THE OMEGA-3 INDEX AND ITS CLINICAL IMPORTANCE

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OUTLINE

- My history in omega-3 research

- The Omega-3 Index

- Birth and Development of the Omega-3 Index

- Accuracy and Precision of the Omega-3 Index test

- Omega-3 Index and Risk for Cardiovascular and Neurocognitive Disease, and Death

MY HISTORY IN OMEGA-3 RESEARCH

- PhD in Nutritional Biochemistry 1978

- First paper on salmon oil and serum lipids in 1980

- 5 NIH grants to study omega-3, lipid metabolism and risk prediction

- Co-invented the Omega-3 Index with 2004 publication

- Currently 263 publications on fatty acids and health

- Founded OmegaQuant Analytics as a fatty acid specialty lab in 2009

- Currently analyzing 3-4000 samples per month

WS HARRIS – TOP AUTHOR FOR OMEGA-3

Top authors for omega 3

- Harris William S (106)
- Serhan Charles N (50)
- Kang Jing X (49)
- Calder Philip C (45)
- Clandinin M T (43)
- McNamara Robert K (43)
- Hibbeln Joseph R (39)
- Holman R T (32)
- Sinclair Andrew J (29)
- von Schacky Clemens (28)

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

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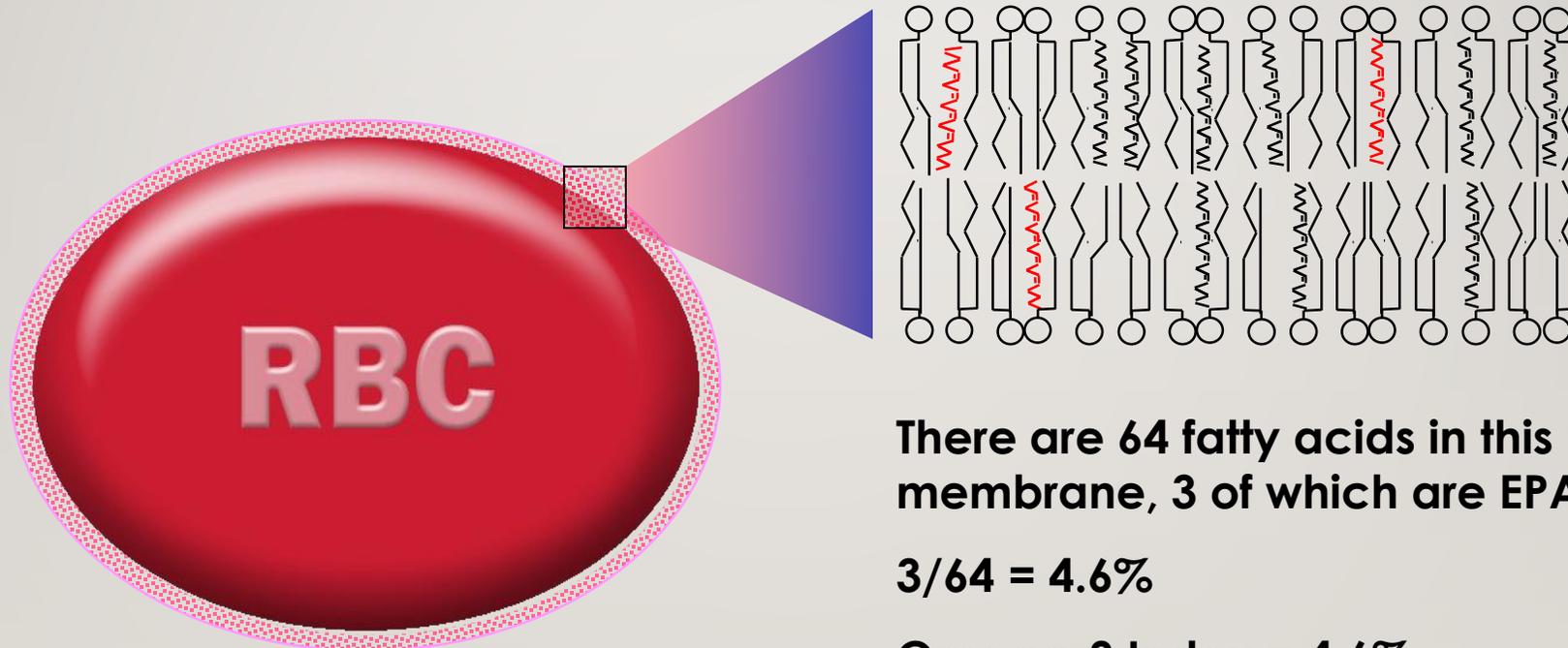
There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

3/64 = 4.6%

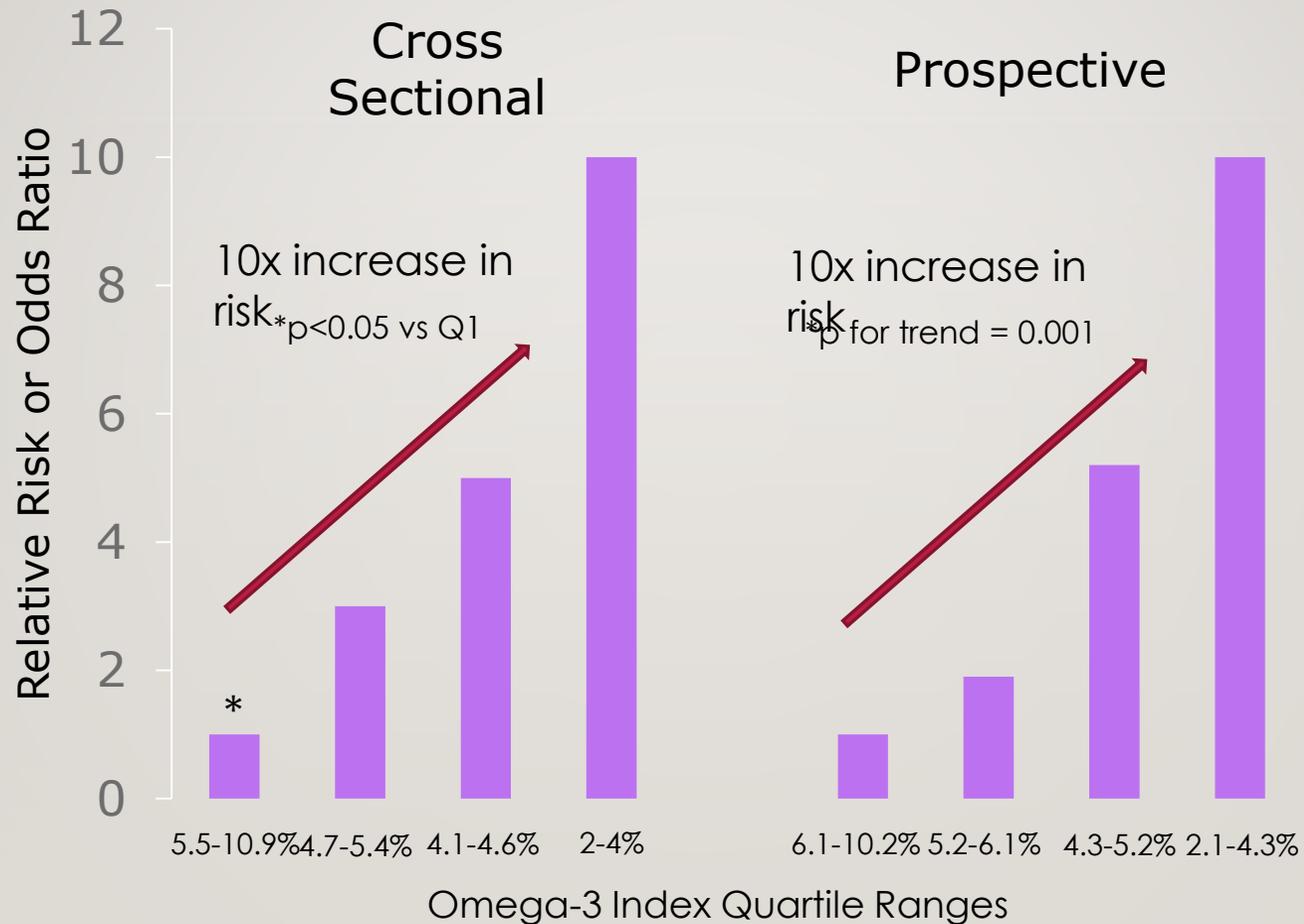**Omega-3 Index = 4.6%**

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

BIRTH AND DEVELOPMENT OF THE OMEGA-3 INDEX

- Conceived November 2002 in Chicago

- Co-inventers were myself and Clemens von Schacky, MD (Munich)

- Siscovick (JAMA 1995) and Albert (NEJM 2002) laid the foundation

- OmegaQuant (USA) and Omegametrix (GDR) established as sister labs

- Omega-3 Index adopted by Health Diagnostic Lab - use exploded

- At least 5 US clinical labs now offering an omega-3 status test

- Test partially reimbursed by third party payers

RISK FOR PRIMARY CARDIAC ARREST AND RED BLOOD CELL EPA+DHA LEVEL

Cross Sectional

Prospective

Relative Risk or Odds Ratio

10x increase in risk *p<0.05 vs Q1

10x increase in risk p for trend = 0.001

*

5.5-10.9% 4.7-5.4% 4.1-4.6% 2-4%

6.1-10.2% 5.2-6.1% 4.3-5.2% 2.1-4.3%

Omega-3 Index Quartile Ranges
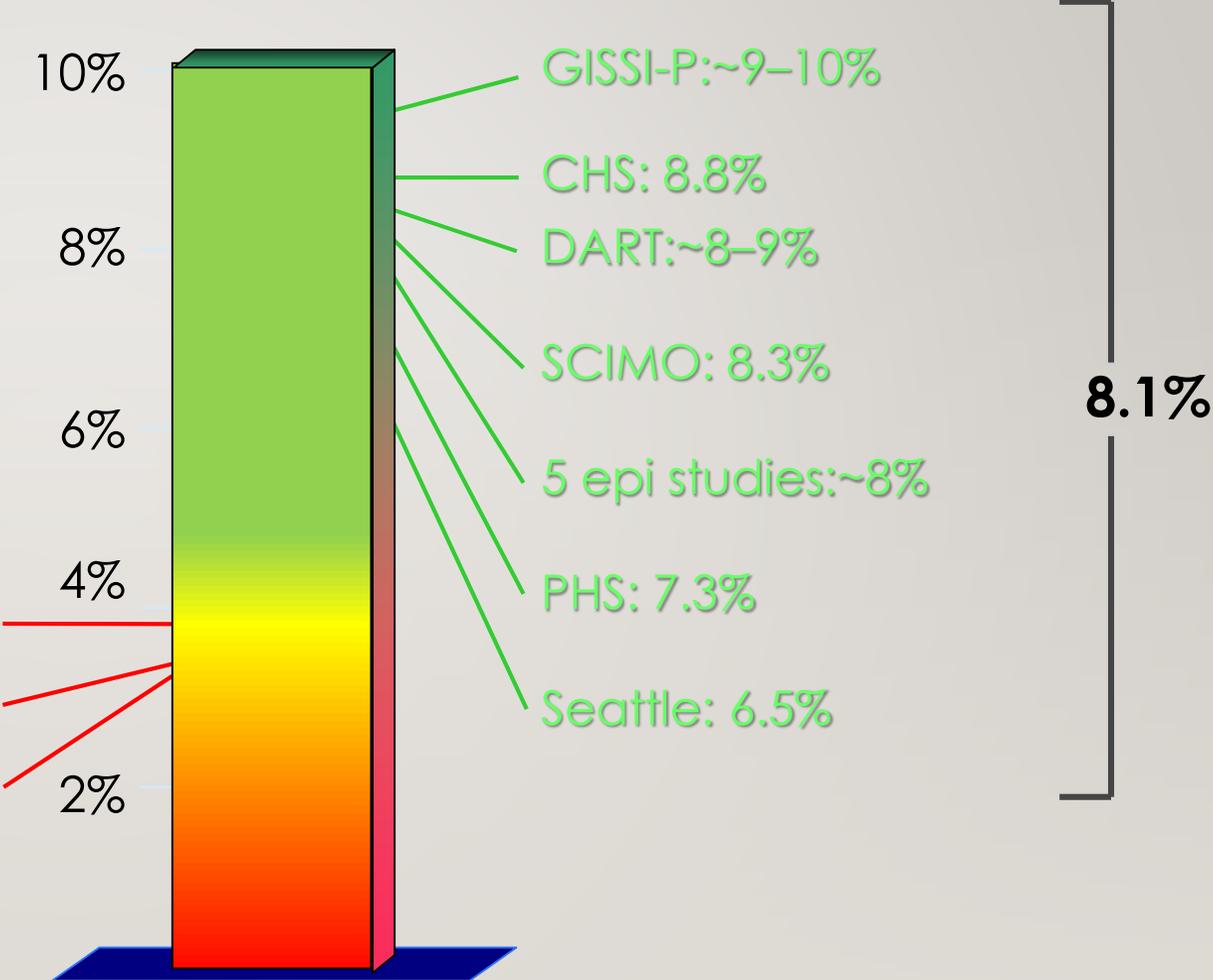
Adapted from Siscovick et al. JAMA 1995;274:1363-1367.

Adapted from Albert et al. N Engl J Med 2002:346:1113-1118.
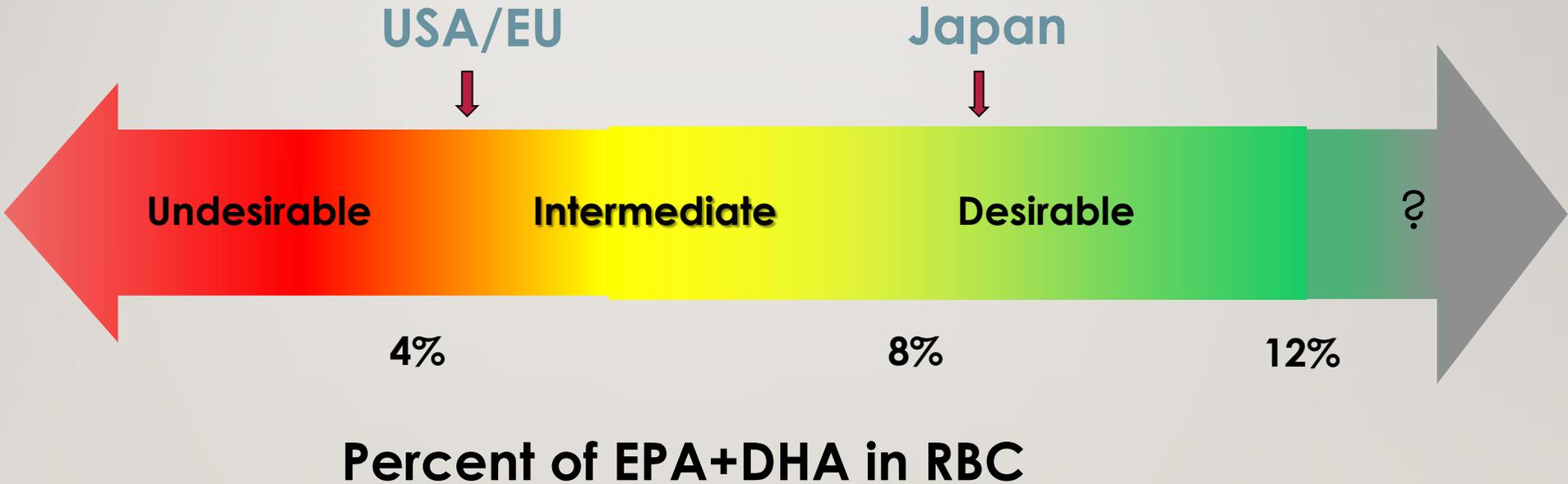
RATIONALE FOR SELECTING OMEGA-3 INDEX TARGETS

Greatest Protection

10%

GISSI-P:~9–10%

CHS: 8.8%

DART:~8–9%

8%

SCIMO: 8.3%

6%

5 epi studies:~8%

Least Protection

4%

PHS: 7.3%

PHS: 3.9%

SCIMO: 3.4%

Seattle: 6.5%

Seattle: 3.3%

2%

8.1%

Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.
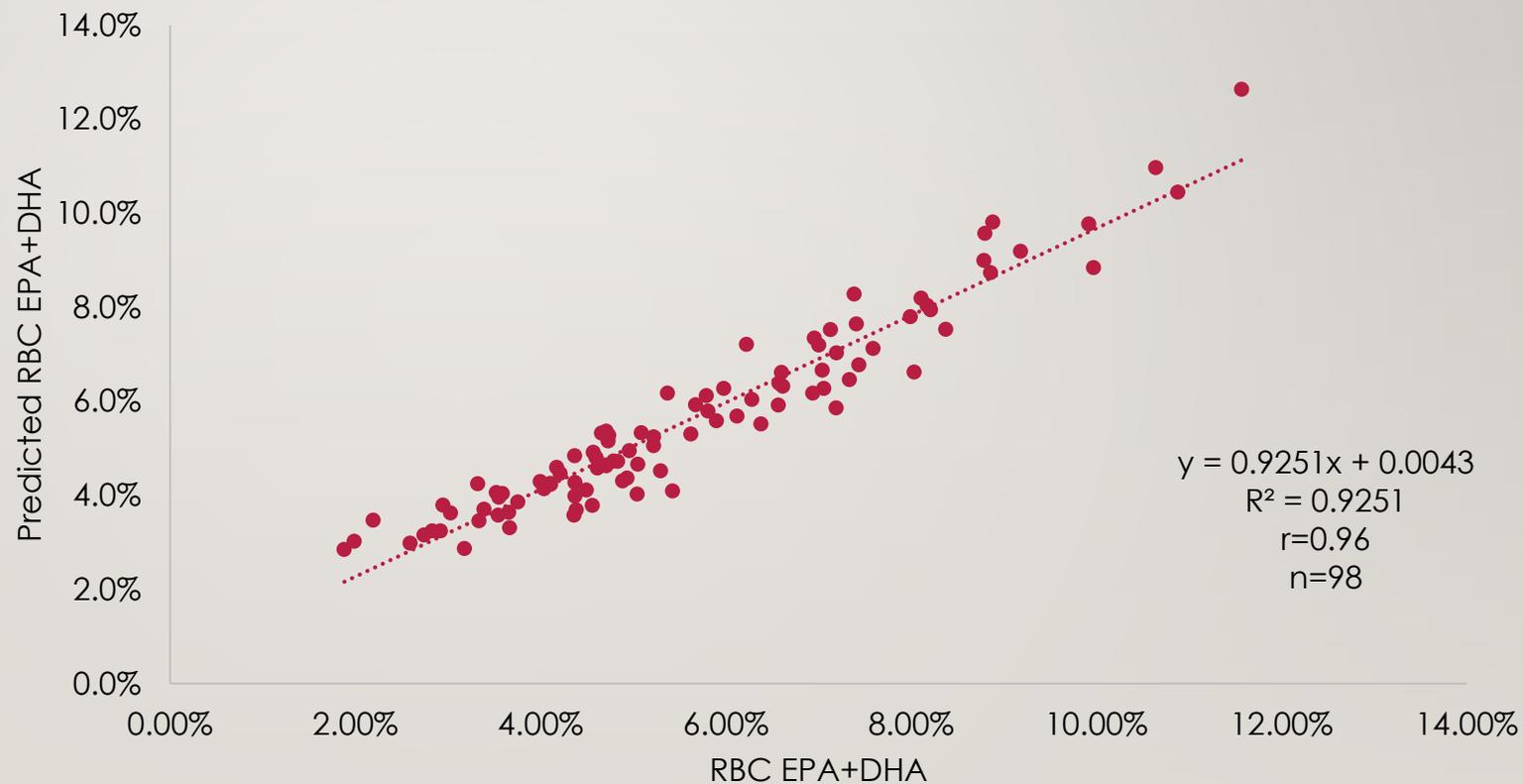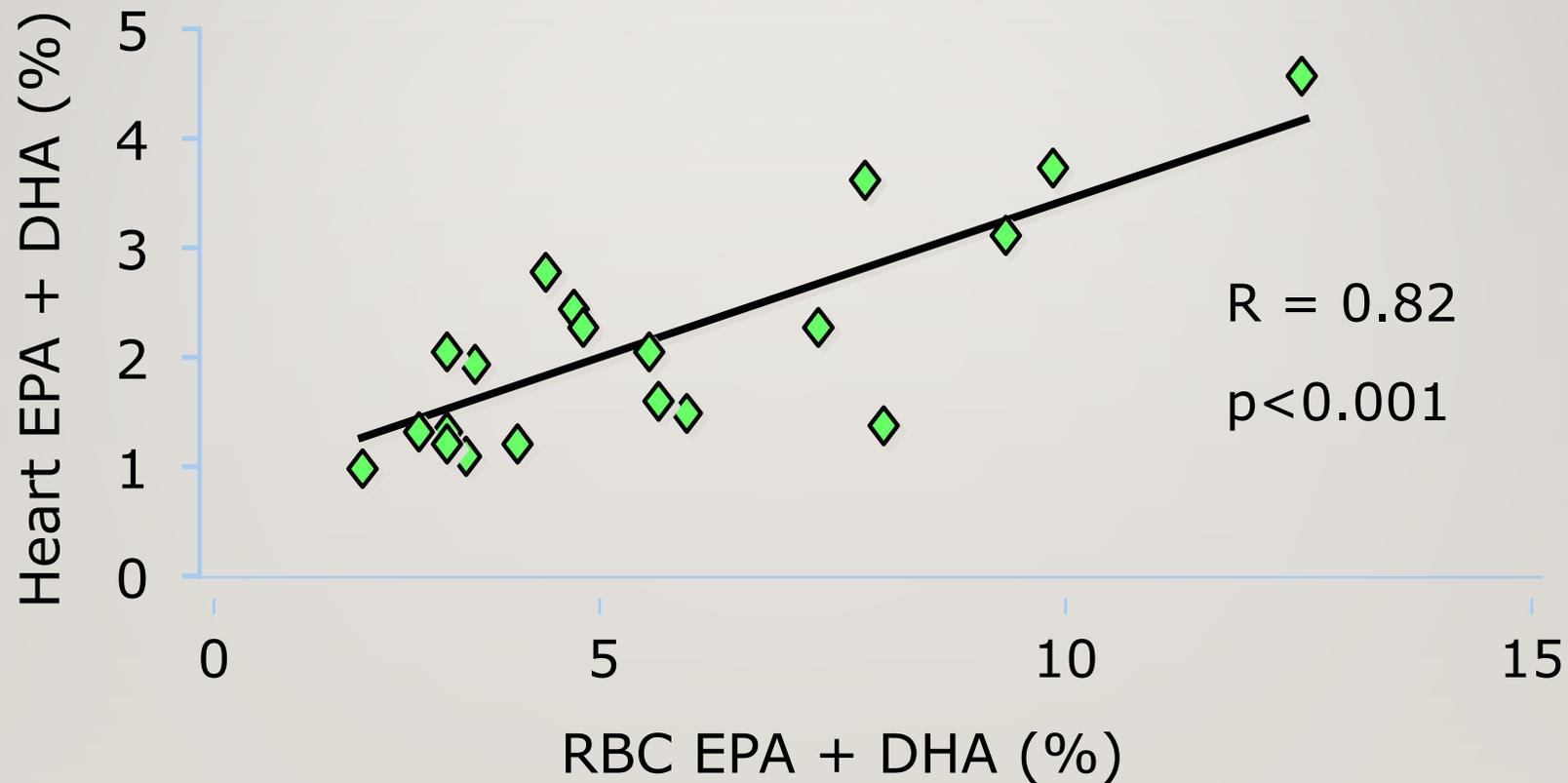
ACCURACY AND PRECISION OF THE DRIED BLOOD SPOT OMEGA-3 INDEX TEST

Precision: <5%

Minimum amount of blood needed on DBS card: 2 uL

$y = 0.9251x + 0.0043$
$R^2 = 0.9251$
$r=0.96$
$n=98$

RED BLOOD CELL EPA+DHA LEVELS ARE HIGHLY CORRELATED WITH HUMAN MYOCARDIAL OMEGA-3 (N=20)

R = 0.82

p<0.001

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

THE OMEGA-3 INDEX CORRELATES WITH THE EPA+DHA CONTENT OF MANY TISSUES (IN MICE)

Fenton J et al. *PLEFA* 2016;112:12-23

Plasma EPA+DHA

RBC EPA+DHA
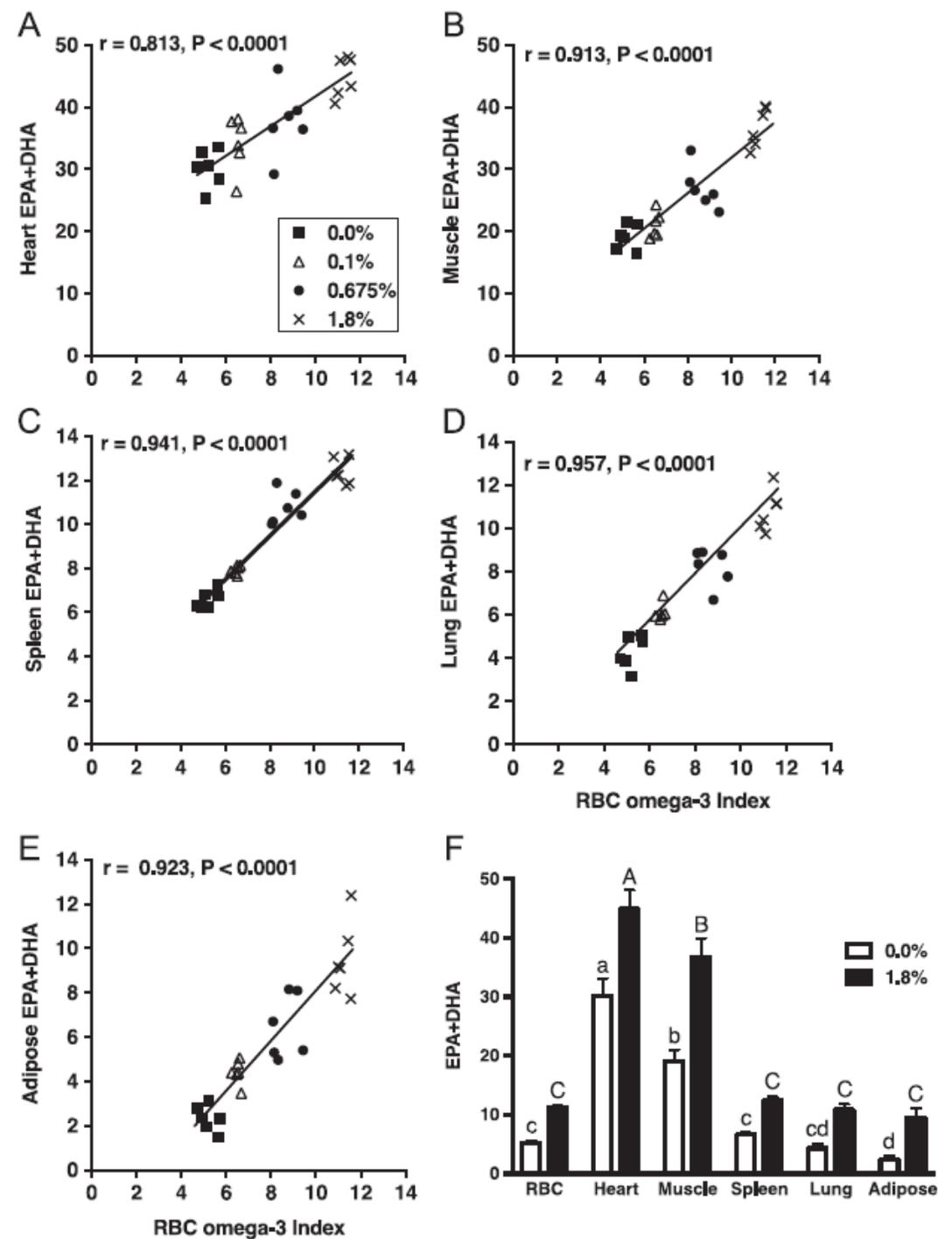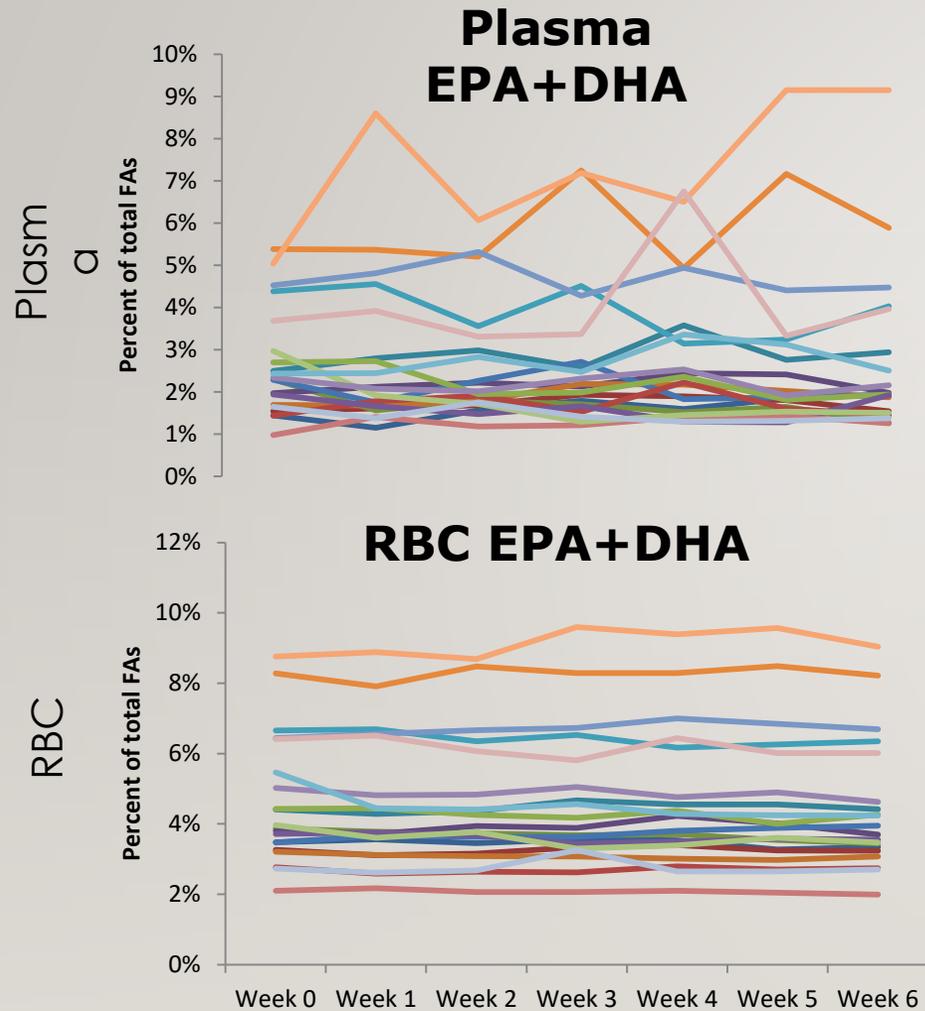
20 healthy volunteers tested weekly for 6 weeks

Total Coefficients of Variability (CVs)

EPA+DHA in…
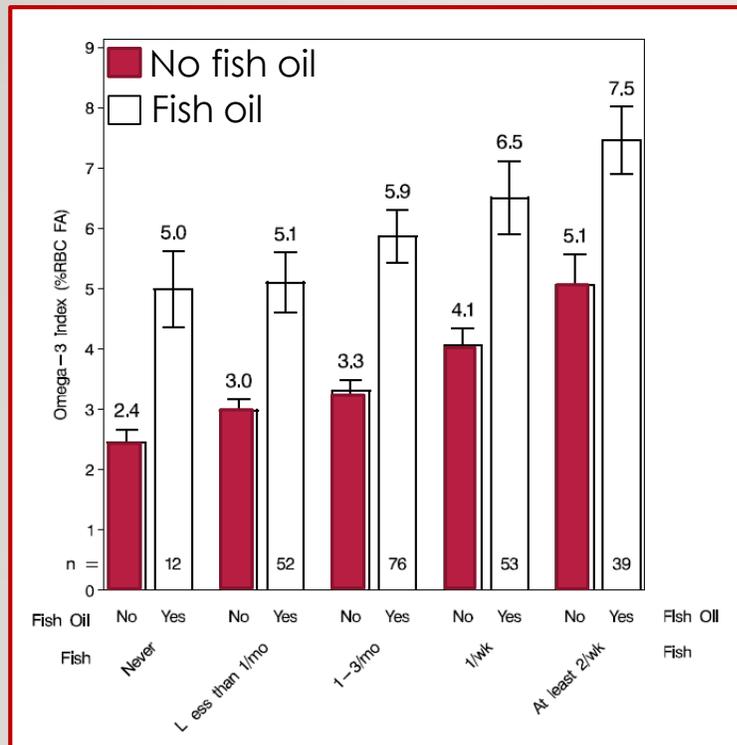• RBC = 4.1%
• Whole Blood = 6.7%
• Plasma = 16%
• Plasma PL = 15%

The Omega-3 Index Has Low Biological Variability

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

THE OMEGA-3 INDEX IS A VALID MARKER OF INTAKE

Relations with Oily Fish Intake ± Fish Oil Capsule Use

Dose response with Fish Oil Capsules (5 months; n=21-24/grp)
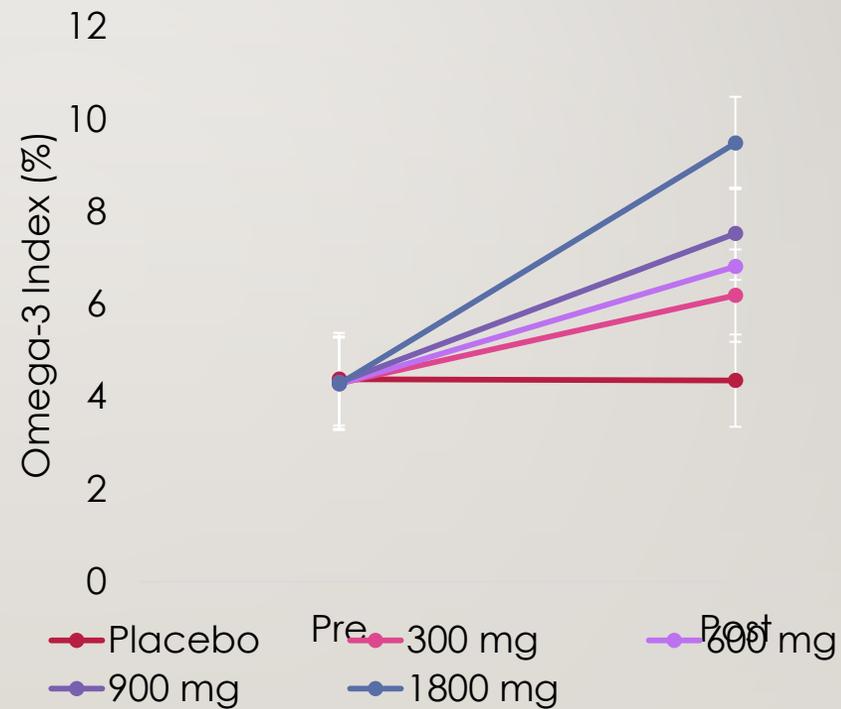
Block, et al. Open Biomark J 2008;1:1-8   Flock, et al. *J Am Heart* Assoc. 2013;2:e000513

OUTLINE

- My history in omega-3 research

- The Omega-3 Index

- Birth and Development of the Omega-3 Index

- Accuracy and Precision of the Omega-3 Index test

- Other Methods to Assess Omega-3 Status – Advantage of the Omega-3 Index test
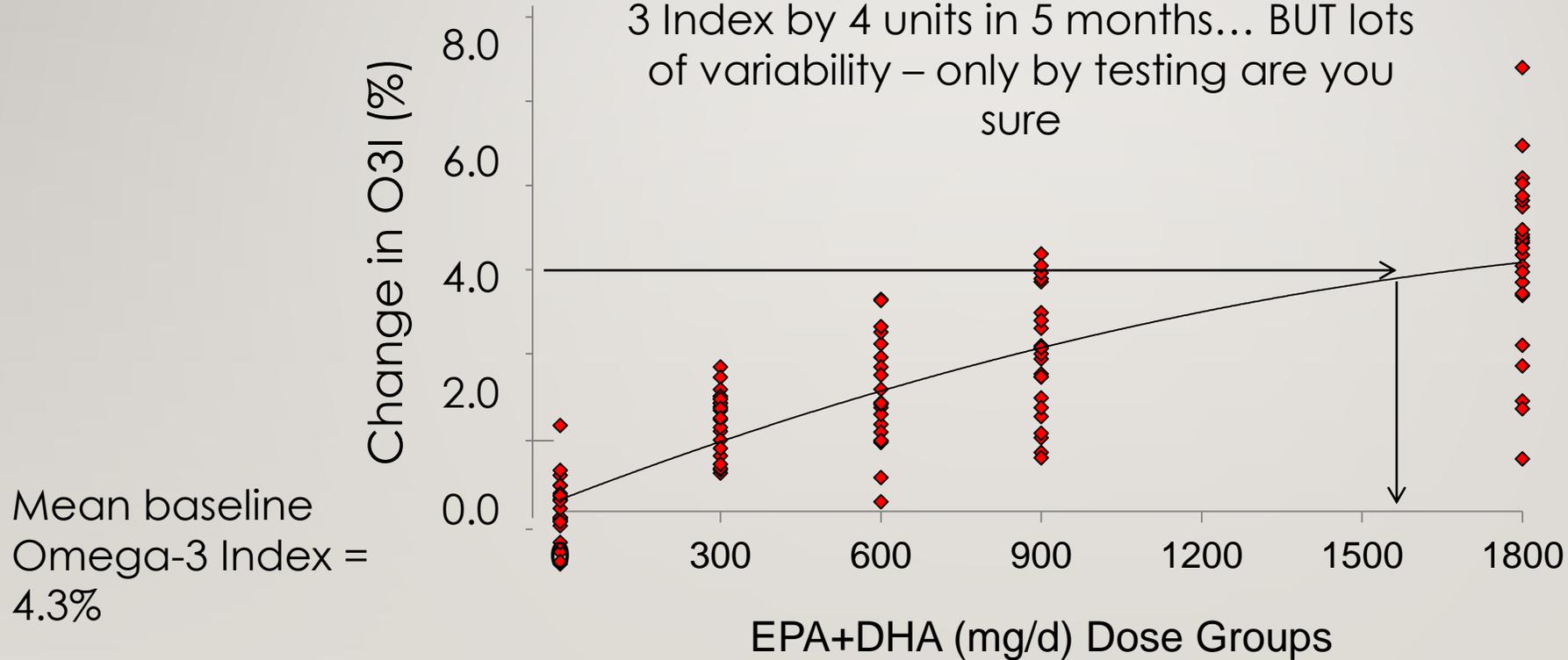
- Omega-3 Index and Risk for Cardiovascular and Neurocognitive Disease, and Death

- Can the Omega-3 Index be too High?
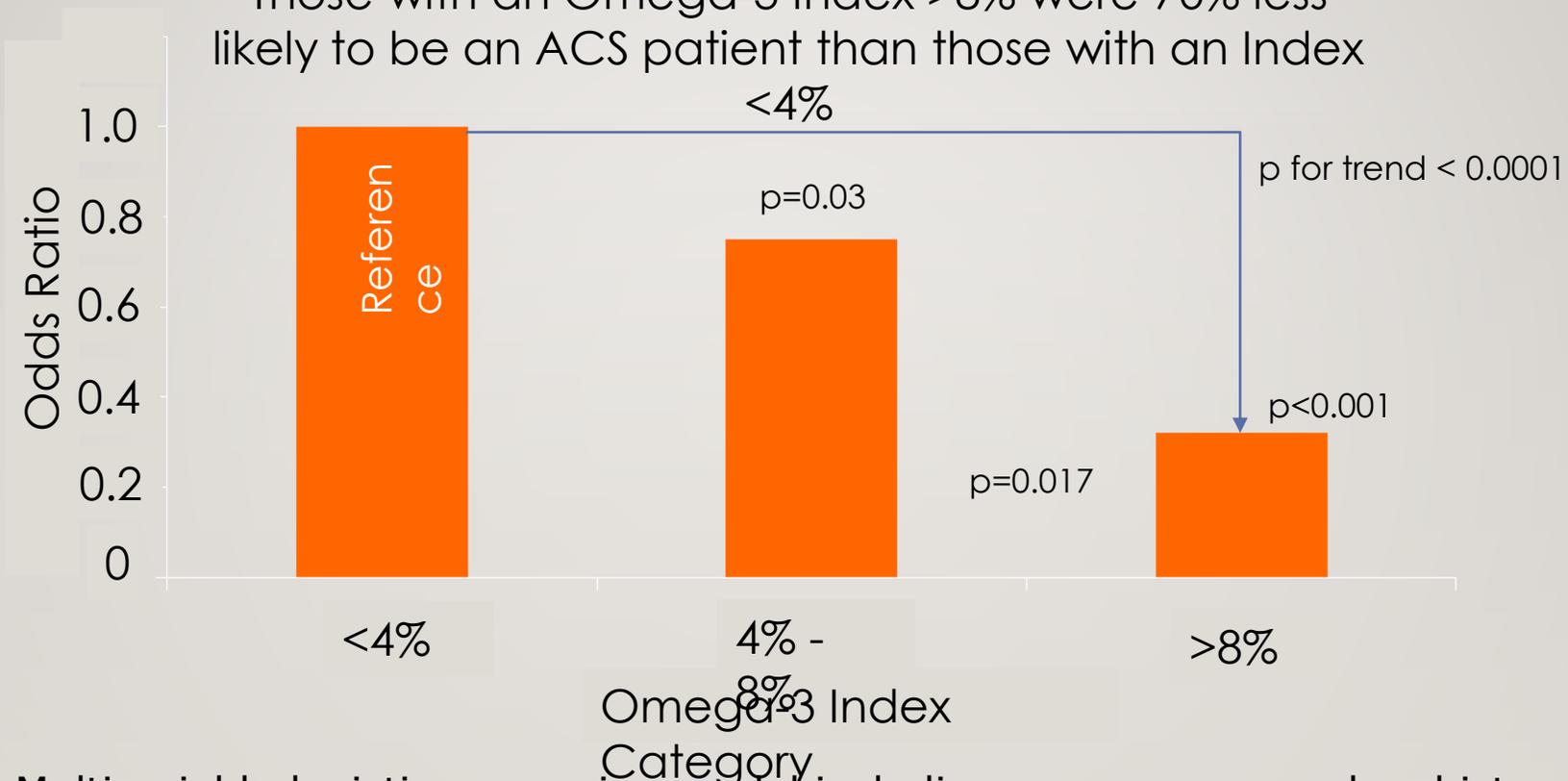
- How to obtain the Omega-3 Index for your patients

HOW MUCH OMEGA-3 IS NEEDED TO MOVE THE INDEX FROM 4% TO 8%?

On average, about 1500 mg/d of EPA+DHA is needed to raise the Omega-3 Index by 4 units in 5 months... BUT lots of variability – only by testing are you sure

Mean baseline Omega-3 Index = 4.3%

Change in O3I (%) vs EPA+DHA (mg/d) Dose Groups

Flock et al. JAHA 2013:2:e000513

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

Those with an Omega-3 Index >8% were 70% less likely to be an ACS patient than those with an Index <4%

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.

CHD Death Rates* and the Omega-3 Index

*http://circ.ahajournals.org/content/123/4/e18

Harris (unpublished data, 2016)
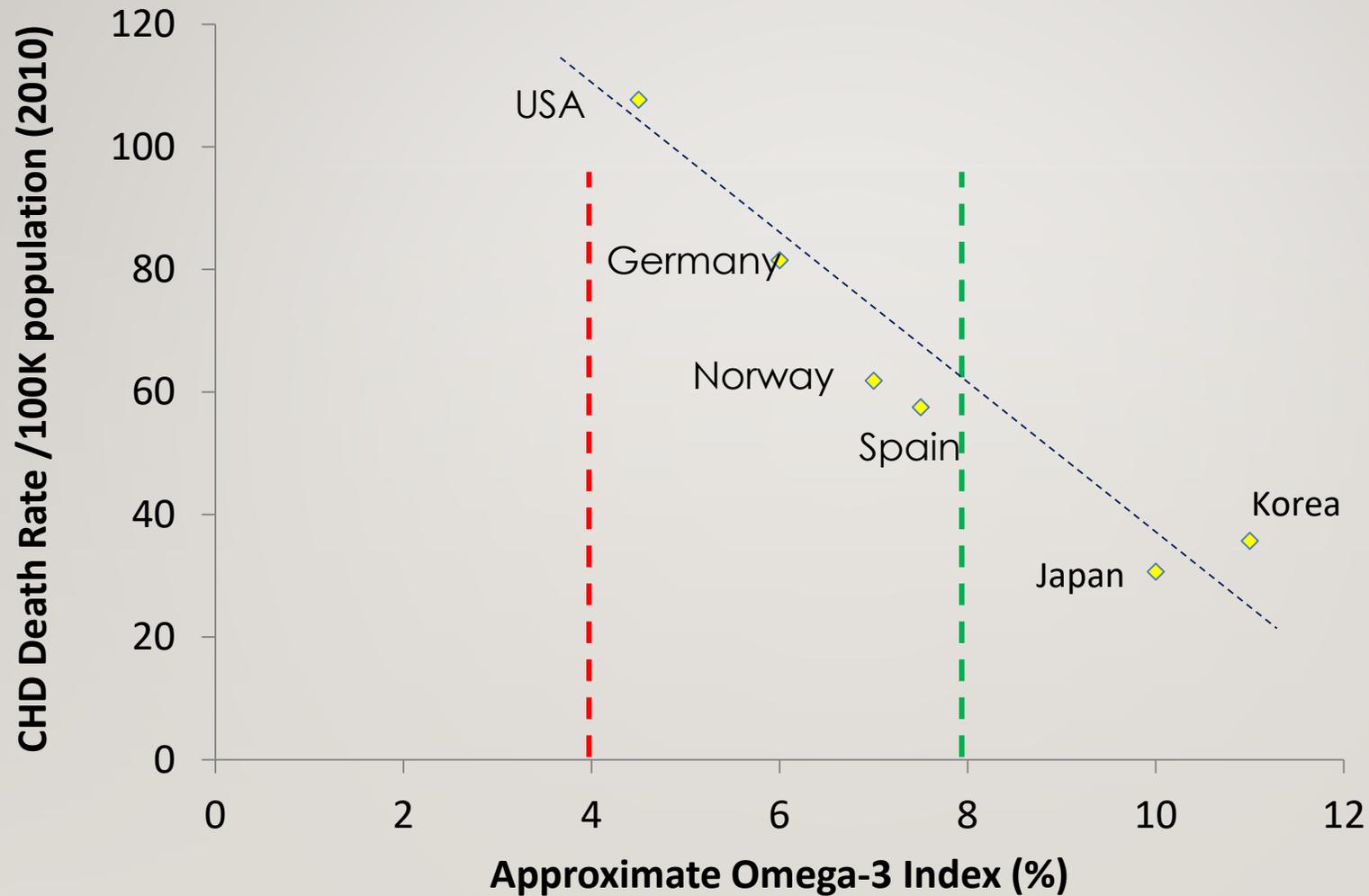
Circulating EPA+DHA levels taken from

- 24,129 individual subjects

- 54 countries

- 398 data sets

- Converted to Omega-3 Index equivalents based on Stark et al.[b]

% EPA+DHA of total fatty acids in erythrocyte equivalents*

- ≤ 4%
- > 4 to 6%
- > 6 to 8%
- > 8%

GLOBAL OMEGA-3 INDEX[A]
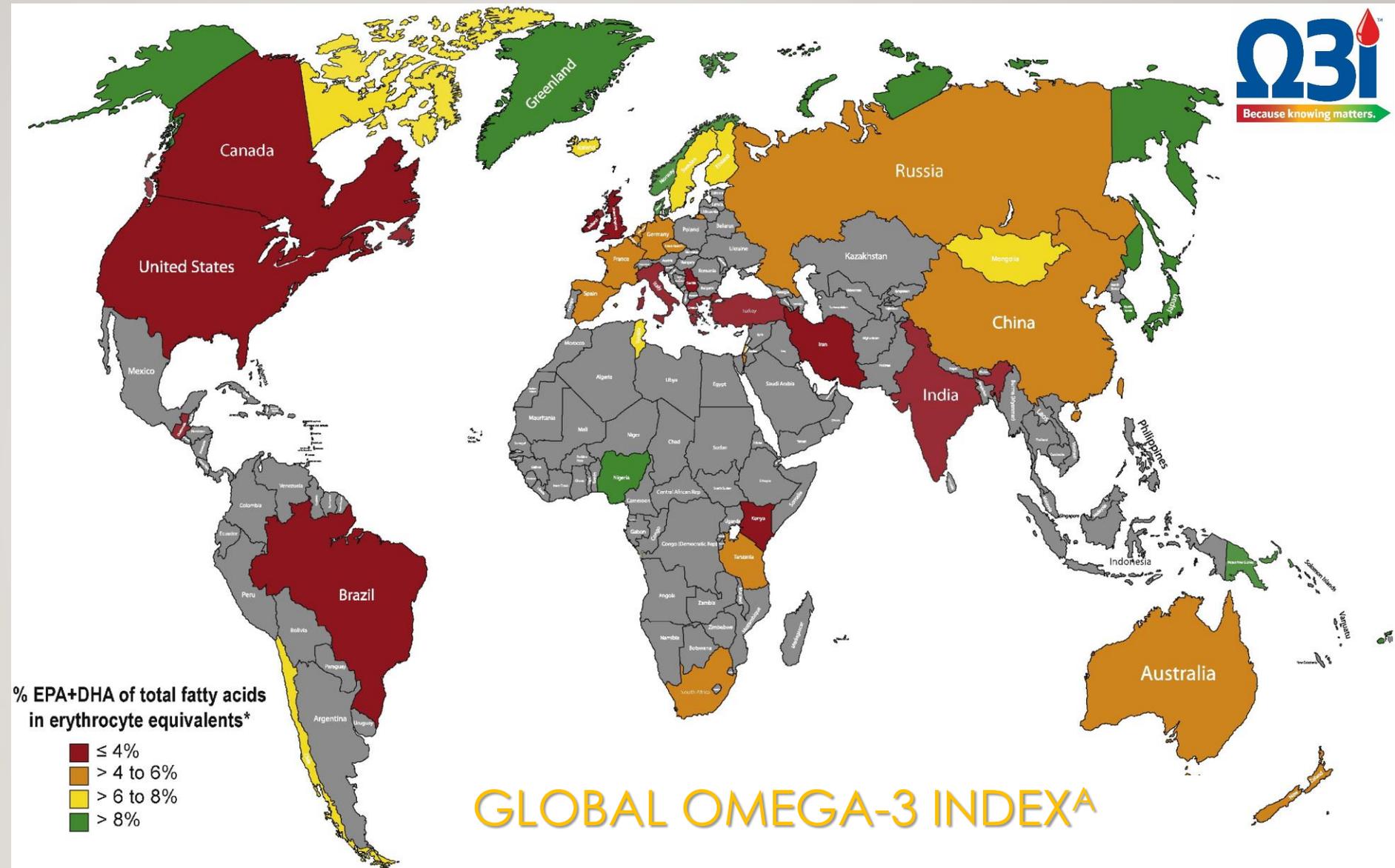
[A] Stark et al. Global survey of the omega-3 fatty acids, DHA and EPA in the blood stream of healthy adults. Prog Lipid Res. 2016;63:132-152.

[b] Stark et al. PLEFA 2016;104:1–10

Table 2

Age- and sex-adjusted and multivariable-adjusted correlations between the inflammatory biomarkers and erythrocyte omega-3 index. (N=2724)

Adjustment	Age and sex		Multivariable[a]	
	r	p-value	r	p-value
Biomarkers				
C-reactive protein	−0.12	<0.001	−0.08	<0.001
Interleukin-6	−0.11	<0.001	−0.10	<0.001
Intercellular adhesion molecule-1	−0.14	<0.001	−0.08	<0.001
Urinary isoprostanes/creatinine ratio	−0.18	<0.001	−0.16	<0.001
LpPLA2 Activity	−0.10	<0.001	−0.08	<0.001
LpPLA2 Mass	−0.13	<0.001	−0.11	<0.001
Monocyte chemoattractant protein-1	−0.08	<0.001	−0.05	0.006
Osteoprotegerin	−0.07	<0.001	−0.06	0.0018
P-selectin	−0.11	<0.001	−0.06	<0.001
Tumor necrosis factor receptor 2	−0.08	<0.001	−0.08	<0.001

[a] Multivariable model: Age; sex; cohort (Offspring vs. Omni) current smoking; systolic blood pressure; body mass index; total cholesterol, high density lipoprotein cholesterol, triglycerides, glucose, diabetes, aspirin use (≥3 times per week); hormone replacement therapy; lipid lowering treatment; blood pressure, fish oil supplement or self-reported diet intake, prevalent cardiovascular disease (myocardial infarct, stroke, congestive heart failure).
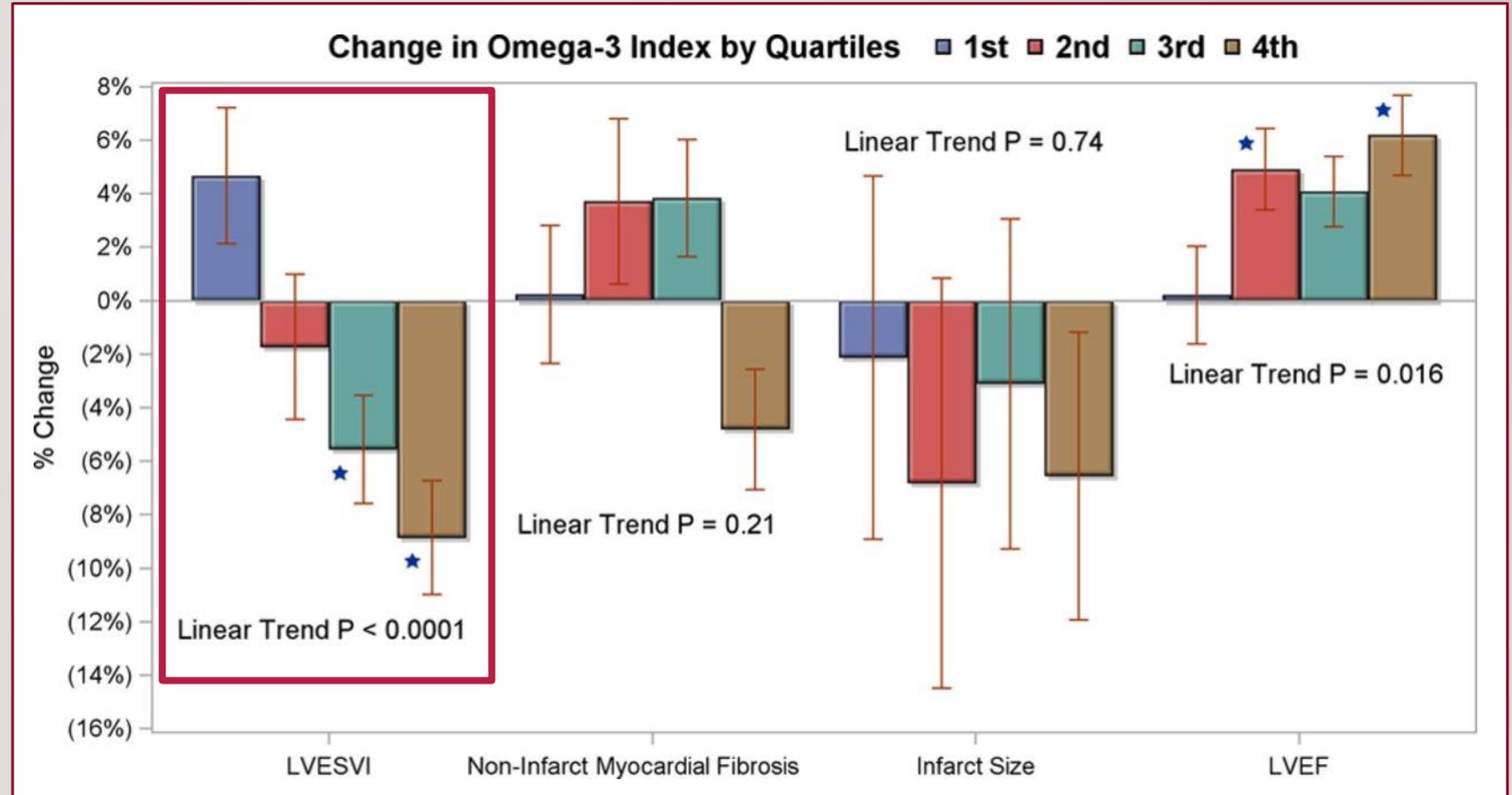
Ω3i

Because knowing matters.

CORRELATIONS BETWEEN THE OMEGA-3 INDEX AND MULTIPLE INFLAMMATORY BIOMARKERS: THE FRAMINGHAM OFFSPRING STUDY

Higher Omega-3 Index = Lower Inflammation

Effects of Lovaza (4 g/d x 6 months) on Cardiac Remodeling in Post-MI Patients (n=227)

There was a strong and significant relationship between an increase in the Omega-3 Index and a decrease in pathological cardiac remodeling

Change in Omega-3 Index by Quartiles ▪ 1st ▪ 2nd ▪ 3rd ▪ 4th

% Change

Linear Trend P < 0.0001

Linear Trend P = 0.21

Linear Trend P = 0.74

Linear Trend P = 0.016

LVESVI   Non-Infarct Myocardial Fibrosis   Infarct Size   LVEF

LVESVI=left ventricular end systolic volume index

Is Blood Omega-3 Associated with the Rate of Cellular Aging?

Blood Omega-3 and Rate of Telomere Attrition: Heart & Soul Study

Figure. Absolute and Relative Mean Changes in Telomere Length Over 5 Years by Quartile of Omega-3 Fatty Acid Level, Adjusted for Age and Baseline Telomere Length

Absolute change in telomere length — Absolute Change in Telomere Length, Mean T/S Units — Quartiles of Blood Omega-3 Fatty Content (1, 2, 3, 4)

Relative change in telomere length — Relative Change in Telomere Length, Mean % — Omega-3 Index (%)* (3.0, 4.0, 5.0, 8.1)
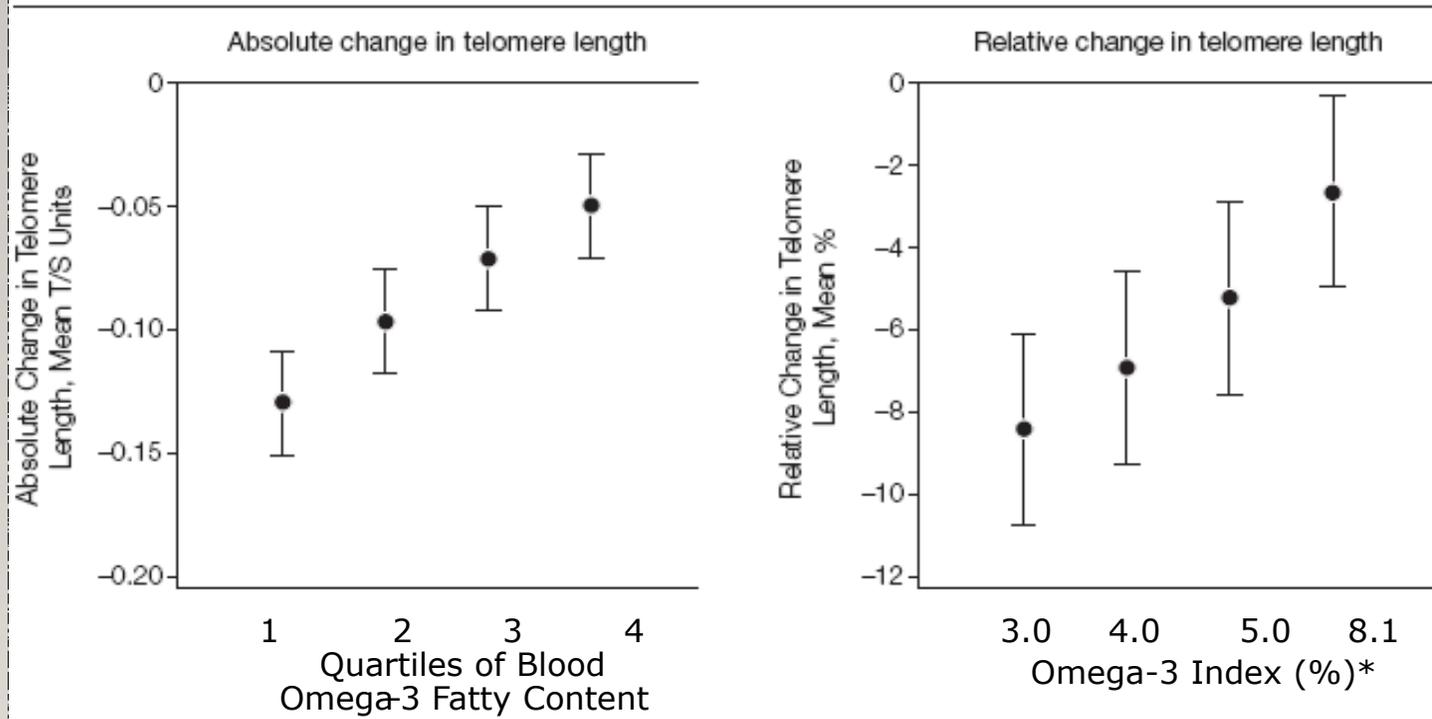
Error bars indicate 95% confidence intervals. T/S indicates telomere-to-single-copy gene ratio. $P < .001$ for linear trend for both absolute and relative change. See Table 1 for definitions of quartiles.
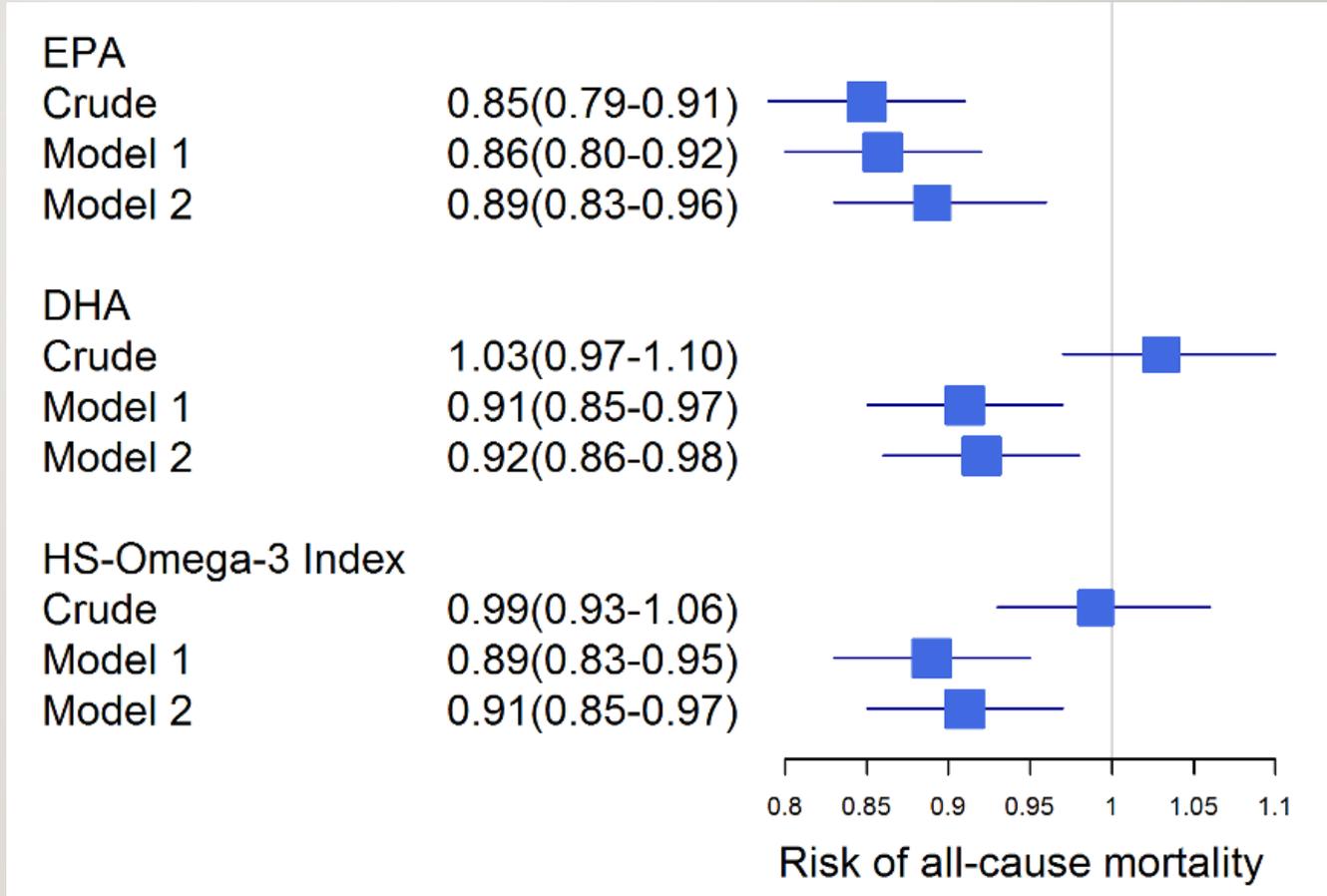
Patients with the highest Omega-3 Index experienced the slowest rate of telomere shortening (cellular aging)

Farzaneh-Far, et al. JAMA 2010;303:250-257.

* Extrapolated from whole blood EPA+DHA (r=0.95)

Model 1: adjusted for age and gender

Model 2: additionally adjusted for BMI, LDL-C, HDL-C, logTG, hypertension, diabetes mellitus, smoking, alcohol intake, physical exercise and lipid lowering therapy.

EPA	
Crude	0.85(0.79-0.91)
Model 1	0.86(0.80-0.92)
Model 2	0.89(0.83-0.96)
DHA	
Crude	1.03(0.97-1.10)
Model 1	0.91(0.85-0.97)
Model 2	0.92(0.86-0.98)
HS-Omega-3 Index	
Crude	0.99(0.93-1.06)
Model 1	0.89(0.83-0.95)
Model 2	0.91(0.85-0.97)

Risk of all-cause mortality

Kleber et al. Atherosclerosis (epub July 1, 2016)

THE OMEGA-3 INDEX AND RISK FOR TOTAL MORTALITY

WOMEN'S HEALTH INITIATIVE MEMORY STUDY
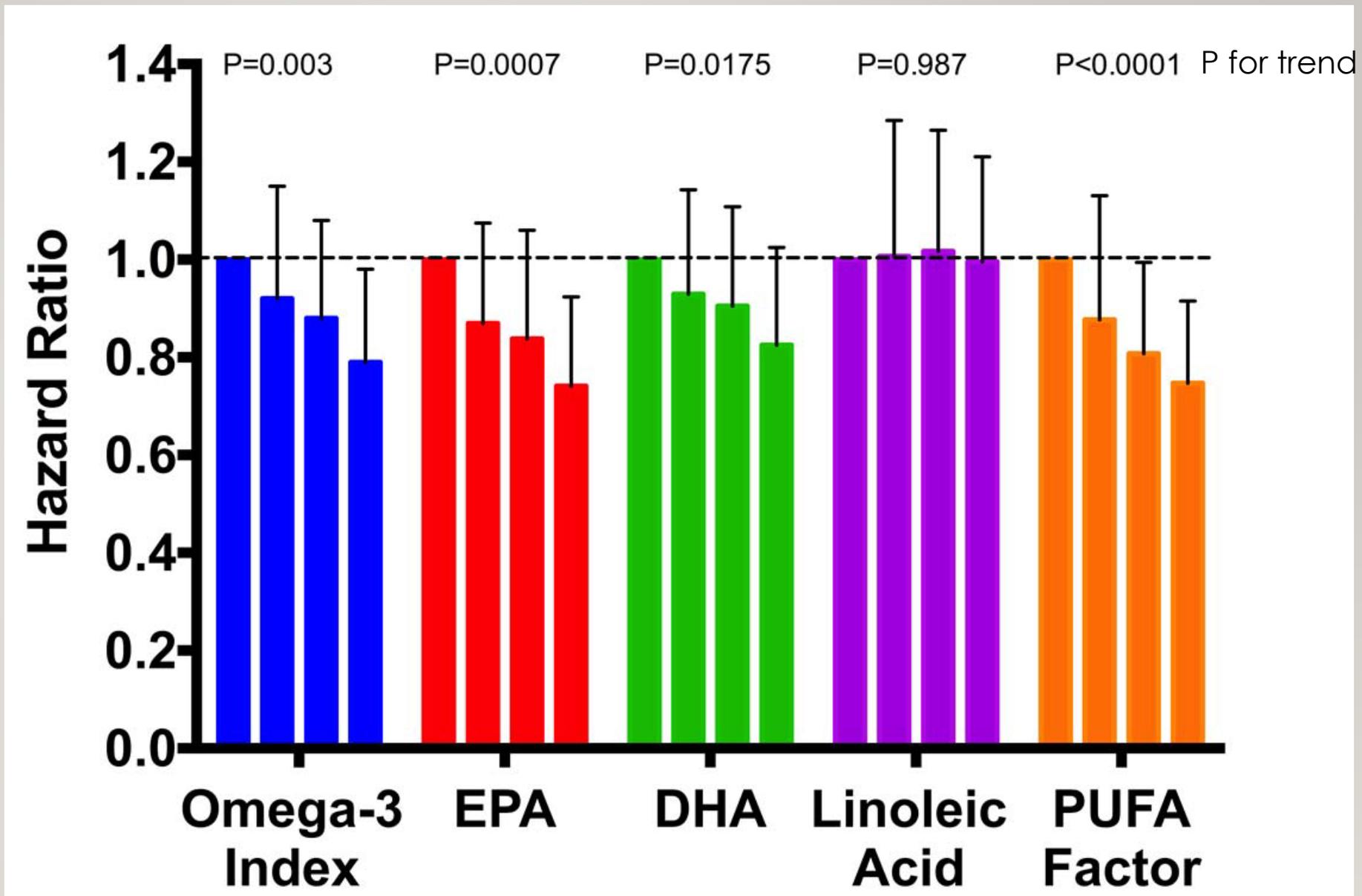
Harris et al. (under review, 2016)
PUFA Score = 0.26 LN(ALA) + 0.85 LN(EPA) + 0.82 (DHA) - 0.63 (AA) - 0.84 (C22:4n6) - 0.81 (C22:5n6),

Fully-adjusted hazard ratios for death from any cause over a 14.9 years in 6501 post-menopausal women.

CIRCULATING OMEGA-3 AND ODDS OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (NV-AMD)[A]
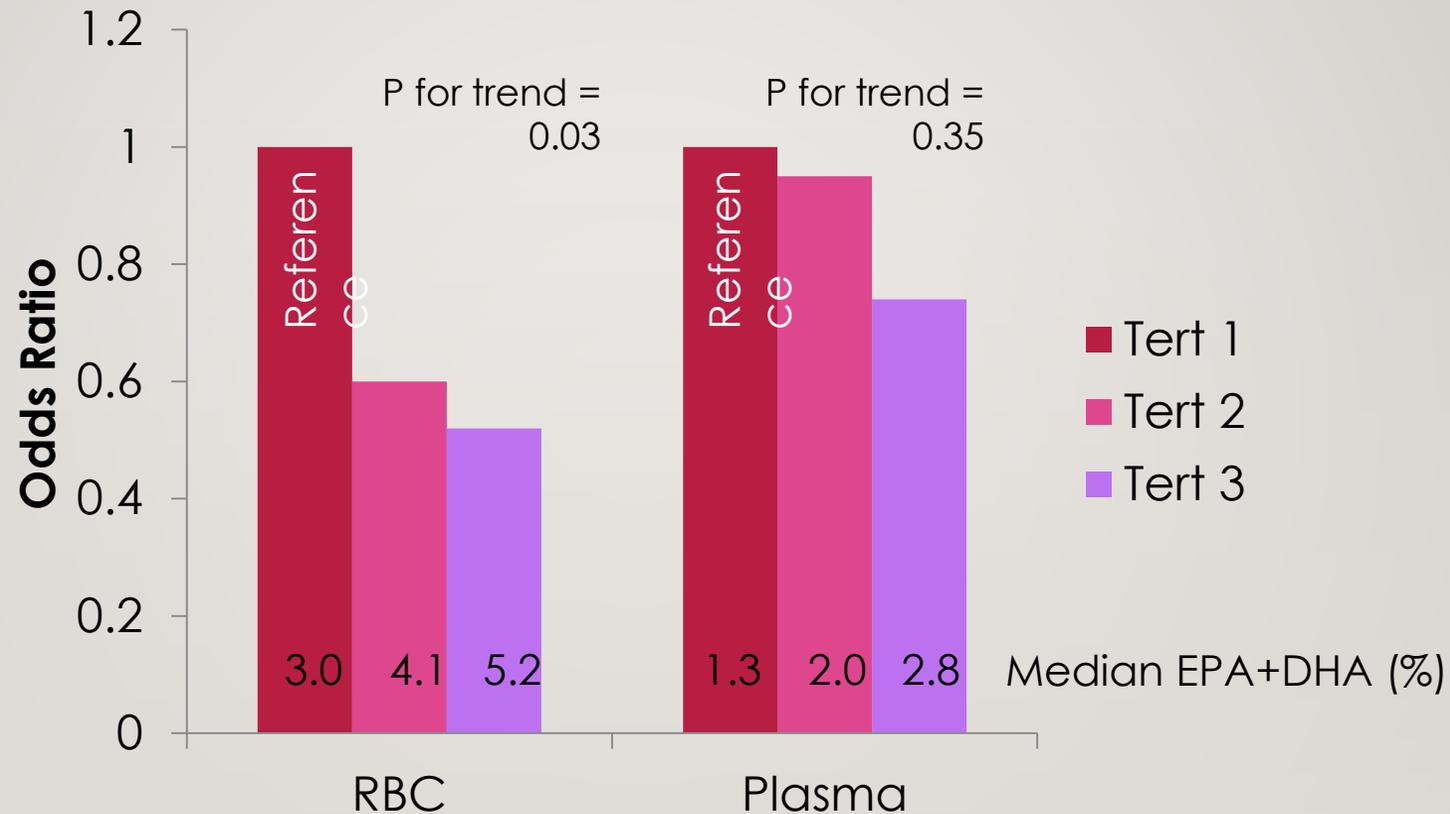
RBC and plasma EPA+DHA were compared between patients with NV AMD (n=290, baseline from Nutritional AMD Treatment Study 2[B]) and healthy controls (n=144). Data from fully adjusted model*.

[A]Merle, et al. *Inv Ophthal Vis Sci* 2014;55:2010-2019.
[B]Souied, et al. *Ophthalmology* 2013;120:1619–1631

*age, sex, CFH Y402H, ARMS2 A69S, and ApoE4 polymorphisms, plasma triglycerides, hypertension, hypercholesterolemia and family history of AMD

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

A HIGHER OMEGA-3 INDEX IS LINKED WITH LESS HOSTILITY AND 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
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

*Brown's Attention Deficit Disorder Scales

THE OMEGA-3 INDEX, BRAIN VOLUME AND COGNITIVE FUNCTION IN FRAMINGHAM*

Model	Covariates	Total Cerebral Brain Volume (%)	Visual Memory	Executive	Abstract Thinking
	Summary	Lower Index = Volume*	Lower Index = Poorer Function		
A	Age, sex, education, time interval	p=0.005	p=0.026	p=0.025	p=0.001
B	A with apoE4 and homocysteine	p=0.005	p=0.026	p=0.038	p=0.002
C	B with physical activity and BMI	p=0.008	p=0.024	p=0.046	p=0.002
D	B with diabetes, sBP, smoking, A-fib, prevalent CVD and serum cholesterol	p=0.011	p=0.079	p=0.108	p=0.001

* Comparing Q1 to Q2-4

Tan Z, et al. Neurology 2012;78:658–664

n=1575; age=67

THE OMEGA-3 INDEX, BRAIN VOLUME AND COGNITIVE FUNCTION IN FRAMINGHAM

"The MRI finding of lower brain volume [in those with an Omega-3 Index <4.4%] represents a change equivalent to approximately 2 years of structural brain aging."

Tan Z, et al. Neurology 2012;78:658–664

EFFECTS OF B-VITAMIN TREATMENT ON EPISODIC MEMORY AS A FUNCTION OF OMEGA-3 FATTY ACID LEVELS IN VITACOG*
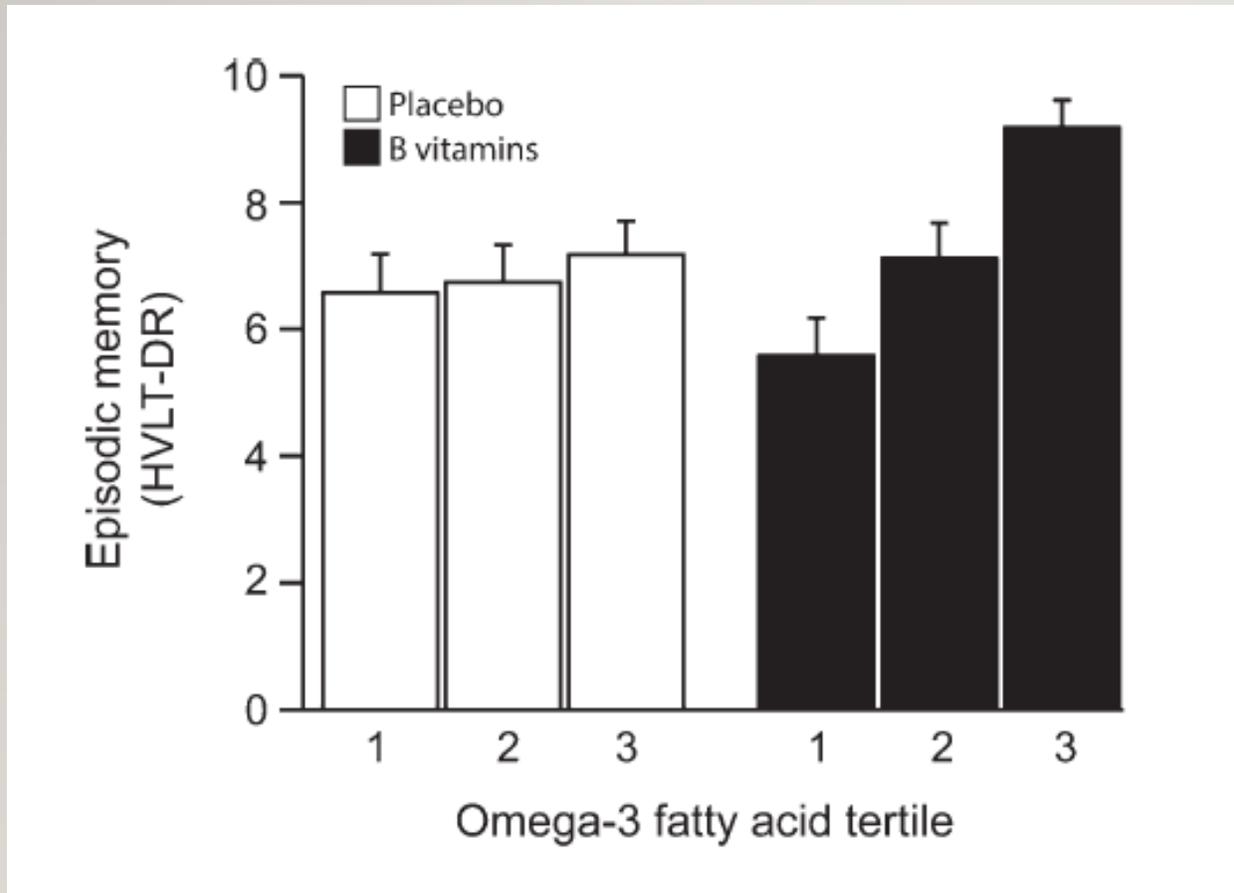
- 277 patients with mild cognitive impairment
- Randomized to B-vitamins vs placebo
- 2 year follow-up on cognitive function
- Tested for an effect modification by baseline omega-3 status
- **In B-vitamin-replete subjects, Omega-3 status was directly related to better memory**

Beginning of 3rd Tertile EPA+DHA (590 uM) ≈ 9.8% Omega-3 Index

Oulhaj et al. J Az Dis Res 2016;50:547-557   *Homocysteine and B-Vitamins in Cognitive Impairment

THE OMEGA-3 INDEX AND 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
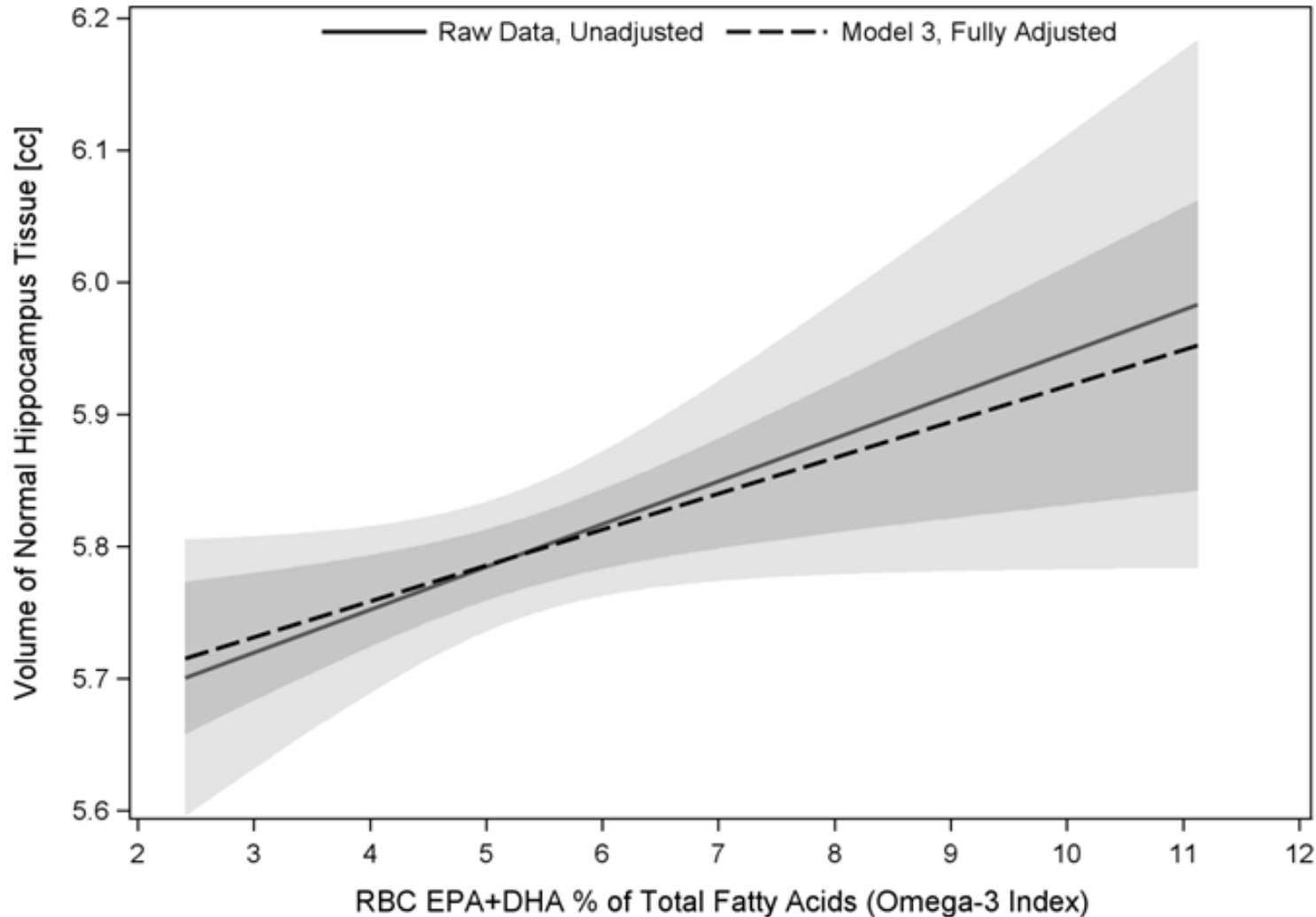
THE OMEGA-3 INDEX WAS DIRECTLY RELATED TO HIPPOCAMPAL VOLUME IN WHIMS*

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

*Women's Health Initiative Memory Study

Why is the Target 8%?

- The average Omega-3 Index estimated from 11 studies was 8.1%

- An Omega-3 Index of >8% was associated with reduced probability for acute coronary syndrome compared to an Index of <4%

- The Omega-3 Index associated with the slowest rate of cellular aging was 8%

- The average Index in Japan (where CHD is rare) is ~9%

- The Omega-3 Index associated with reduced risk for sudden cardiac death was 7.3%[a]

- In B-vitamin supplemented patients, the Omega-3 Index associated with better cognitive function and larger brain size was 9.8%[b]

[a] estimated from plasma omega-3 levels - mid value from 2nd tertile (Virtanen et al. 2012)
[b] estimated from plasma omega-3 levels - lowest value from 3rd tertile (Oulhaj et al. 2016)

From Fish Oil to Medicine

Bernadine Healy, MD. (Former Director of the NIH and President of the Am Heart Assn)
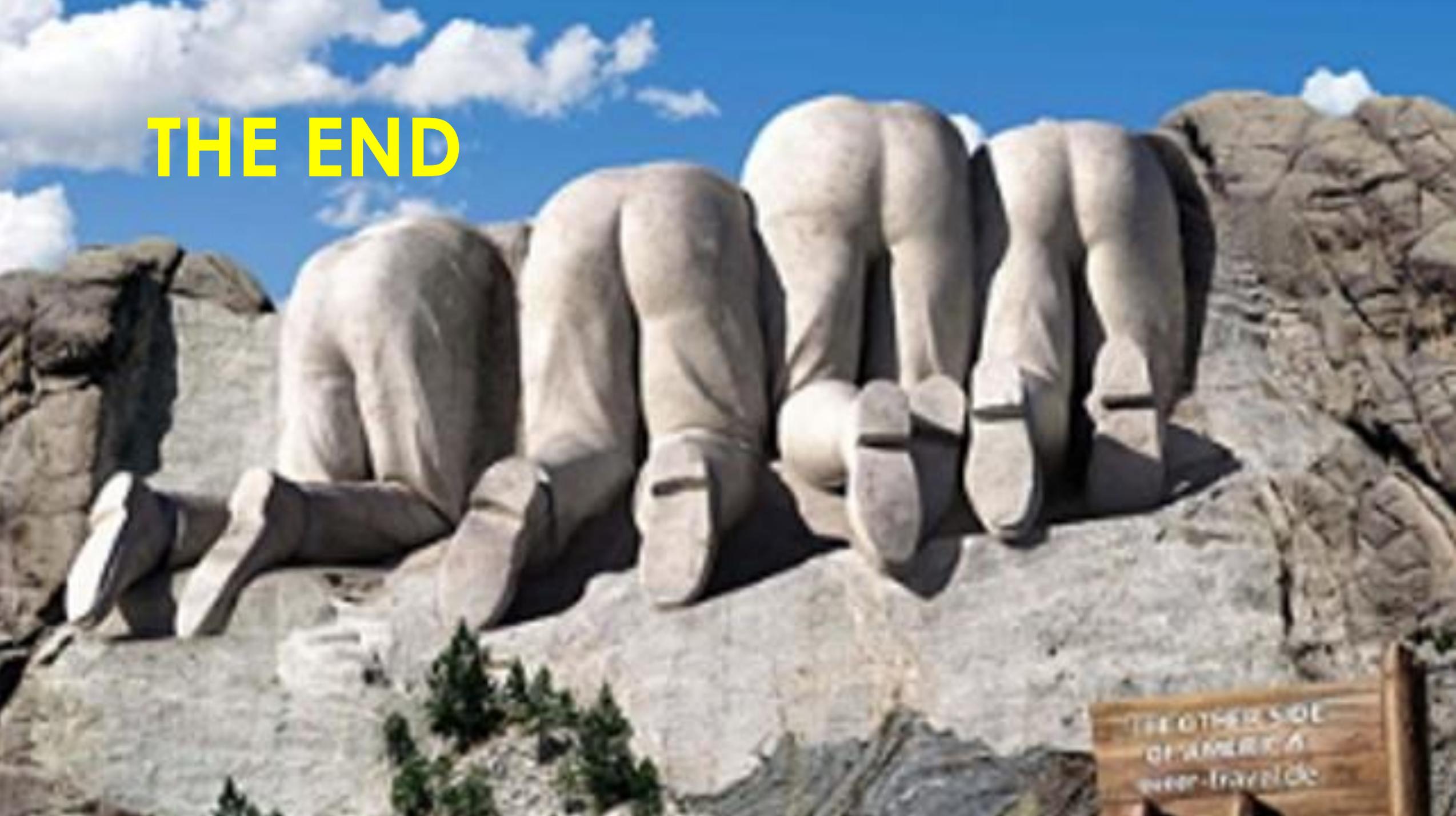*US News and World Report. August 7, 2008*

"This is no fish story: Raising omega-3s could be as important to public health as lowering cholesterol. Think about that comparison. Reining in our nation's cholesterol levels over the past 40 years has yielded great benefit to health and longevity. The change was a grass-roots effort driven by individuals—patients motivated by test results and doctors who helped monitor and manage them. The National Cholesterol Education Program even launched a "know your number" campaign. *But who knows their levels of omega-3s?*"

"Before long, your personal omega-3 index just could be the new cholesterol—the number you want to brag about."