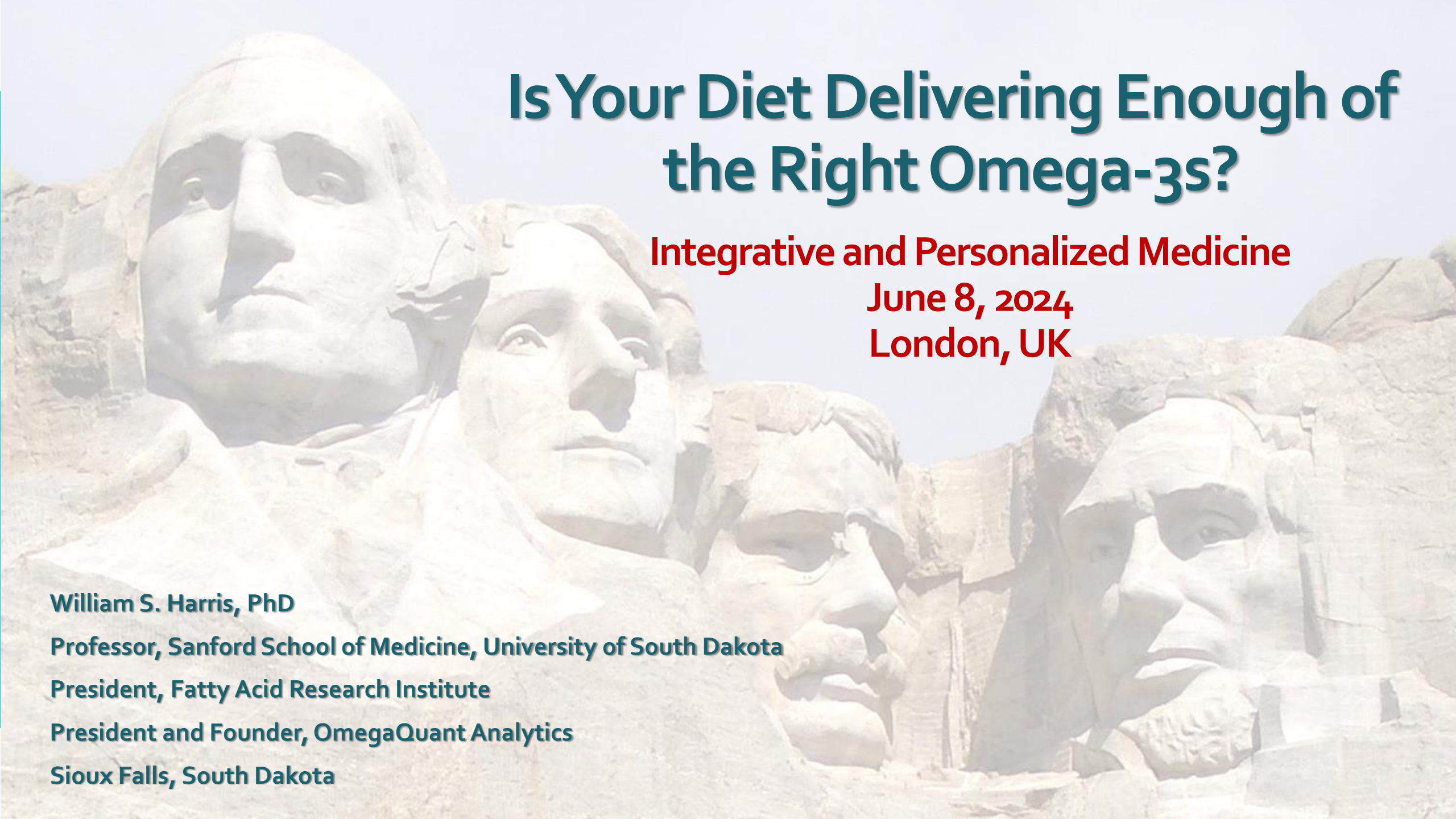


Is Your Diet Delivering Enough of the Right Omega-3s?

Integrative and Personalized Medicine
June 8, 2024
London, UK

William S. Harris, PhD

Professor, Sanford School of Medicine, University of South Dakota

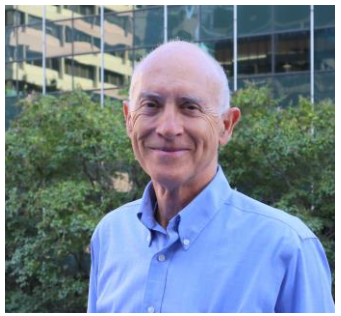
President, Fatty Acid Research Institute

President and Founder, OmegaQuant Analytics

Sioux Falls, South Dakota

Fatty Acid Research Institute

FARI is a non-profit research organization that brings together nutritional, medical and biostatistical scientists with experience in fatty acids to accelerate discovery of the relationships between fatty acids, especially omega-3, and health


WS Harris, PhD


NL Tintle, PhD


JP Schuchardt, PhD


Y Park, PhD


A Sala-Vila, PhD


JH O'Keefe, MD

Since 2020, we have published 21 peer-reviewed papers on fatty acid-related topics


R Patrick, PhD


MI McBurney, PhD


R Marchioli, MD


KH Jackson, PhD


R Wallace, MD

FARI

OmegaQuant

- Independent, CLIA-certified lab specializing in fatty acid analysis based in Sioux Falls, SD, USA. Lab partner in Europe and Australia.
- Offers nutritional status tests to researchers, healthcare providers, supplement brands, sports teams, wellness facilities, and individuals.
- OmegaQuant offers a variety of blood tests that measure fatty acids (omega-3s, omega-6s, *trans* fats, etc.) from a single drop of blood.
- Our Omega-3 Index blood spot tests have been used by *millions of individuals.*

Polyunsaturated Fatty Acid Families

ω-6 family

C18:2 ω-6 — **Linoleic**

- Corn Oil
- Safflower Oil
- Sunflower Oil

C20:4 ω-6 — **Arachidonic**

- Meat
- Eggs

ω-3 family

C18:3 ω-3 — **α-Linolenic**

- Flaxseed Oil
- Canola Oil
- Soybean Oil

C20:5 ω-3 — **Eicosapentaenoic (EPA)**

C22:6 ω-3 — **Docosahexaenoic (DHA)**

- Oily Fish
- Fish Oil

The Birth of the Omega-3 Index

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Preventive Medicine 39 (2004) 212–220

Preventive Medicine

www.elsevier.com/locate/ypmed

The Omega-3 Index: a new risk factor for death from coronary heart disease?☆,☆☆

William S. Harris, Ph.D.[a,*] and Clemens von Schacky, M.D.[b]

[a]*Lipid and Diabetes Research Center, Mid America Heart Institute of Saint Luke's Hospital, University of Missouri-KC School of Medicine, Kansas City, MO 64111, USA*

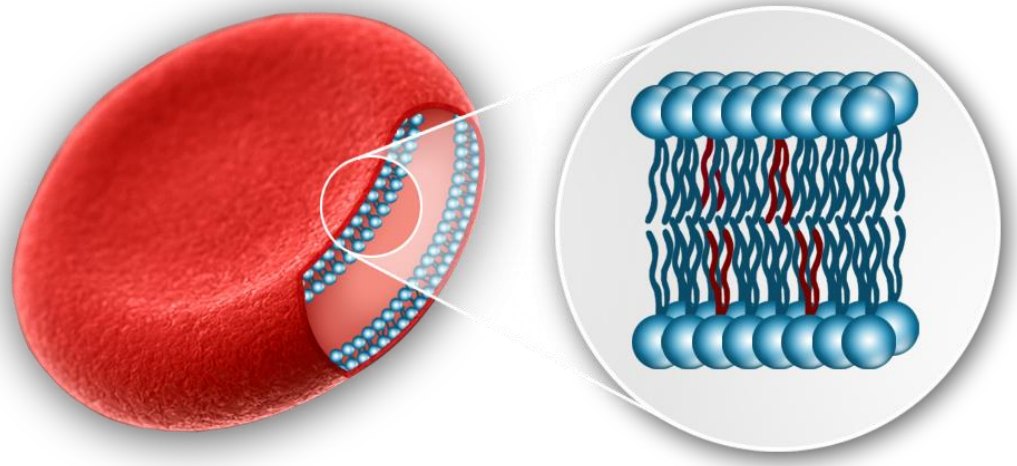
[b]*Medizinische Klinik and Poliklinik Innenstadt, University of Munich, Munich, Germany*

Available online 2 April 2004

The Omega-3 Index: Biomarker and Risk Factor

RBC EPA+DHA % of total RBC fatty acids

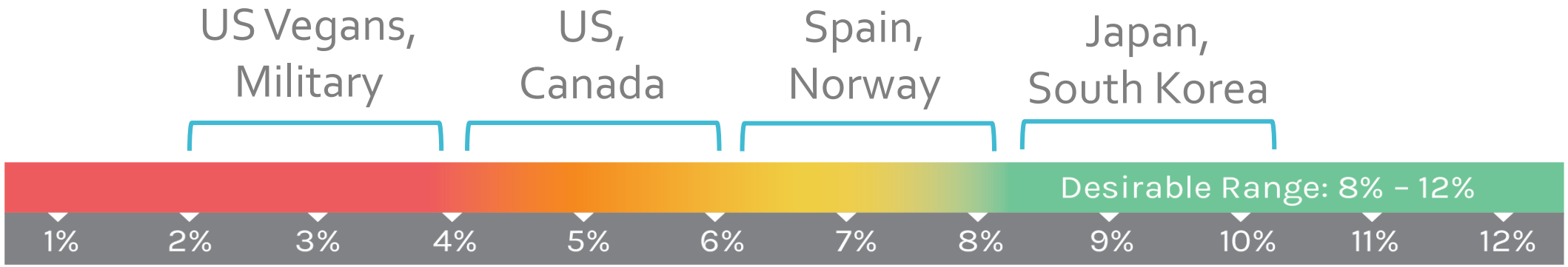
It is a marker of tissue levels of EPA and DHA… and a modifiable risk factor for multiple chronic diseases



Having an Omega-3 Index in the desirable range (8%-12%) has been associated with improved heart, brain, and eye health.

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

Typical vs. Desirable Omega-3 Index Levels

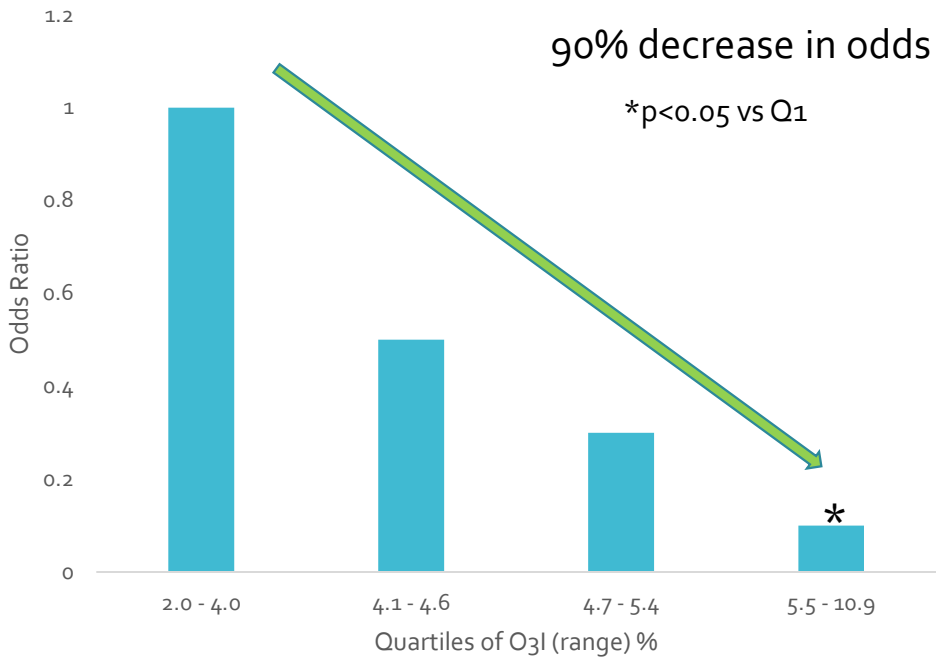


Target Omega-3 Index >8%

Two Studies that inspired the creation of the Omega-3 Index

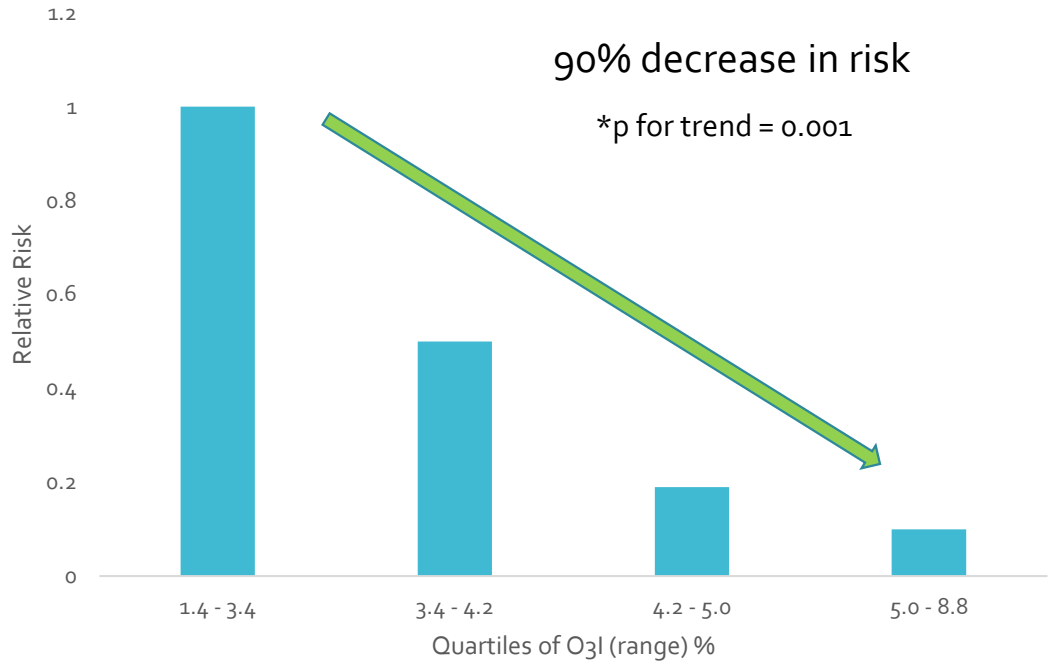
RISK FOR PRIMARY CARDIAC ARREST AND RED BLOOD CELL EPA+DHA LEVEL

Cross Sectional



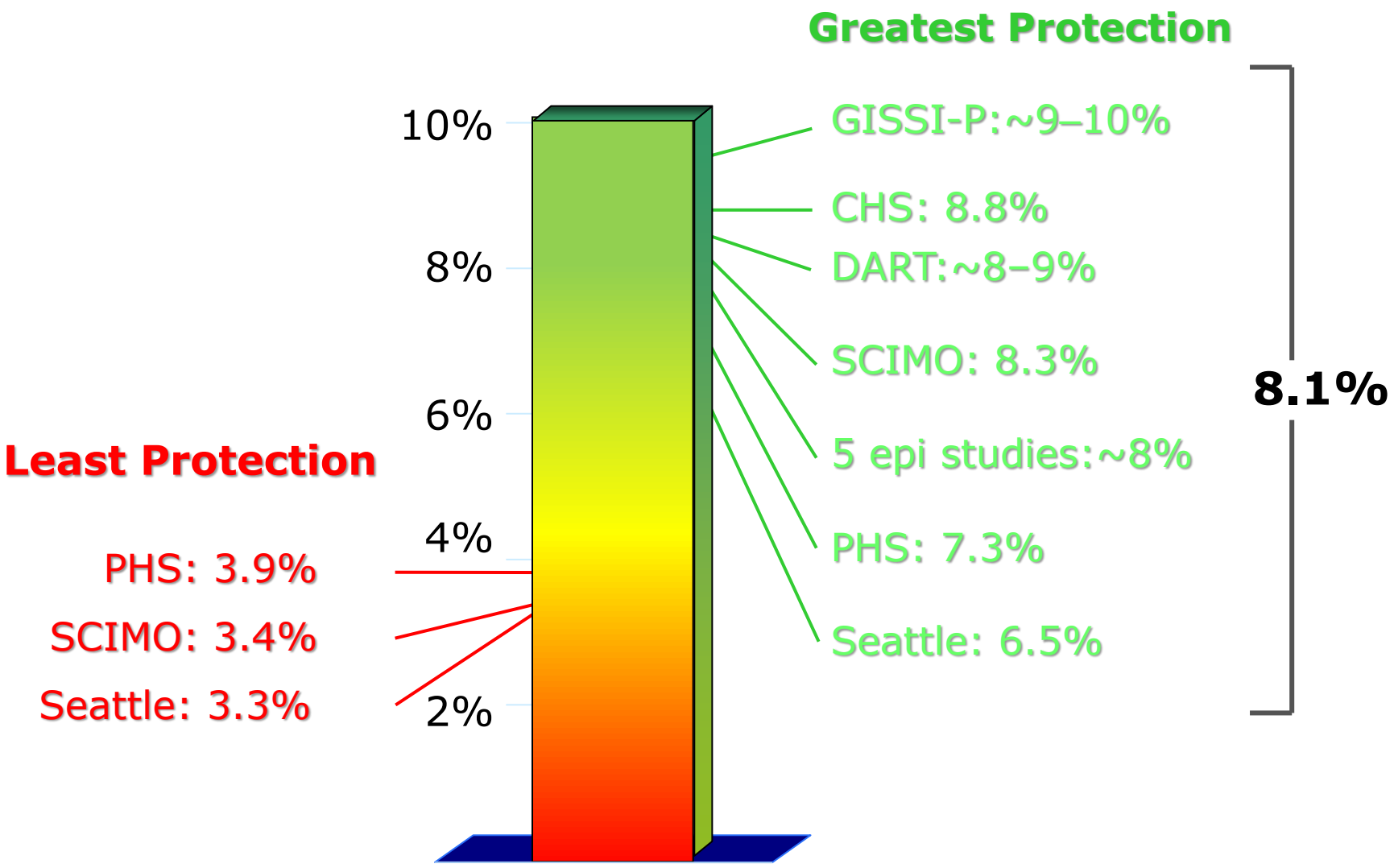
Adapted from Siscovick et al. *JAMA* 1995;274:1363-1367.

Prospective



Adapted from Albert et al. *N Engl J Med* 2002:346:1113-1118.

Selecting a target omega-3 index



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

Polyunsaturated Fatty Acid Families

ω-6 family

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- Corn Oil
- Safflower Oil
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ω-3 family

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- Soybean Oil

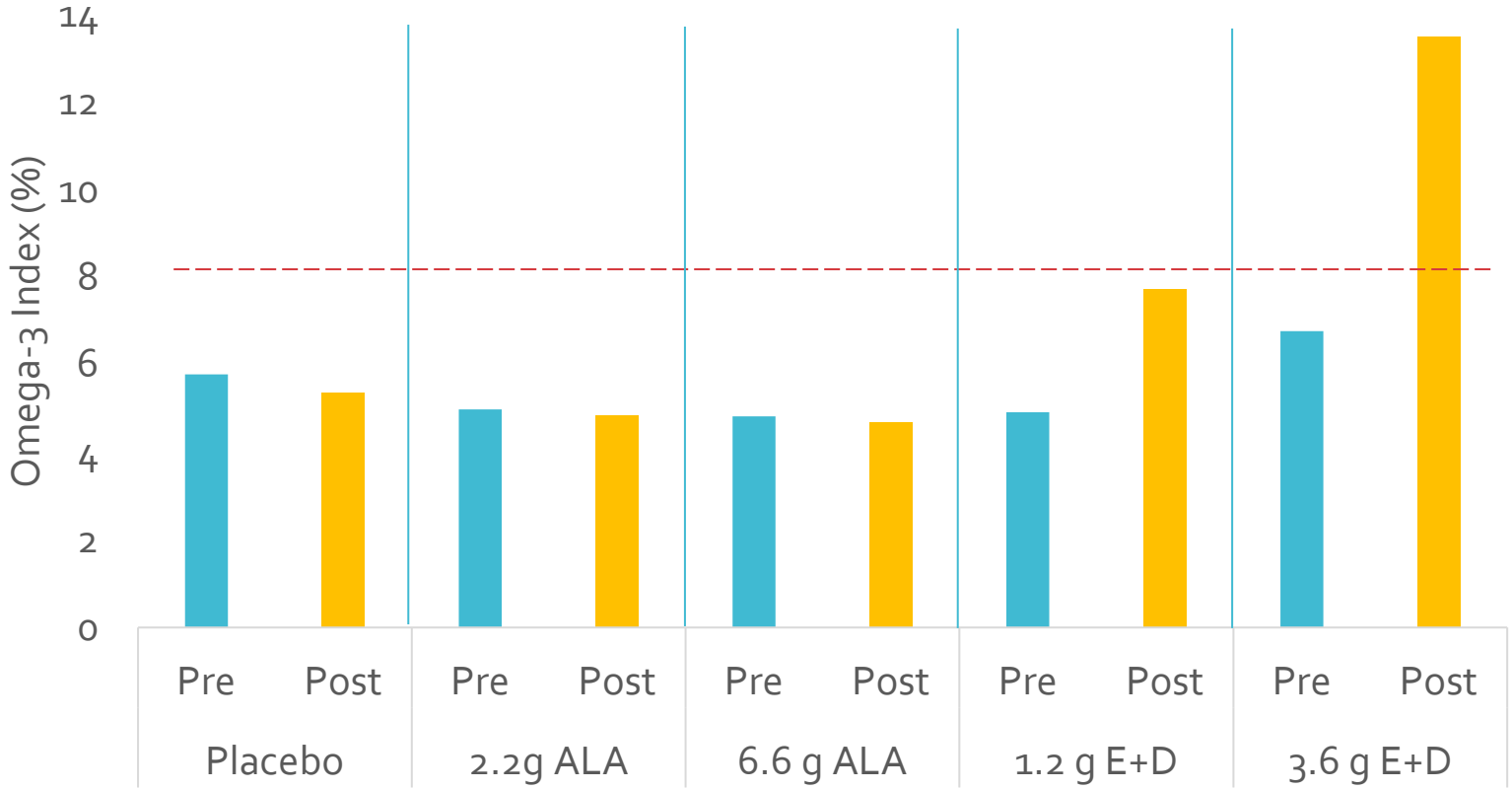
C20:5 ω-3 — **Eicosapentaenoic (EPA)**

C22:6 ω-3 — **Docosahexaenoic (DHA)**

- Oily Fish
- Fish Oil

(Non) Effects of ALA on the Omega-3 Index vs EPA+DHA

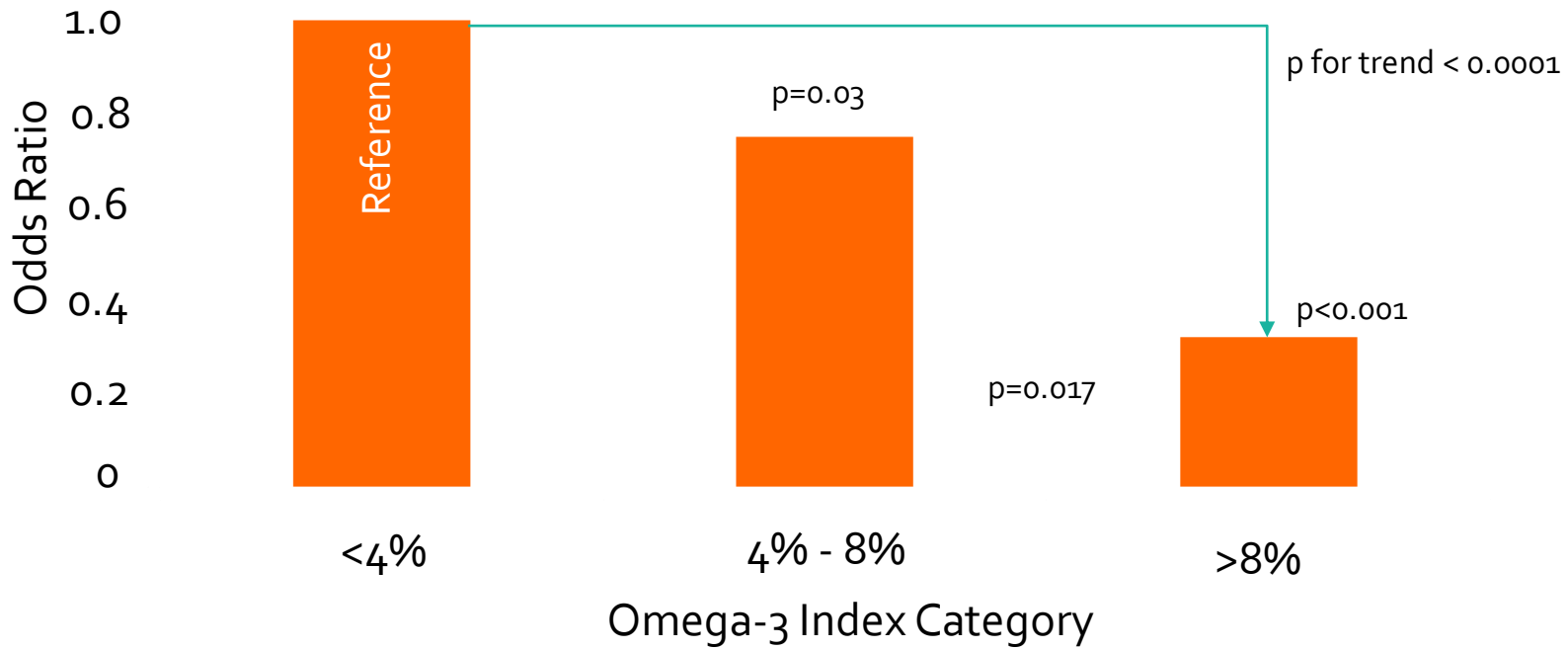
Flaxseed oil vs Fish Oil for 8 weeks (n=20 per arm)



Dewell A, et al. J. Nutr. 141: 2166–2171, 2011

Omega-3 Index and Acute Coronary Syndromes
(768 case-control pairs)

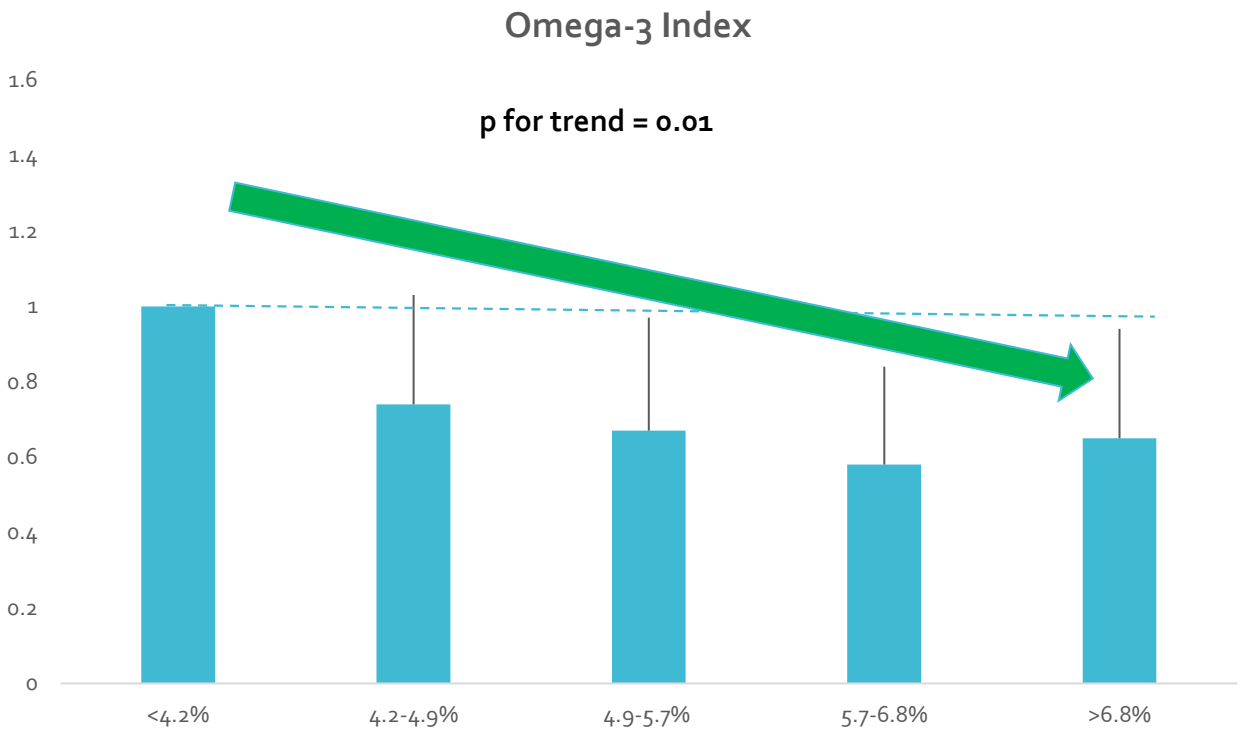
Those with an Omega-3 Index >8% were 70% less likely to be an ACS patient than those with an Index <4%



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.

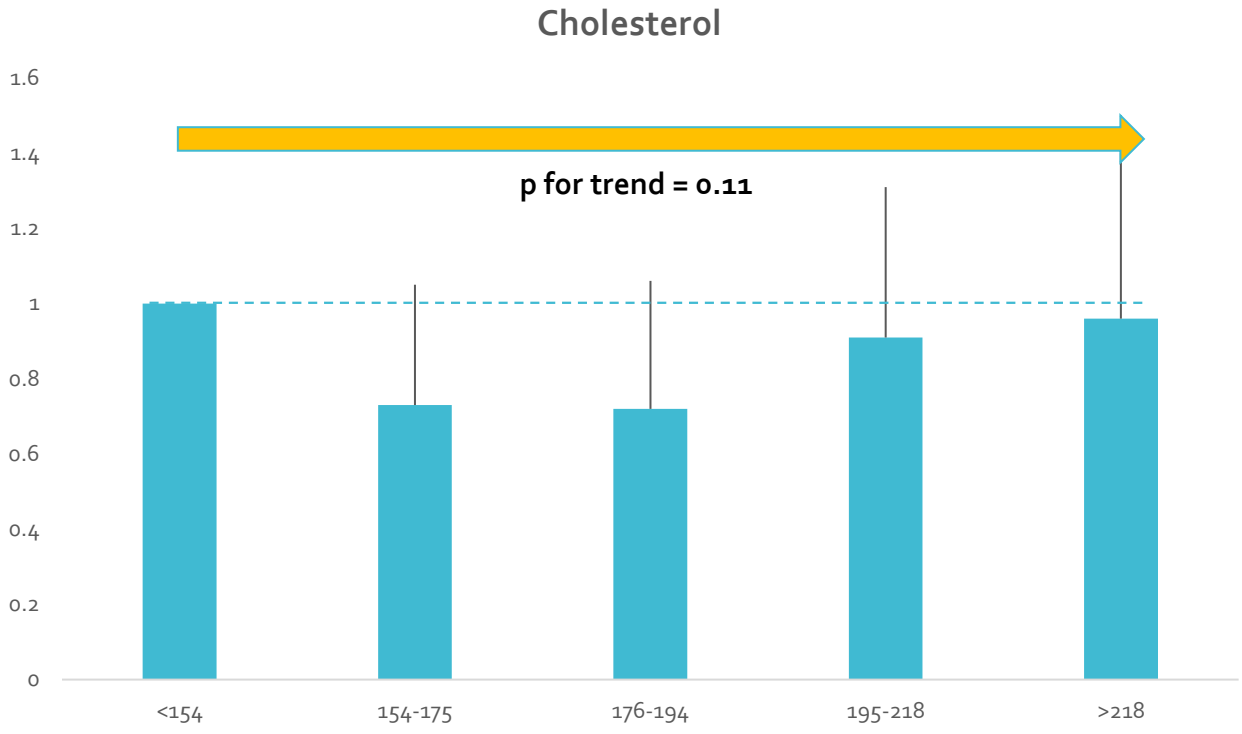
Block RC, et al. Atherosclerosis 2008;197 :821-828.

Relative Risk for Death from Any Cause in The Framingham Offspring Study the Omega-3 Index vs cholesterol



Quintiles (% of RBC fatty acids)

2500 persons free of CVD at baseline (age 66) were followed for median 7.3 years



Quintiles (mg/dL)

In the same model, baseline cholesterol levels were not related to risk for death

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

Omega-3 Levels Linked with Reduced Risk for Premature Death

FORCE

Harris WS, et al. for the FORCE Consortium.
NATURE COMM | (2021) 12:2329

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-22370-2 OPEN

Check for updates

Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies

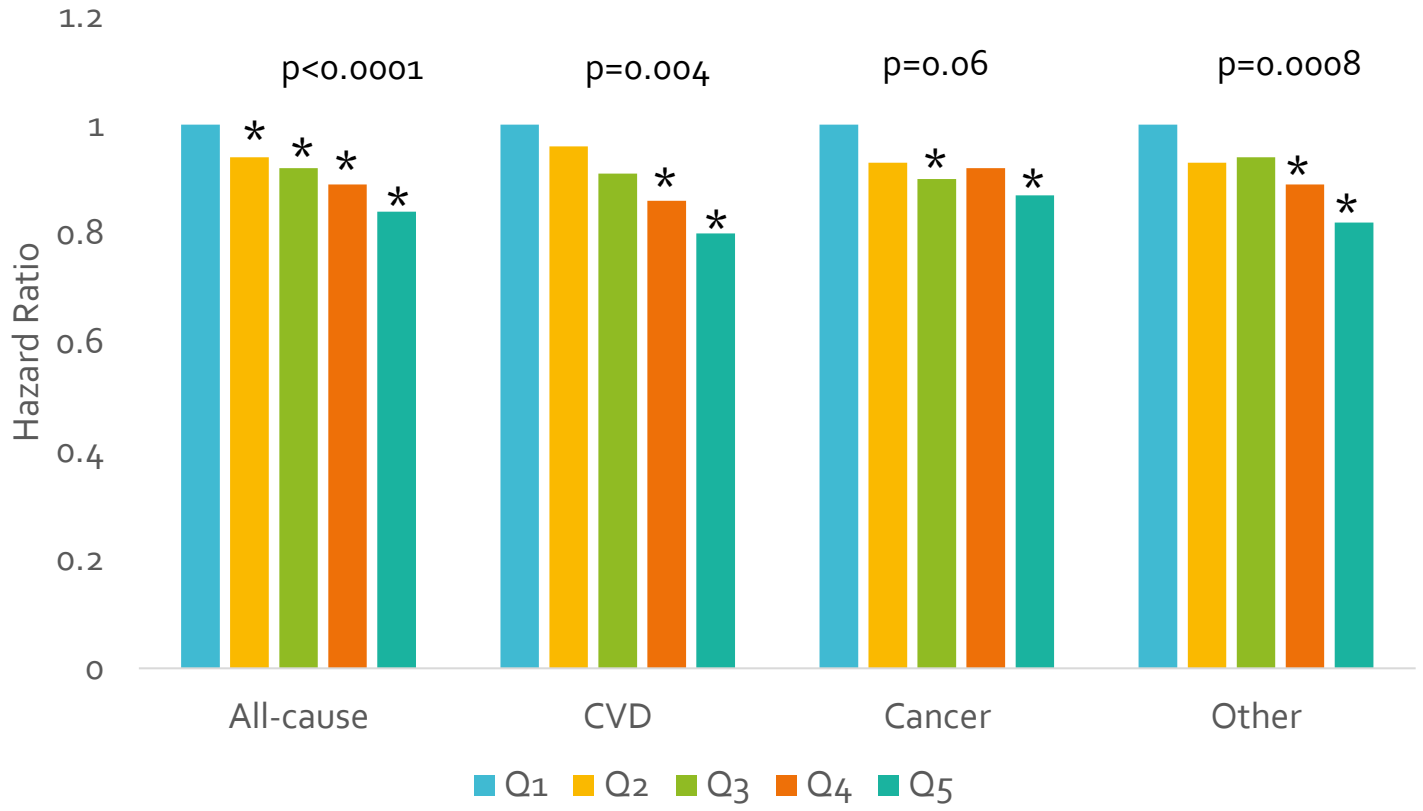
William S. Harris[1,2✉], Nathan L. Tintle[2,3], Fumiaki Imamura[4], Frank Qian[5,6], Andres V. Ardisson Korat[6], Matti Marklund[7,8], Luc Djoussé[6], Julie K. Bassett[9], Pierre-Hugues Carmichael[10], Yun-Yu Chen[11], Yoichiro Hirakawa[12], Leanne K. Küpers[13], Federica Laguzzi[14], Maria Lankinen[15], Rachel A. Murphy[16], Cécilia Samieri[17], Mackenzie K. Senn[18], Peilin Shi[19], Jyrki K. Virtanen[15], Ingeborg A. Brouwer[20], Kuo-Liong Chien[21,22], Gudny Eiriksdottir[23], Nita G. Forouhi[4], Johanna M. Geleijnse[13], Graham G. Giles[24], Vilmundur Gudnason[23,25], Catherine Helmer[17], Allison Hodge[24], Rebecca Jackson[26], Kay-Tee Khaw[4], Markku Laakso[27], Heidi Lai[19,28], Danielle Laurin[10,29], Karin Leander[14], Joan Lindsay[30], Renata Micha[19], Jaako Mursu[15], Toshiharu Ninomiya[31], Wendy Post[9], Bruce M. Psaty[32], Ulf Risérus[33], Jennifer G. Robinson[34,35], Aladdin H. Shadyab[36], Linda Snetselaar[35], Aleix Sala-Vila[2,37], Yangbo Sun[35,38], Lyn M. Steffen[39], Michael Y. Tsai[40], Nicholas J. Wareham[4], Alexis C. Wood[18], Jason H. Y. Wu[7], Frank Hu[5,6], Qi Sun[5,6], David S. Siscovick[41], Rozenn N. Lemaitre[32], Dariush Mozaffarian[19] & The Fatty Acids and Outcomes Research Consortium (FORCE)*

Subject Characteristics

- 42,466 individuals in 17 studies and 10 countries
- Mean age, 64 years and 54% women
- Median follow-up time of 16 years (range 5 to 32 years)
- 15,720 deaths occurred during follow-up
  - 30% CVD
  - 30% cancer
  - 39% other causes

Harris WS, et al. for the FORCE Consortium.
NATURE COMM | (2021) 12:2329

Associations of omega-3 index with risk of total and cause-specific mortality



Estimated O3I
Q1 ~ 4.0%
Q5 ~ 7.7%

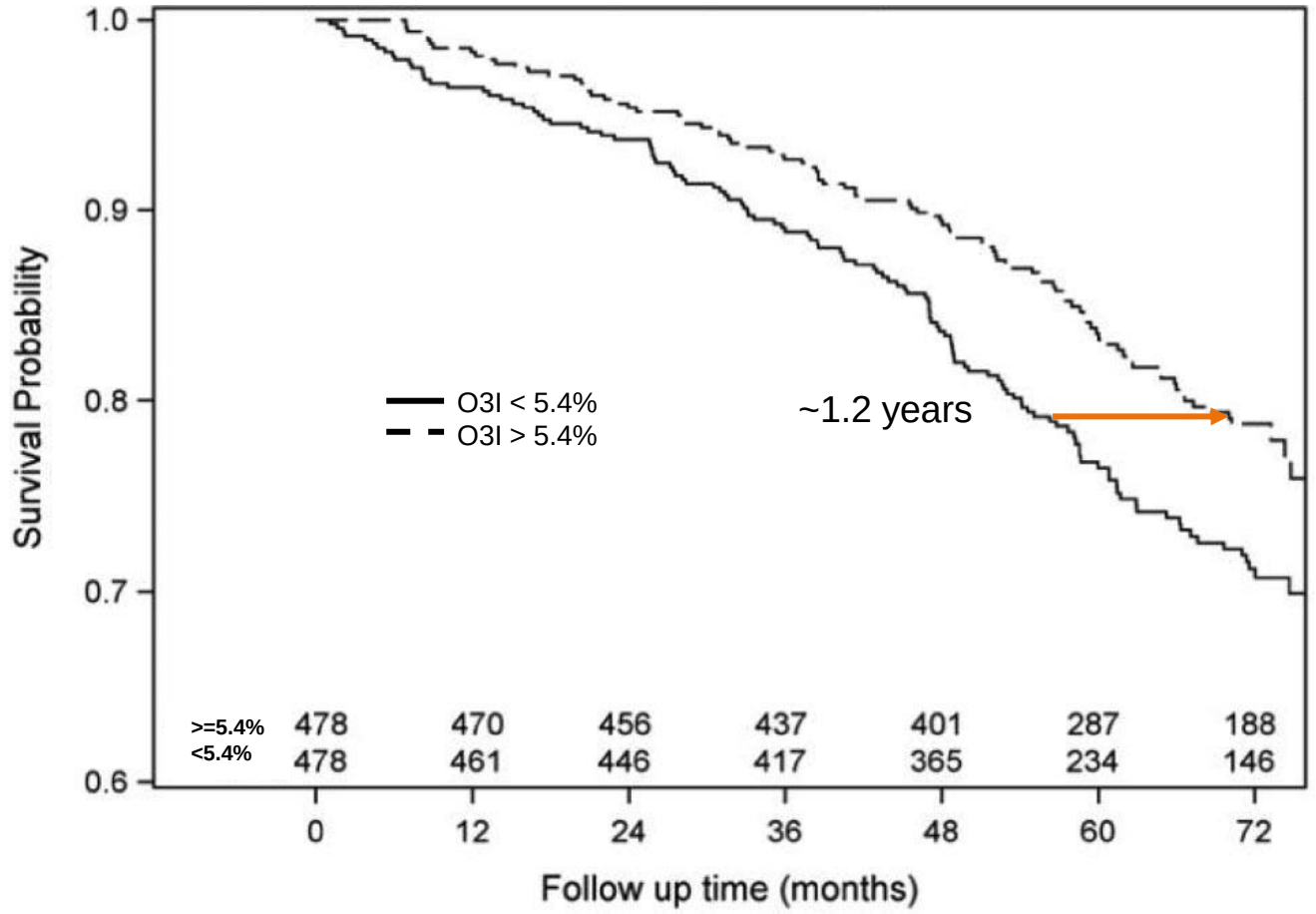
Harris WS, et al. for the FORCE Consortium.
NATURE COMM | (2021) 12:2329

*p at least <0.05 versus reference group. Category p-values are for trends

THE HEART & SOUL STUDY: THE HIGHER THE OMEGA-3 INDEX, THE GREATER THE PROBABILITY OF SURVIVAL

It took about 1.2 years longer for 20% of the above-average group to die compared with the below-average group (n=956 total).

* Extrapolated from whole blood EPA+DHA (r=0.96)



Pottala, et al. Circ: CV Qual Outcomes 2010;3:406-412

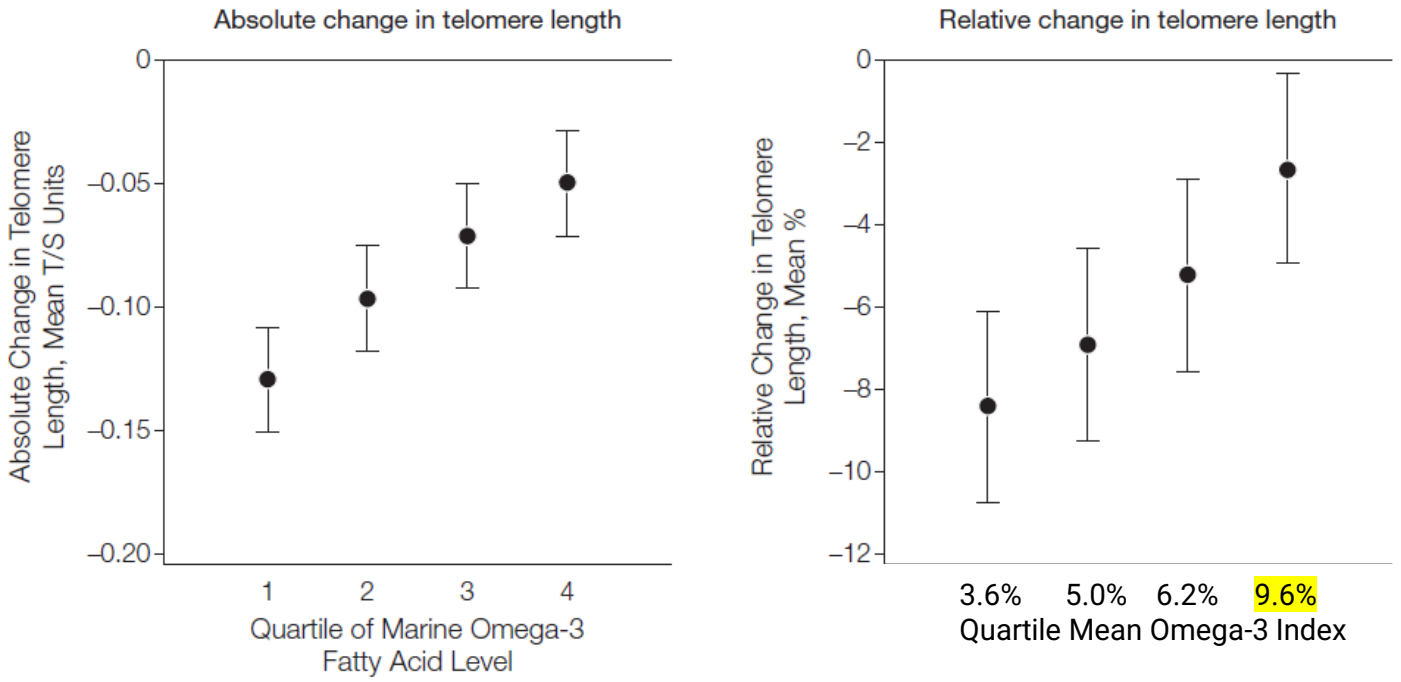
The Heart & Soul Study: Blood Omega-3 and Rate of Telomere Attrition

Patients with the highest Omega-3 Index experienced the slowest rate of telomere shortening (cellular aging)

A 1-SD increase in the O3I was associated with a 32% reduction in the odds of telomere shortening.

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

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

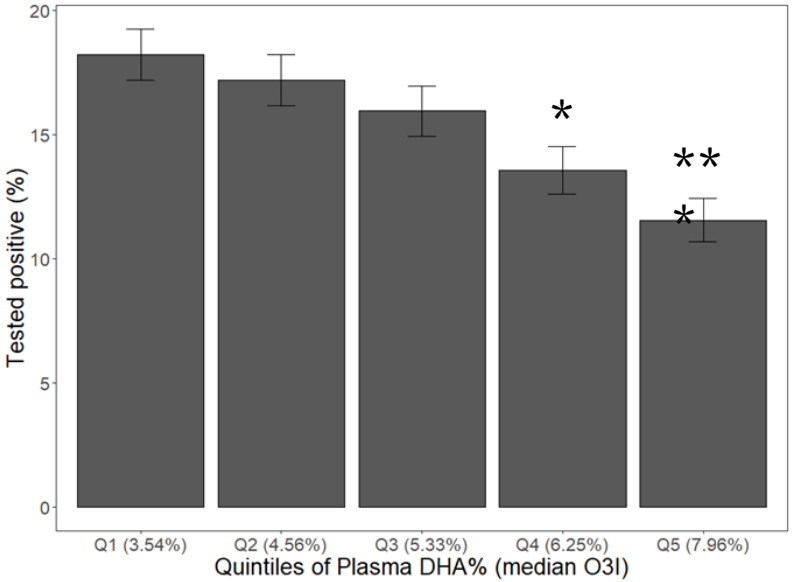


Error bars indicate 95% confidence intervals. T/S indicates telomere-to-single-copy gene ratio. $P<.001$ for linear trend for both absolute and relative change. See Table 1 for definitions of quartiles.

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

Relations between the Plasma DHA% and COVID-19 Outcomes UK Biobank

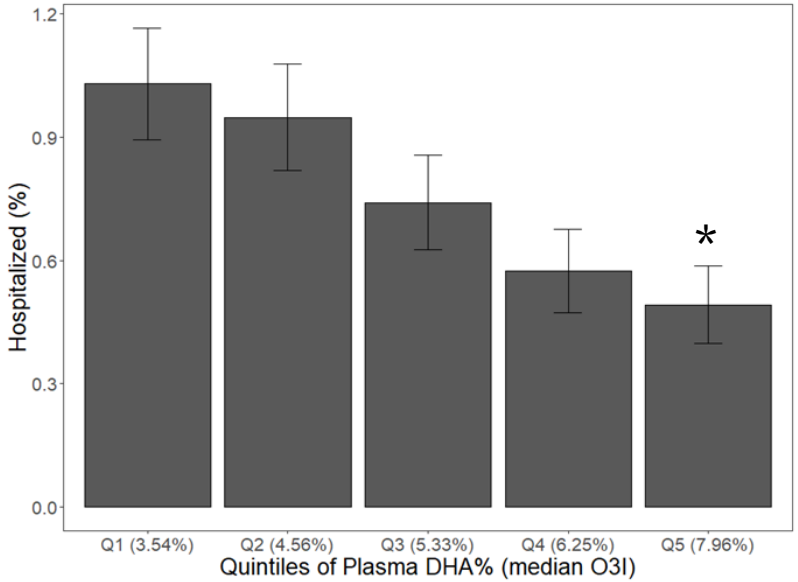
Tested Positive



N=4084 of 26,620 tested

8% lower risk per 1 SD DHA%***

Hospitalized

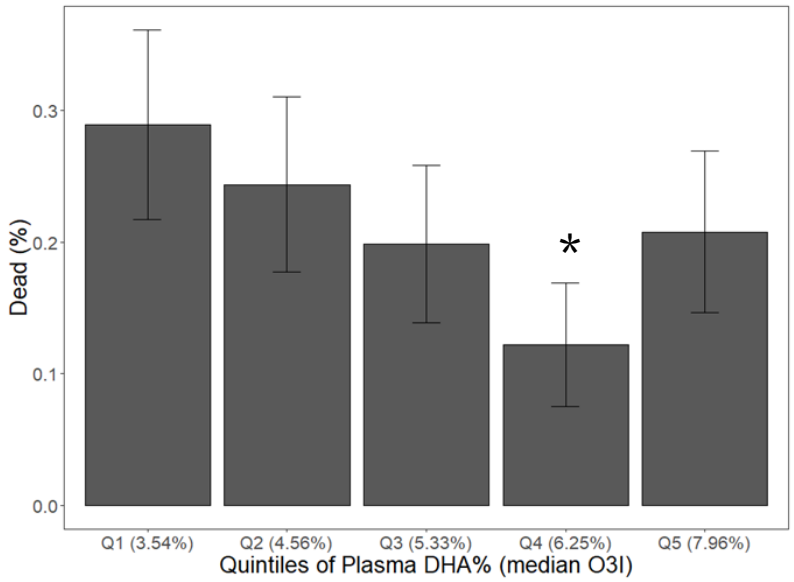


eO3I: Q1=3.54% and Q5=7.96%

N=838 of 110,6888

11% lower risk per 1 SD DHA%**

Dead



N=235 of 110,688

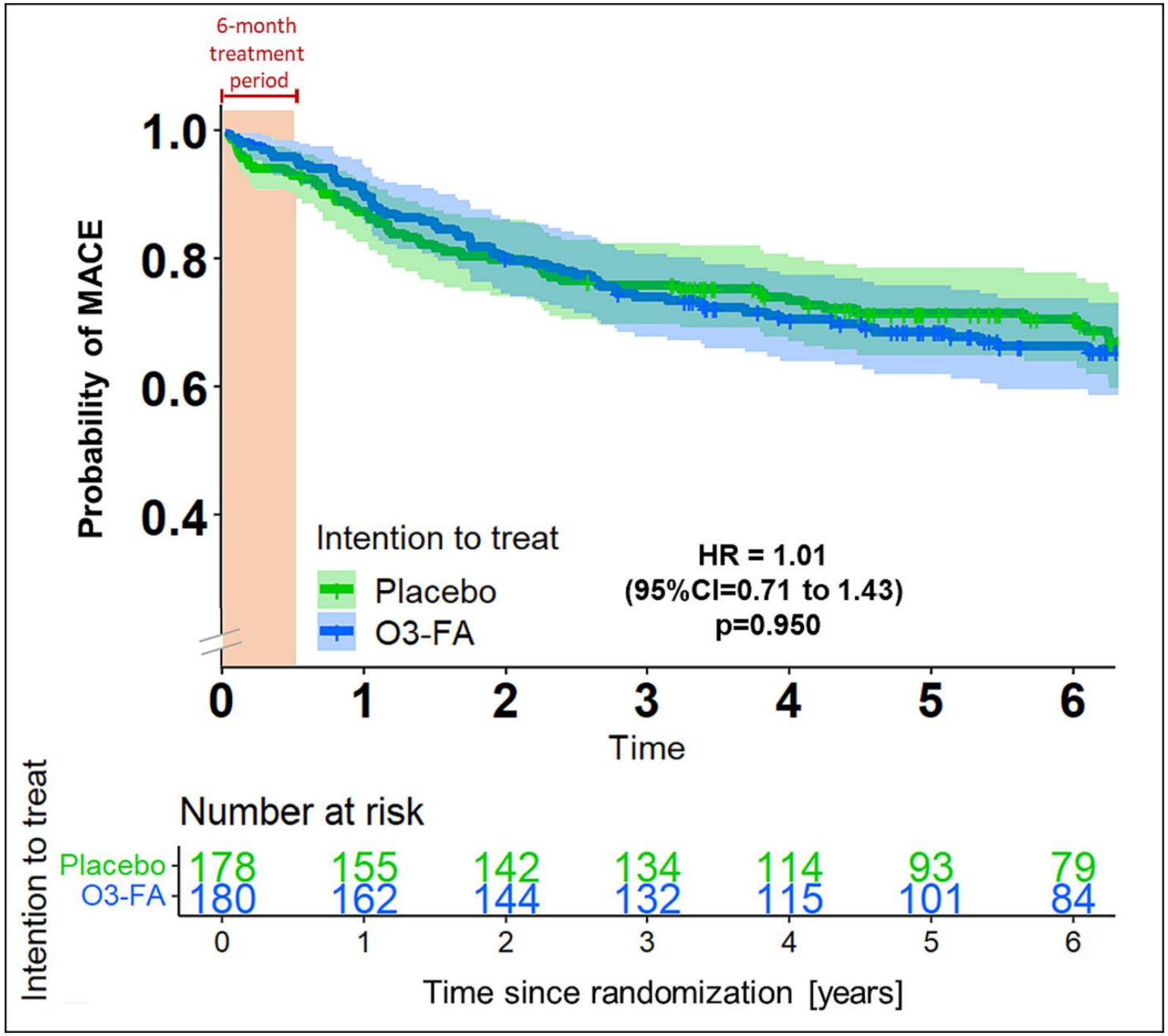
6% lower risk per 1 SD DHA% (NS)

Harris WS, et al. AJCN 2023;117:357-363

In fully-adjusted model vs Q1: * p<0.05; ** p<0.01; *** p<0.001

Long-term (6 yr) Major Adverse Cardiac Events (MACE) were compared in post-MI patients assigned to 6 months of treatment with Omacor vs Placebo

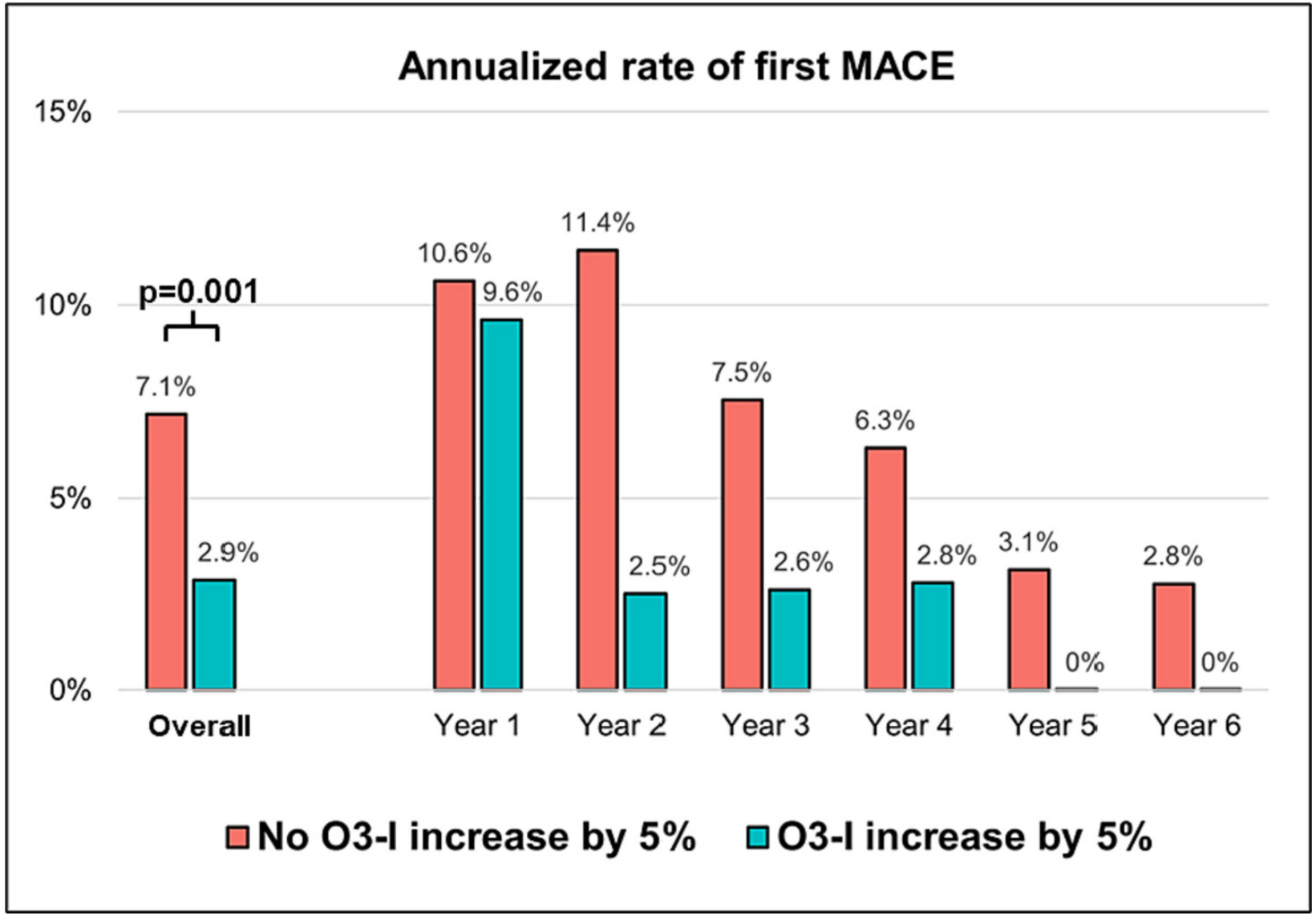
There was no difference in MACE outcomes *by treatment group.*



Bernhard et al. Int J Cardiology 399 (2024) 131698

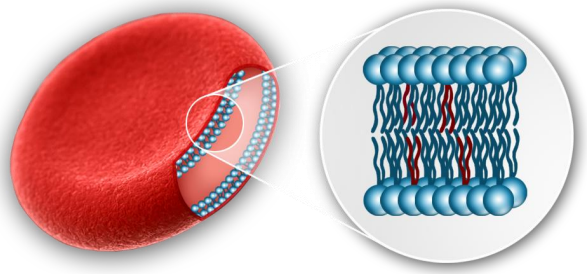
There was a 59% reduction in risk for MACE in those who had an **increase** in the O3I ≥5% (n=43) during treatment vs those who did not (n=211).

Achieving target tissue Om3 levels is more important than just being told to take Omega-3.

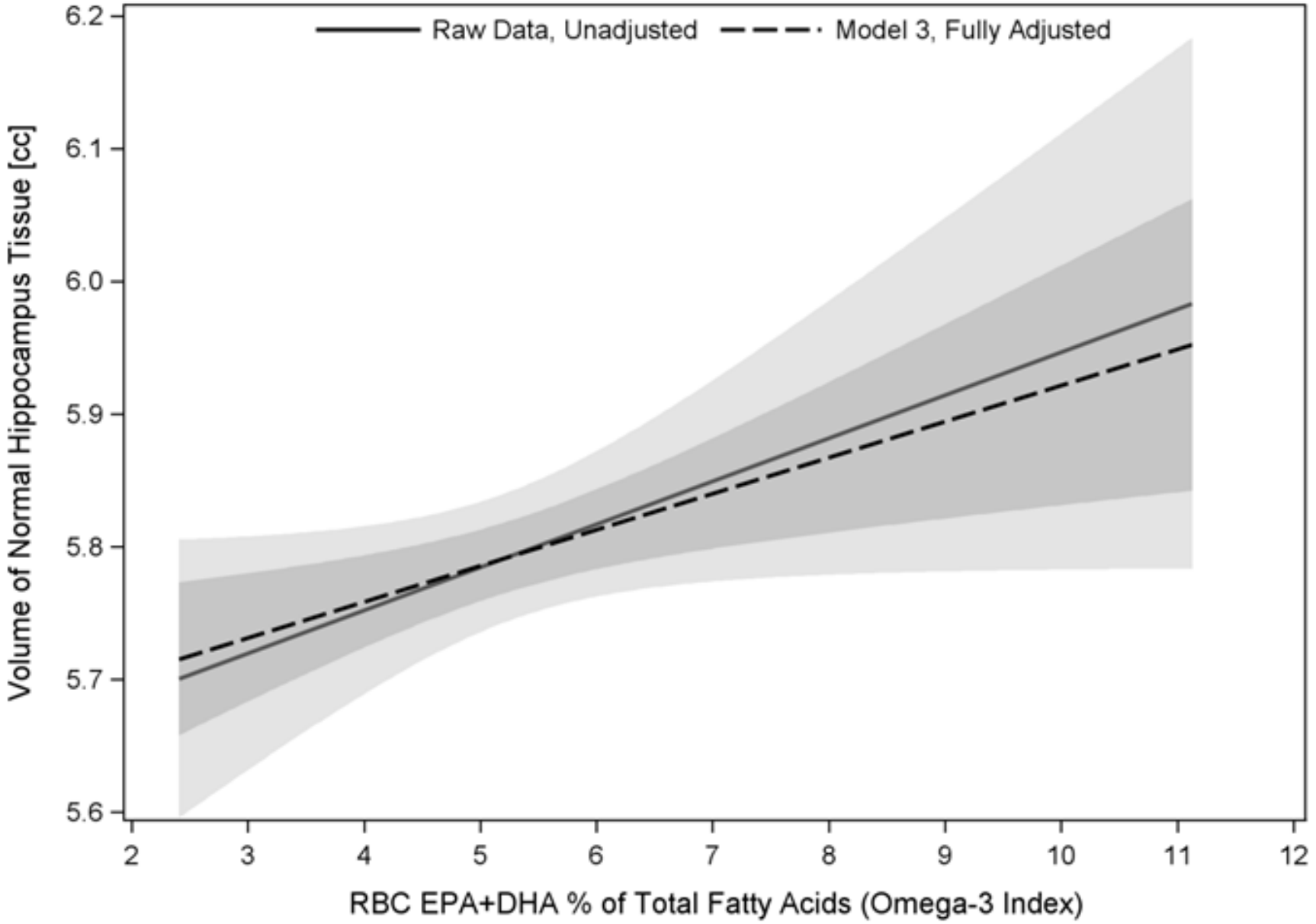


Bernhard et al. Int J Cardiology 399 (2024) 131698

The Omega-3 Index and Hippocampal Volume in the Women's Health Initiative Memory Study



The Omega-3 Index (EPA+DHA as a % of erythrocyte fatty acids) is a marker of tissue levels of EPA and DHA.



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

Risk for developing Alzheimer's disease over an average of 7.3 years as a function of baseline RBC DHA in Framingham

Endpoint	HR (95% CI) for quintiles of red blood cell DHA				
	Q1 (<3.8%, median = 3.4%) (n = 300)	Q2 (3.8% to <4.5%, median = 4.2%) (n = 298)	Q3 (4.5% to <5.2%, median = 4.8%) (n = 297)	Q4 (5.2% to 6.1%, median = 5.6%) (n = 297)	Q5 (>6.1%, median = 6.97%) (n = 295)
Alzheimer's disease					
N. of cases	29	30	24	29	19
Hazard Ratio	1.00	0.77 (0.45, 1.33)	0.64 (0.35, 1.18)	0.75 (0.42, 1.33)	0.51 (0.27, 0.96)
All-cause dementia					
N. of cases	35	38	29	40	26
Hazard Ratio	1.00	0.79 (0.49, 1.29)	0.64 (0.37, 1.11)	0.87 (0.53, 1.44)	0.56 (0.32, 0.97)

= 8.13% O3I

49% lower risk for AD comparing Q5 to Q1

Sala-Vila et al. *Nutrients* 2022;14:2408

Omega-3 and Risk for Atrial Fibrillation

Circulating And Tissue Omega-3 Fatty Acid Biomarkers And Incident Atrial Fibrillation: An Individual Participant-level Pooled Analysis Of Prospective Studies

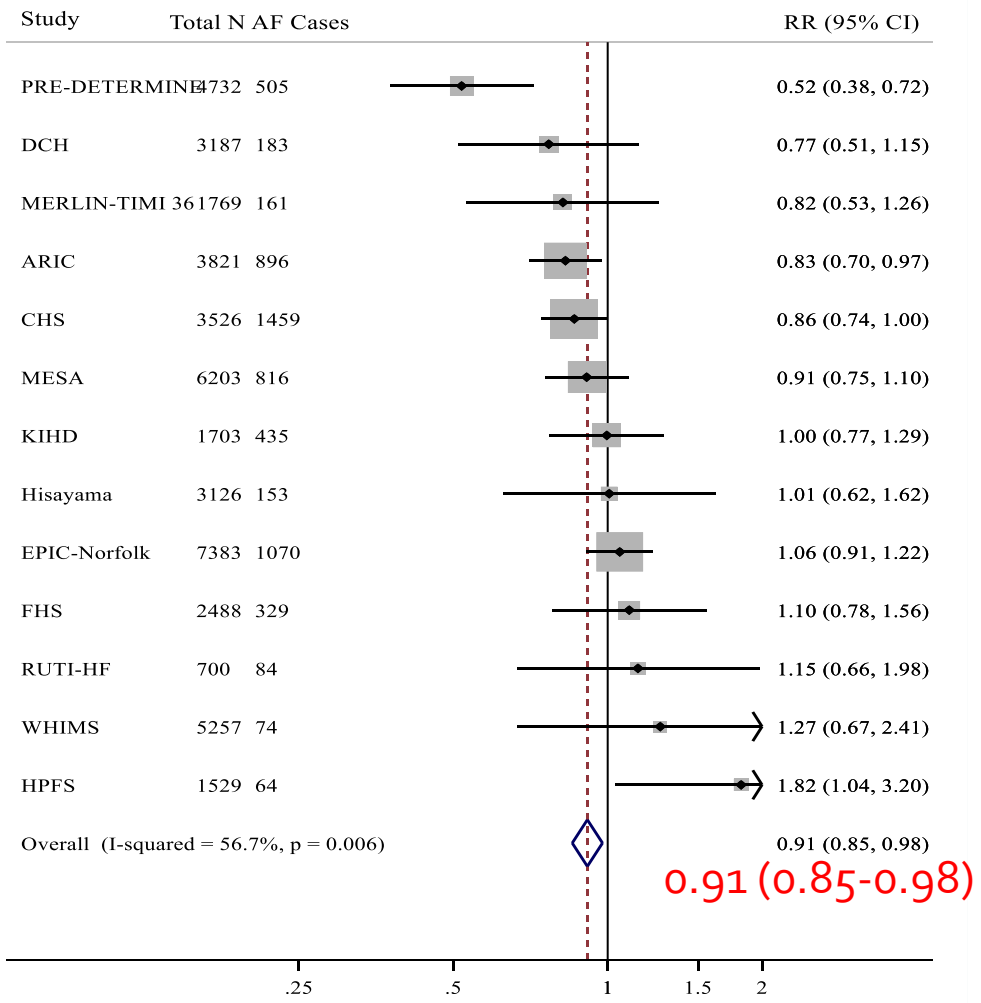
Frank Qian et al.

17 prospective cohorts
54,799 participants
7720 incident cases of AF
Weighted Median follow-up 13.3 yrs

(Abstract: 7 Apr 2022 https://doi.org/10.1161/circ.145.suppl_1.P212 Circulation. 2022;145:AP212. Paper currently (1/20/2023) under review at JACC

Omega-3 and Risk for Atrial Fibrillation

Pooled Relative Risk for incident Atrial Fibrillation comparing Circulating EPA+DHA levels, 90th vs 10th percentile



(Qian et al. https://doi.org/10.1161/circ.145.suppl_1.P212 Circulation. 2022;145:AP212

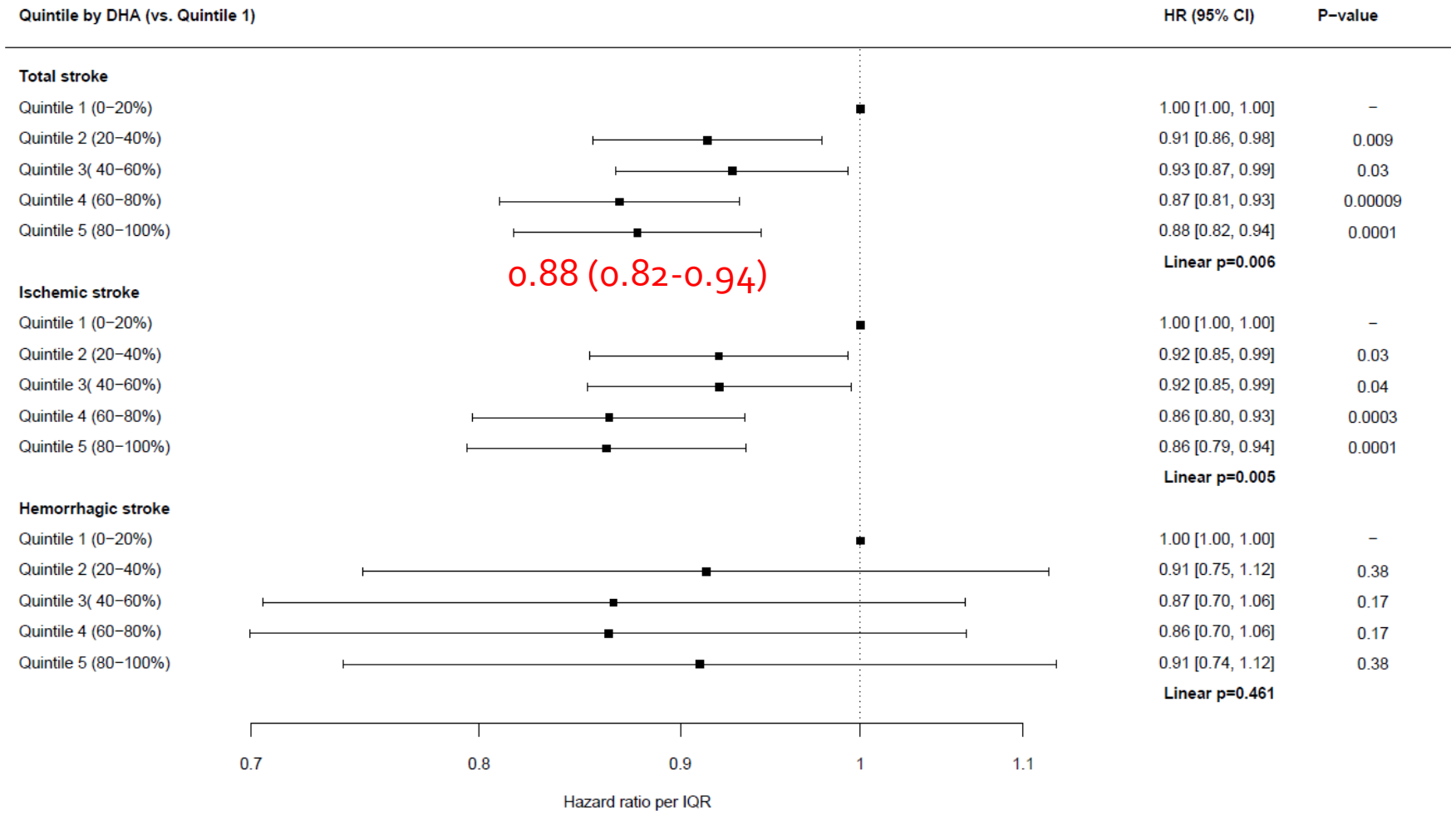
Omega-3 and Stroke

- Outcome: Incident stroke (total, ischemic, and hemorrhagic)
- 29 international prospective cohorts.
- Total n=183,291
- Median of 14.3 years follow-up
- 10,561 total strokes
  - 8220 ischemic strokes
  - 1142 hemorrhagic strokes

James H O'Keefe, MD
Professor of Medicine, UMKC School of Medicine
Saint Luke's Mid America Heart Institute, Kansas City, MO

O'Keefe et al. *Stroke* 2024;55:50–58.

Omega-3 and Stroke



Higher DHA levels were associated with ~12% reduction in risk for total and ischemic stroke; Trend towards *lower* risk for hemorrhagic stroke

O'Keefe et al. *Stroke* 2024;55:50–58.

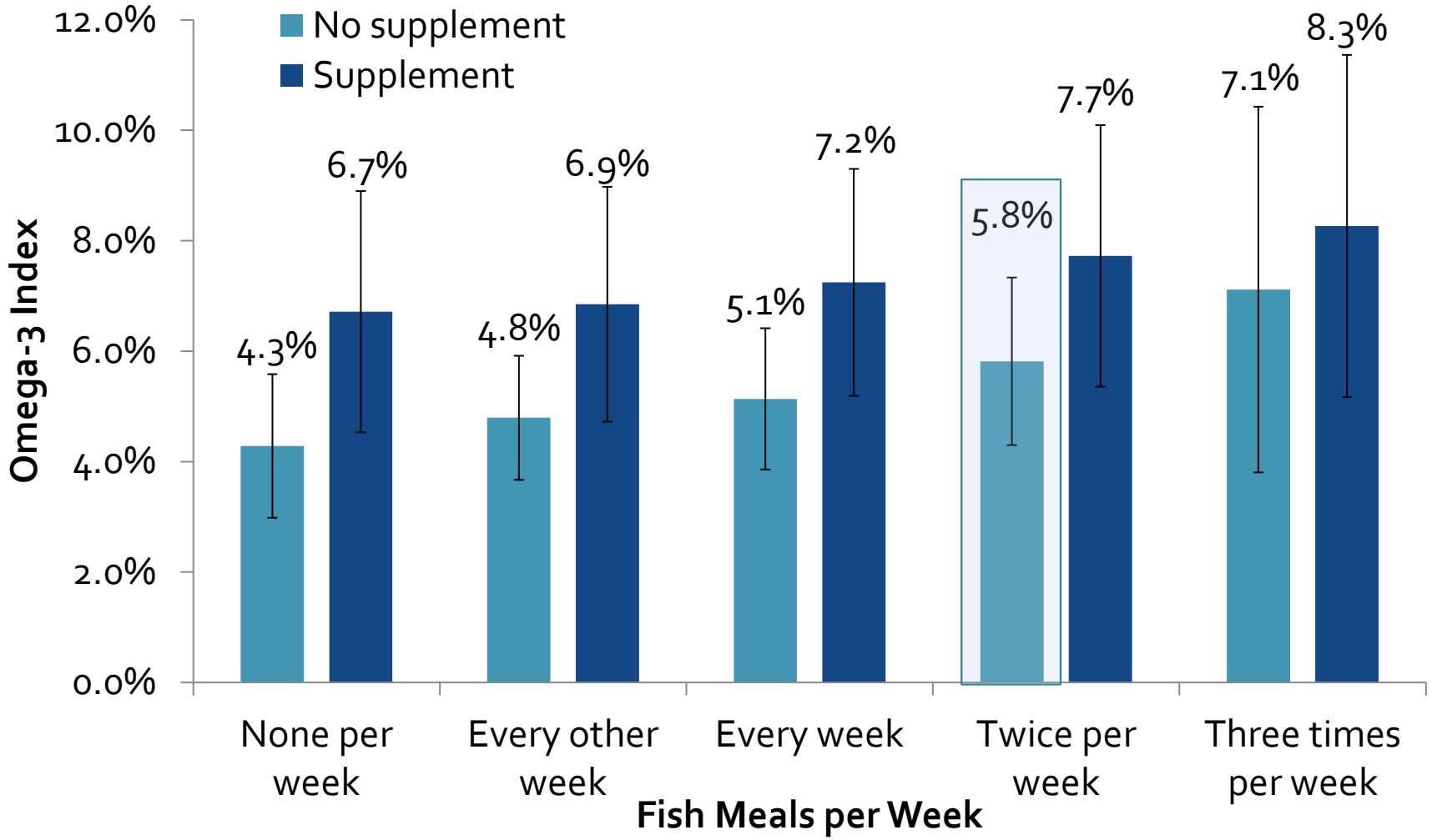
Associations between Blood Omega-3 Levels and Risk for Diseases

Summary of FORCE Findings (May 2024)

Disease	Favorable	Neutral	Adverse
Coronary	X		
Type 2 Diabetes	X		
All-Cause Mortality	X		
CV Mortality	X		
Cancer Mortality	X		
Other Mortality	X		
Atrial Fibrillation	X		
Stroke	X		
Ischemic Stroke	X		
Hemorrhagic Stroke		X	
Kidney	X		
Peripheral Arterial		Pending	
Heart Failure		Pending	
Dementia		Pending	
Depression		Pending	

Higher blood omega-3 levels are uniformly associated with lower risk for multiple diseases

Eating fish 1-2 times per week is associated with an Omega-3 Index of ~5.5%



Jackson KH et al. *PLEFA* 2019:142:4-10

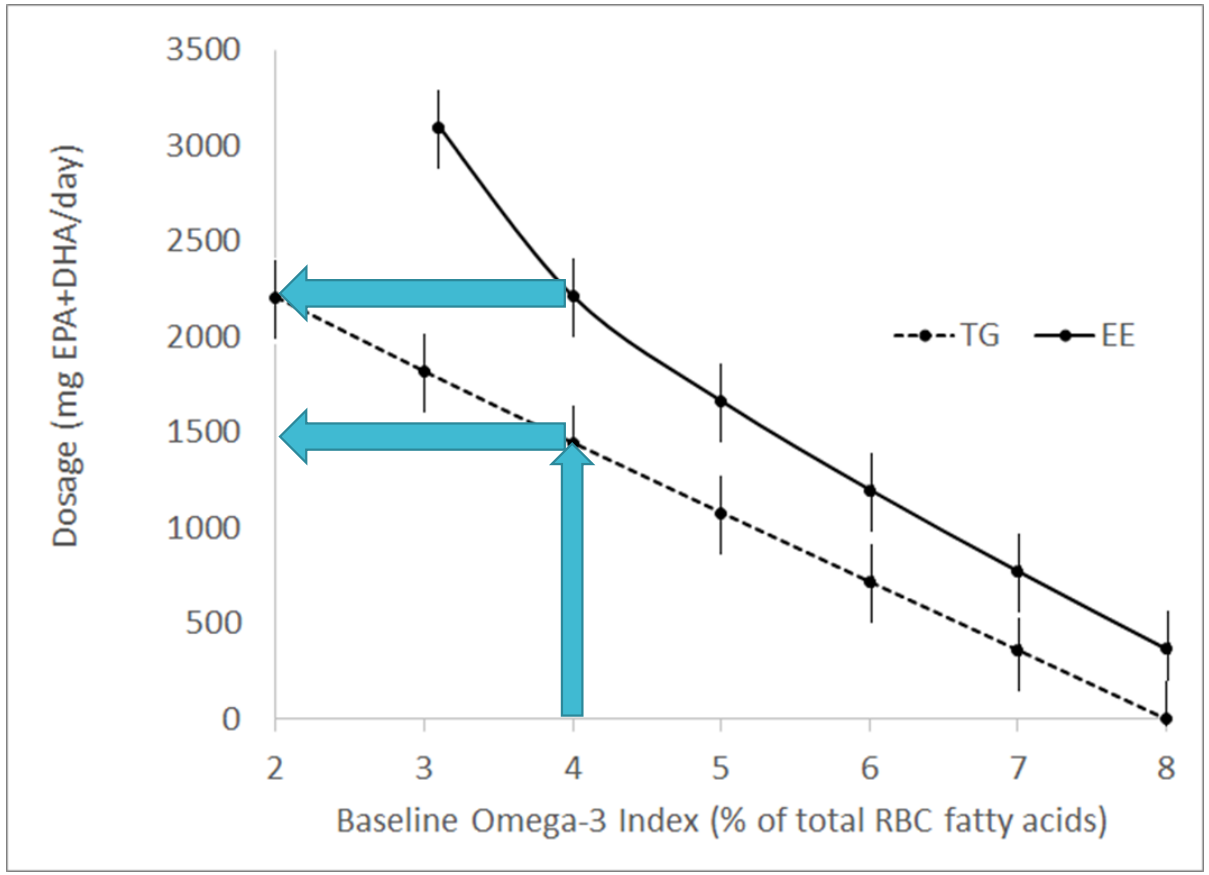
Data from 3458 blood samples

The omega-3 index calculator

Dose of EPA+DHA needed to move from baseline Omega-3 Index to 8%

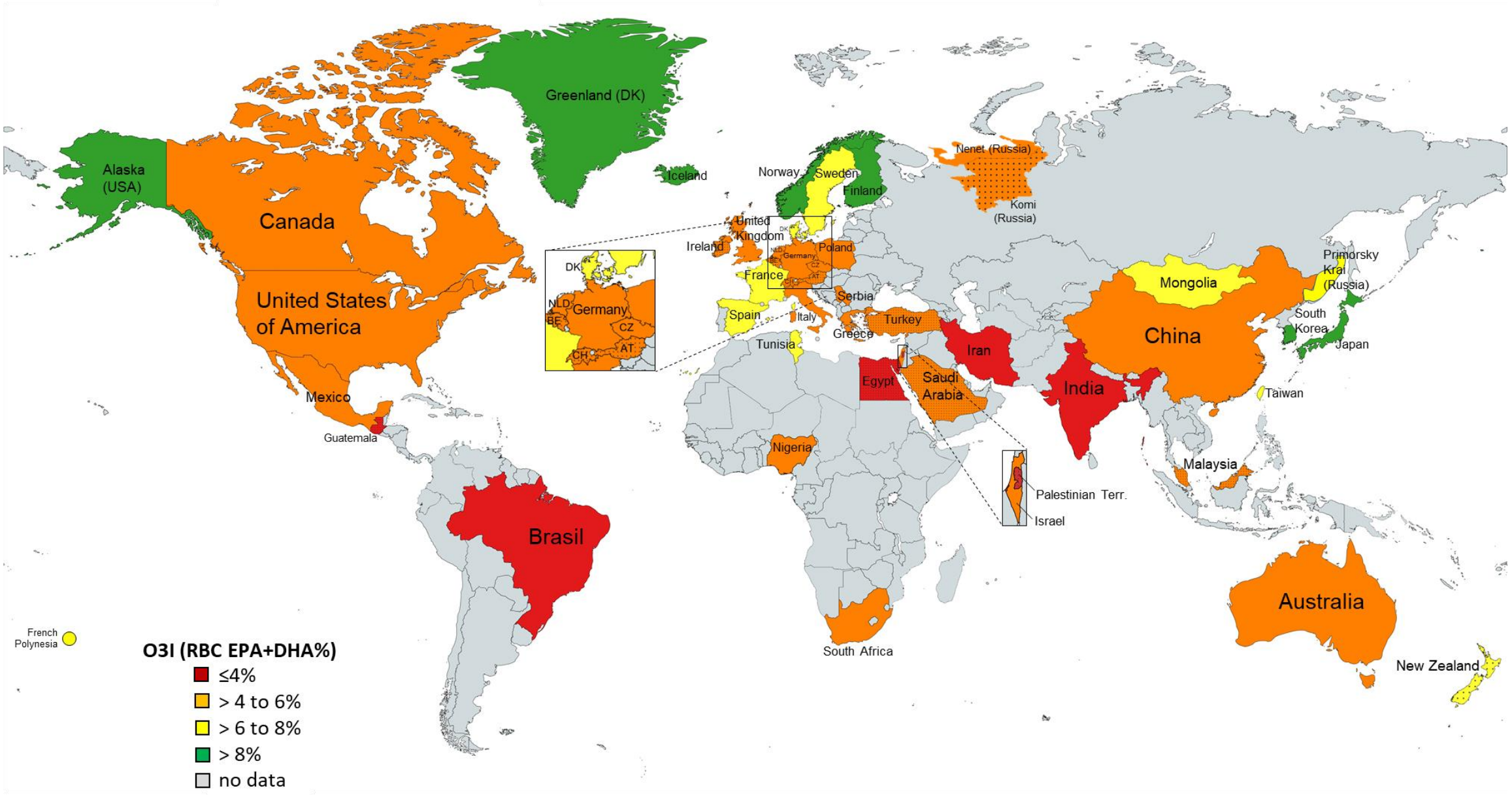
Pooled data on 1422 individuals from 14 RCTs

1500 mg EPA+DHA (TG)
7.5 mL of cod liver oil
5 capsules (300 mg/cap)
2 capsules (750 mg/cap)



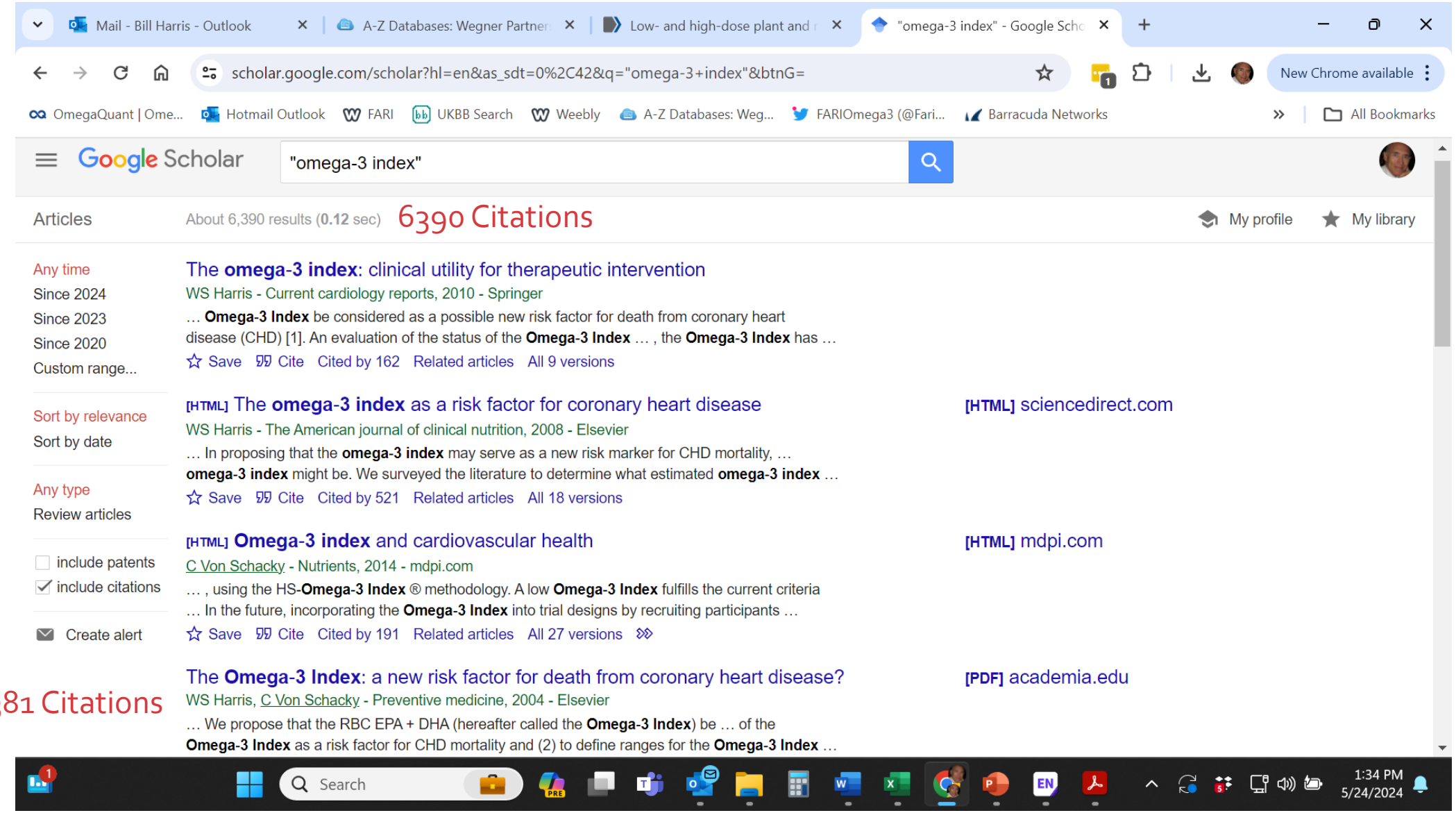
https://omegaquant.com/omega-3-index-calculator/

Walker, et al. Am J Clin Nutr 2019;110(4):1034-1040



Schuchardt JP, et al. Prog Lipid Res (in press, 2024)

The Omega-3 Index is Widely Accepted in Medical Research



SUMMARY

The Omega-3 Index is a valid and stable marker of omega-3 (EPA+DHA) status

Can be determined on a dried blood spot

It can be used in both research and in "personalized nutritional counseling" to help patients achieve an optimal omega-3 status

The response to supplementation is quite variable – testing is required

A higher Omega-3 Index is independently associated with lower risk for acute coronary syndromes, for death from all causes (and CVD, cancer, and others) and for many other diseases


THE END

WebMD

Fish Oil Supplements Linked to First-Time Heart Problems

Written by Lisa O'Mary

MEDICALNEWSTODAY

Regular use of fish oil supplements may increase first time heart disease and stroke risk

Written by Bob Curley on May 23, 2024 — Fact checked by Sarah Myers, PharmD

HEALTH NEWS ✓ Fact Checked

Fish Oil Supplements May Raise Your Risk of Heart Disease and Stroke If You're Healthy

Written by Nancy Schimelpfening, MS on May 21, 2024 — Fact checked by Jennifer Chesak, MSJ

healthline

CNN Health

Fish oil supplements may raise risk of stroke, heart issues, study suggests

By Sandee LaMotte, CNN

FOX NEWS FLASH

HEALTH

Fish oil supplements linked to greater first-time heart attack risk in study: 'Not universally good or bad'

Cardiologist, dietitians share cautions, tips on fish oil supplements and new study: 'More isn't always better'

By Melissa Rudy · Fox News

Published May 23, 2024 7:15pm EDT | Updated May 26, 2024 5:29pm EDT

bmjmedicine

Check for updates

Regular use of fish oil supplements and course of cardiovascular diseases: prospective cohort study

Ge Chen,[1] Zhengmin (Min) Qian,[2] Junguo Zhang,[1] Shiyu Zhang,[1] Zilong Zhang ,[1]
Michael G Vaughn,[3] Hannah E Aaron,[2] Chuangshi Wang,[4] Gregory YH Lip,[5,6] Hualiang Lin [1]

OBJECTIVE To examine the effects of fish oil supplements on the clinical course of cardiovascular disease (CVD), from a healthy state to atrial fibrillation (AF), major adverse cardiovascular events, and subsequently death.
DESIGN Prospective cohort study.
SETTING UK Biobank study, median follow-up 11.9 years.
PARTICIPANTS 415 737 participants, 40-69 years.
MAIN OUTCOME MEASURES Incident cases of AF, major adverse CV events (MACE), and death, identified by linkage to hospital inpatient records and death registries.

Role of fish oil supplements in different progressive stages of CVDs, from healthy status (primary stage), to AF (secondary stage), MACE (tertiary stage),

There were 24 different pathways in this study, each of which examined the difference in risk between FOS users and non-users over about 12 years for going down each pathway

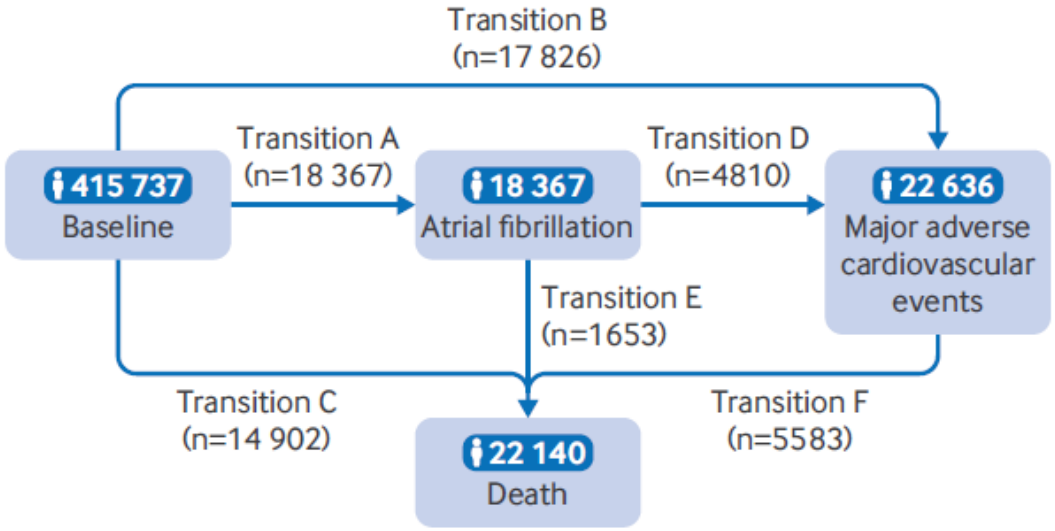


Figure 2 | Numbers of participants in transition pattern I, from baseline to atrial fibrillation, major adverse cardiovascular events, and death

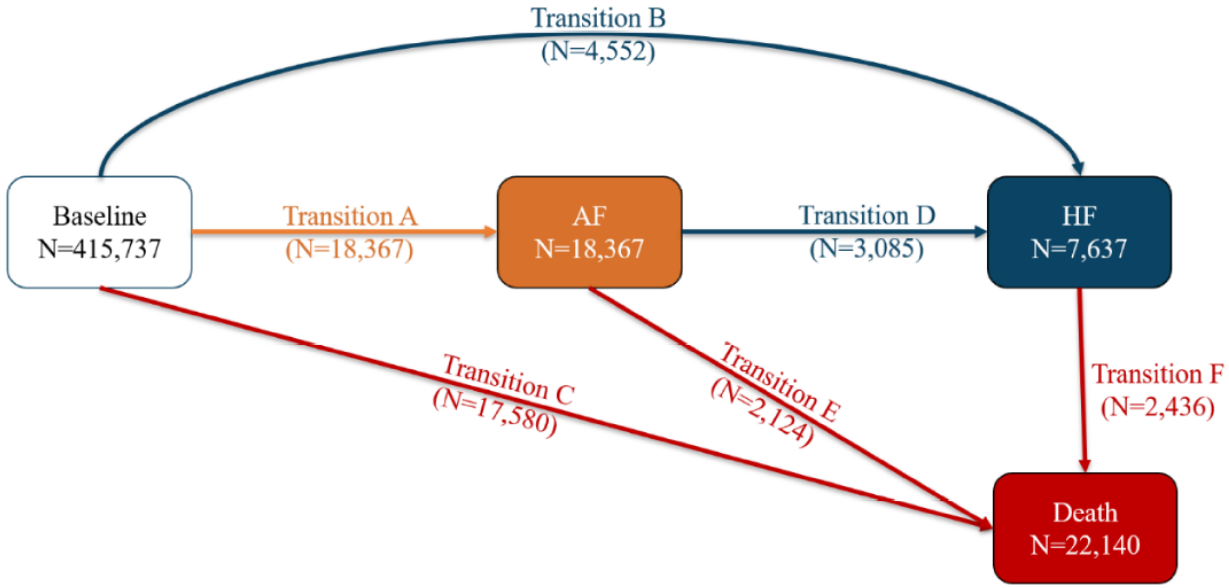


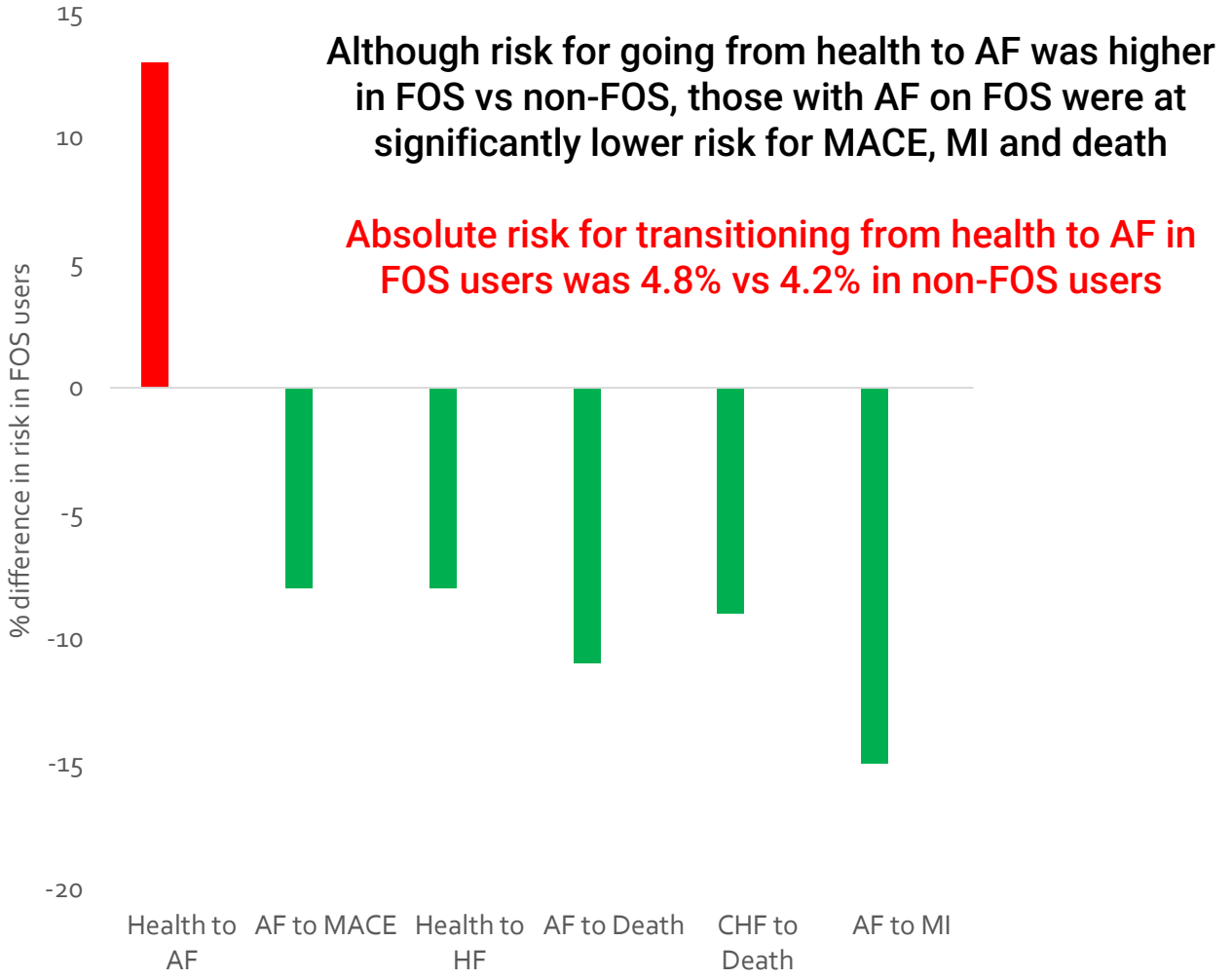
Figure S1. Numbers of participants in transition pattern II from baseline to atrial fibrillation, heart failure (HF), and death.

Of the 24 possible outcome pathways, FOS users differed significantly from non-users as follows:

No difference – 18

Better outcome – 5

Worse outcome -1



Adapted from Chen et al. BMJMED 2024;3:e000451. doi:10.1136/bmjmed-2022-000451

OUTLINE

Associations of habitual fish oil supplementation with cardiovascular outcomes and all cause mortality: evidence from a large population based cohort study

Zhi-Hao Li,[1] Wen-Fang Zhong,[1] Simin Liu,[2] Virginia Byers Kraus,[3] Yu-Jie Zhang,[1] Xiang Gao,[4] Yue-Bin Lv,[5] Dong Shen,[1] Xi-Ru Zhang,[1] Pei-Dong Zhang,[1] Qing-Mei Huang,[1] Qing Chen,[1] Xian-Bo Wu,[1] Xiao-Ming Shi,[5] Dong Wang,[6] Chen Mao[1]

UK Biobank study of 427,678 participants who reported on habitual use of fish oil supplements: Follow-up for total mortality for ~10 years

Table 2 | Associations of use of fish oil supplements with the risk of cardiovascular outcomes and all cause mortality. Values are numbers (percentages) unless stated otherwise

Outcomes	Fish oil non-users (n=294 240)	Fish oil users (n=133 438)	Model 1*		Model 2†	
			HR (95% CI)	P value	HR (95% CI)	P value
All cause mortality	8781 (3.0)	4147 (3.1)	0.83 (0.80 to 0.86)	<0.001	0.87 (0.83 to 0.90)	<0.001
Cardiovascular mortality	2274 (0.8)	1008 (0.8)	0.77 (0.72 to 0.83)	<0.001	0.84 (0.78 to 0.91)	<0.001
Myocardial infarction mortality	1017 (0.3)	406 (0.3)	0.73 (0.65 to 0.81)	<0.001	0.80 (0.70 to 0.91)	<0.001
Stroke mortality	441 (0.2)	223 (0.2)	0.83 (0.71 to 0.98)	0.03	0.87 (0.73 to 1.04)	0.14
Cardiovascular events	12 388 (4.2)	5909 (4.4)	0.88 (0.85 to 0.91)	<0.001	0.93 (0.90 to 0.96)	<0.001
Myocardial infarction	5306 (1.8)	2448 (1.8)	0.86 (0.82 to 0.90)	<0.001	0.92 (0.88 to 0.96)	<0.001
Stroke	2680 (0.9)	1329 (1.0)	0.88 (0.82 to 0.94)	<0.001	0.90 (0.84 to 0.97)	0.01

"Habitual use of fish oil seems to be associated with a lower risk of all cause and CVD mortality and to provide a marginal benefit against CVD events among the general population."

Li, Z.-H., *et al.* **Associations of habitual fish oil supplementation with cardiovascular outcomes and all cause mortality: evidence from a large population-based cohort study**. *BMJ (Clinical Research Ed.)* **368**, m456 (2020).

	Li et al.	Chen et al.
N	427,678*	415,737*
Mean Age	55.9%	55.9%
Females	55.1%	55%
White people	91.9%	94.5%
Never Smoked	56.4%	56%
Fruit ≥ 4/d	16%	31.4%
Vegetable ≥ 4/d	13.7%	64.5%
No alcohol	30.1%	4.3%
Oily fish ≥ 2/wk	55.1%	17.5%

Chen et al. BMJ-MED 2024;3:e000451 vs Li et al. BMJ (Clin Res Ed) 368, m456 (2020)

Some problem with data extraction from the UKBB dataset – Li or Chen or both?

* Chen et al. apparently excluded patients with AF or HF at baseline that Li et al. included

Outcome	UKBB Cohort	Findings
Incident CHD (2)	T2DM/pre-diabetes	9%↓/13%↓
Kidney Stones (3)	All	16%↓ low genetic risk NS in high genetic risk
Atrial Fibrillation (4)	All	10%↑ (6.2% vs 5.2%)
Liver Cancer (5)	All	44%↓
Total and CV Mortality (6)	>1 Cardiometabolic Disease*	17%↓ total 19↓ CV
Total, vascular and AD dementia (7)	All	10%↓ total 15%↓ vascular NS AD
Total dementia (8)	>60 yrs	13%↓ total
Inflammatory Bowel Disease (9)	All	12%↓
Fractures (10)	All	7%↓ total 17%↓ hip 15%↓ vertebral
All-cause mortality (12)	All	13%↓
CV mortality		16%↓
MI mortality		20%↓
Stroke mortality		NS
CV events		7%↓
MI		8%↓
Stroke		10%↓

All participants free of the outcome of interest at baseline; down arrow = lower risk in FOS users and up arrow = higher risk in FOS users. *CHD, T2DM, HTN, stroke

‡ Excluding Chen et al. BMJ-MED 2024;3:e000451

Associations between plasma DHA levels by quintile and risk for all-cause and cause-specific mortality in the UK Biobank.

From O'Keefe et al. Mayo Clin Proc 2024;99:534-54

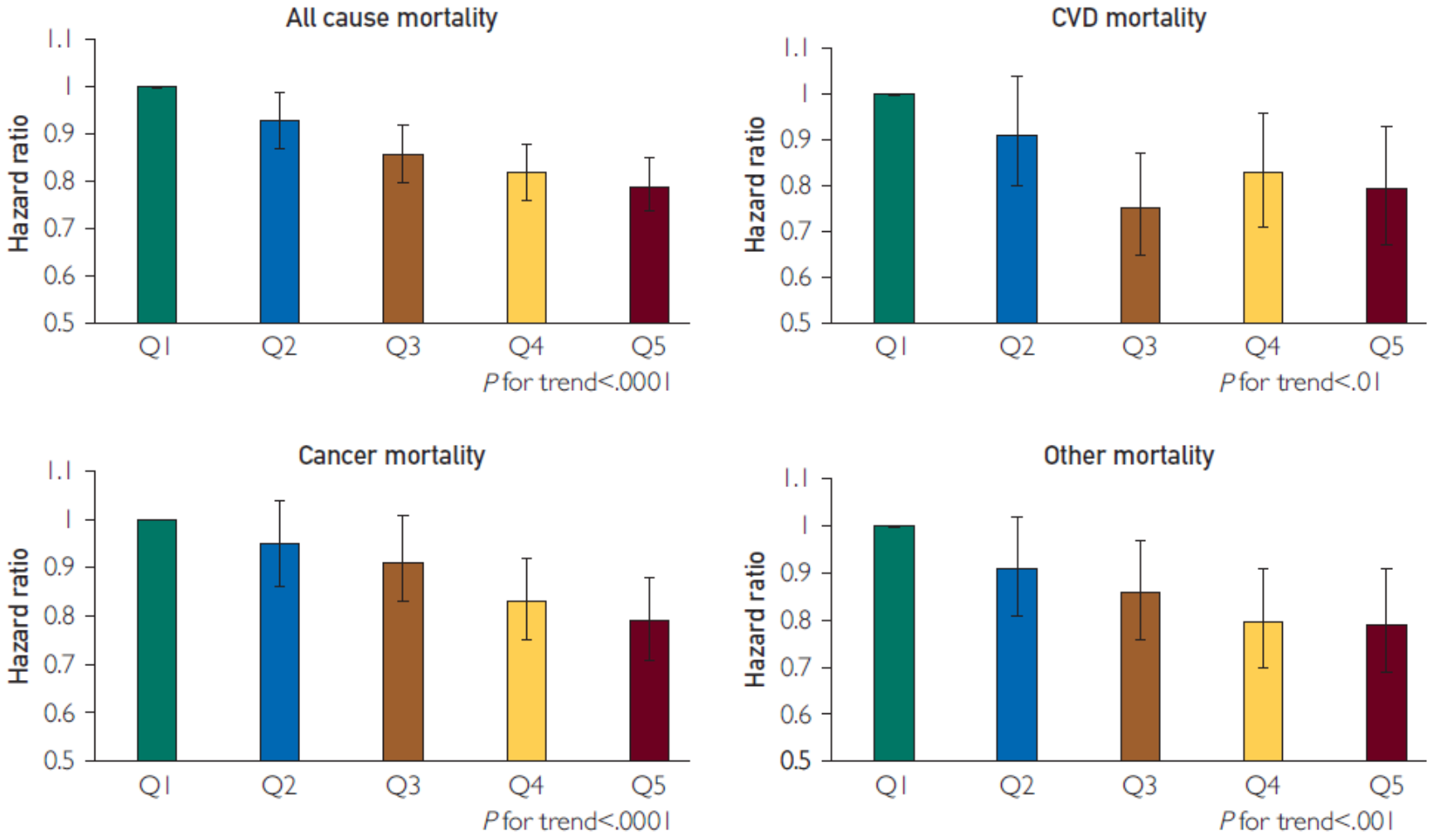


FIGURE 2. Associations of circulating docosahexaenoic acid levels with all-cause and cause-specific mortality in the updated 18-cohort meta-analysis.

Associations between *in vivo* omega-3 fatty acid levels and clinical outcomes from FORCE

Disease/Outcome		Favorable	Neutral	Adverse
Coronary Heart Disease (1)		X		
Type 2 Diabetes (2)		X		
Mortality (3)	All Cause	X		
	CV	X		
	Cancer	X		
	Other	X		
Atrial Fibrillation (4)		X		
Stroke (5)	Total	X		
	Ischemic	X		
	Hemorrhagic		X	
Chronic Kidney Disease (6)		X		

1. Del Gobbo et al. JAMA internal medicine 2016;176(8):1155-66.
2. Qian F, et al. Diabetes Care 2021;44(5):1133-42.
3. Harris WS, et al. Nat Comm 2021;12(1):2329.
4. Qian F, et al. J Am Coll Cardiol 2023;82(4):336-49.
5. O'Keefe JH, et al. Stroke 2024;55(1):50-8.
6. Ong KL, et al. BMJ (Clinical research ed) 2023;380:e072909.

CHEN

- **Found 5 favorable links with FOS use but emphasized the 1 unfavorable link**
- **Failed to consider prior studies on the same question in the same cohort that reached very different (favorable) conclusions.**
- **FOS use in the UKBB has been associated in 10 other studies with lower risk for 18 different outcomes, unrelated with 3, and with higher risk for 1 (AF)**
- **Comparing blood levels of EPA/DHA is a more objective way to examine the associations between omega-3 status and disease than is a yes/no question about FOS use. In the UKBB higher omega-3 levels are associated with significantly lower risk for all-cause mortality, and CV, cancer and other causes of death. This was not mentioned by Chen et al.**

THE PRESS

- **Emphasized only the 1 bad outcome**
- **Equated developing AF with "heart disease"**
- **Failed to mention past studies that had favorable outcomes**

Assessing the Efficacy of Omega-3 Fatty Acids + Statins vs. Statins Only on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of 40,991 Patients from 14 RCTs

- **"The result shows that adding omega-3 fatty acids to statin therapy significantly reduces the incidence of MACE, MI, unstable angina, and hospitalization for unstable angina."**
- "This analysis reported no significant increase in the risk of adverse outcomes."
- "Our research reinforces that all patients, regardless of their CV health, may benefit from adding omega- 3 fatty acids to their statin therapy."

Adapted from Ifram et al. Curr Prob Cardiol 2024, 102245

Associations between reported intake of EPA and DHA from diet and supplements and risk for death from any cause

"These results suggest that intake of long-chain ω-3 fatty acids may reduce risk of total and cancer-specific mortality."

Supplement Use or Intake, by Quartile	No. of Participants	Multivariate-Adjusted[b]		
EPA + DHA from diet and supplements, g/day		HR	95% CI	*P* for Trend
1 (0–0.082)	17,703	1.00	Reference	0.004
2 (>0.082–0.174)	17,485	0.97	0.87, 1.07	
3 (>0.174–0.322)	17,601	0.89	0.80, 1.00	
4 (>0.322)	17,498	0.86		

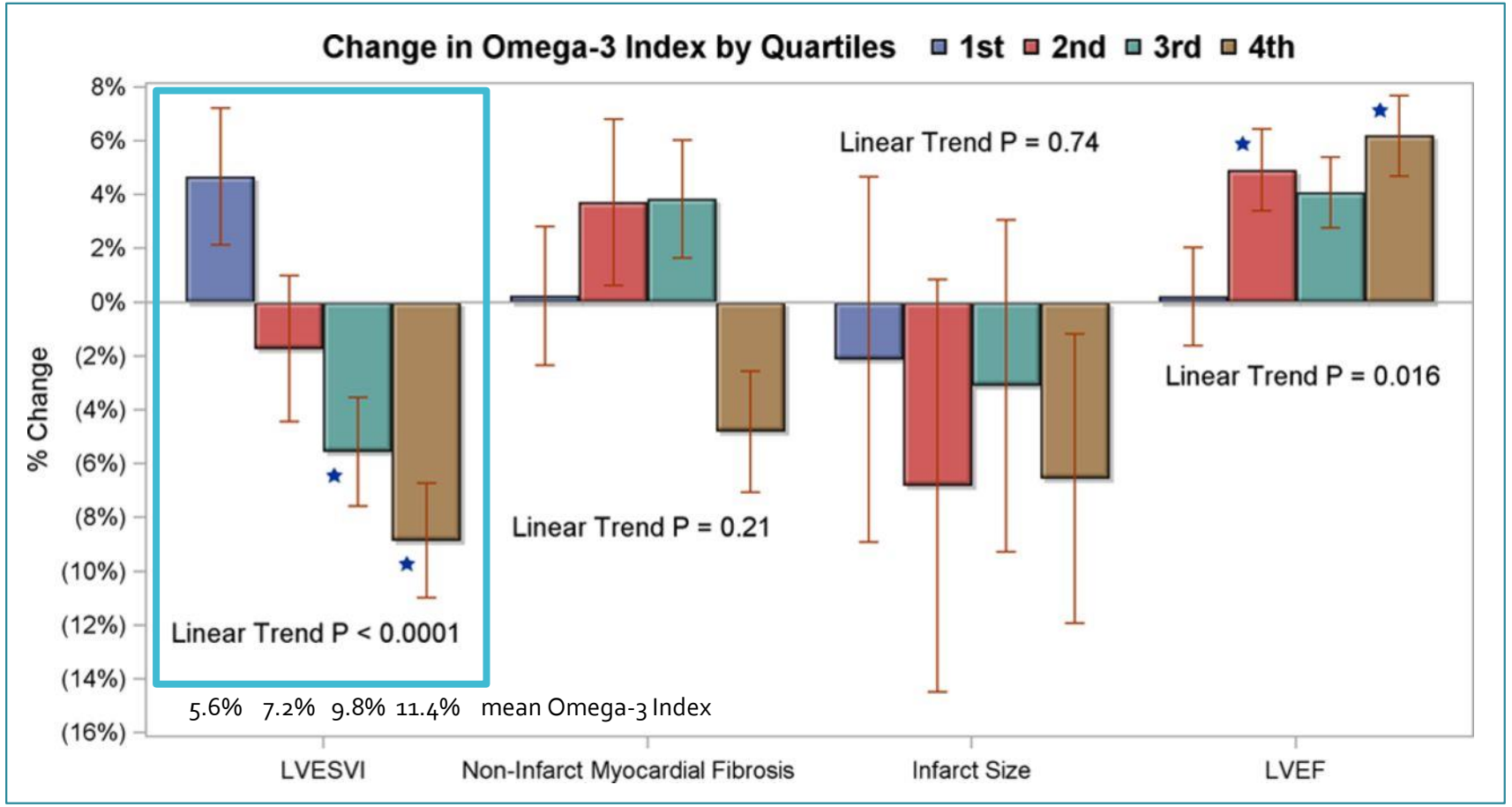
14% reduction in risk at >322 mg/day

Data on intake collected from 70,495 residents of Washington State who were followed for ~5 years for death from any cause. There were 3051 deaths.

Bell, G.A., *et al.* **Intake of long-chain omega-3 fatty acids from diet and supplements in relation to mortality.** *American journal of epidemiology* **179**, 710-720 (2014).

Effects of Omacor (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



LVESVI=left ventricular end systolic volume index

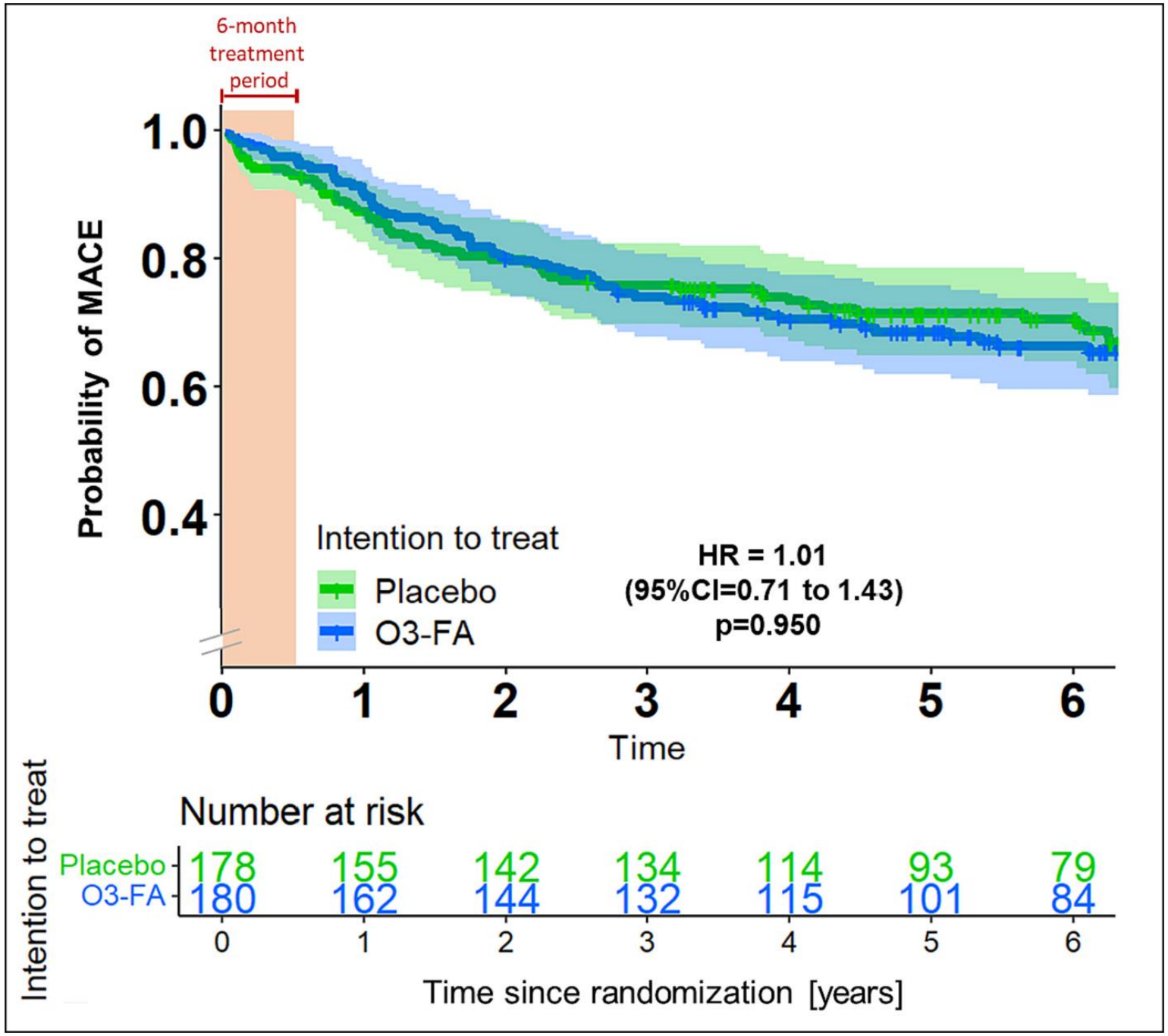
Heydari et al. Circulation. 2016;134:378-391

Long-term (6 yr) Major Adverse Cardiac Events (MACE) were compared in those patients

1) Assigned to Omacor vs Placebo, or
2) Whose Omega-3 Index increased during the trial by ≥5% vs those in whom the increase was <5%

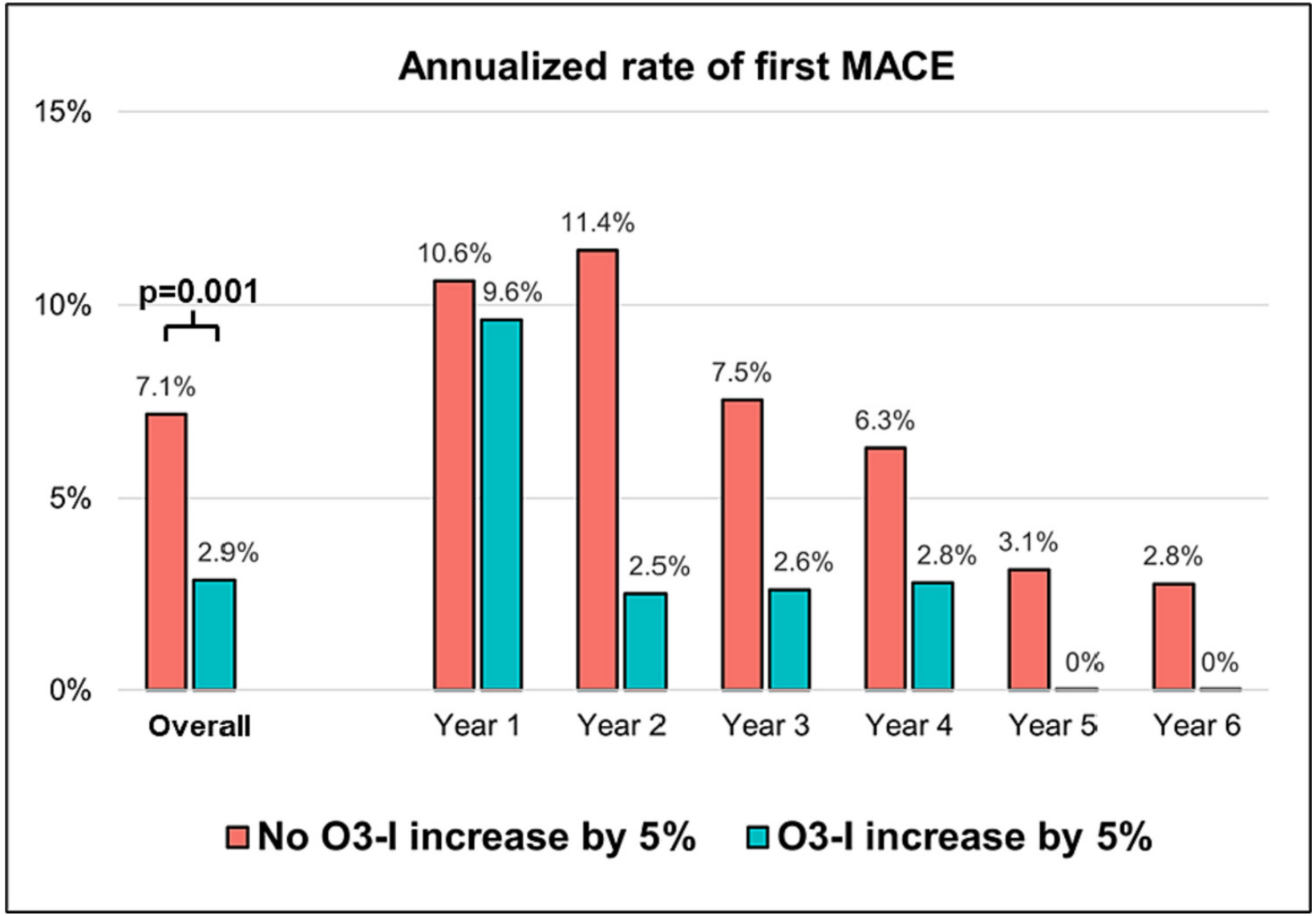
There was no difference in MACE outcomes *by treatment group.*

Bernhard et al. Int J Cardiology 399 (2024) 131698



There was a 59% reduction in risk for MACE in those who had an increase in the O3I ≥5% (n=43) during treatment vs those who did not (n=211).

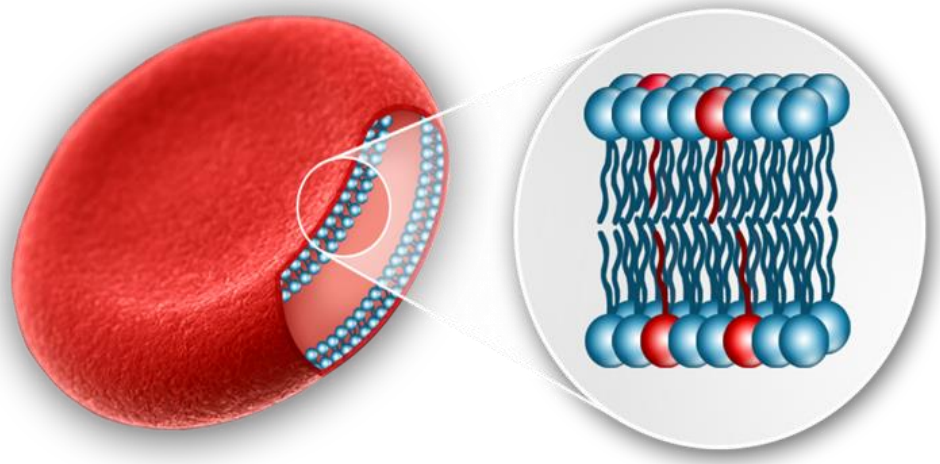
Achieving target tissue Om3 levels is more important than just being told to take Omega-3.



Bernhard et al. Int J Cardiology 399 (2024) 131698

WHAT IS THE OMEGA-3 INDEX?

The Omega-3 Index is a measure of the amount of EPA and DHA in red blood cell membranes, expressed as a percent of total fatty acids.

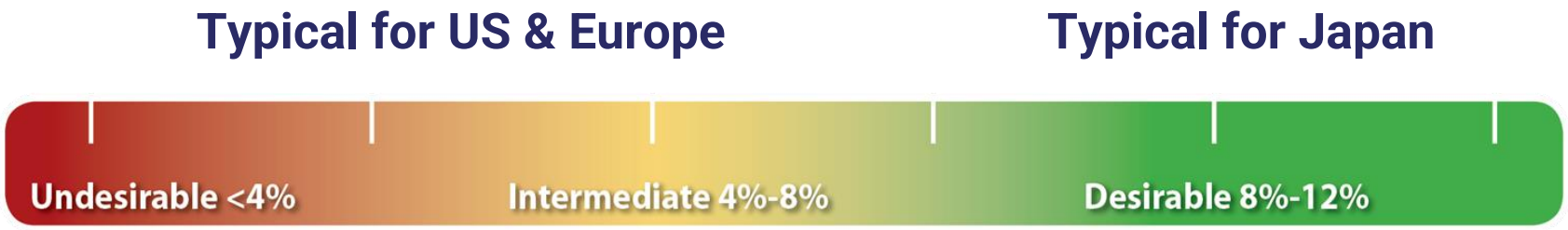


There are 64 fatty acids in this model membrane, 4 of which are EPA and DHA

4/64 = 6.25%

Omega-3 Index = 6.25%

THE OMEGA-3 INDEX SCALE



Red Blood Cell EPA+DHA (% of total fatty acids)

A desirable Omega-3 Index is 8-12%

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

META-ANALYSIS OF PROSPECTIVE DATA FROM 17 COHORTS

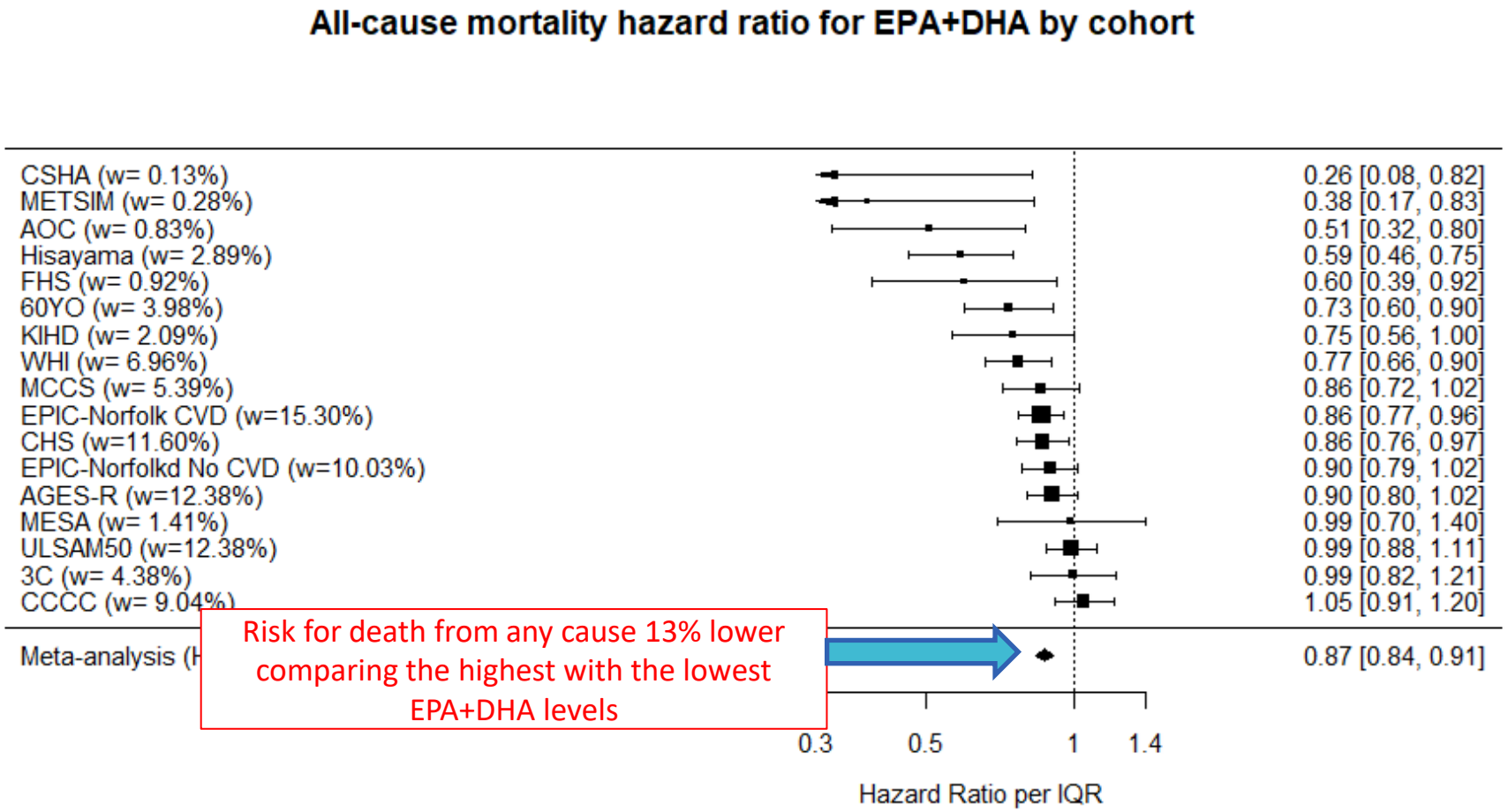
Baseline

- 42,466 individuals in 17 studies and 10 countries
- Mean age, 64 years and 54% women
- Median follow-up time of 16 years (range 5-32 y)
- 15,720 deaths occurred during follow-up
  - 30% CVD
  - 30% cancer
  - 39% other causes

Omega-3 blood levels and risk for all-cause and cause-specific mortality

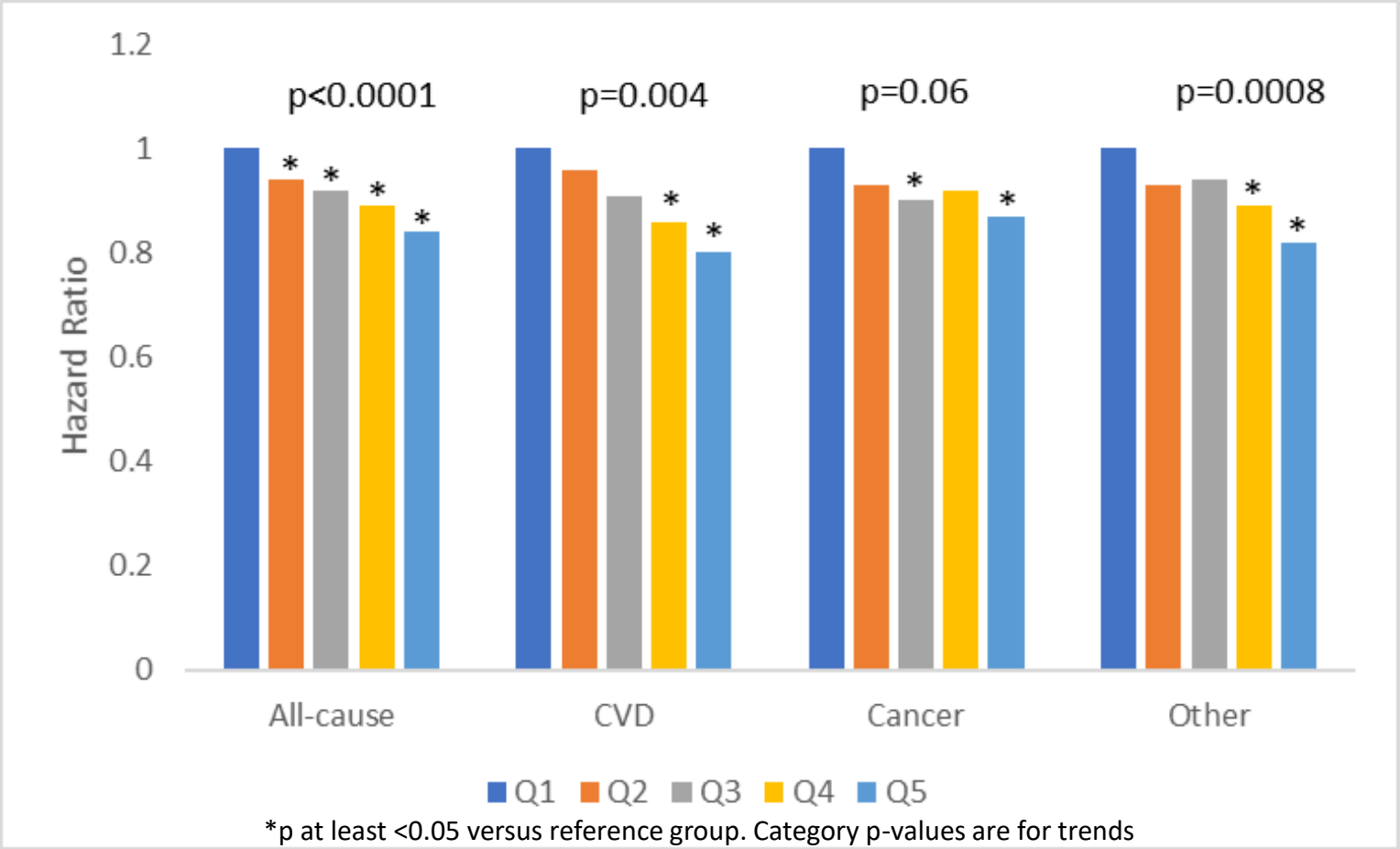
Harris WS, et al. for the FORCE Consortium. Nature Comm (2021) 12:2329

COMPARISON OF RISK FOR DEATH FROM ANY CAUSE COMPARING THE 90TH PERCENTILE TO THE 10TH PERCENTILE OF EPA+DHA IN EACH STUDY



Harris WS, et al. for the FORCE Consortium. Nature Comm (2021) 12:2329

ASSOCIATIONS OF OMEGA-3 INDEX WITH RISK OF TOTAL AND CAUSE-SPECIFIC



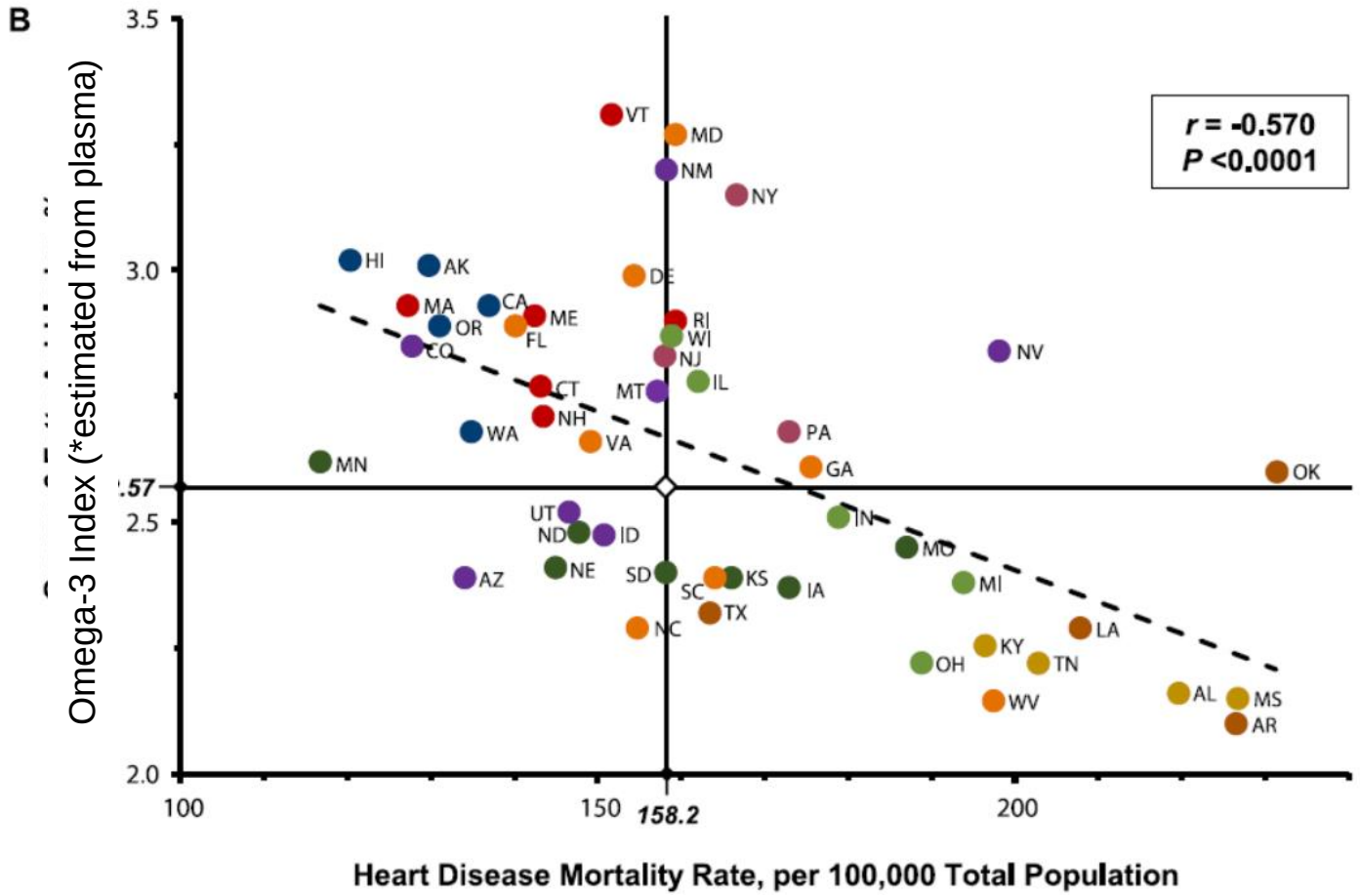
*p at least <0.05 versus reference group. Category p-values are for trends

Omega-3 blood levels were inversely linked with risk for death from all-causes, CVD and other causes

Estimated O3I from Framingham
Q1 mean ~ 3.6%
Q5 mean ~ 7.8%

Harris WS, et al. for the FORCE Consortium. Nature Comm (2021) 12:2329

A HIGHER OMEGA-3 INDEX* IS LINKED WITH A LOWER CORONARY HEART DISEASE MORTALITY RATE BY STATE



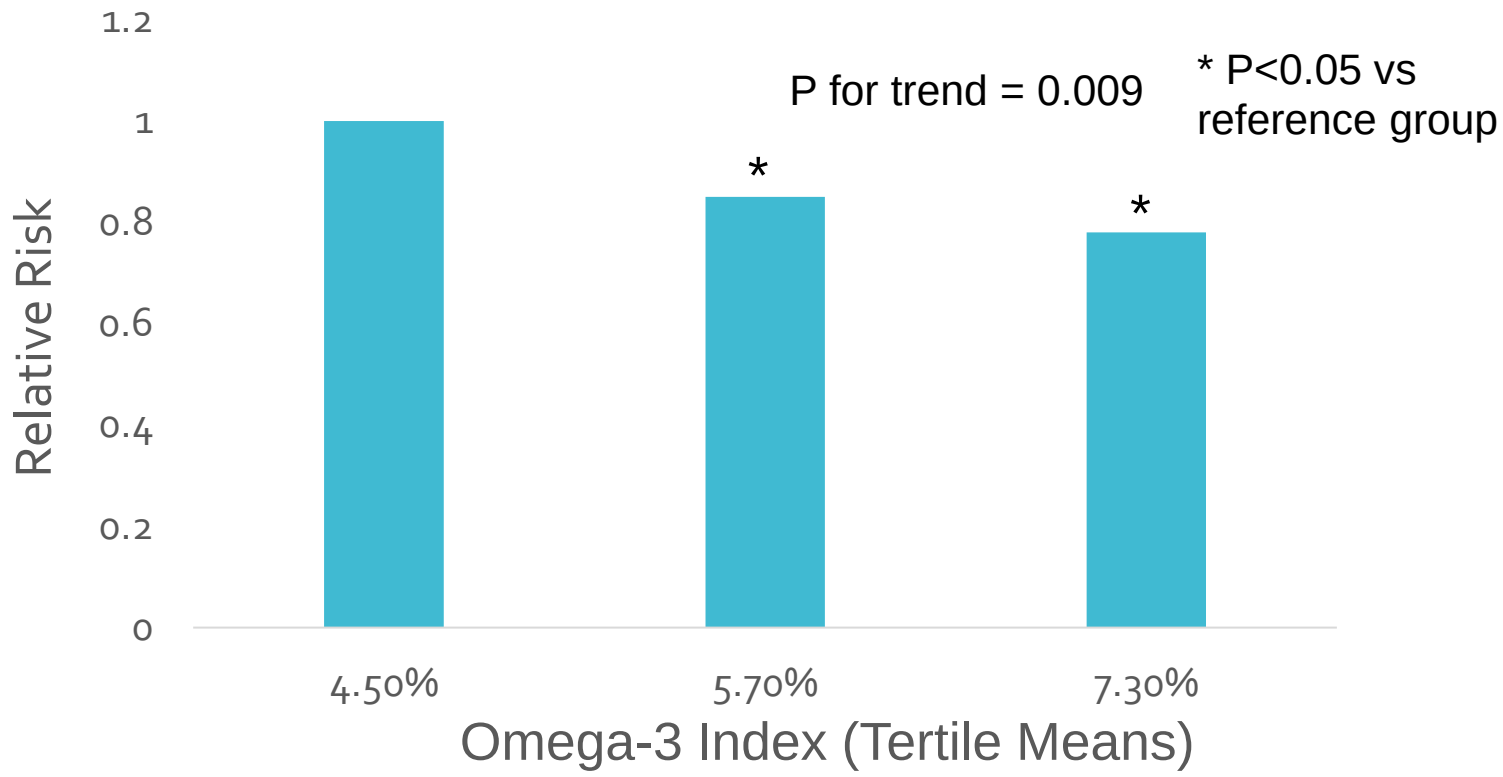
Omega-3 Levels and Risk for Death from CHD in the USA

(Data from Boston Heart Lab, n=1.17M)

Diffenderfer MR et al, J Clin Lipidol 2022 Jan 5;S1933-2874(21)00352-4.

RELATIVE RISK FOR DEATH FROM ANY CAUSE AND THE OMEGA-3 INDEX: THE LURIC STUDY

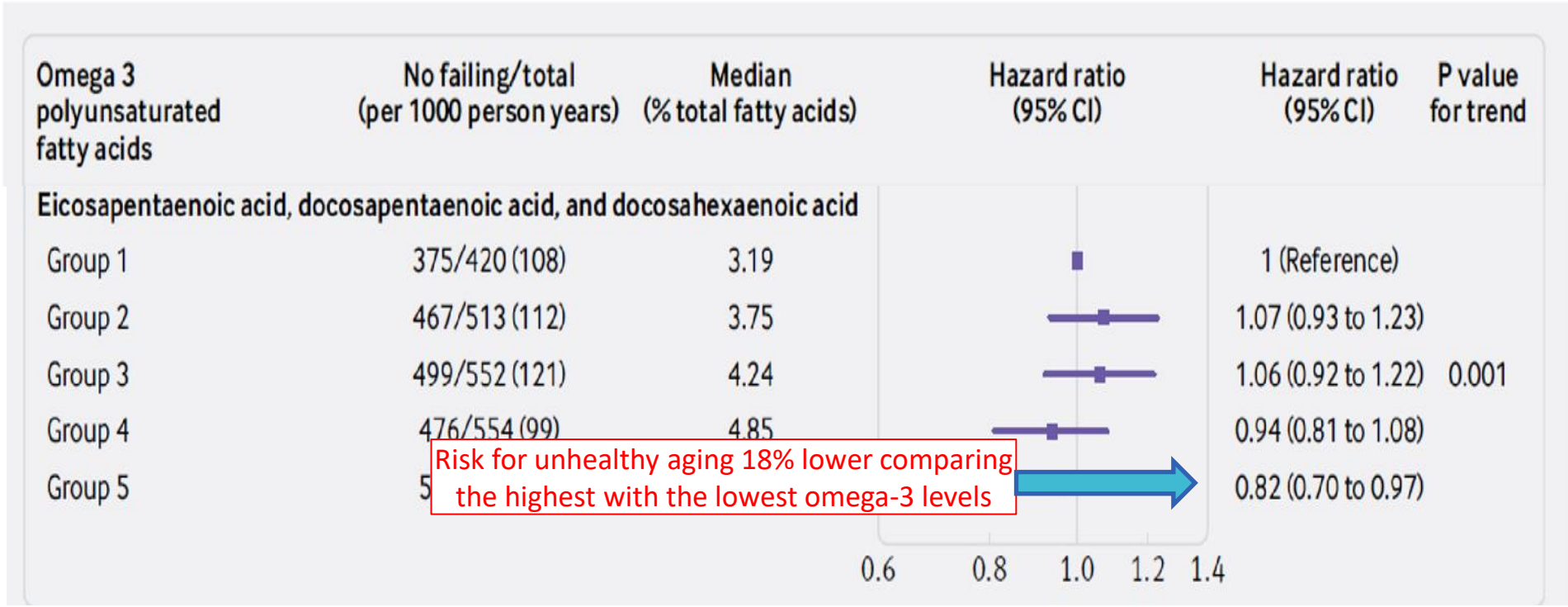
Risk for death was 22% lower at an Omega-3 Index of 7.3% vs 4.5%



Multivariable-adjusted risk for death from any cause between ages 63 and 73 in 3259 patients undergoing diagnostic catheterization

Kleber et al. Atherosclerosis 2016;253175-181 (personal communication)

BLOOD OMEGA-3 LEVELS LINKED WITH RISK FOR "UNHEALTHY AGING" : THE CARDIOVASCULAR HEALTH STUDY



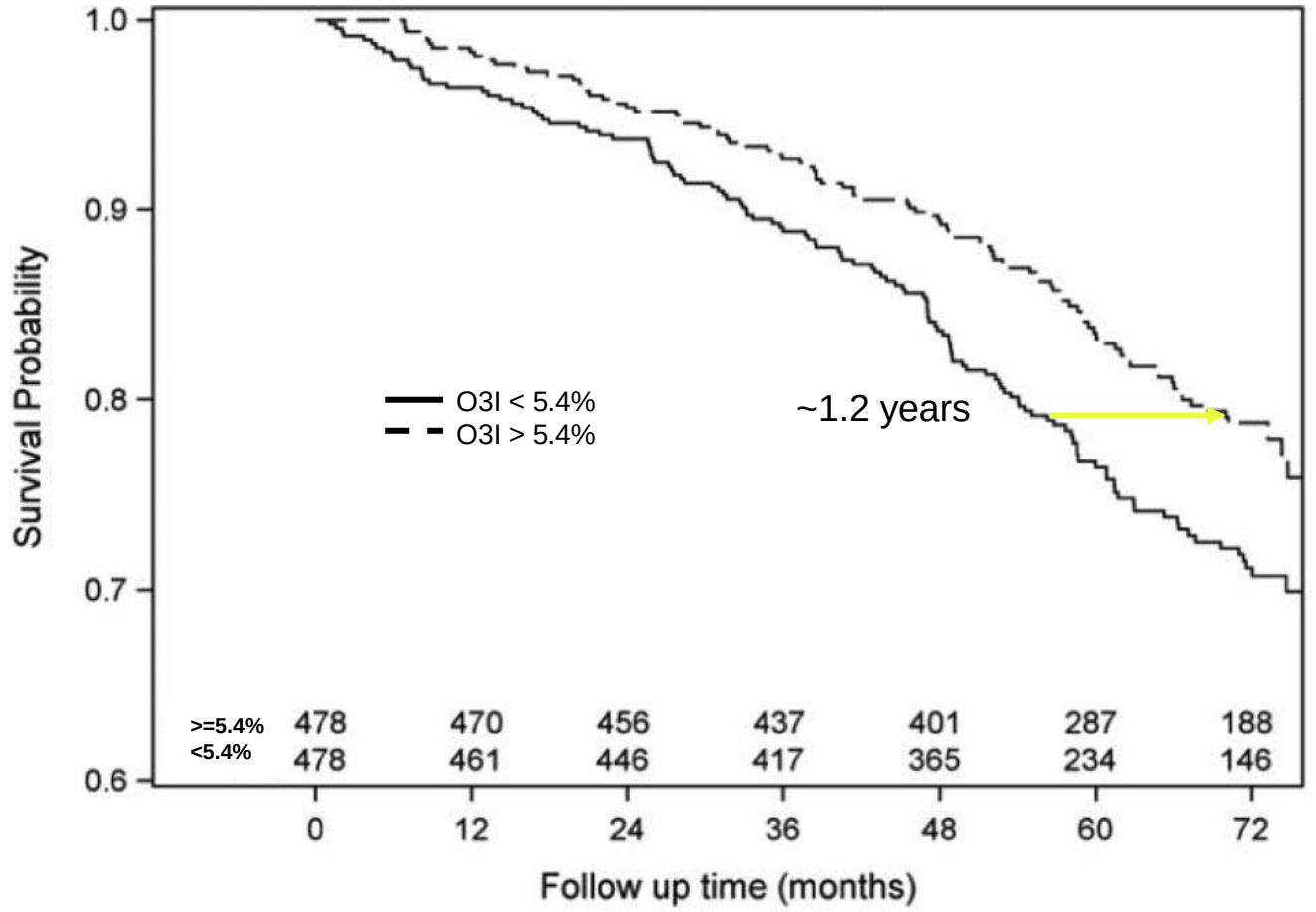
Unhealthy aging defined as developing any of the following after age 65: CVD, cancer, lung disease, severe CKD, cognitive or physical dysfunction, or death. N=2369, Median follow-up, 9 yrs.

Lai et al. BMJ 2018;363:k4067 | doi: 10.1136/bmj.k4067

THE HEART & SOUL STUDY: THE HIGHER THE OMEGA-3 INDEX, THE GREATER THE PROBABILITY OF SURVIVAL

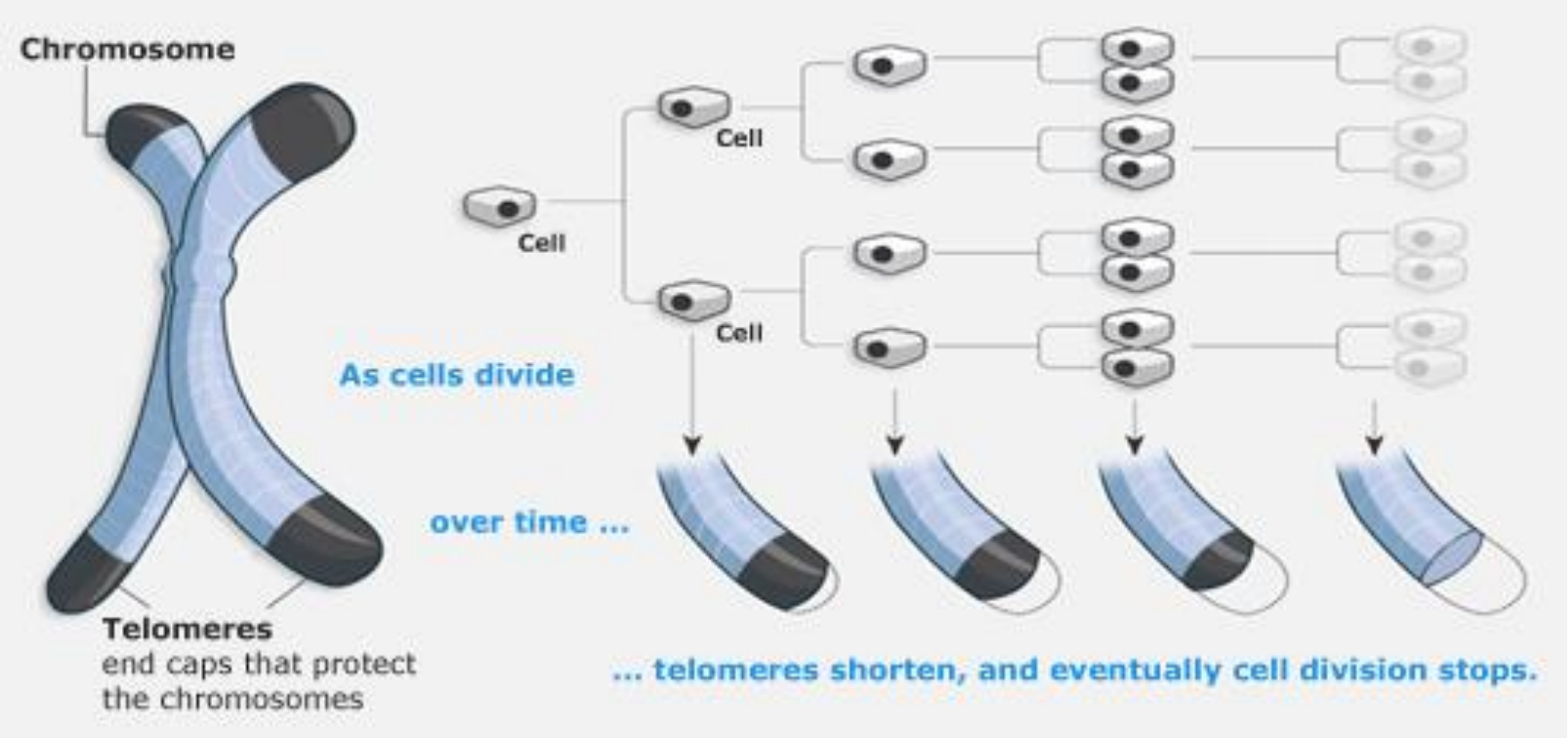
It took about 1.2 years longer for 20% of the above-average group to die compared with the below-average group (n=956 total).

* Extrapolated from whole blood EPA+DHA (r=0.96)



Pottala, et al. Circ: CV Qual Outcomes 2010;3:406-412

TELOMERIC AGING



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

Patients with the highest Omega-3 Index experienced the slowest rate of telomere shortening (cellular aging)

A 1-SD increase in the O3I was associated with a 32% reduction in the odds of telomere shortening.

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

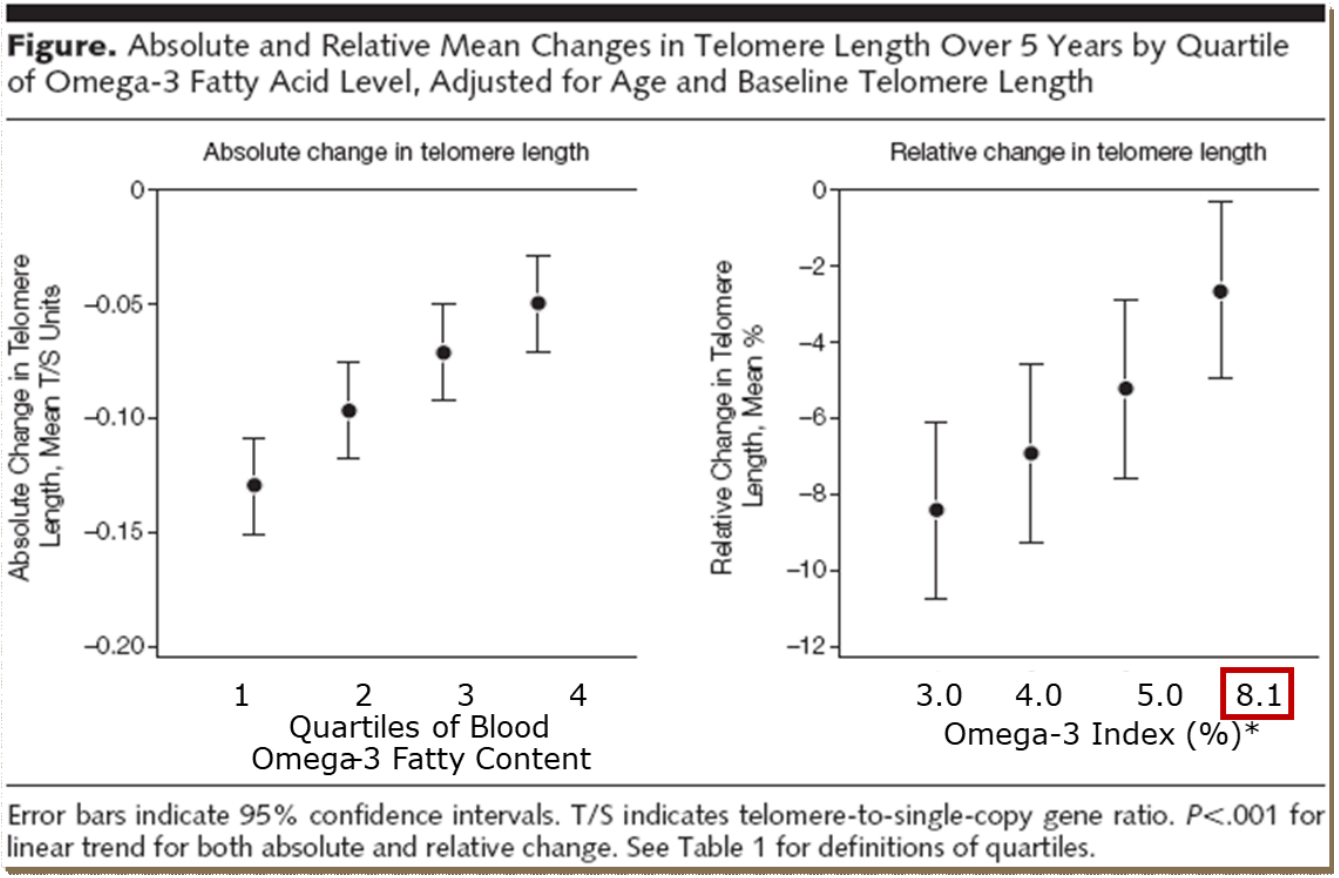


Figure. Absolute and Relative Mean Changes in Telomere Length Over 5 Years by Quartile of Omega-3 Fatty Acid Level, Adjusted for Age and Baseline Telomere Length

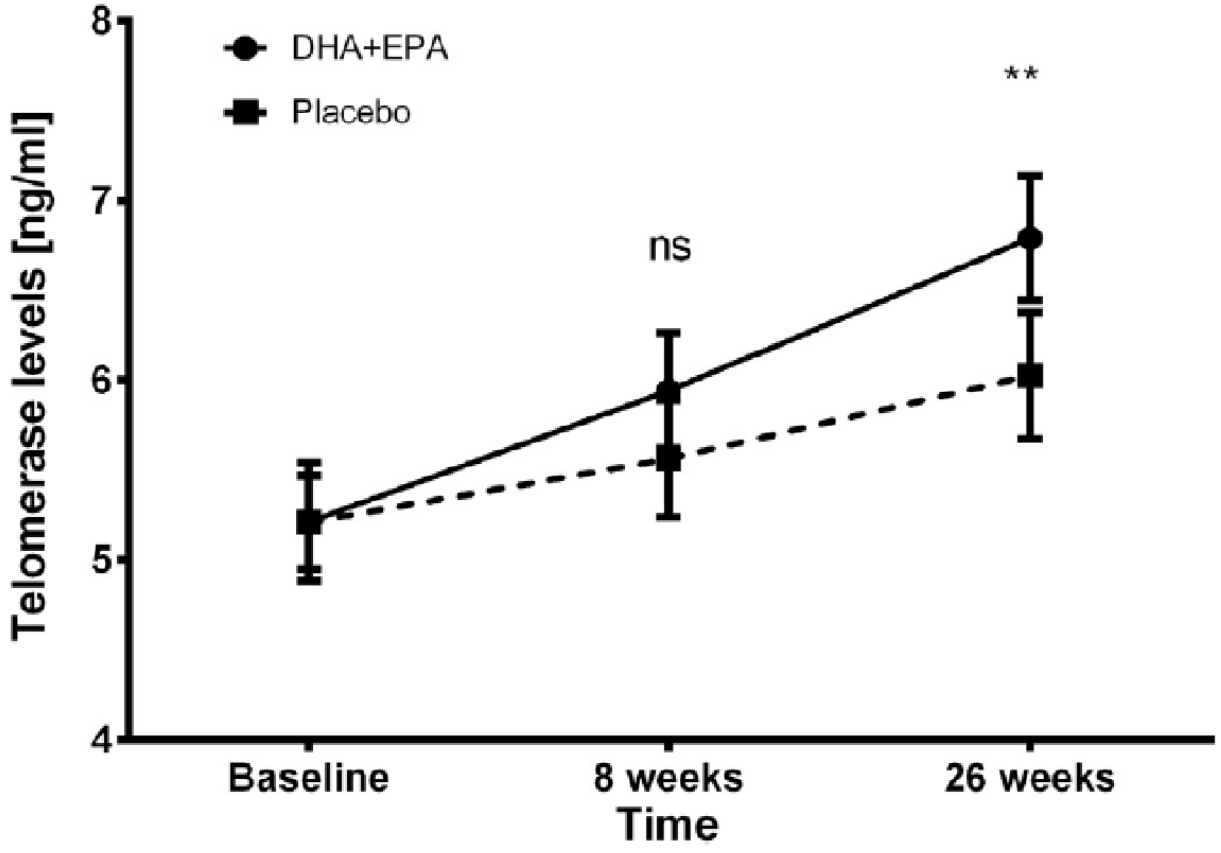
Error bars indicate 95% confidence intervals. T/S indicates telomere-to-single-copy gene ratio. *P*<.001 for linear trend for both absolute and relative change. See Table 1 for definitions of quartiles.

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

OMEGA-3 SUPPLEMENTATION RAISES TELOMERASE* LEVELS IN HUMANS

Schizophrenic patients (n=71) randomized to 2.2 g EPA+DHA or placebo for 26 weeks. Effects on telomerase enzyme levels in white blood cells and on clinical symptoms were measured.

* Telomerase is an enzyme that LENGTHENS telomeres



Pawełczyk T, et al. Prog Neuropsychopharma Biol Psychiatry 2018;83:142-148.

OUTLINE

Observational

Diet

Biomarker

Interventional

>> **N-3 PUFA supplementation**

Mechanisms

META-ANALYSIS EFFECTS OF EPA+DHA DOSE ON CVD OUTCOMES

17 RCTs
>1 yr duration
n=83,617
Compared EPA+DHA doses
- <0.84 g/day
- 0.84-1.7 g/day
- 1.7-2.5 g/day
- >2.5 g/day +

Combined, P<0.05

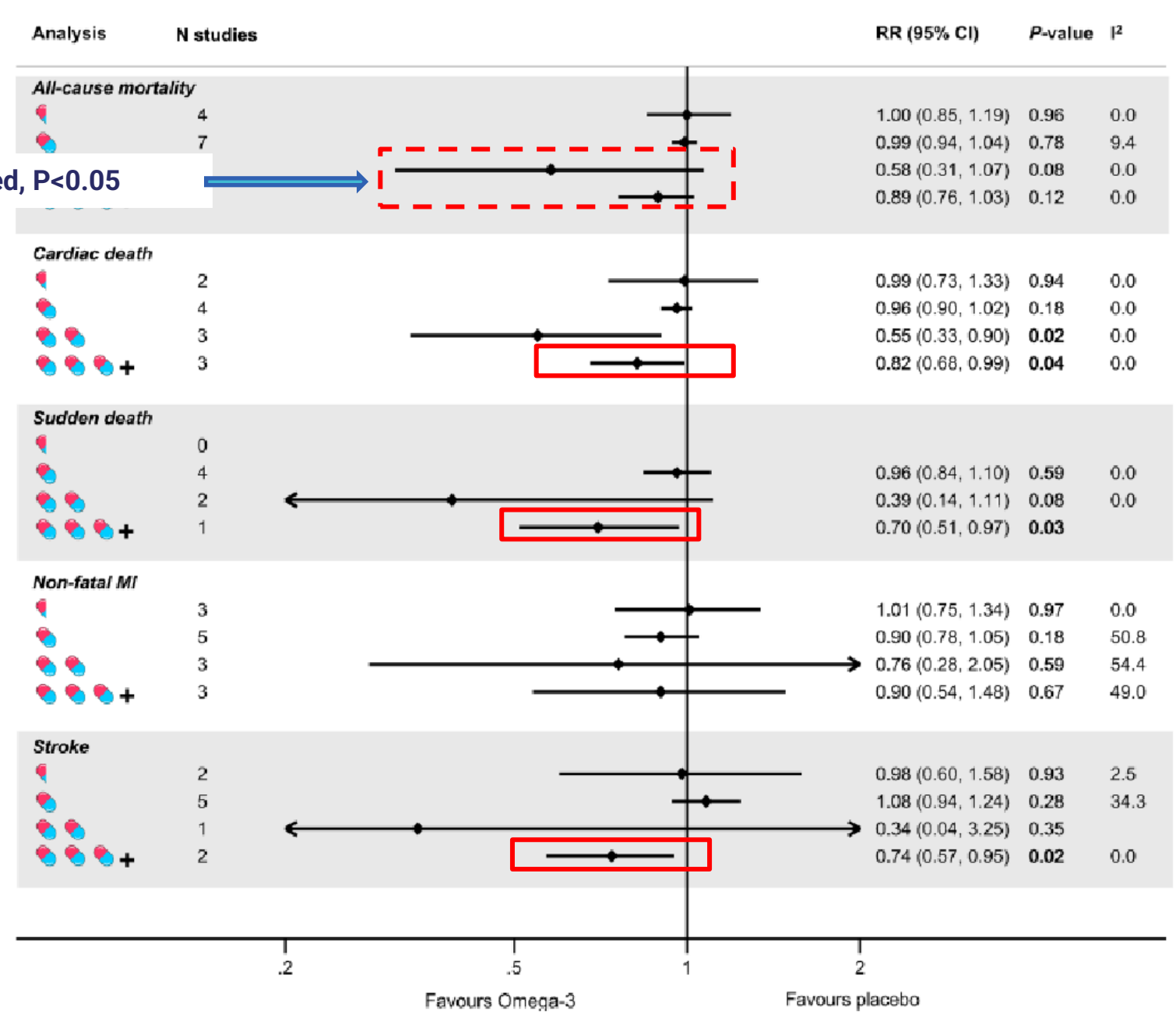
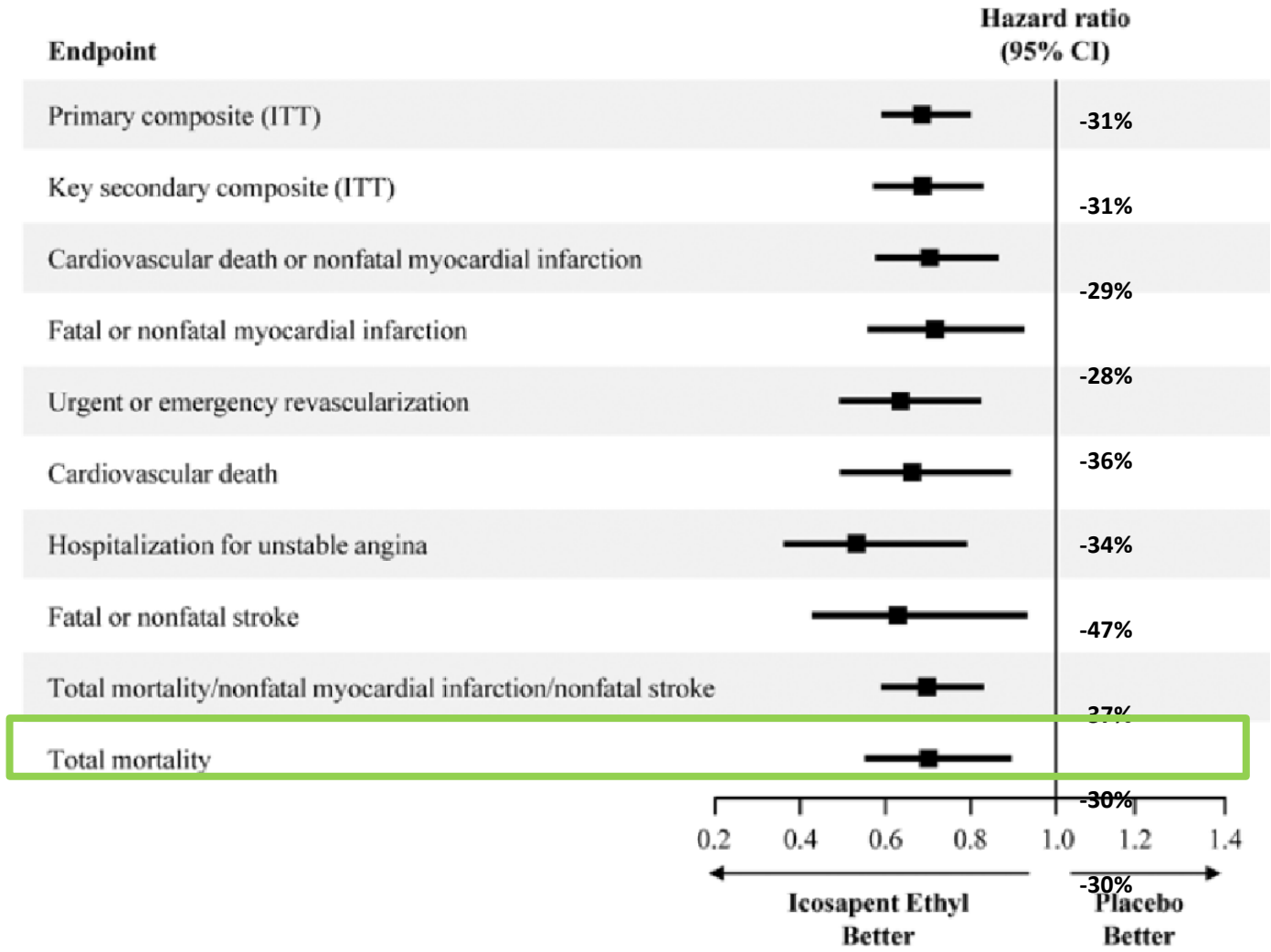


Figure 2 Results from the main analysis on omega-3 dosage formulation. CI, confidence interval; MI, myocardial infarction; RR, relative risk. Bold denotes a statistically significant p value. 💊: <1 capsule/day (<0.84 g); 💊💊: 1 capsule/day (0.84–1.68 g); 💊💊💊: 2 capsules/day (1.68–2.52 g); 💊💊💊+: ≥3 capsules/day (>2.52 g).

Rizos EC, et al. Heart 2021;**107**:150–158

REDUCE-IT USA

EPA treatment at 4 g/day reduced total mortality in REDUCE-IT USA



3146 US patients treated with 4 g Vascepa or placebo and followed up for 4.9 years.

Bhatt et al. *Circulation.* 2020;141:367–375.

OUTLINE

Observational

Diet

Biomarker

Interventional

N-3 PUFA supplementation

>> Mechanisms

MULTIPLE MECHANISMS OF ACTION

- **Reductions in heart rate**

Mozaffarian, et al. Circulation 2005; 12:1945-1952

- **Reduced inflammation**

Fontes, et al. Atherosclerosis 2015;240:431-436

- **Slowed telomere shrinkage**

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

- **Anti-thrombotic**

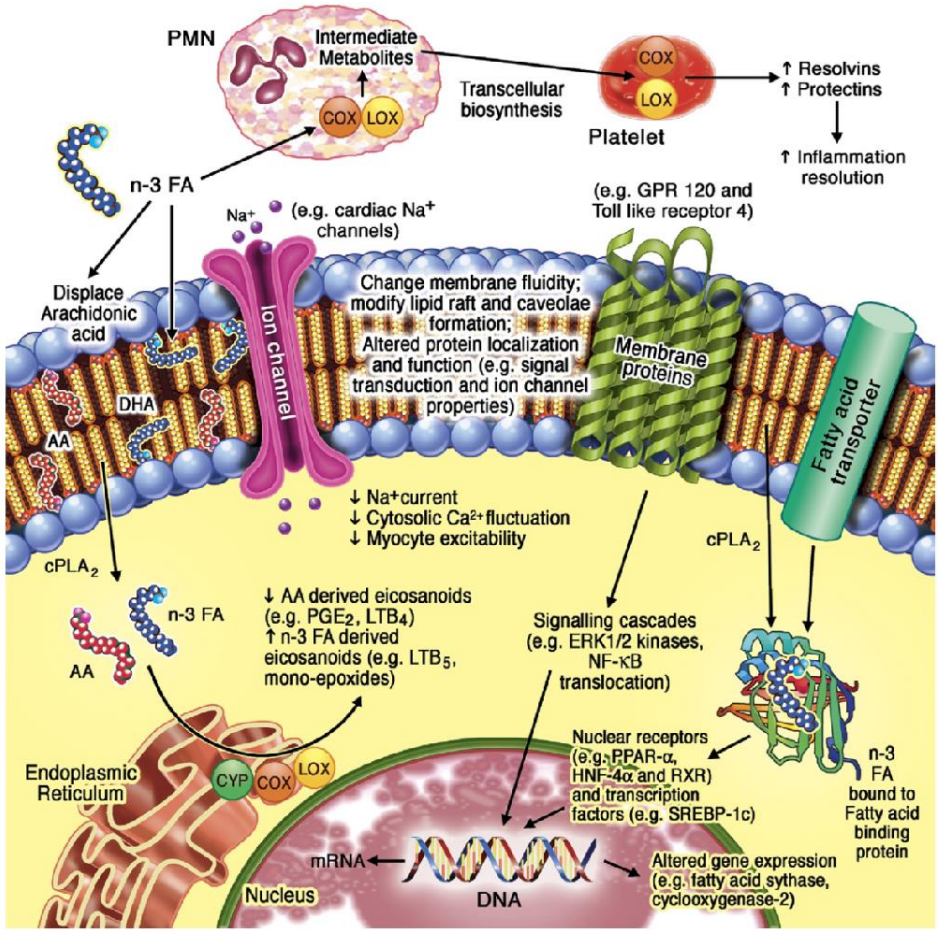
Gao et al. Atherosclerosis 2013;226:328-334

- **Triglyceride lowering**

Harris. J Lipid Res 1989;30:7

- **Reduce Blood pressure**

Zhang et al. J Am Heart Assoc. 2022;11:e025071



Mozaffarian and Wu. J Am Coll Cardio 2011;58:2047-67

Omega-3 and Risk for Atrial Fibrillation

Circulating And Tissue Omega-3 Fatty Acid Biomarkers And Incident Atrial Fibrillation: An Individual Participant-level Pooled Analysis Of Prospective Studies

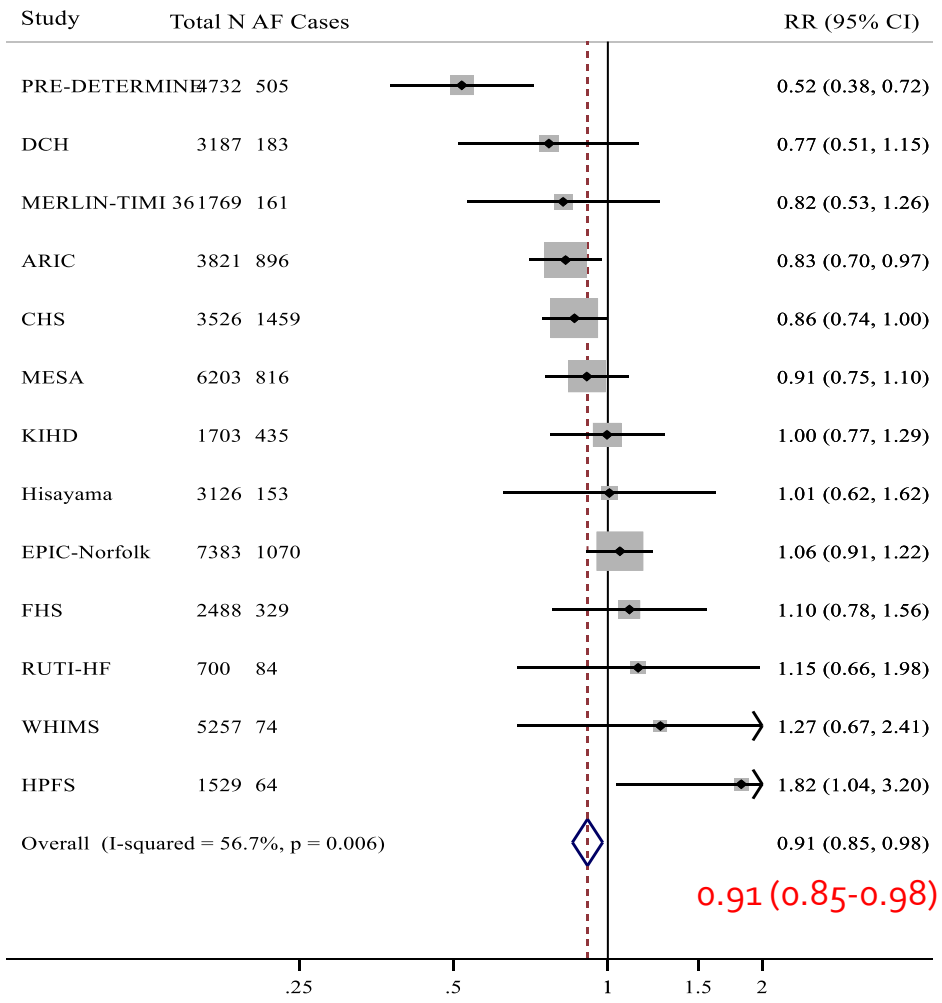
Frank Qian et al.

17 prospective cohorts
54,799 participants
7720 incident cases of AF
Weighted Median follow-up 13.3 yrs

(Abstract: 7 Apr 2022 https://doi.org/10.1161/circ.145.suppl_1.P212 Circulation. 2022;145:AP212. Paper currently (1/20/2023) under review at JACC

Omega-3 and Risk for Atrial Fibrillation

Pooled Relative Risk for incident Atrial Fibrillation comparing Circulating EPA+DHA levels, 90th vs 10th percentile



(Qian et al. https://doi.org/10.1161/circ.145.suppl_1.P212 Circulation. 2022;145:AP212

Circulating And Tissue Omega-3 Fatty Acid Biomarkers And Incident Atrial Fibrillation: An Individual Participant-level Pooled Analysis Of Prospective Studies
Frank Qian et al.

Omega-3 and Risk for Atrial Fibrillation

"Biomarkers of omega-3 fatty acids including DPA, DHA, and EPA+DHA demonstrated an inverse association with incident AF. In the absence of RCTs examining long-term dietary omega-3 intake and AF risk, our results do not suggest that higher levels of these fatty acids are associated with harm."

(7 Apr 2022 https://doi.org/10.1161/circ.145.suppl_1.P212 Circulation. 2022;145:AP212