individual subjects
- 54 countries
- 398 data sets
- Converted to Omega-3 Index equivalents based on Stark et al.^b



^a Stark et al. Global survey of the omega-3 fatty acids, DHA and EPA in the blood stream of healthy adults. *Prog Lipid Res.* 2016;63:132-152.

^b Stark et al. *PLEFA* 2016;104:1-10

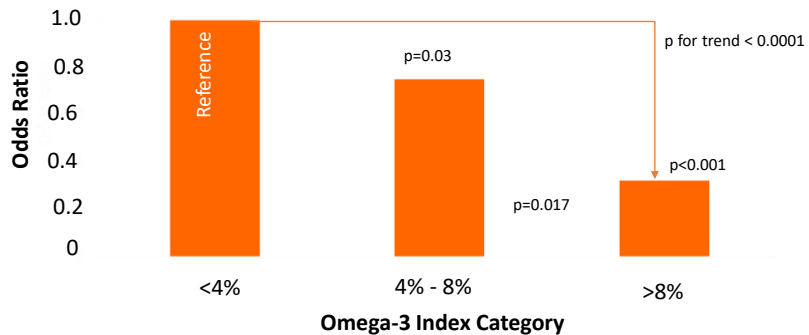


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Omega-3 Index and Acute Coronary Syndromes

768 case-control pairs



Multivariable logistic regression model including: age; race; gender; history of diabetes mellitus, hypertension, hyperlipidemia and/or myocardial infarction; a family history of coronary artery disease; and LDL-C, HDL-C, and triglycerides.

Block RC, et al. *Atherosclerosis* 2008;197 :821-828.

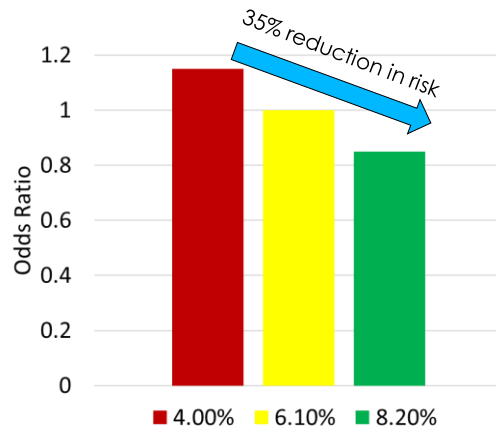


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Meta-Analysis: Omega-3 Index as a Predictor of Risk for Fatal Coronary Heart Disease

10 studies worldwide - over 27,000 subjects



Risk for fatal CHD was **35% lower** in persons with an Omega-3 Index of 8% compared with those with an Index of 4%

Harris WS, et al. Atherosclerosis 2017;262:51-54

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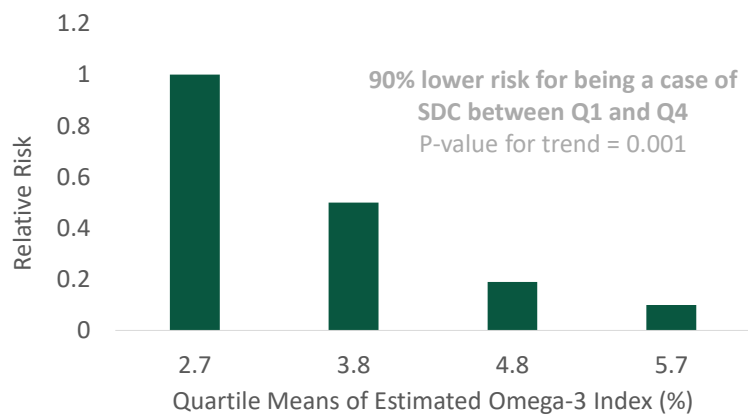
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Sudden Cardiac Death and the Omega-3 Index

Physicians' Health Study

- 15,008 male physicians 40-84 yrs in 1982 with no history of CVD or cancer provided a blood sample
- After 17 years of follow up, 94 men experienced sudden cardiac death
- Omega-3 levels were compared to those of healthy controls (n=184)



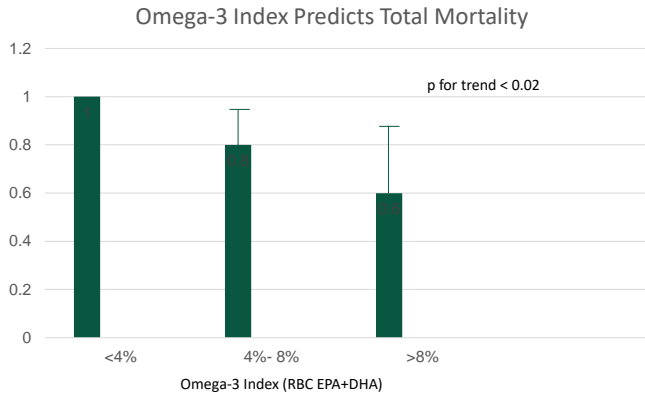
Albert et al. N Engl J Med 2002;346:1113-8

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Relative Risk for Death from Any Cause and the Omega-3 Index: The Women's Health Initiative Memory Study



Multivariable-adjusted risk for death from any cause between age 70 and 85 in 6501 post-menopausal women was 31% lower with an Omega-3 Index of >8% vs <4%

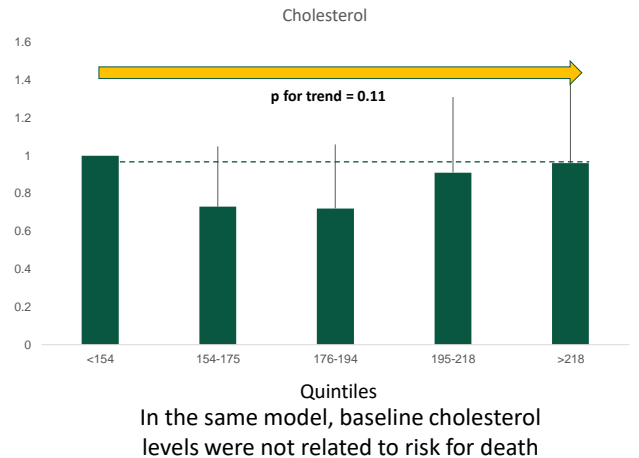
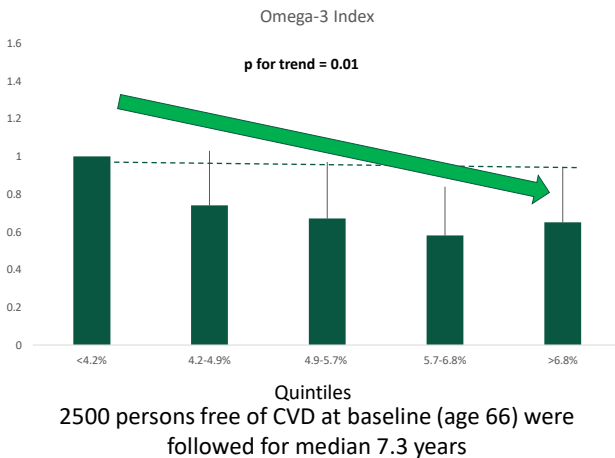
Harris WS, et al. J Clin Lipidol 2017;11:250-259



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Relative Risk for Death from Any Cause and the Omega-3 Index: The Framingham Offspring Study



Harris WS, et al. J Clin Lipidol 2018;12:718-727



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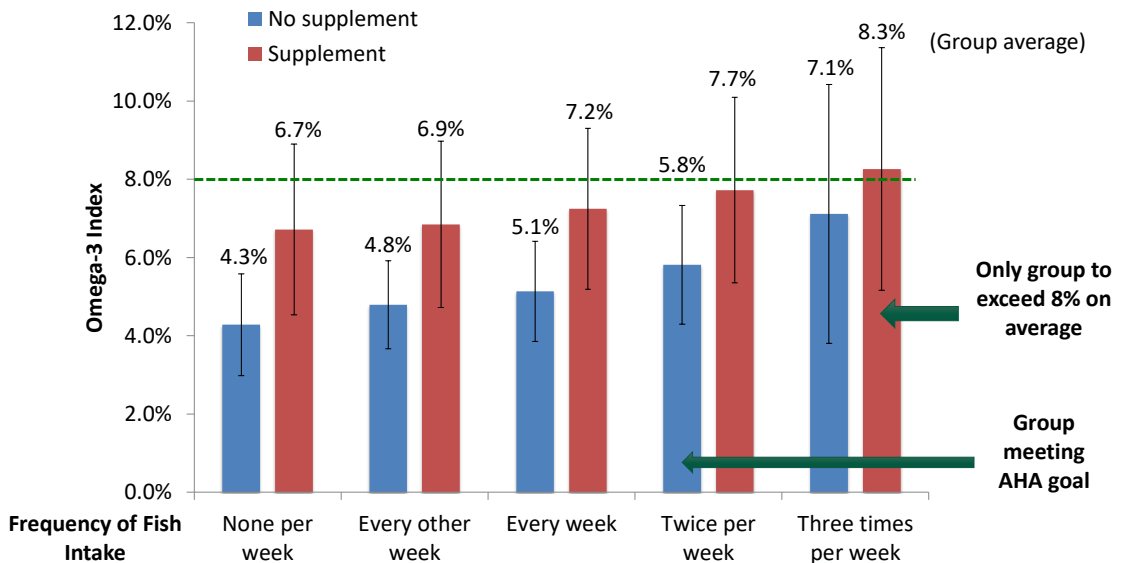
Safety of Omega-3



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The Omega-3 Index Reflected Fish + Supplementation



Jackson et al. Prostaglandins, Leukotrienes and Essential Fatty Acids 142 (2019) 4–10

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2018 TRIALS: OMEGA-3 & HEART DISEASE

ASCEND

EFFECT OF N-3 DIETARY SUPPLEMENTS IN DIABETES MELLITUS

VITAL

MARINE N-3 FATTY ACIDS AND VITAMIN D FOR THE PREVENTION OF CARDIOVASCULAR DISEASE AND CANCER.

REDUCE-IT

REDUCTION OF CARDIOVASCULAR EVENTS WITH ICOSAPENT ETHYL—INTERVENTION TRIAL



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ASCEND

Effect of n-3 dietary supplements in diabetes mellitus

- Design: Randomized controlled trial
- Study subjects: 15,480 patients with diabetes – but without evidence of atherosclerotic cardiovascular disease
- Treatments: n-3 FAs (1 g, containing 840 mg EPA+DHA) or olive oil placebo (1 g)
- Compliance: 76%

ASCEND Study Collaborative Group. NEJM Aug 26, 2018 DOI: 10/NEJMoa1804989.



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ASCEND

Effect of n-3 dietary supplements in diabetes mellitus

- Duration: Median 7.4 years
- Primary endpoint: Serious vascular events (composite of non-fatal MI or stroke, transient ischemic attack, or vascular death)
- Primary finding: “No significant difference in serious vascular events with n-3 FA treatment”

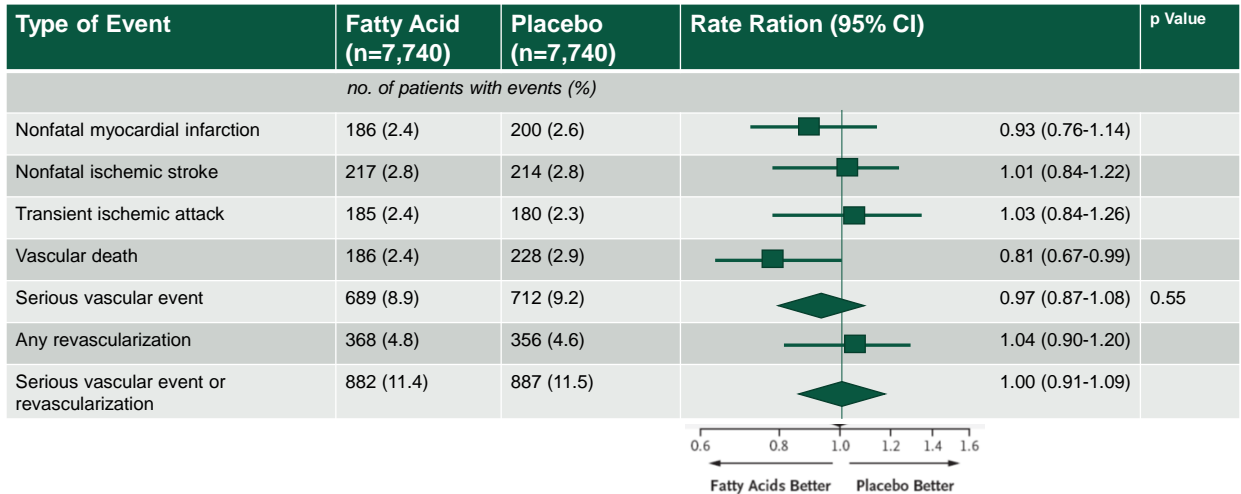
ASCEND Study Collaborative Group. NEJM Aug 26, 2018 DOI: 10/NEJMoa1804989.



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Primary Outcomes in ASCEND



Adapted from ASCEND Study Collaborative Group. NEJM Aug 26, 2018 DOI: 10/NEJMoa1804989.



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ASCEND

Despite negative conclusions from the authors, EPA+DHA significantly reduced risk for fatal vascular events.

It should be considered a successful trial.



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VITAL

Marine n-3 Fatty Acids and VITAMIN D FOR THE Prevention of Cardiovascular Disease and Cancer.

- Design: 2x2 factorial randomized controlled trial
- Study subjects: 25,871 US subjects >50 yoa with no history of CHD or cancer
- Treatments: n-3 FAs (1 g, containing 840 mg EPA+DHA) and/or 2000 IU Vitamin D (with matching placebos)

Manson JE, et al. NEJM 2018. doi: 10.1056/NEJMoa1811403.

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VITAL

- Duration: Median 5.3 years
- Primary endpoint: major CV events (composite of myocardial infarction, stroke, and death from CV causes)
- Primary finding: “Supplementation with n–3 fatty acids did not result in a lower incidence of major CV or cancer than placebo.”

Manson JE, et al. NEJM 2018. doi: 10.1056/NEJMoa1811403.

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VITAL

Table 2. Hazard Ratios and 95% Confidence Intervals for Primary, Secondary, and Other End Points, According to Randomized Assignment to n-3 Fatty Acids or Placebo, in Intention-to Treat Analyses

End Point	N-3 Group (n=12,933)	Placebo Group (n=12,938)	Hazzard Ratio (95% CI)
Cardiovascular(CV) Disease			
	<i>no. of participants with event</i>		
Primary End point: major CV event	386	419	.92 (0.80-1.06)
Total myocardial infraction	527	567	0.93 (0.82-1.04)
Total Stroke	145	200	0.72 (0.59-0.90)
Death from cardiovascular causes	142	148	0.96 (0.76-1.21)

Adapted from Manson JE, et al. NEJM 2018. doi: 10.1056/NEJMoa1811403.



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VITAL

Despite negative conclusions from the authors,
EPA+DHA significantly reduced risk for several
important cardiovascular events.

It should be considered a successful trial.



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REDUCE-IT

- Design: Randomized controlled trial
- Study subjects: 8179 patients with median LDL-C 75 mg/dL (all on statins) and median TG of 216 mg/dL with either a history of CVD or diabetes
- Treatments: EPA ethyl esters (Vascepa, Amarin Corp) or placebo (4 g/d)
- Duration: 4.9 yrs
- Primary Outcome: Major Adverse Cardiovascular Events

Bhatt et al. NEJM Nov 10, 2018 DOI: 10.1056/NEJMoa1812792.



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REDUCE-IT

Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis.

Bhatt et al. NEJM Nov 10, 2018 DOI: 10.1056/NEJMoa1812792.



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Safety of Fish Oil Supplements

Gastrointestinal: Side effects of n-3 FA can include fishy taste, eructation, diarrhea, and nausea. The PIs for the pharmaceutical forms list GI side effect rates as low (<5%) and similar to placebo.

Bleeding: Due to the known anti-platelet effect of all n-3 FA products, PIs suggest that patients taking both n-3 FA and an anticoagulant or anti-platelet agent “be monitored periodically.” Nonetheless, it is also stated that use of n-3-FA in combination with such agents “do not produce clinically-significant bleeding episodes.”

Fish/Seafood Allergies: n-3 FA products contain highly purified oils (no peptides) and do not appear to be allergenic*. Thus, patients with fish allergies need not avoid these products, although the FDA labels state “use with caution.”

*Mark BJ, Beatty AD, Slavin RG. Are fish oil supplements safe in finned fish-allergic patients? *Allergy Asthma Proc.* 2008;29:528-529.



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Less Bleeding with Omega-3 Treatment in the OPERA Study

- 1516 patients undergoing open heart surgery in 28 centers US, Argentina and Italy
- Given 10 g EPA+DHA over 3-5 days pre-surgery and 2 g/d until discharge
- Shown Significant Difference ($p < 0.001$) reduction in total unit of blood transfusion for those who received omega 3 vs placebo

Adapted from Akintoye et al. Circ Cardiovasc Qual Outcomes. 2018 Nov;11(11):e004584



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Omega-3 & Heart Health

- Omega-3 fatty acids – EPA+DHA – have beneficial effects on multiple systems in the body.
- Higher intakes than are typical for Americans are needed to achieve cardioprotective levels
- There are no safety concerns
- Omega-3 status can be measured and used to titrate patients to a desirable level
- Omega-3 fatty acids do “work” to reduce risk for CVD – dose, patient type, formulation, duration



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The Omega-3 Index is Reduced in Patients with Depression

Author	Country	N Controls / Cases	Omega-3 Index Controls / Cases	P-value
Baek ^a	Korea	80 / 80	9.47% / 8.61%	0.006
Baghai ^b	Germany	86 / 80	5.1% / 3.9%	0.001
Amin ^c	USA	641 / 118	3.3% / 2.9%	0.002

^a Baek and Park. PLEFA 2013;89:291-296

^b Baghai et al. J Clin Psych 2011;72:1242-1247

^c Amin et al. Psychosom Med 2008;70:856-862



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A Higher Omega-3 Index is Linked with Less Hostility & Better Attention in Prisoners

	Correlation	Adj P-value
7 pt scale of aggressive behavior	-0.207	0.023
Total Aggression	-0.234	0.023
Physical Aggression	-0.174	0.065
Verbal Aggression	-0.159	0.087
Anger	-0.222	0.023
Hostility	-0.239	0.023
Indirect Aggression	-0.188	0.051
Total BADDS*	-0.263	0.023
<small>*Brown's Attention Deficit Disorder Scales</small>		
Activation	-0.236	0.023
Attention	-0.192	0.051
Effort	-0.253	0.023
Affect	-0.330	<0.001
Memory	-0.240	0.023

Meyer et al. PLoS ONE 2015;10(3): e0120220. doi:10.1371/journal.pone.0120220



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The Omega-3 Index and Incident Dementia Women's Health Initiative Memory Study

6706 women; median age, 70 and follow-up, 9.8 yrs

Probable Dementia (587 cases)		Mild Cognitive Impairment (671 cases)		PD or MCI (1047 cases)	
HR*	P value	HR	P value	HR	P value
0.91	<0.03	0.95	0.23	0.94	0.07

Hazard ratio per 1-SD increase in the Omega-3 Index. Model adjusted for HT trial arm, age, education, race/ethnicity, cardiovascular disease, hypertension, diabetes, education, BMI, smoking status, alcohol use and baseline 3MS score.

Ammann, et al (manuscript under review, 2017)



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Higher Omega-3 Index is Associated with Larger Brain Hippocampal Volume in Whims

Postmenopausal women (n=1111) participating in the Women's Health Initiative Memory Study (WHIMS) had blood was drawn and red blood cells frozen (~1996), and brain volumes measured by MRI in 2004.

RBC EPA+DHA levels were measured and correlated with brain dimensions.

There was a positive correlation between the Omega-3 Index and total brain volume and hippocampal volume.

Pottala et al. Neurology 2014;82:435-442



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The Omega-3 Index was Directly Related to Hippocampal Volume in WHIMS*

Larger volume \approx better memory

*Women's Health Initiative Memory Study

Pottala et al. Neurology 2014;82:435–442



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Conclusion

The Omega-3 Index is an essential tool to help recommend omega-3 supplements for optimal patient health.



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