Omega-3 Index: From biomarker to risk marker to risk factor

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State of The Science
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BIG PICTURE

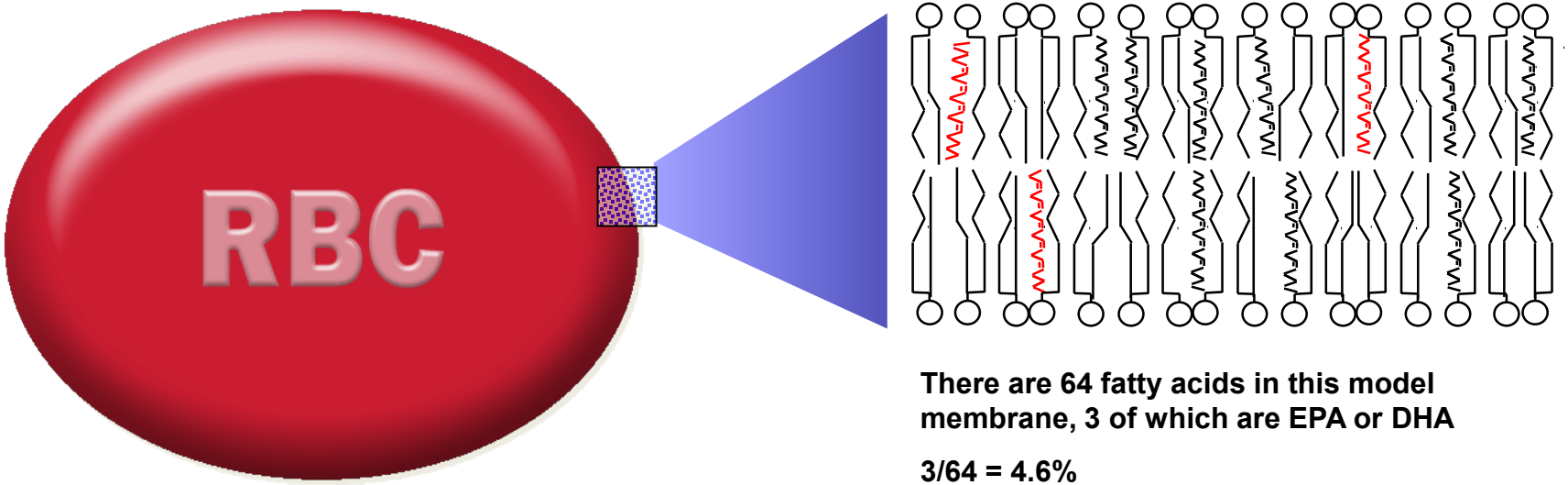
Why include this topic in the SNP Conference?

Once consumers find out via a blood test that they are low (deficient*) in omega-3 fatty acids then they should be more motivated to “fix” it, and that should drive them to eat more omega-3 rich fish

* At increased risk for disease or death

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

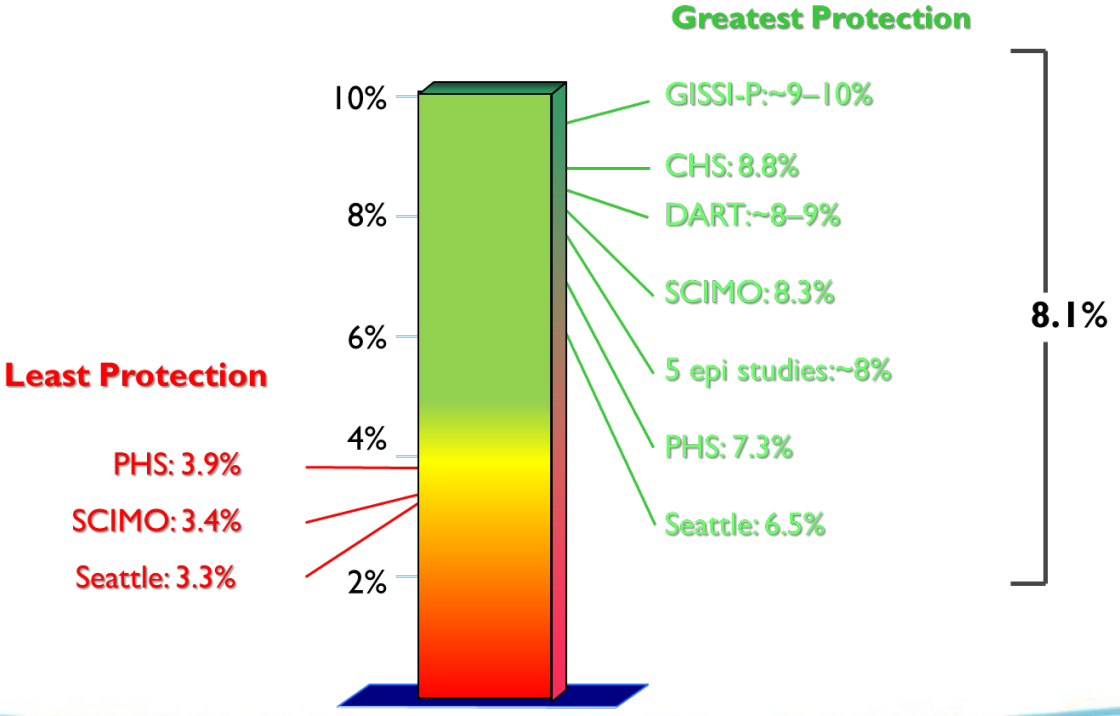
3/64 = 4.6%

Omega-3 Index = 4.6%

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

OMEGA-3 INDEX AND RISK FOR CARDIOVASCULAR DISEASE

Selecting Omega-3 Index Targets



Harris WS and von Schacky C.
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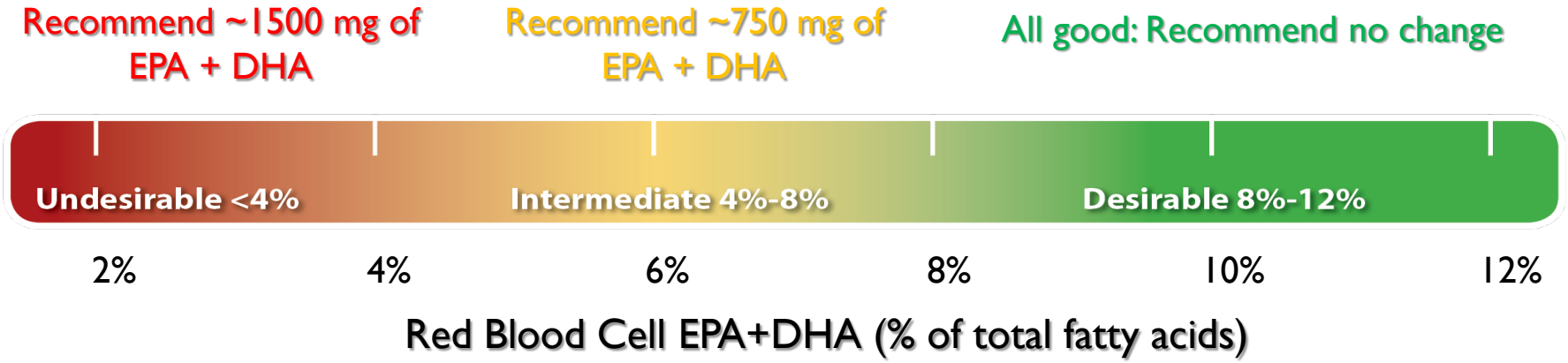
Omega-3 Index Target



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

Omega-3 Index:
A *bio*-marker of omega-3 intake

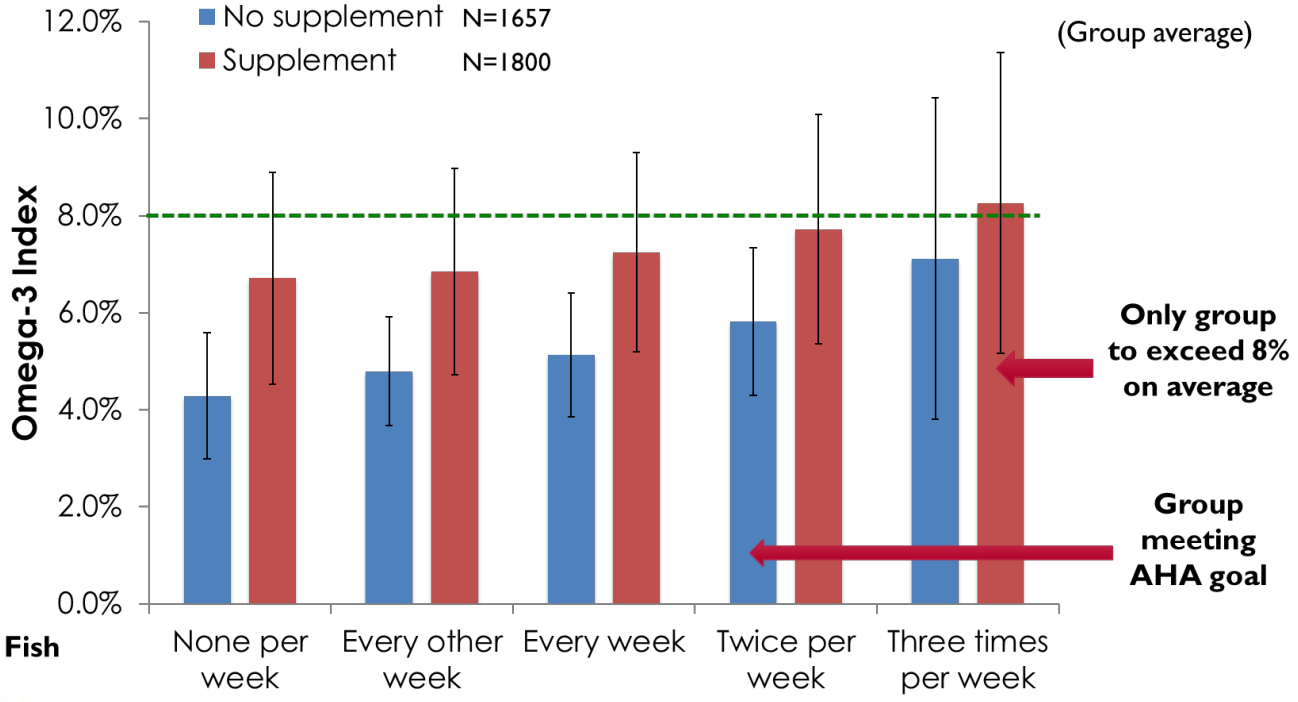
Docosahexaenoic acid status of preterm infants at birth and following feeding with human milk or formula[1–3]

Susan E Carlson, PhD, Philip G Rhodes, MD, and Mitzi G Ferguson, MD

ABSTRACT The docosahexaenoic acid (DHA) status of preterm infants (< 32 wk gestation) was measured as the molar percent of DHA in individual red blood cell phospholipids: *1*) in cord venous blood immediately following delivery, *2*) after infants were receiving > 60 kcal · kg · day of energy from oral-gastric feedings, and *3*) at a mean of 7 wk later. Infants on full feeding received either preterm human milk or formula. The DHA concentration of all phospholipid classes declined between birth and the time at which enteral feedings constituted the primary source of energy. Subsequent feeding with preterm human milk increased the molar percent of red blood cell phospholipid DHA, while DHA declined further in infants fed formula. Infants fed human milk compared to those fed formula had a significantly higher molar percent of DHA in all red blood cell phospholipids studied. *Am J Clin Nutr* 1986;44:798–804.

KEY WORDS
Human milk, formula, preterm, infants, docosahexaenoic acid, arachidonic acid

The Omega-3 Index: A validated biomarker of omega-3 intake



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

Omega-3 Index: A *risk* marker for cardiovascular disease

AHA Phases of Evaluation of a Novel Risk Marker		
Criterion	Description	Satisfied by the omega-3 index?
Proof of concept	Do novel marker levels differ between subjects with and without the outcome?	Yes
Prospective validation	Does the novel marker predict development of future outcomes in a prospective cohort or nested case-cohort/case-cohort study?	Yes
Incremental value	Does the novel marker add predictive information to established, standard risk markers?	Uncertain; prediction is independent of standard risk markers
Clinical utility	Does the novel risk marker change predicted risk sufficiently to change recommended therapy?	Yes, given the safety and low cost of treating
Clinical outcomes	Does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?	Yes (in secondary analyses of RCTs)
Cost-effectiveness	Does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?	Yes, given the low cost of testing and treating

Hlatky MA, et al. Criteria for evaluation of novel markers of cardiovascular risk: *Circulation*. 2009;119:2408-2416.

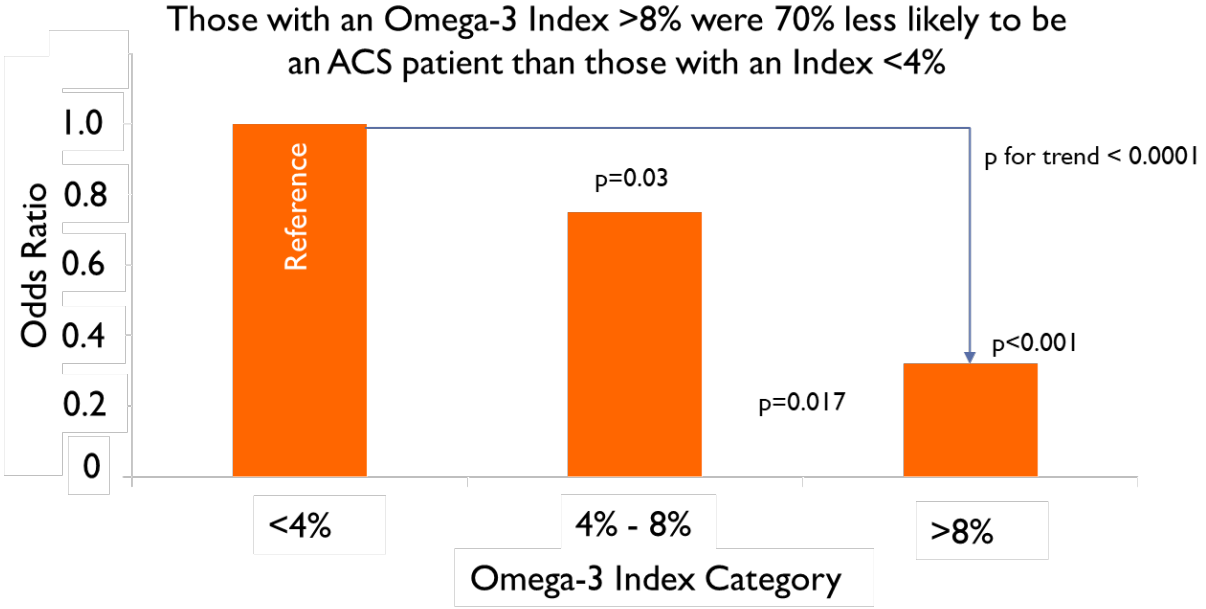
Omega-3 Index:
A *risk factor* for cardiovascular disease (and beyond!)

Hill Criteria for Causation		
Criterion	**Description**	**Satisfied by the omega-3 index?**
Temporal Relation	Exposure to the factor always precedes the disease.	Yes
Strength	The stronger the association, the more likely the causal relation.	Yes
Dose-Response Relation	The greater the exposure, the lesser the incidence (or prevalence) of the disease.	Yes
Consistency and Coherence	The association between the factor and the disease is consistent across different study designs, using different analytical methods, endpoints and populations. In addition, data from several disciplines (epidemiology, biochemistry, randomized trials, cell culture, animal models, etc.) harmonize.	Yes, but more studies always needed Yes
Plausibility	The association between the factor and the disease is reasonable given the current understanding of biology.	Yes
Experiment	Changing exposure to the factor changes the incidence of the disease.	Yes
Specificity	A specific factor is associated with a specific disease.	No – linked to several disease outcomes

Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. 1965;58:295-300.

OMEGA-3 INDEX AND ACUTE CORONARY SYNDROMES (768 CASE-CONTROL PAIRS)

Do novel marker levels differ between subjects with and without the outcome?



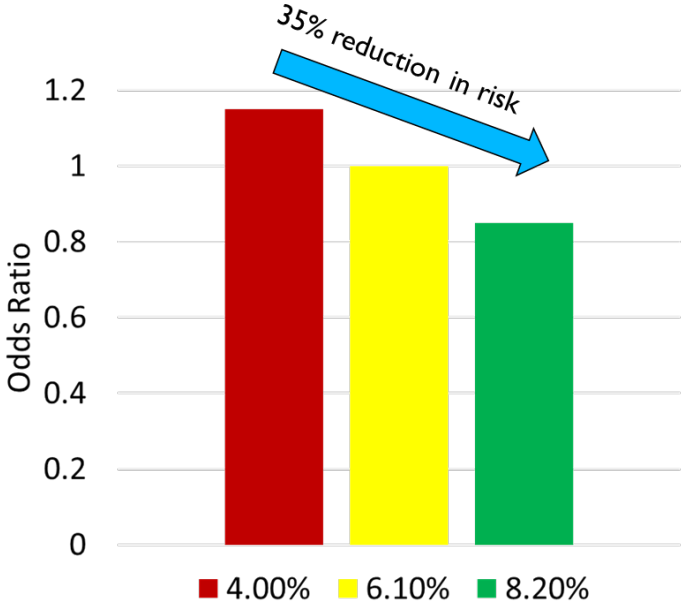
Block RC, et al. Atherosclerosis 2008;197 :821-828.

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.

META-ANALYSIS: OMEGA-3 INDEX AS A PREDICTOR OF RISK FOR FATAL CORONARY HEART DISEASE

(10 STUDIES WORLDWIDE - OVER 27,000 SUBJECTS)

Does the marker predict development of future outcomes in a prospective cohort studies?

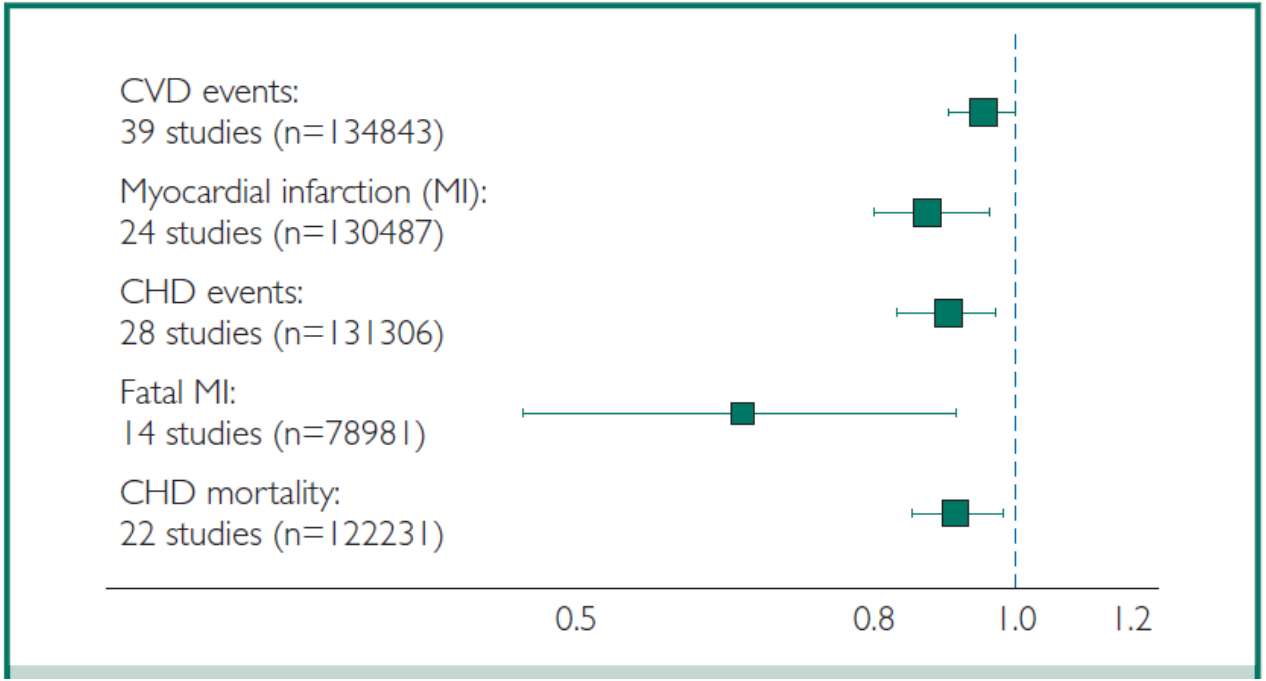


Risk for fatal CHD was 35% lower in persons with an Omega-3 Index of 8% compared with those with an Index of 4%

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

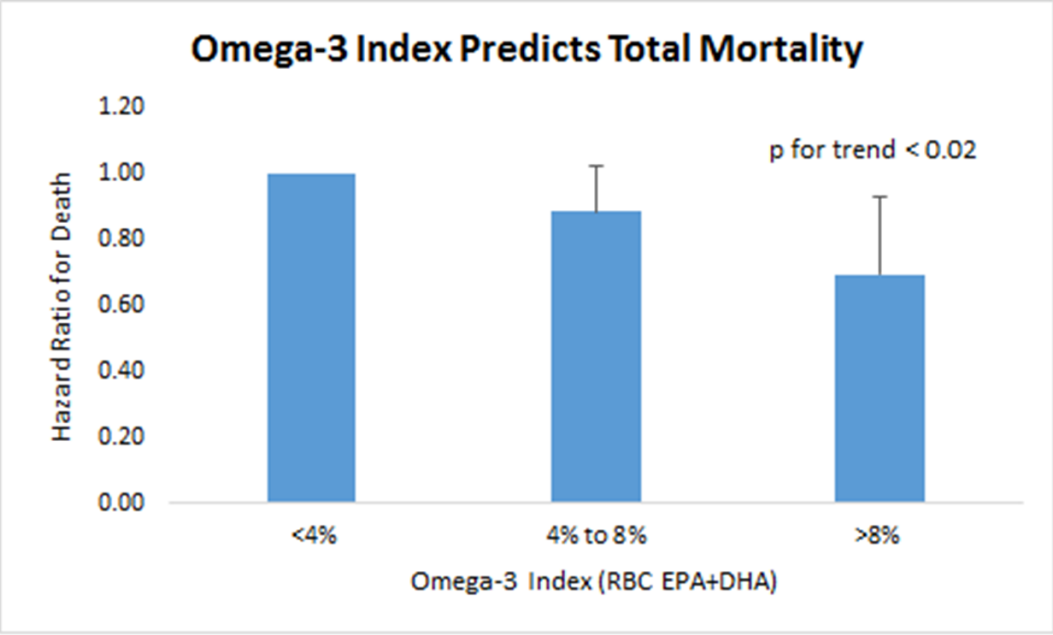
Latest Meta-analysis of Randomized Omega-3 Trials

Changing exposure to the factor changes the incidence of the disease.



Relative risk reduction in each outcome in the omega-3 vs the placebo groups

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

OMEGA-3 INDEX

Validated biomarker of omega-3 intake
- Better than dietary intake questionnaire
- More stable than plasma omega-3 levels

Satisfies 6 of 7 AHA Criteria as a Risk Marker
- Incremental value needs further study

Satisfies 6 of 7 Hill Criteria for a Causal (Risk) Factor
- Fails to be "specific" for heart disease (but that's not a weakness)

Omega-3 Index – Biomarker to Risk Factor Conclusions

- Higher Omega-3 Index levels are clearly associated with better health
- The primary way to raise the Omega-3 Index is by eating more “oily” fish (salmon, herring, sardines, albacore tuna, etc.)
- Omega-3 (EPA+DHA) capsules can also raise the Omega-3 Index