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KLINIKUM

DER UNIVERSITÄT MÜNCHEN

Some things we learned with the Omega-3 Index

Ankara, Dec 04, 2019

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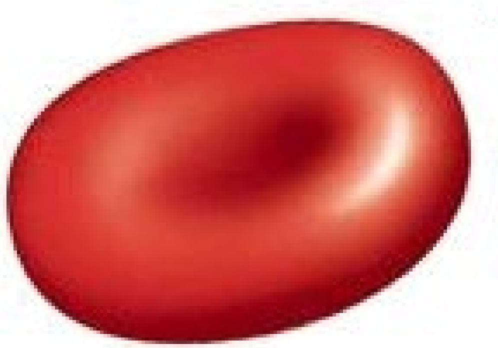
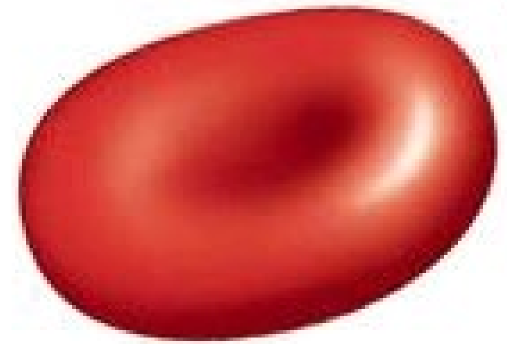
Ω metrix®

Conflicts of Interest

- Omegametrix
- Honoraria for speaking and consulting:
  BASF/Pronova, EPAX, Huntsworth Medical, Abbott, DSM, Marine Ingredients, Norsan

HS-Omega-3 Index®





Seminal Publication 2004

Biomarker for Fatty Acid Comp., correlating with tissue FA Comp.

Measured in Erythrocytes (low biologic Variability)

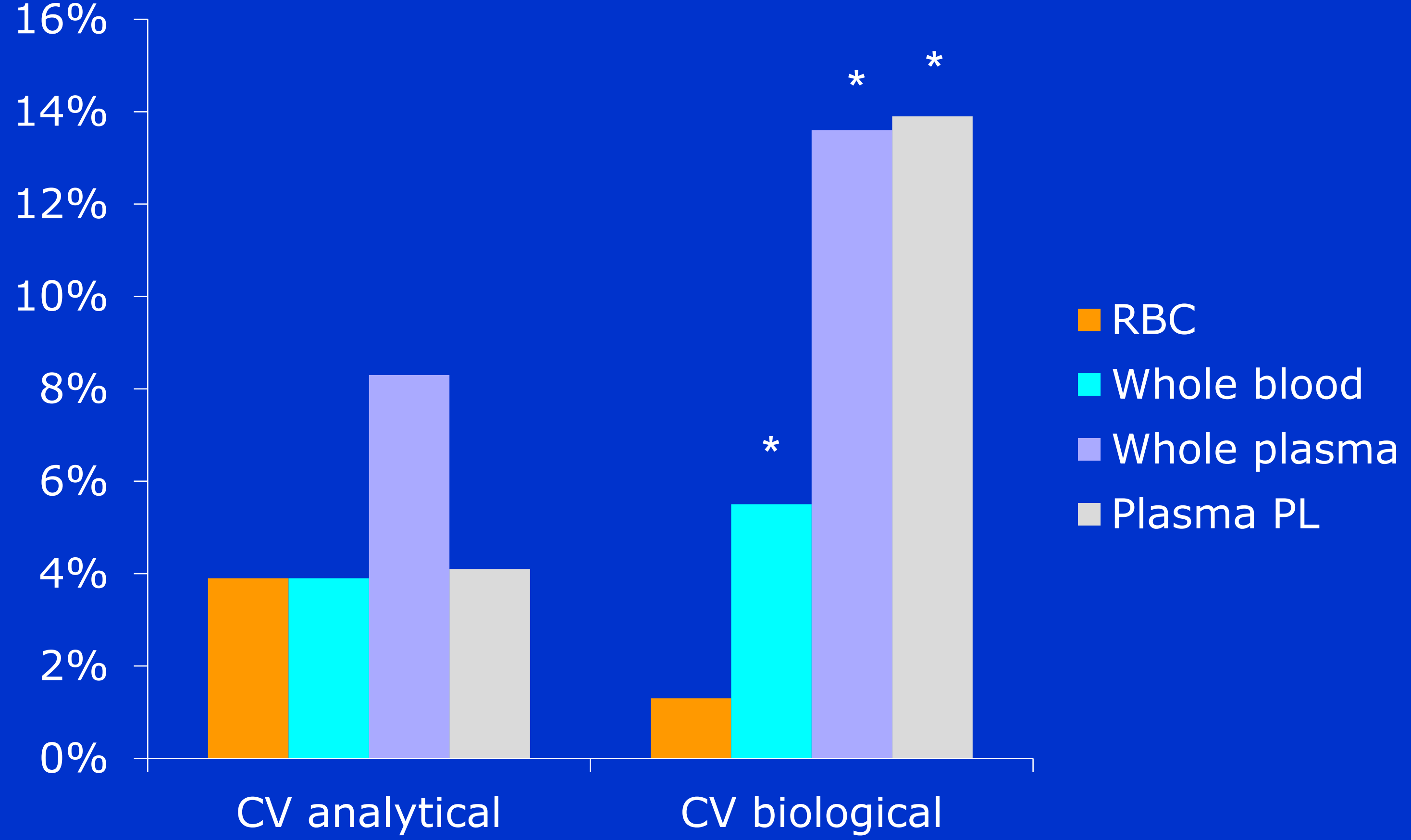
Standardized and validated Method for 26 Fatty Acids
(low analytical Variability)

> 280 Publications, >50 current Research Projects

QM according DIN ISO 15189

Ω metrix®

Biological and analytical Variability of EPA+DHA in various Compartments



* p<0.03 vs RBC

Harris WS, Thomas R Clin Biochem 2009;43:338-40

…one sample in 6 Labs…

August 2018 – Measuring the Omega-3 Index in Germany

	Results	Target	Recommendation
Omegametrix:	6.43%	8 – 11%	more omega-3
Labor B1:	4.36%	>8%	is normal
Labor B2:	7.29%	>8%	more omega-3
Labor G:	5.69%	>8%	more omega-3
Labor M:	3.70%	>4%	more omega-6
Labor W:	4.30%	6 – 8%	-

Standardization !!!
Ethical Issues!!!

In humans representative for tissue

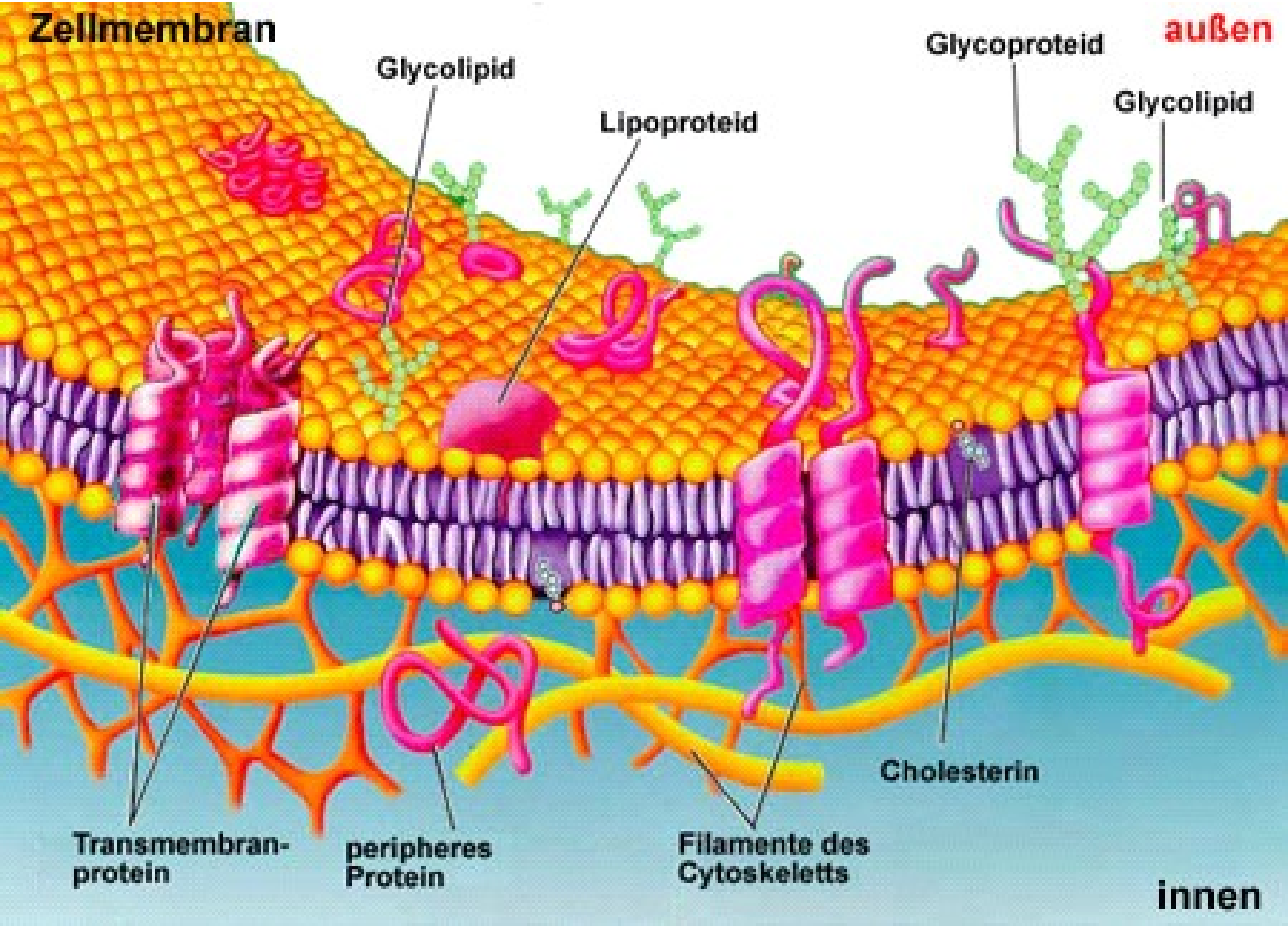
Heart, Breast, Muscle, Cheek cells, Placenta

In experimental animals representative for tissue

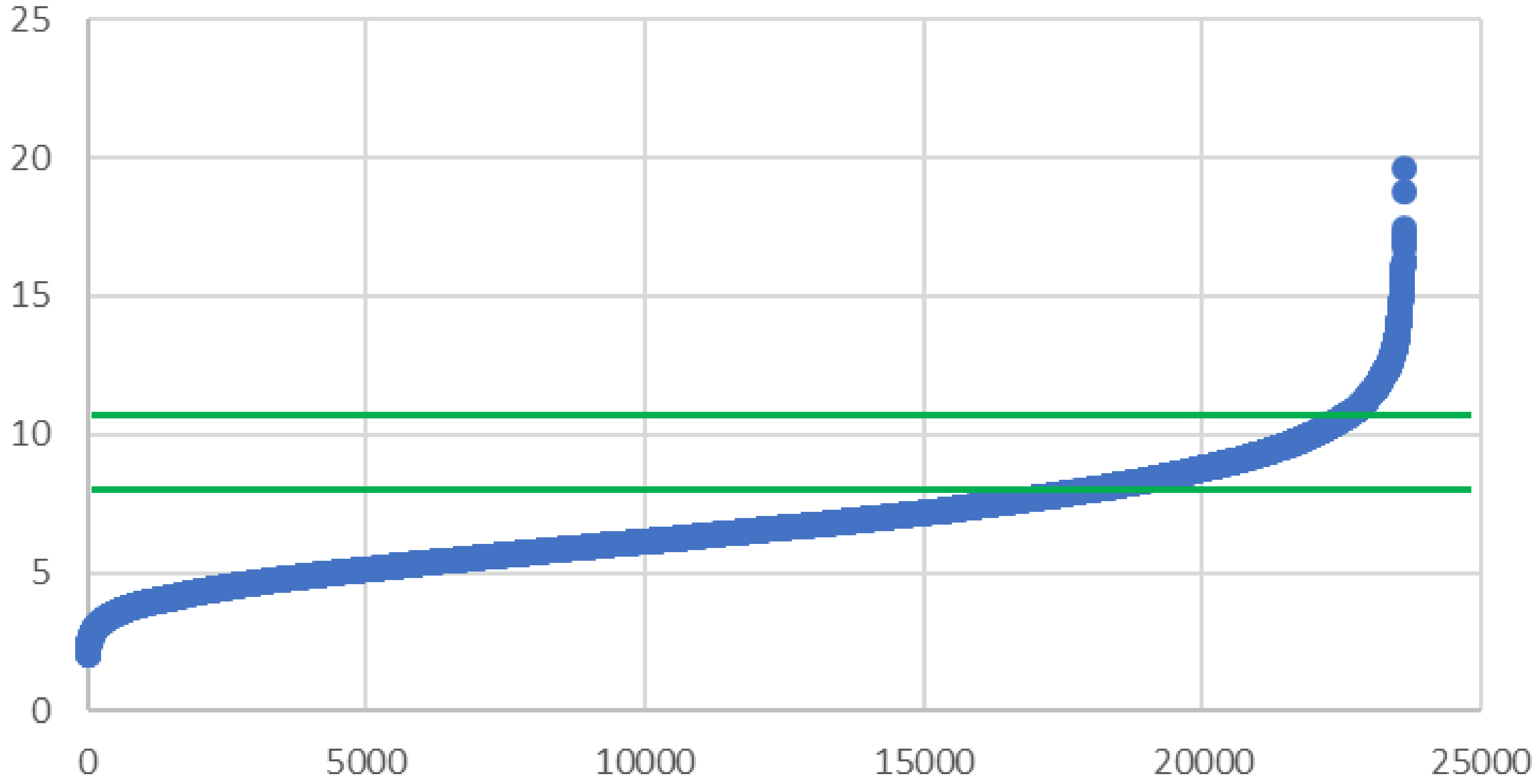
Kidney, Cerebral Cortex, Liver, Lung, Gut, asf.

Almost no correlation with intake

Harris WS et al Circulation 2004;110:1645
Arnold et al, JBC, 2010; 285:32720-33; ;
Gurzell et al, PLEFA 2014;91:87
Roy et al, Int J Canc 2015; e-pub July 2
u.a. Köhler et al, Br J Nutr 2010;104:729
Lager et al, J Clin Endo Metab 2017;102:4557

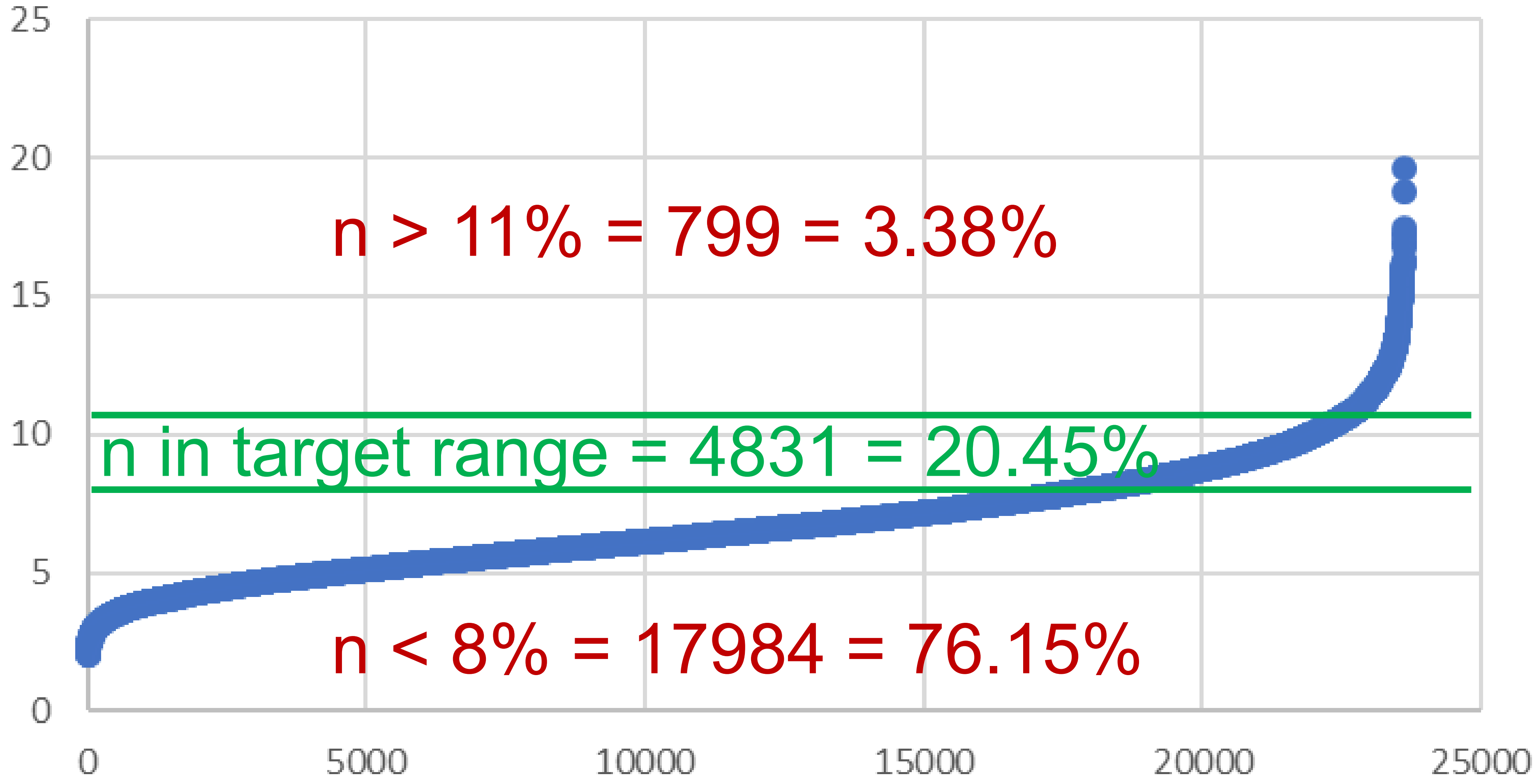

Zellmembran
außen
Glycolipid
Lipoproteid
Glycoproteid
Glycolipid
Cholesterin
Transmembran-
protein
peripheres
Protein
Filamente des
Cytoskeletts
innen

HS-Omega-3 Index in 23615 Erythrocyte-Samples from Europe

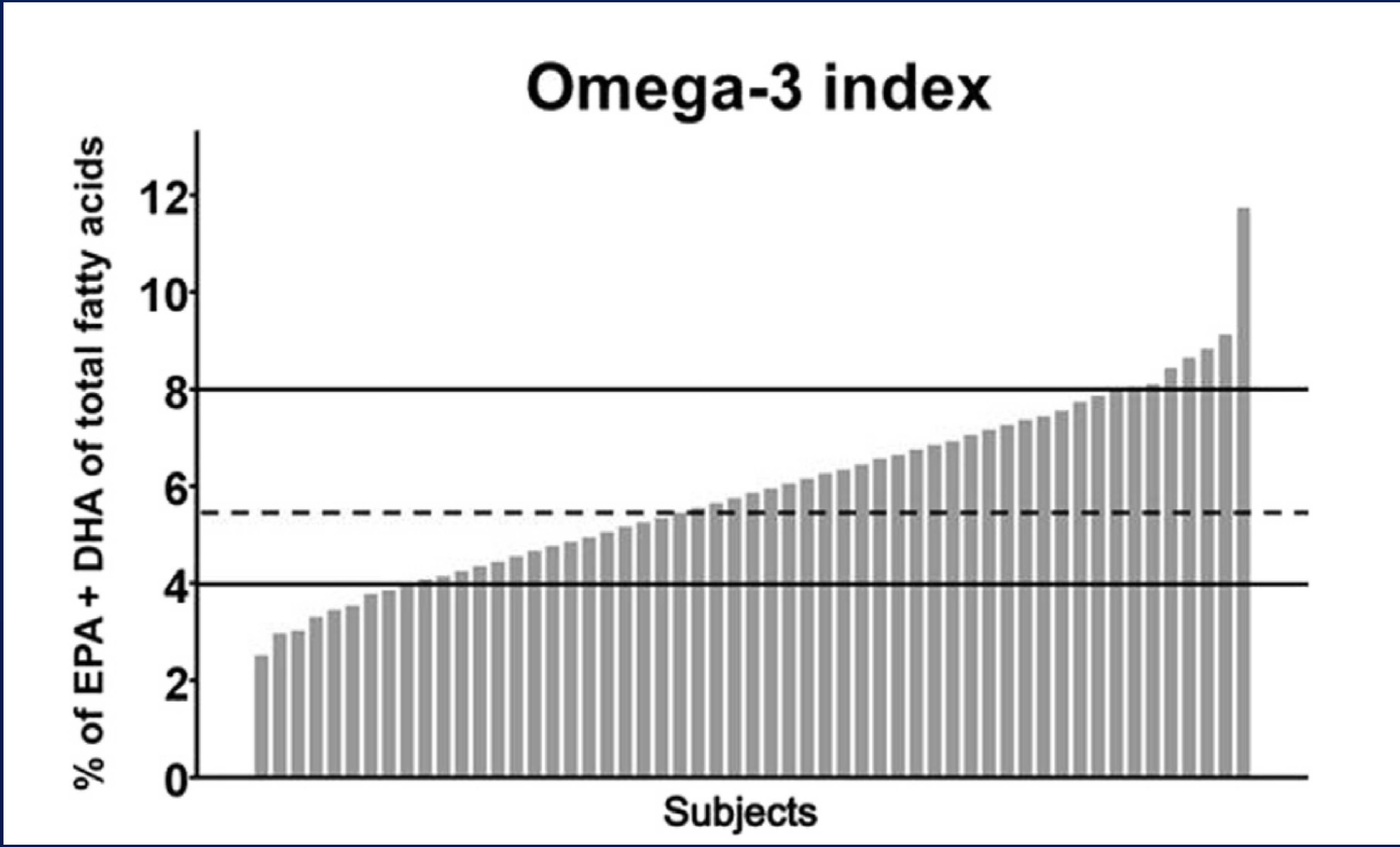


n < 2% = 0, n > 18% = 2

HS-Omega-3 Index in 23615 Erythrocyte-Samples from Europe



446 German Women between 40 and 60 Years old
Semi-representative
Mean 5.49+1.17%, <8%: 97.3% of all women



Gellert et al, PLEFA 2017;117:54

Health Reports

Omega-3 Index of Canadian adults

4.5%

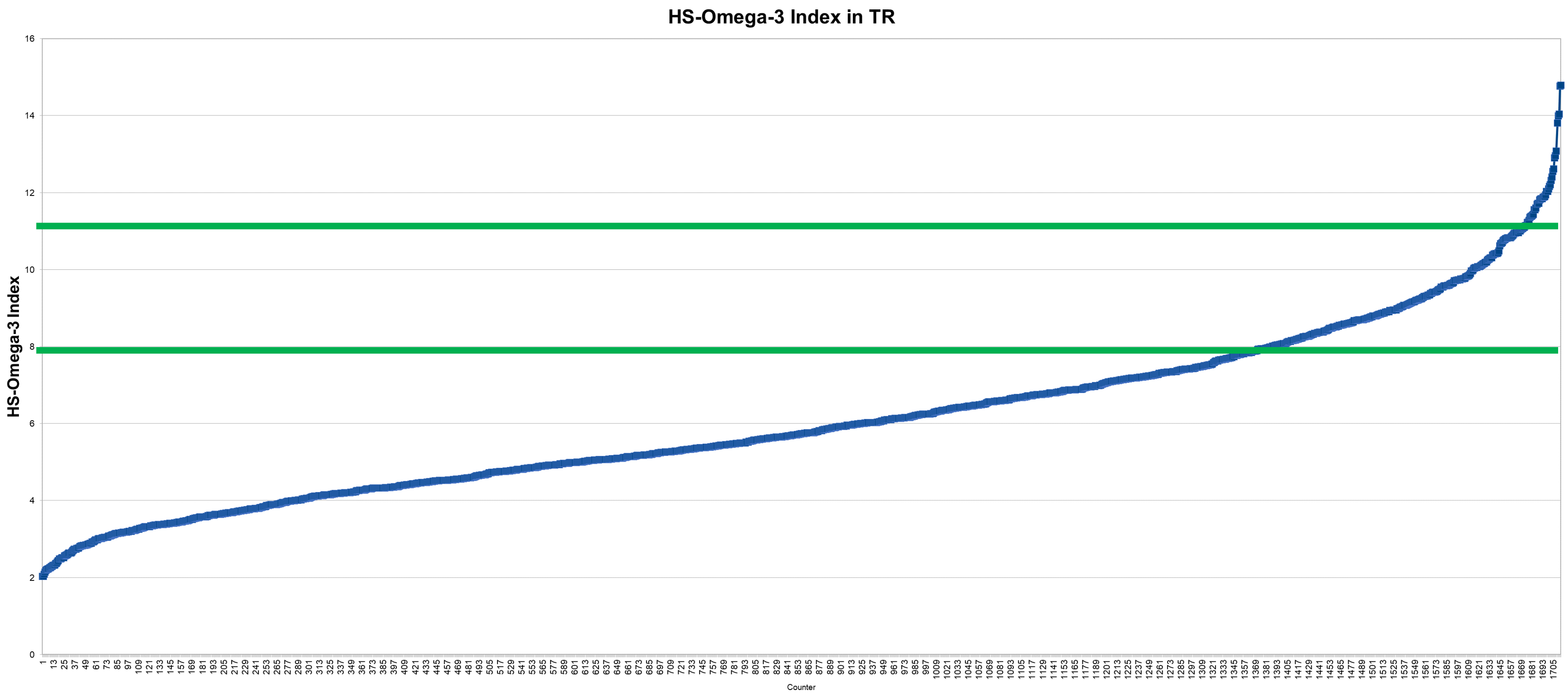
by Kellie Langlois and Walisundera M. N. Ratnayake

Release date: November 18, 2015

Statistics Canada Statistique Canada

Canada

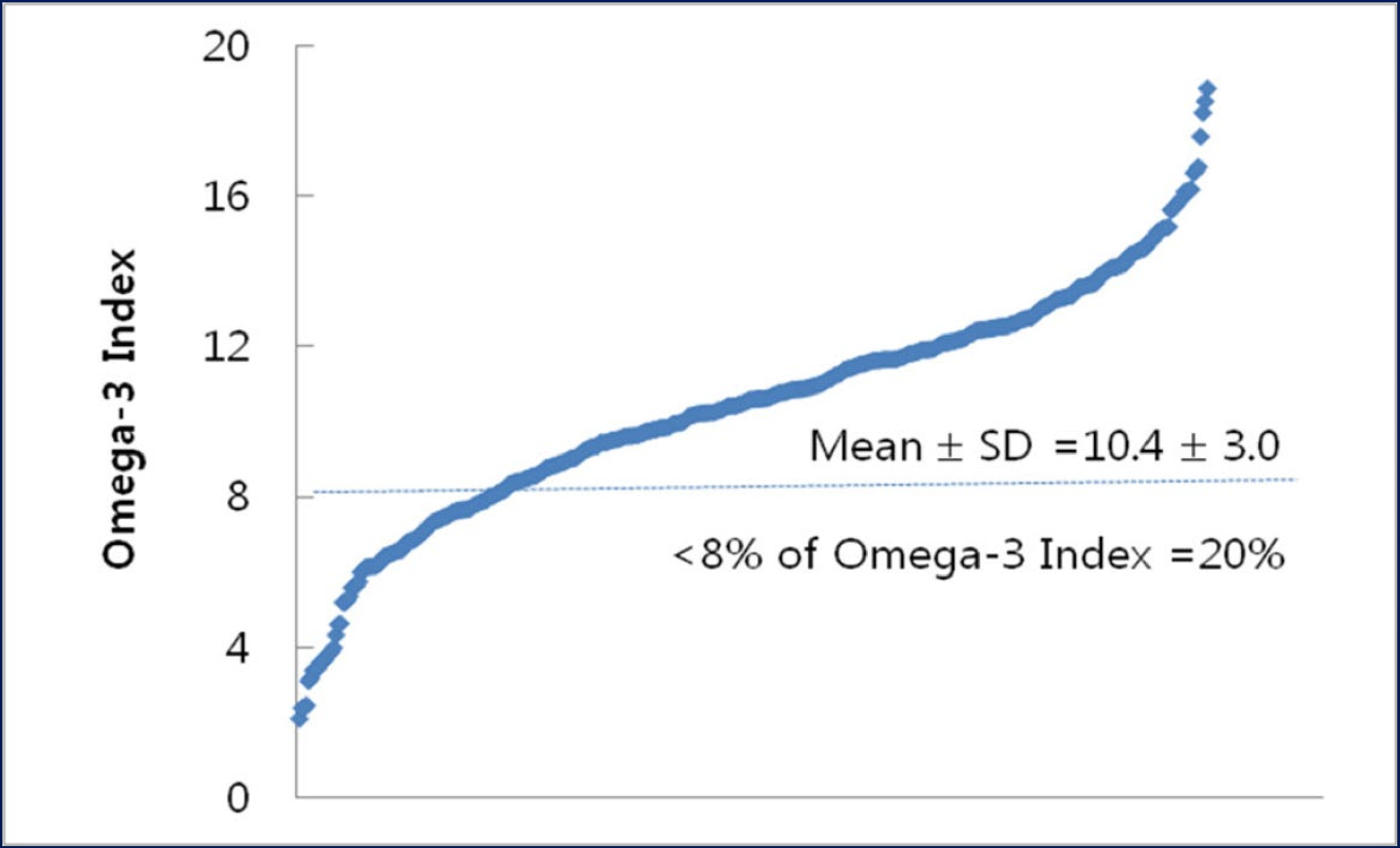
HS-Omega-3 Index in 1711 Turks, uppermost social stratum
Mean 6.08±2.20 %
81%<8%; 16.2% in target range, 2.8%>11%



Overestimation, real situation worse

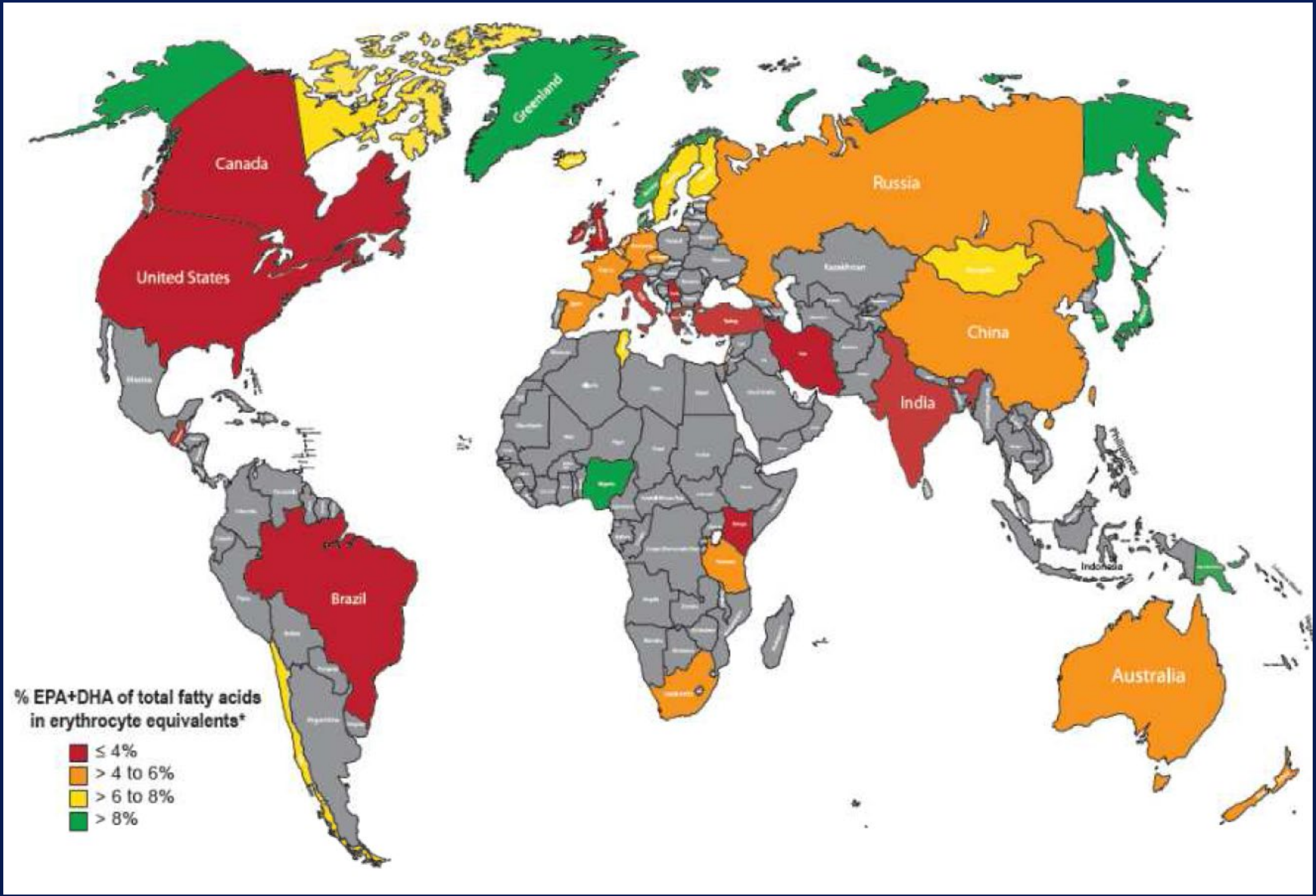
Omegametrix, data on file

HS-Omega-3 Index in 1000 South-Koreans No Supplementation, Mean 10.4 ± 3.0 %



Park et al, unpublished

Omega-3 Index around the World

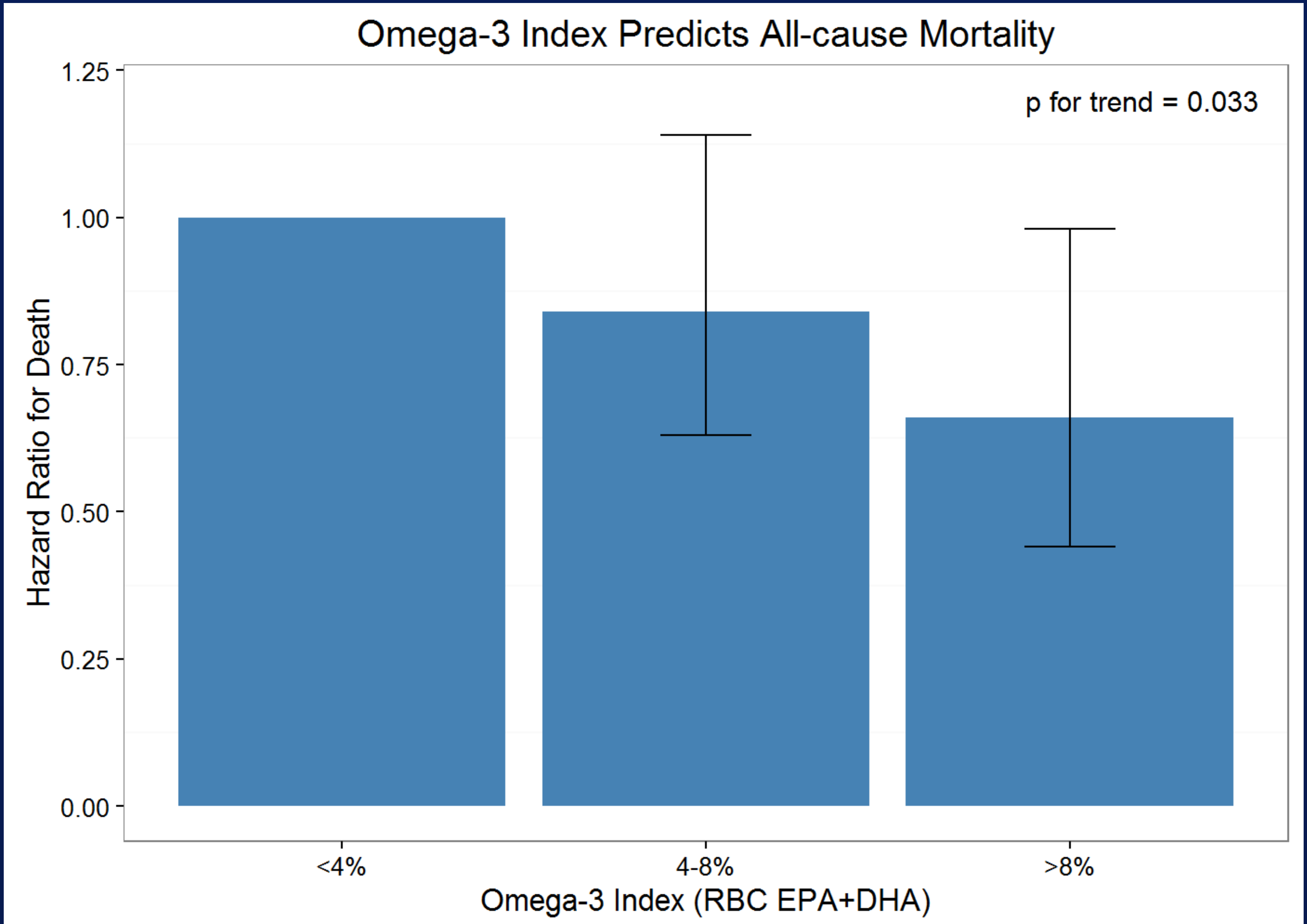


Stark K et al, Prog Lipid Res 2016, e-pub May 20

Omega-3 Index: Epidemiology

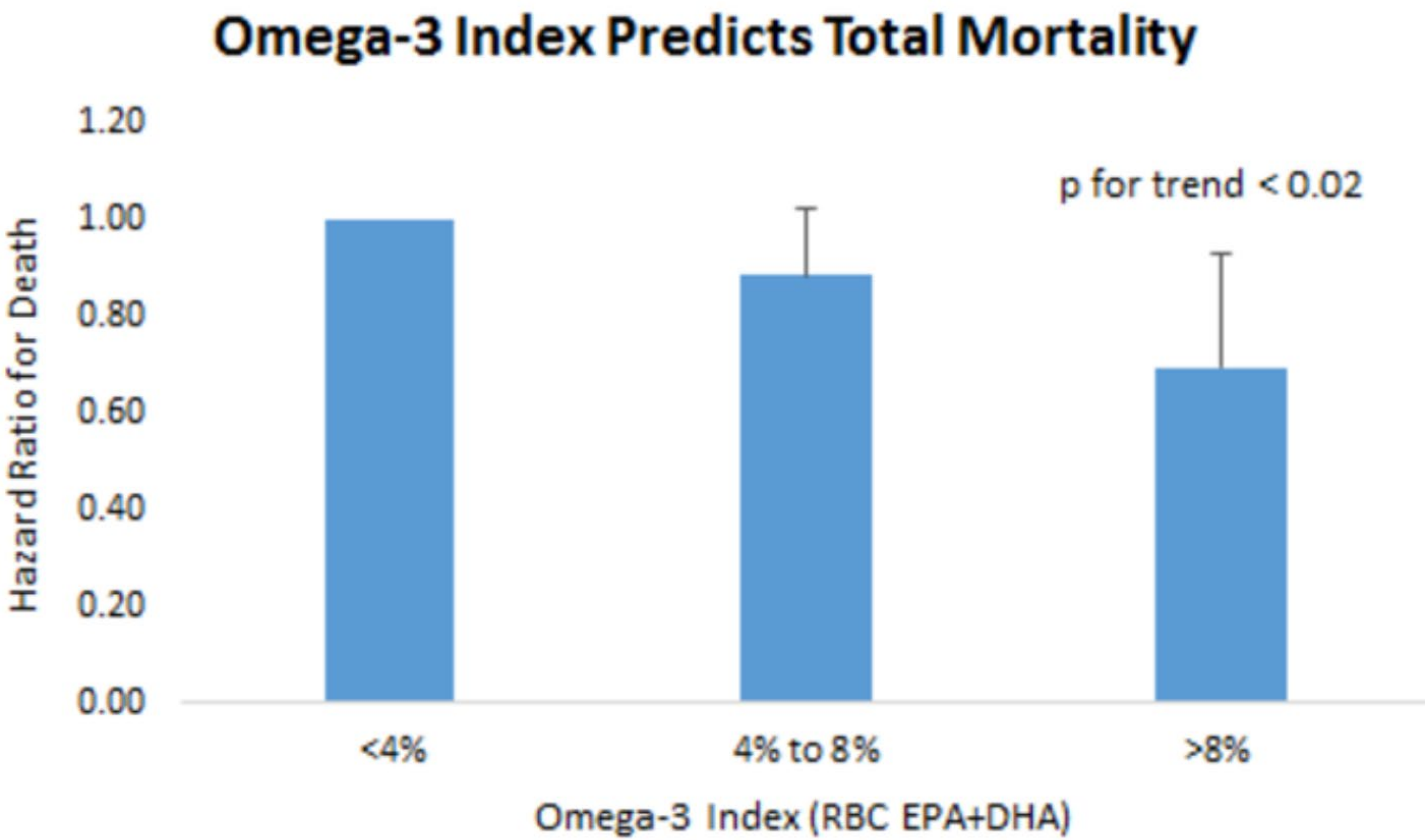
Total Mortality

Omega-3 Index and Risk for Total Mortality in LURIC



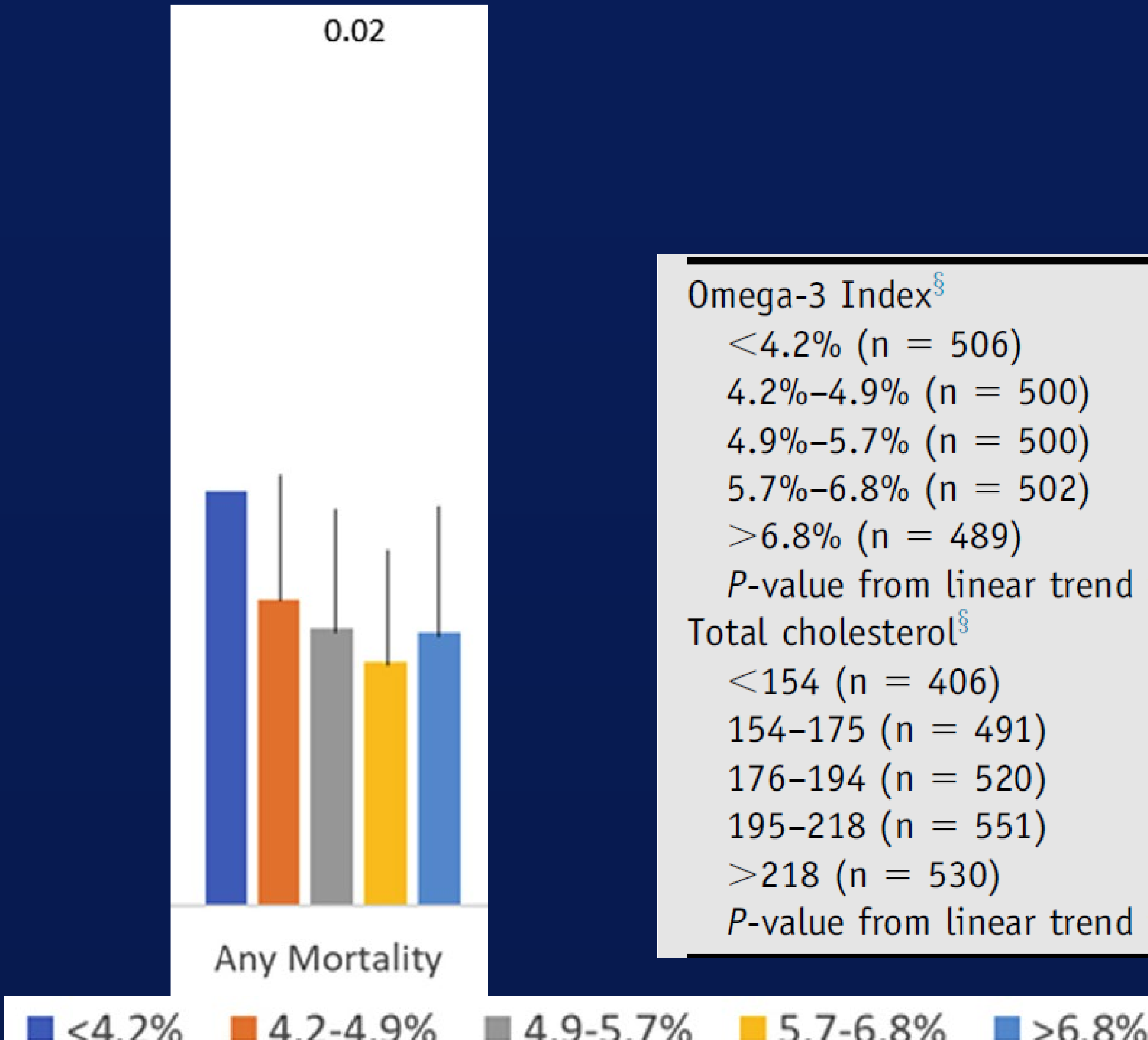
Kleber et al, Atherosclerosis 2016;252:157

Women's Health Initiative Memory Study: 6501 Women, Age 65-80 Years, 15 Y Follow-up, 1851 (28,5%) dead



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

Omega-3 Index and Total Mortality in Framingham



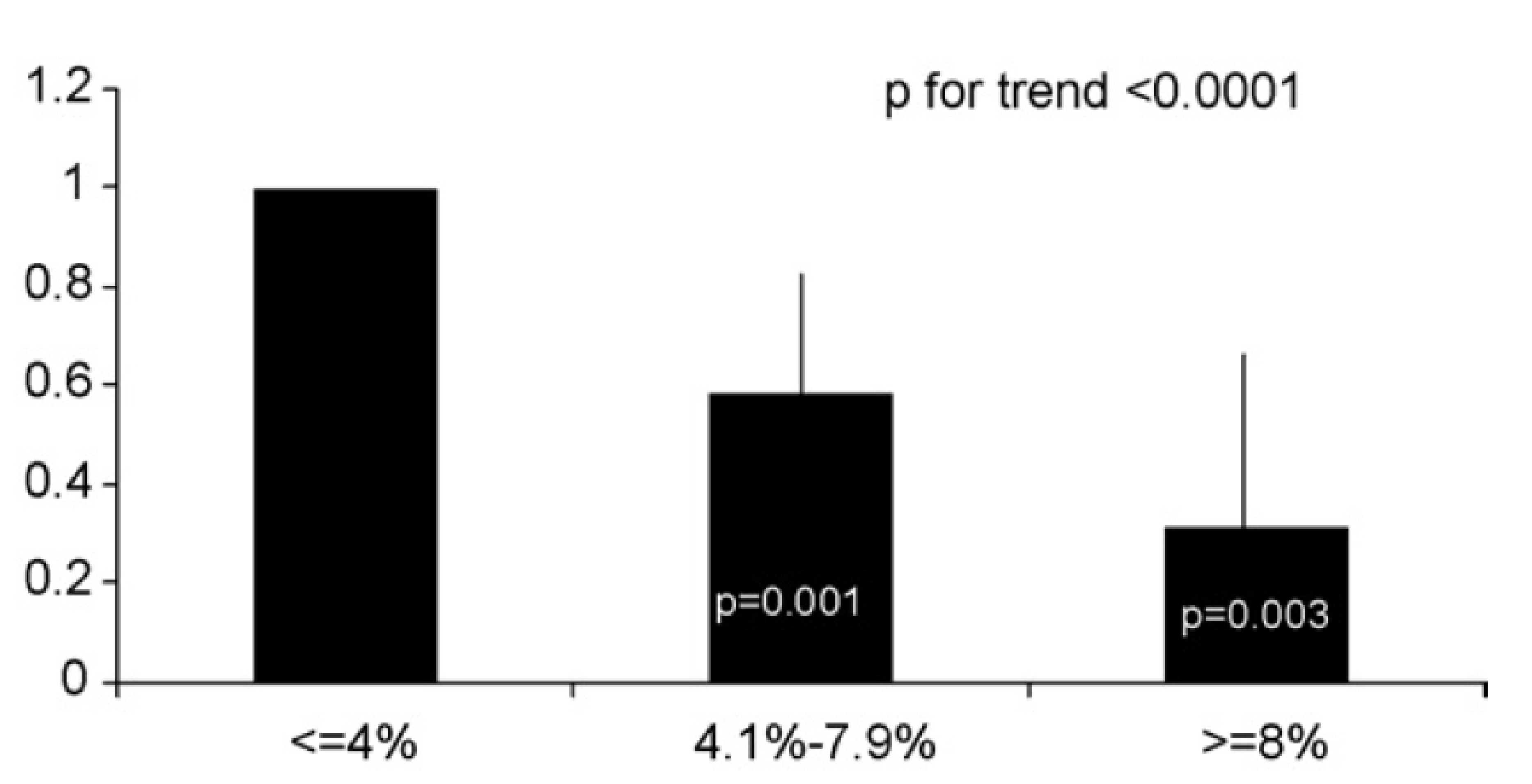
	Any Mortality
Omega-3 Index[§]	
<4.2% (n = 506)	1.0
4.2%–4.9% (n = 500)	0.74 (0.53, 1.03)
4.9%–5.7% (n = 500)	***0.67 (0.47, 0.97)***
5.7%–6.8% (n = 502)	***0.58 (0.41, 0.84)***[†]
>6.8% (n = 489)	***0.65 (0.45, 0.94)***
P-value from linear trend test[‖]	***.01***[*]
Total cholesterol[§]	
<154 (n = 406)	1.0
154–175 (n = 491)	0.73 (0.50, 1.05)
176–194 (n = 520)	0.72 (0.49, 1.06)
195–218 (n = 551)	0.91 (0.64, 1.31)
>218 (n = 530)	0.96 (0.66, 1.40)
P-value from linear trend test[‖]	.11

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

Omega-3 Index: Epidemiology

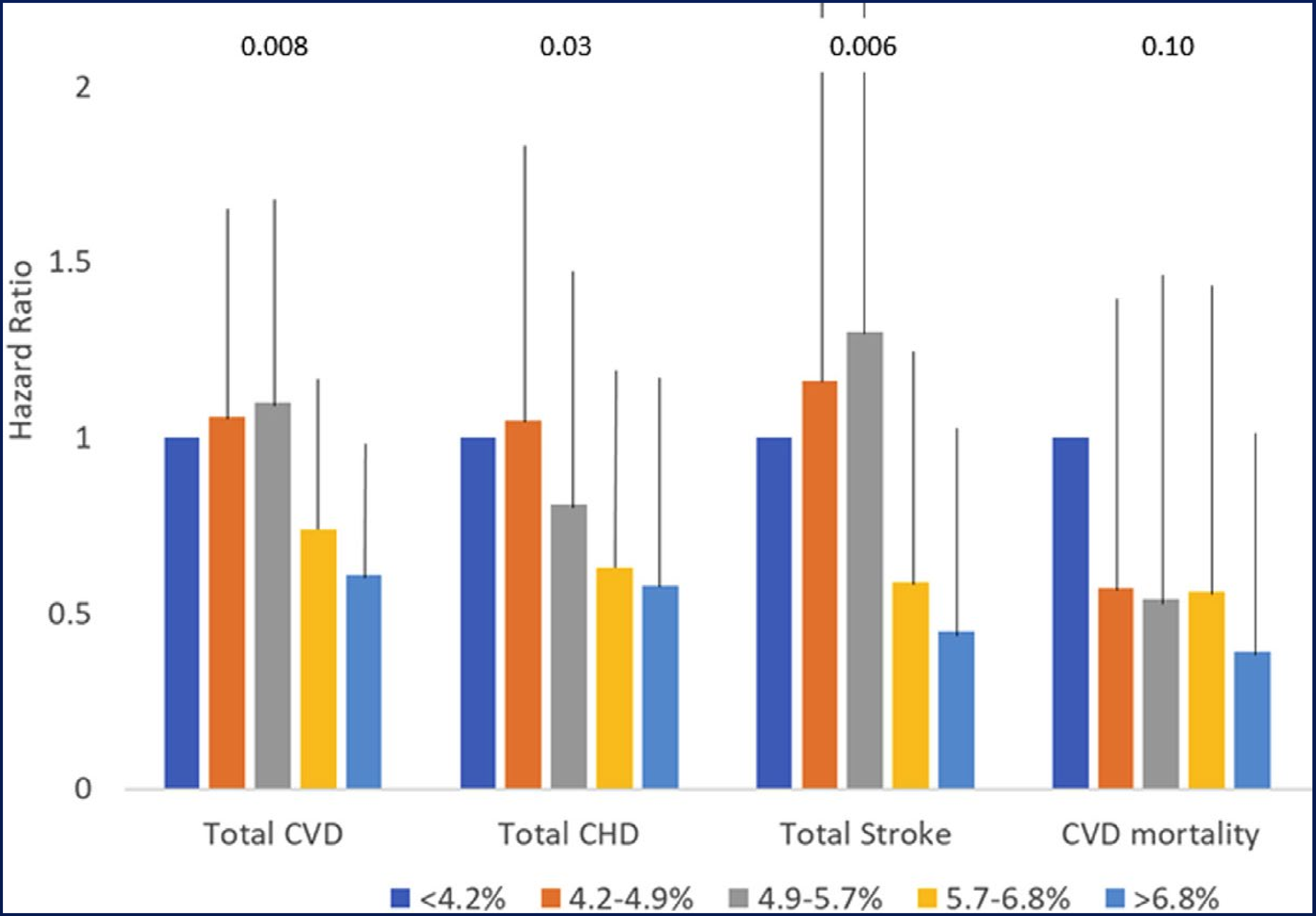
Clinical Events

Omega-3 Index and Acute Coronary Syndrome



Block RC et al, Atherosclerosis 2008;197:821

Omega-3 Index and Cardiovascular Events in Framingham



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

Table 4 Omega-3 Index and total cholesterol: Associations with risk for disease outcomes (n = 2500)

	Hazard ratios (95% CIs)				
	Total CVD	Total CHD	Total Stroke	CVD mortality	Any Mortality
Omega-3 Index§					
<4.2% (n = 506)	1.0	1.0	1.0	1.0	1.0
4.2%–4.9% (n = 500)	1.08 (0.70, 1.65)	1.06 (0.61, 1.85)	1.20 (0.63, 2.27)	0.65 (0.27, 1.54)	0.74 (0.53, 1.03)
4.9%–5.7% (n = 500)	1.11 (0.73, 1.68)	0.81 (0.44, 1.47)	1.32 (0.69, 2.50)	0.53 (0.19, 1.49)	***0.67 (0.47, 0.97)***
5.7%–6.8% (n = 502)	0.74 (0.47, 1.17)	0.63 (0.34, 1.19)	0.61 (0.29, 1.27)	0.58 (0.22, 1.55)	***0.58 (0.41, 0.84)***†
>6.8% (n = 489)	0.63 (0.39, 1.01)	0.59 (0.30, 1.17)	0.47 (0.21, 1.06)	0.44 (0.16, 1.91)	***0.65 (0.45, 0.94)***
P-value from linear trend test‖	***.009***†	***.03****	***.006***†	.19	***.01****
Total cholesterol§					
<154 (n = 406)	1.0	1.00	1.0	1.0	1.0
154–175 (n = 491)	1.03 (0.69, 1.56)	1.02 (0.55, 1.89)	0.88 (0.47, 1.66)	1.22 (0.53, 2.77)	0.73 (0.50, 1.05)
176–194 (n = 520)	0.95 (0.62, 1.45)	1.29 (0.71, 2.37)	0.63 (0.31, 1.27)	0.67 (0.26, 1.77)	0.72 (0.49, 1.06)
195–218 (n = 551)	0.89 (0.56, 1.39)	1.01 (0.53, 1.92)	0.69 (0.32, 1.40)	1.07 (0.30, 3.79)	0.91 (0.64, 1.31)
>218 (n = 530)	1.09 (0.66, 1.80)	1.59 (0.81, 3.11)	0.89 (0.41, 1.93)	0.31 (0.72, 1.34)	0.96 (0.66, 1.40)
P-value from linear trend test‖	.99	.26	.50	.27	.11

CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

**P* < .05; †*P* < .01; ‡*P* < .001.

§Hazard ratios presented here were adjusted for all variables in Table 1 with the addition of grouped total cholesterol (and removing total cholesterol to high-density lipoprotein cholesterol ratio) and the grouped Omega-3 Index.

‖Linear trend test models were fit for both the Omega-3 Index and TC simultaneously, after adjusting for variables as described in footnote "§".

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

Omega-3's and Cardiovascular / Primary – secondary Prevention

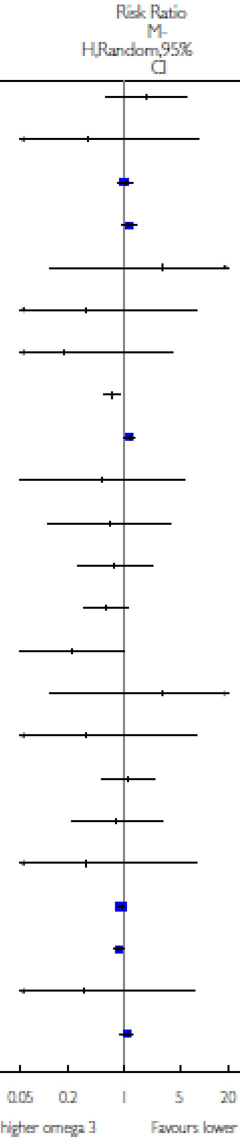
Analysis 1.1. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 1 All-cause mortality (overall) - LCn3.

Review: Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes)

Outcome: 1 All-cause mortality (overall) - LCn3

Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Weight	Risk Ratio M-H,Random,95% CI
ADCS 2010	11/238	4/164	0.2 %	1.89 [0.61, 5.85]
AFFORD 2013	0/153	1/163	0.0 %	0.35 [0.01, 8.65]
AlphaOmega - EPA+DHA 2010 (1)	186/2404	184/2433	6.0 %	1.02 [0.84, 1.24]
AREDS2 2014	200/2147	168/2056	6.0 %	1.14 [0.94, 1.39]
Bates 1989	1/155	0/157	0.0 %	3.04 [0.12, 74.02]
Berson 2004	0/105	1/103	0.0 %	0.33 [0.01, 7.94]
Brox 2001	0/80	1/40	0.0 %	0.17 [0.01, 4.05]
DART 1989	94/1015	131/1018	4.0 %	0.72 [0.56, 0.92]
DART2 2003	283/1571	242/1543	8.4 %	1.15 [0.98, 1.34]
Derosa 2016	1/138	2/143	0.1 %	0.52 [0.05, 5.65]
DIPP 2015	2/104	3/101	0.1 %	0.65 [0.11, 3.79]
DISAF 2003	6/201	8/206	0.3 %	0.77 [0.27, 2.18]
DO IT 2010	14/282	24/281	0.7 %	0.58 [0.31, 1.10]
Doi 2014	2/119	9/119	0.1 %	0.22 [0.05, 1.01]
EPIC-1 2008	1/183	0/180	0.0 %	2.95 [0.12, 71.97]
EPIC-2 2008	0/189	1/190	0.0 %	0.34 [0.01, 8.17]
FAAT 2005	13/200	12/202	0.5 %	1.09 [0.51, 2.34]
FORWARD 2013	4/289	5/297	0.2 %	0.82 [0.22, 3.03]
FOSTAR 2016	0/101	1/101	0.0 %	0.33 [0.01, 8.09]
GISSI-HF 2008	955/3494	1014/3481	18.8 %	0.94 [0.87, 1.01]
GISSI-P 1999	472/5666	545/5658	12.2 %	0.86 [0.77, 0.97]
HARP 1995	0/41	1/39	0.0 %	0.32 [0.01, 7.57]
JELIS 2007	286/9326	265/9319	7.8 %	1.08 [0.91, 1.27]



Abdelhamid et al Cochrane Database Syst Rev. 2018;11:CD003177

(. . . Continued)

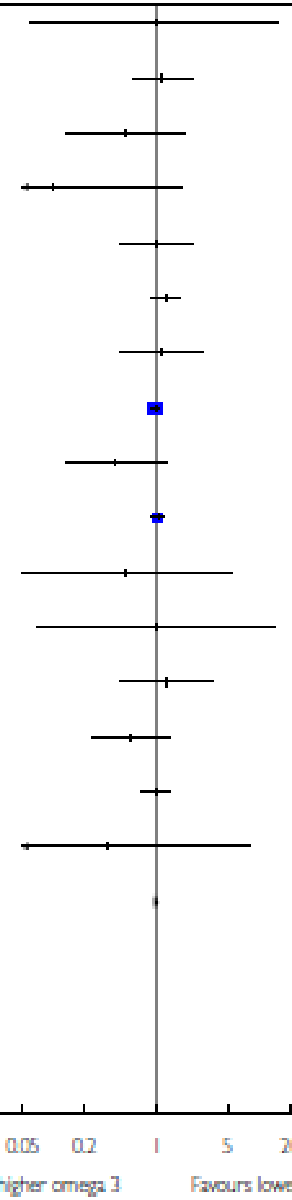
Study or subgroup	Favours higher omega 3 n/N	Lower omega 3 fats n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kumar 2013	1/39	1/39		0.0 %	1.00 [0.06, 15.43]
MAPT 2017	18/840	16/840		0.6 %	1.13 [0.58, 2.19]
NAT2 2013	3/150	6/150		0.2 %	0.50 [0.13, 1.96]
Nutristroke 2009	0/38	4/34		0.0 %	0.10 [0.01, 1.79]
OFAMI 2001	11/150	11/150		0.4 %	1.00 [0.45, 2.24]
OMEGA 2009	88/1919	70/1885		2.7 %	1.23 [0.91, 1.68]
OPAL 2010	9/434	8/433		0.3 %	1.12 [0.44, 2.88]
ORIGIN 2012	951/6281	964/6225		17.5 %	0.98 [0.90, 1.06]
Raitt 2005	4/100	10/100		0.2 %	0.40 [0.13, 1.23]
Risk % Prevention 2013	348/6239	337/6266		9.3 %	1.04 [0.90, 1.20]
SCIMO 1999	1/112	2/111		0.1 %	0.50 [0.05, 5.39]
Shinto 2014	1/13	1/13		0.0 %	1.00 [0.07, 14.34]
SHOT 1996	8/317	6/293		0.3 %	1.23 [0.43, 3.51]
SOFA 2006	8/273	14/273		0.4 %	0.57 [0.24, 1.34]
SU.FOL.OM3 2010	66/1253	68/1248		2.4 %	0.97 [0.70, 1.34]
Zhang 2017	0/120	1/120		0.0 %	0.33 [0.01, 8.10]
Total (95% CI)	**46479**	**46174**		**100.0 %**	**0.98 [0.93, 1.03]**

Total events: 4048 (Favours higher omega 3), 4141 (Lower omega 3 fats)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 43.01$, df = 38 (P = 0.27); $I^2 = 12\%$

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable



Abdelhamid et al Cochrane Database Syst Rev. 2018;11:CD003177

The Issue of Bioavailability

Variability in Uptake of Omega-3‘s Ingested

- Low Fat vs / High Fat Meal:	up to Factor 13
- Chemical Form:	up to Factor 2
- Emulsion / Fish vs. caps	up to Factor 22
- Matrix Effects	up to Factor 10
- Inter-individually:	up to Factor 13

Intake ≠ Uptake

Bioavailability not predictable individually

One Dose doesn‘t fit all!

Levels count, not dose – Omega-3 Index!!

Schuchardt PLEFA 2013;89:1; Köhler et al, Br J Nutr 2010, 104:729; Flock, JAHA 2013; 2:e000513
Davidson et al J Clin Lipidol. 2012;6:573-84; Hussey et al, Clin Pharm Drug Develop 2012;1:14;
Neubronner et al, Eur J Clin Nutr 2011;65:247; Köhler et al, Nutrients 2017;9:629

Low Fat vs / High Fat Meal: up to Factor 13

* 1 Capsule with Breakfast

Table. Characteristics of Included Trials

Study (Year)	Patients, No.	Dose of EPA/ DHA (mg/d)	Male, No (%)	Mean Trial Duration, y	Mean (SD) Age, y	No (%)			
						Prior CHD	Prior Stroke	Prior Diabetes	Statin Use
DOIT (2010) *	563	1150/800	563 (100)	3	70 (3)	133 (23.6)	37 (6.6)	46 (8.2)	NA
AREDS-2 (2014) *	4203	650/350	1816 (43.2)	4.5	74 (NA)	405 (9.7)	211 (5.0)	546 (13.0)	1866 (44.4)
SU.FOL.OM3 (2010) *	2501	400/200	1987 (79.4)	4.7	61 (NA)	1863 (74.5)	638 (25.5)	440 (17.9)	2079 (83.1)
JELIS (2007)[a,b] +	18 645	1800/NA	5859 (31.4)	4.6	61 (8)	NA	NA	3040 (16.3)	18 645 (100.0)
Alpha Omega (2010) *	4837	226/150	3783 (78.2)	3.3	69 (6)	4837 (100.0)	345 (7.2)	1014 (21.0)	4122 (85.2)
OMEGA (2010) *	3818	460/380	2841 (74.4)	1	64 (NA)	796 (22.5)	192 (5.5)	948 (27.0)	3566 (94.2)
R&P (2013) *	12 505	500/500	7687 (61.5)	5	64 (NA)	Not stated (30)	594 (4.8)	7494 (59.9)	12 505 (100.0)
GISSI-HF (2008) +	6975	850/950	5459 (78.3)	3.9	67 (11)	3614 (51.8)	346 (5.0)	1974 (28.3)	NA
ORIGIN (2012) *	12 536	465/375	8150 (65.0)	6.2	64 (8)	8094 (64.6)	10 877 (86.8)	11 081 (88.4)	6739 (53.8)
GISSI-P[b] (1999) +	11 334	850/1700	9658 (85.2)	3.5	59 (11)	11 334 (100.0)	NA	2139 (18.9)	NA
Total	77 917	NA	47 803 (61.4)	4.4	64	31 076/46 767 (66.4)	13 240/47 938 (27.6)	28 722 (36.9)	49 522 (83.4)

Abbreviations: AREDS-2, Age-Related Eye Disease Study 2; DOIT, Diet and Omega-3 Intervention Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; JELIS, Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study; NA, not available; OMEGA, Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; ORIGIN, Outcome Reduction With Initial Glargine Intervention; SU.FOL.OM3, Supplémentation en Folates et Omega-3; R&P, Risk and Prevention Study.

[a] All trials used eicosapentaenoic acid and docosahexanoic acid supplements, with the exception of the JELIS trial (eicosapentaenoic acid only).

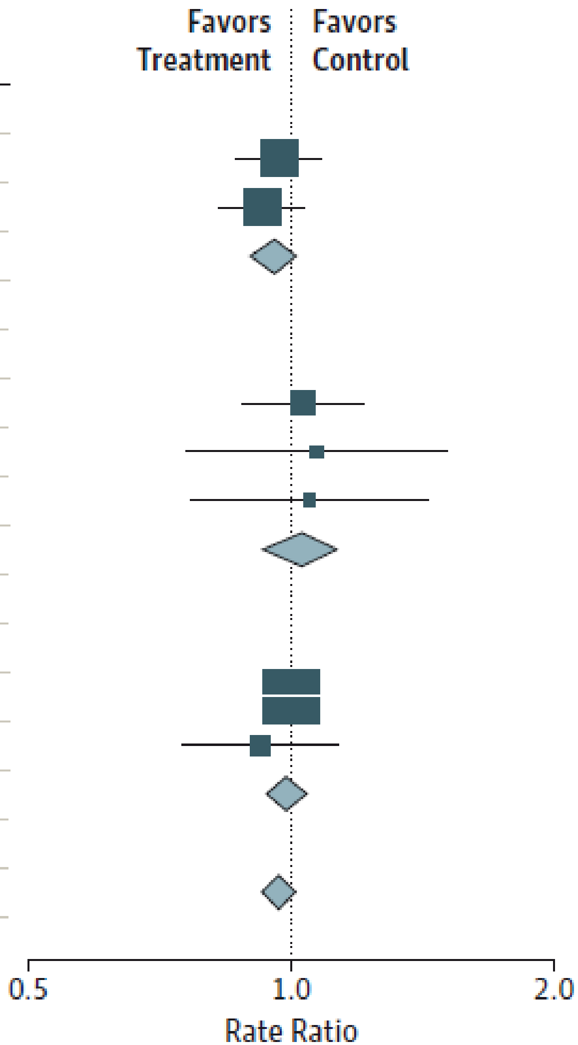
[b] All trials were blind, placebo-controlled randomized clinical trials with the exception of JELIS and GISSI-P, which were open-label without placebo.

Aung et al JAMA Cardiol 2018; e-pub Jan 31

No Uptake – No Effect

Figure 1. Associations of Omega-3 Fatty Acids With Major Vascular Events

Source	No. of Events (%) Treatment	No. of Events (%) Control	Rate Ratios (CI)
Coronary Heart Disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/Other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P = .60
Revascularization			
Coronary	3044 (9.3)	3044 (9.3)	1.00 (0.93-1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75-1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94-1.04)
			P = .60
Any major vascular event	3230 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P = .10



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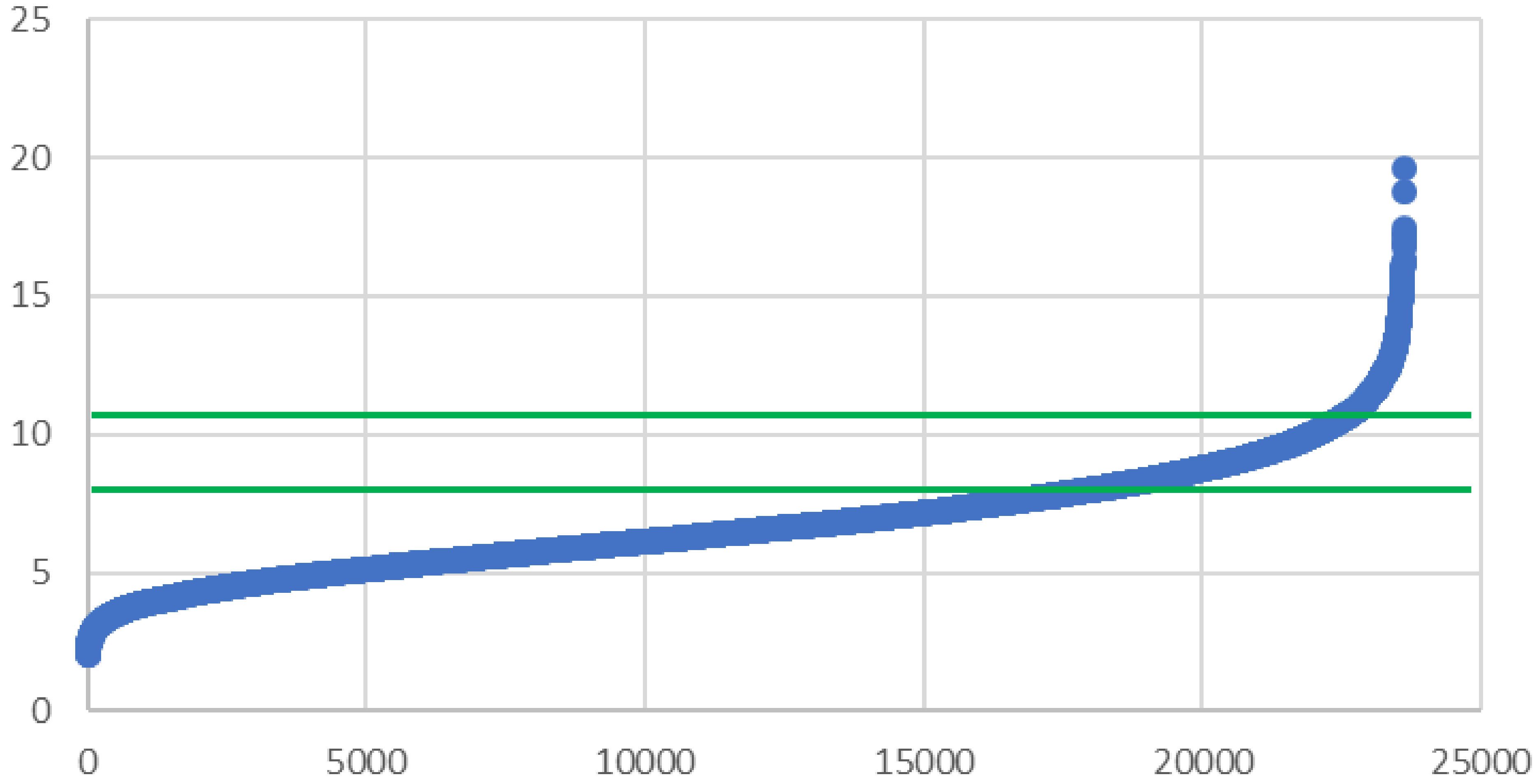
HS-Omega-3 Index in 23615 Erythrocyte-Samples from Europe



n < 2% = 0, n > 18% = 2

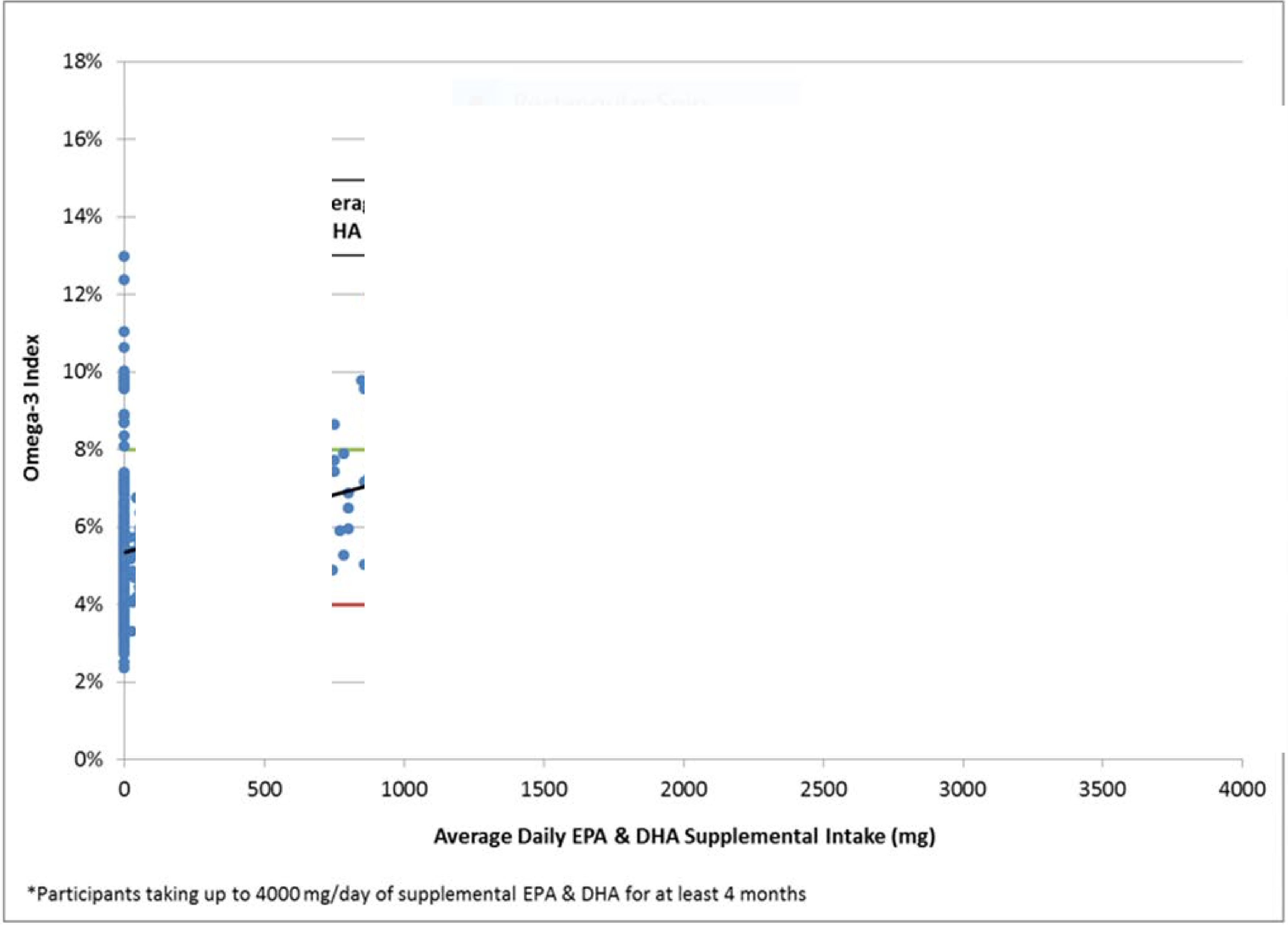
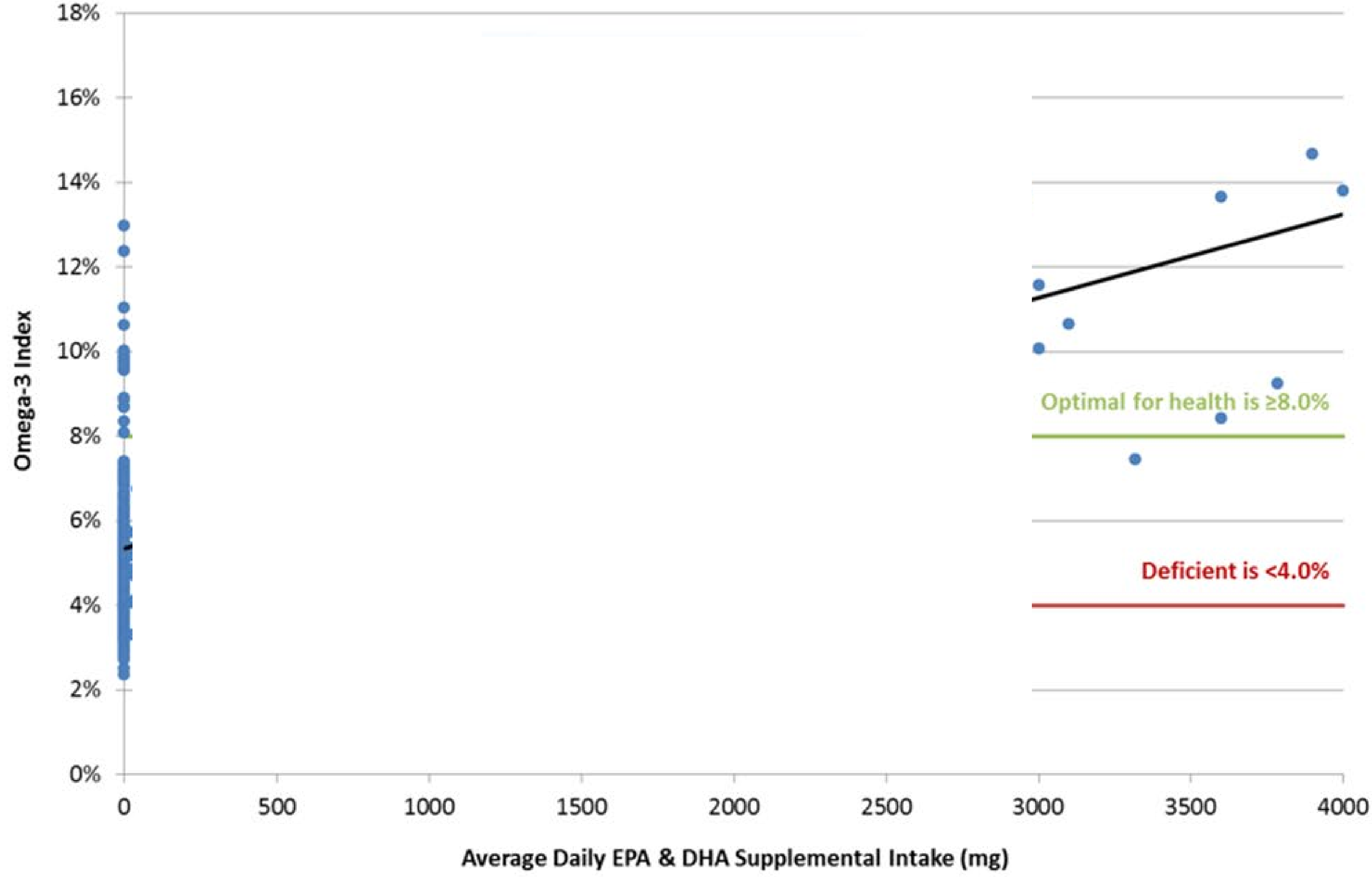


Figure 1© 2018 GrassrootsHealth

https://www.naturalproductsinsider.com/lipids/optimal-illusive-omega-3-level



*Participants taking up to 4000 mg/day of supplemental EPA & DHA for at least 4 months

Figure 1© 2018 GrassrootsHealth

https://www.naturalproductsinsider.com/lipids/optimal-illusive-omega-3-level

Recruitment for trials never
depended on baseline levels

That‘s nonsense

Like a trial with an antihypertensive,
with no baseline blood pressure

or like a statin trial with no baseline LDL

DART, Diet and Reinfarction Trial, two-year Nutrition Trial, randomized, Mono-center, factorial Design in 2033 Pat shortly after first MI

2 x fatty Fish per Week

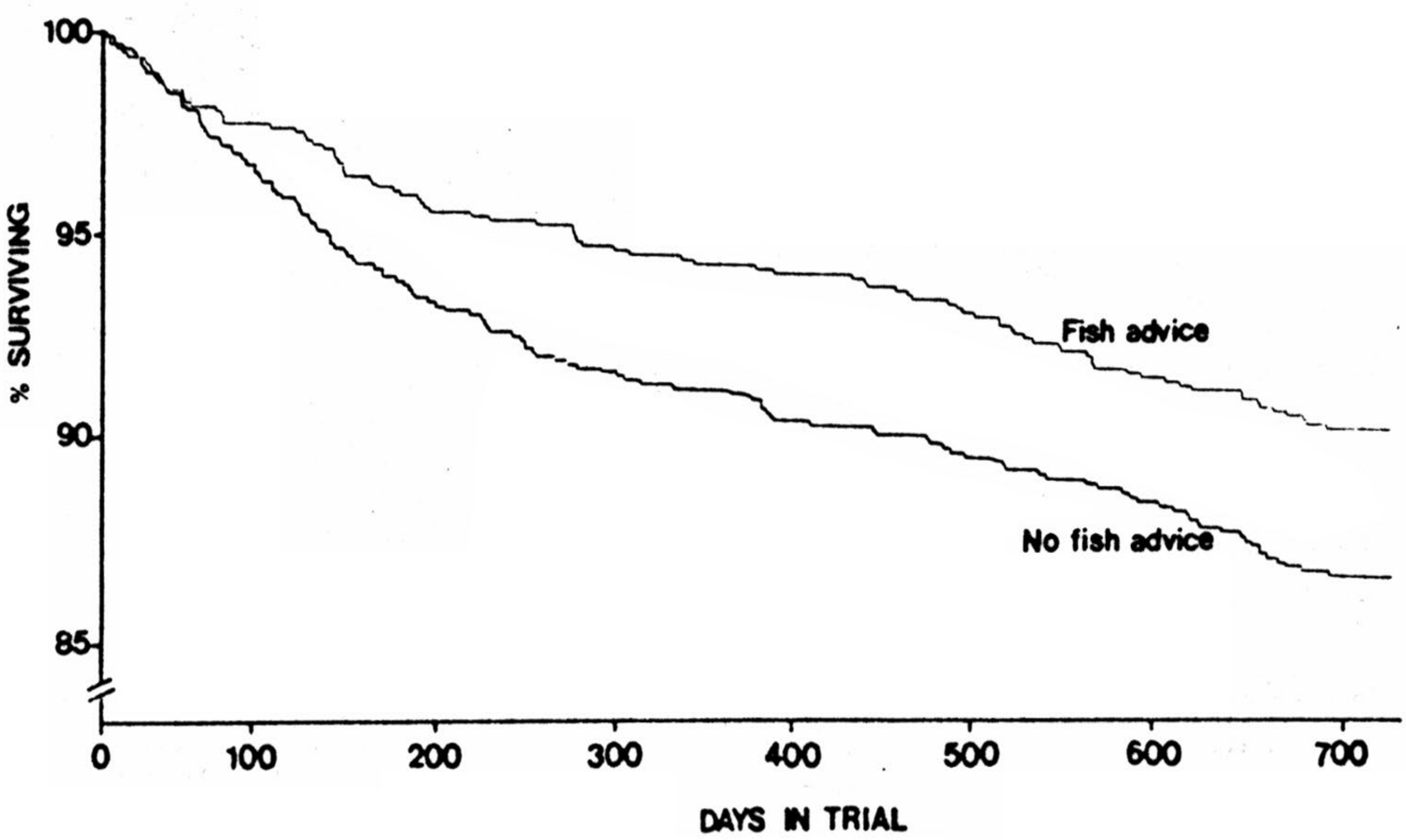


Fig 2—Survival: fish advice.

Burr et al, Lancet 1989; II:554:757

Gruppo Italiano per lo Studio della Sopravvivenza nell´Infarto miocardico

3.5 Years randomized, open, multi-center, factorial Design, 11324 Pat shortly after first MI

0.85 g ω-3 Fatty Acids / Day

300 mg Vitamin E / Day

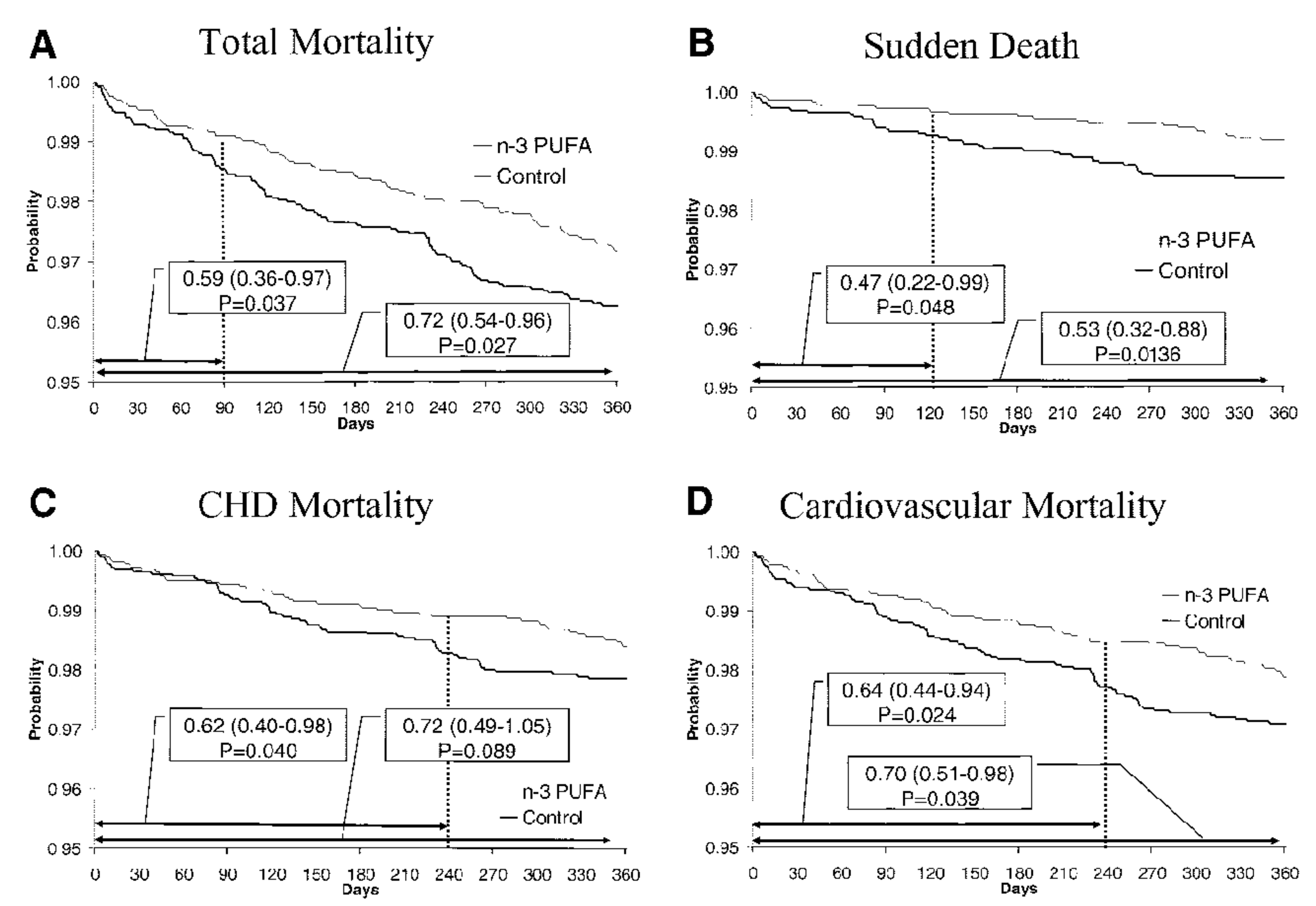
Combination

Neither

Timepoint of Intake free

GISSI-P, Lancet 1999; 354:447

Total C 154, n-3 111

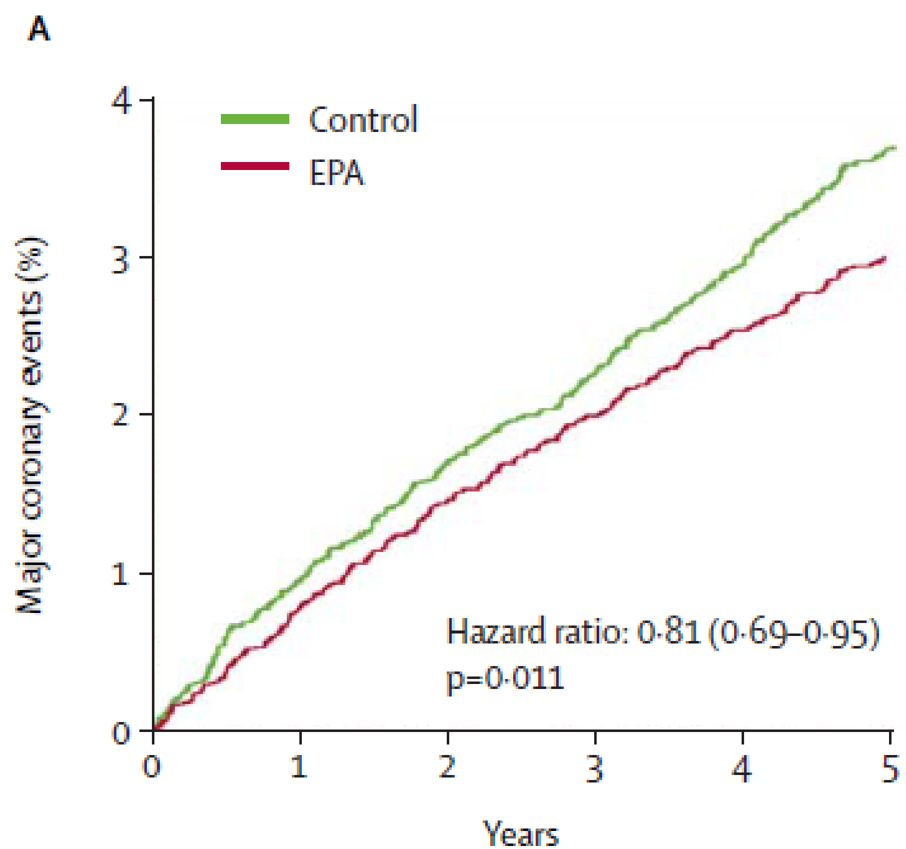


Marchioli et al Circulation 2002;105:1897-1903

JELIS: RCT in 19 466 Hyperlipidemics, ± cardiovasc. Disease,

Of them 9326 1.8 g / day EPA

9319 Controls, Mean Follow-up 4.6 Years.



Numbers at risk

	0	1	2	3	4	5
Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

Primary End Point: coronary Event, fatal and non-fatal Myocardial Infarction, others like Revascularization

Yokoyama et al, Lancet 2007;369:1090

REDUCE-IT

RCT with 8179 Participants with CV Risk, all Statin

4 g EPA-Ethylester vs. Placebo

4.9 Years mean Trial Duration

Primary End Point: MACE

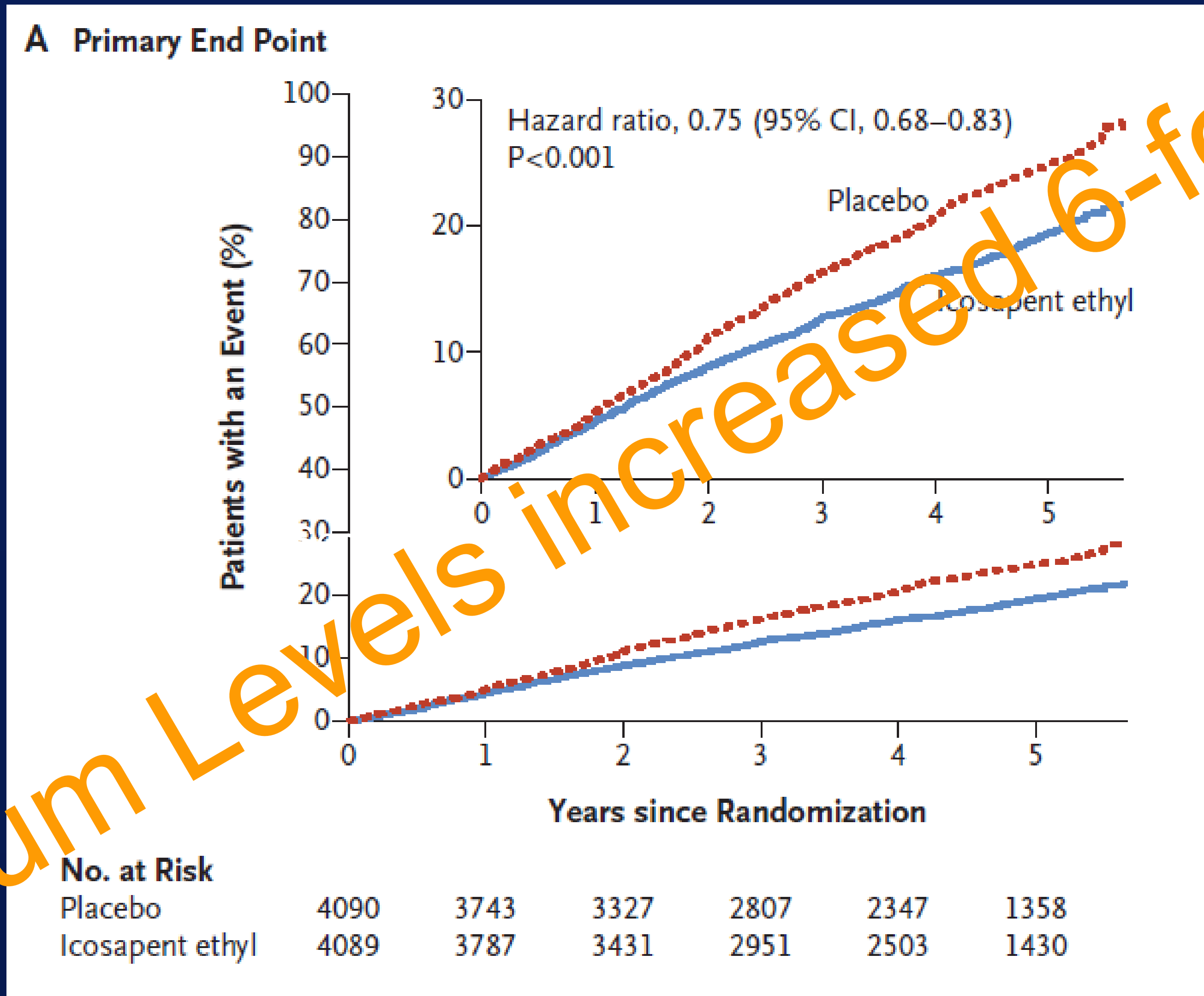
CV Death, non-fatal Myocardial Infarction,

non-fatal Stroke, coronary Revascularization,

unstable AP with Hospitalization

Bhatt et al, N Engl J Med 2018, e-pub Nov 10

REDUCE-IT



25% rel. Risk Reduction, p<0.001

Bhatt et al, N Engl J Med 2018, e-pub Nov 10

AHA Scientific Advisory on EPA+DHA Supplements

Overall, there was a lack of consensus on whether current evidence from RCTs suggested no benefit of omega-3 PUFA supplements among patients at high CVD risk, in part because of differences in the weight given to the results of the JELIS trial. Although the majority of co-authors concluded that treatment is not indicted (*Class III: No Benefit Recommendation*), a minority of coauthors concluded that treatment of these patients is reasonable (*Class IIb Recommendation*).

Primary Prevention

outweighs any risk of treatment, the majority of co-authors concluded that treatment with omega-3 PUFA supplements is reasonable for the secondary prevention of CHD death (*Class IIa Recommendation*); a minority of coauthors preferred a slightly lower strength of recommendation for treatment of patients with this indication (*Class IIb Recommendation*).

Secondary Prevention

Siscovick et al AHA statement on omega-3's Circulation 2017 March 13

Summary EPA & DHA in CVD

Epidemiology: low levels – later CVD, high mortality, MI, Stroke

Mechanisms of Action, if HS-Omega-3 Index around 10%

- TG's↓
- Blood Pressure ↓
- Heart Rate ↓
- inflammatory Cytokines ↓
- Plaque Stabilization

Intermediate endpoints positive: e.g. SCIMO

Some Endpoint Trial positive – few issues in trial methods

Many Endpoint Trials neutral – many issues in trial methods

Guidelines positive for Cardiovascular Prevention and Secondary Prevention, no clear Recommendation of Dose

Intake ≠ Uptake

My Suggestion: Aim for HS-Omega-3 Index around 10%

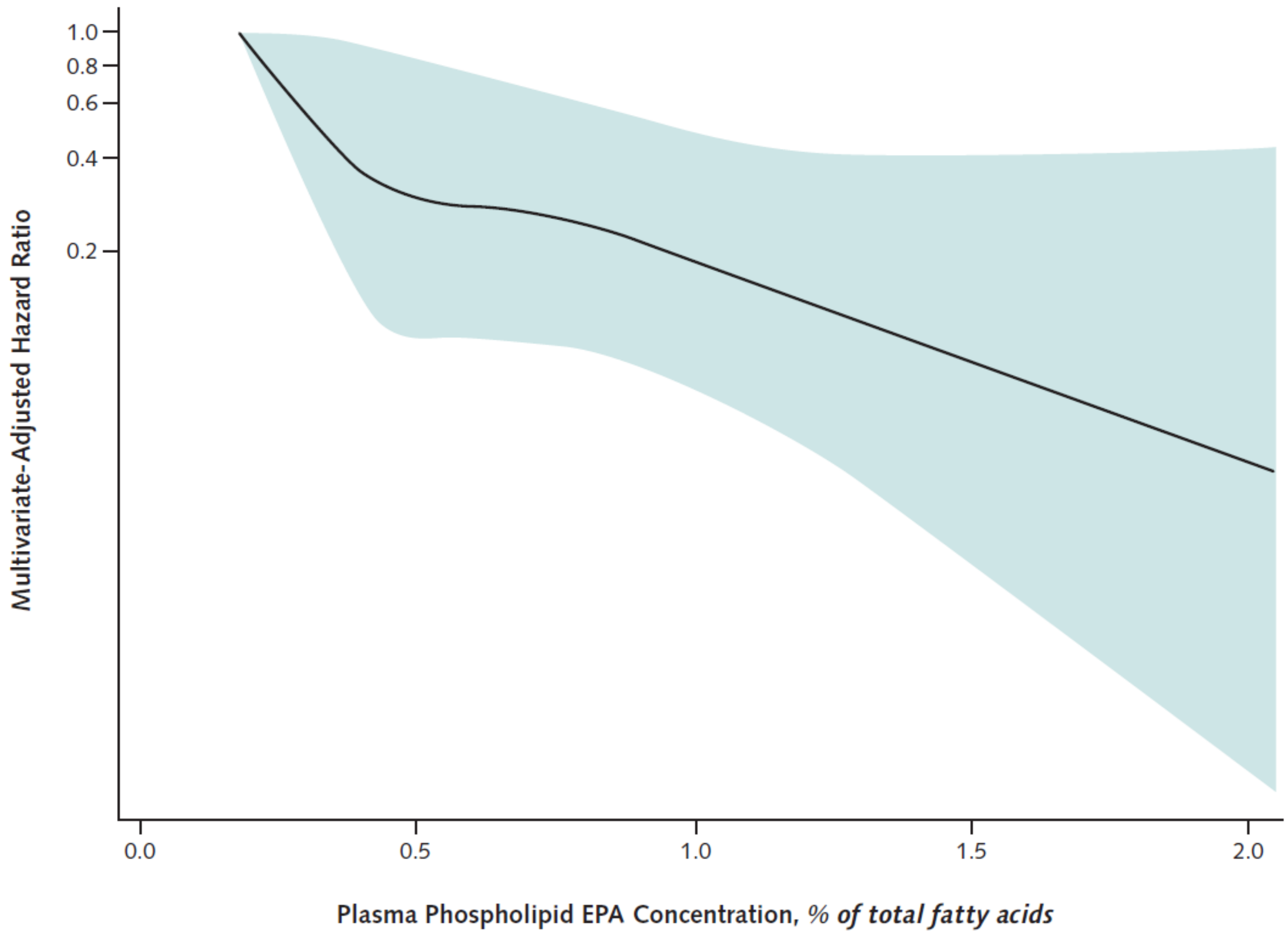
Integrate Omega-3 Index into Clinical Routine

Standardization needed

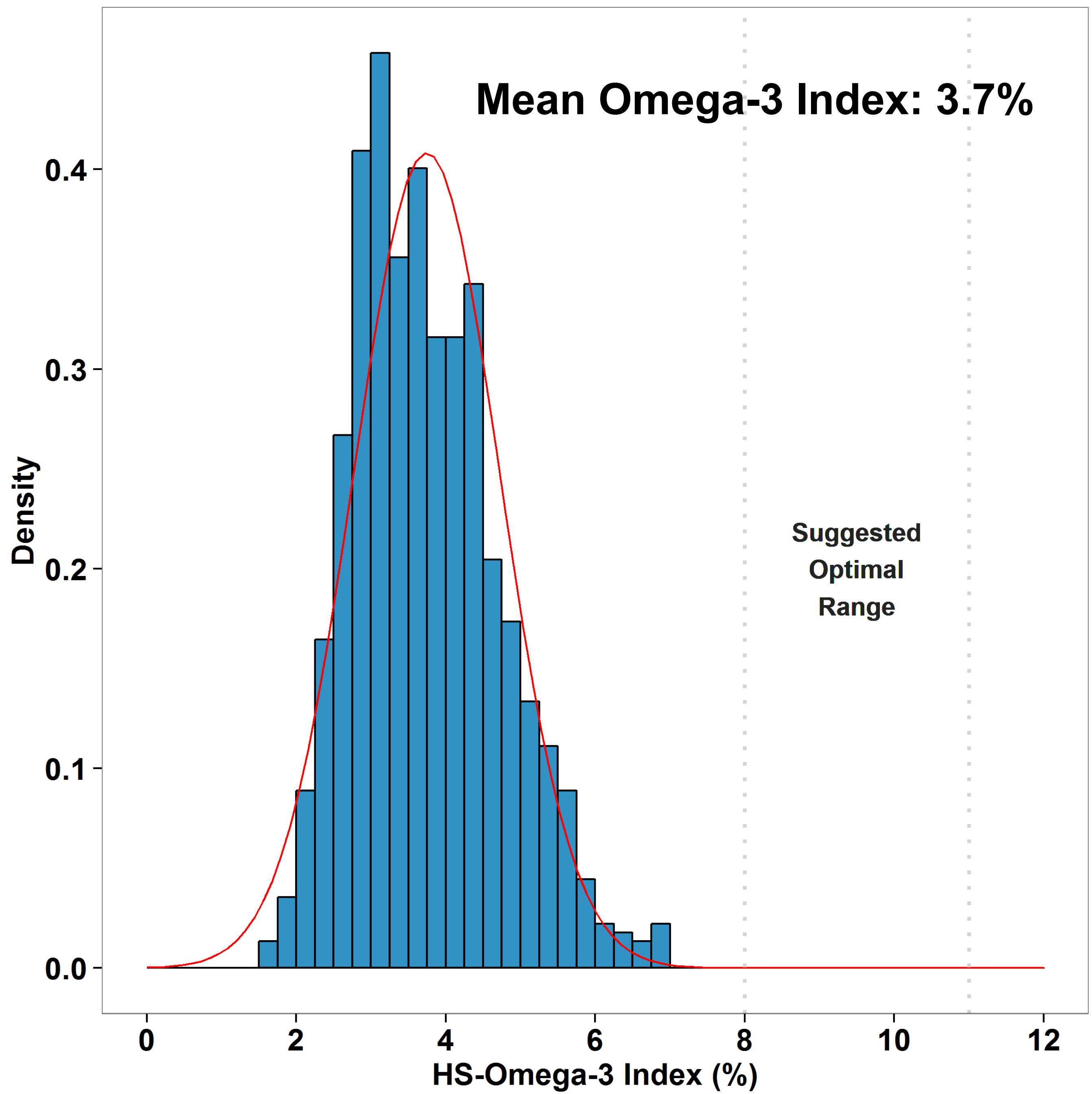
Congestive Heart Failure
HFrEF

Cardiovasc Health Study: Later development CHF
2763 CV Healthy, 10 Y Observation, 555 cases of CHF

Figure. **Nonparametric multivariate-adjusted relationship between plasma phospholipid EPA concentrations and incidence of CHF.**



Mozaffarian et al Ann Int Med 2011;155:160


Mean Omega-3 Index: 3.7%
Suggested
Optimal
Range
Density
0.0
0.1
0.2
0.3
0.4
0
2
4
6
8
10
12
HS-Omega-3 Index (%)

Endpoint Trial

	n-3 PUFA (n=3494)	Placebo (n=3481)
Patients' characteristics		
Age (years)	67 (11)	67 (11)
Age >70 years	1465 (41·9%)	1482 (42·6%)
Women	777 (22·2%)	739 (21·2%)
Heart disease risk factors		
BMI (kg/m²)	27 (5)	27 (5)
SBP (mm Hg)	126 (18)	126 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	72 (13)	73 (14)
Current smoking	502 (14·4%)	485 (13·9%)
History of hypertension	1886 (54·0%)	1923 (55·2%)
NYHA class		
II	2226 (63·7%)	2199 (63·2%)
III	1178 (33·7%)	1187 (34·1%)
IV	90 (2·6%)	95 (2·7%)
LVEF (%)	33·0% (8·5)	33·2% (8·5)
LVEF >40%	333 (9·5%)	320 (9·2%)
Medical history		
Admission for HF in previous year	1746 (50·0%)	1638 (47·1%)
Previous AMI	1461 (41·8%)	1448 (41·6%)
Previous stroke	168 (4·8%)	178 (5·1%)
Diabetes mellitus	992 (28·4%)	982 (28·2%)
CABG	614 (17·6%)	657 (18·9%)
PCI	425 (12·2%)	441 (12·7%)
ICD	248 (7·1%)	249 (7·2%)
Pacemaker	471 (13·5%)	421 (12·1%)
History of atrial fibrillation	682 (19·5%)	643 (18·5%)
Peripheral vascular disease	292 (8·4%)	318 (9·1%)
COPD	740 (21·2%)	793 (22·8%)
Neoplasia	125 (3·6%)	131 (3·8%)
Cause of heart failure		
Ischaemic	1717 (49·1%)	1750 (50·3%)
Dilatative	1053 (30·1%)	972 (27·9%)
Hypertensive	493 (14·1%)	543 (15·6%)
Other	107 (3·1%)	89 (2·6%)
Non-detectable/unknown	124 (3·6%)	127 (3·6%)
Physical examination		
Pulmonary rales	887 (25·4%)	882 (25·3%)
Third heart sound	897 (25·7%)	840 (24·1%)
Mitral insufficiency	2222 (63·6%)	2189 (62·9%)
Aortic stenosis	82 (2·4%)	61 (1·8%)

(Continues in next column)

	n-3 PUFA (n=3494)	Placebo (n=3481)
(Continued from previous column)		
ECG findings		
QRS >120 ms*	1171 (33·9%)	1185 (34·4%)
Atrial fibrillation	573 (16·4%)	567 (16·3%)
Pathological Q waves	797 (22·8%)	807 (23·2%)
Left ventricular hypertrophy	660 (18·9%)	678 (19·5%)
Medical treatment		
ACE inhibitors	2696 (77·2%)	2678 (76·9%)
ARBs	673 (19·3%)	648 (18·6%)
ACE inhibitors/ARBs	3268 (93·5%)	3252 (93·4%)
β blockers	2275 (65·1%)	2247 (64·6%)
Spironolactone	1347 (38·6%)	1393 (40·0%)
Diuretic drugs	3127 (89·5%)	3133 (90·0%)
Digitalis	1296 (37·1%)	1292 (37·1%)
Oral anticoagulant drugs	1027 (29·4%)	982 (28·2%)
Aspirin	1673 (47·9%)	1685 (48·4%)
Other antiplatelet agents	345 (9·9%)	371 (10·7%)
Nitrates	1236 (35·4%)	1236 (35·5%)
Calcium-channel blockers	343 (9·8%)	366 (10·5%)
Amiodarone	668 (19·1%)	690 (19·8%)
Statin (open)	778 (22·3%)	801 (23·0%)

GISSI-HF, Lancet 2008,372:1231

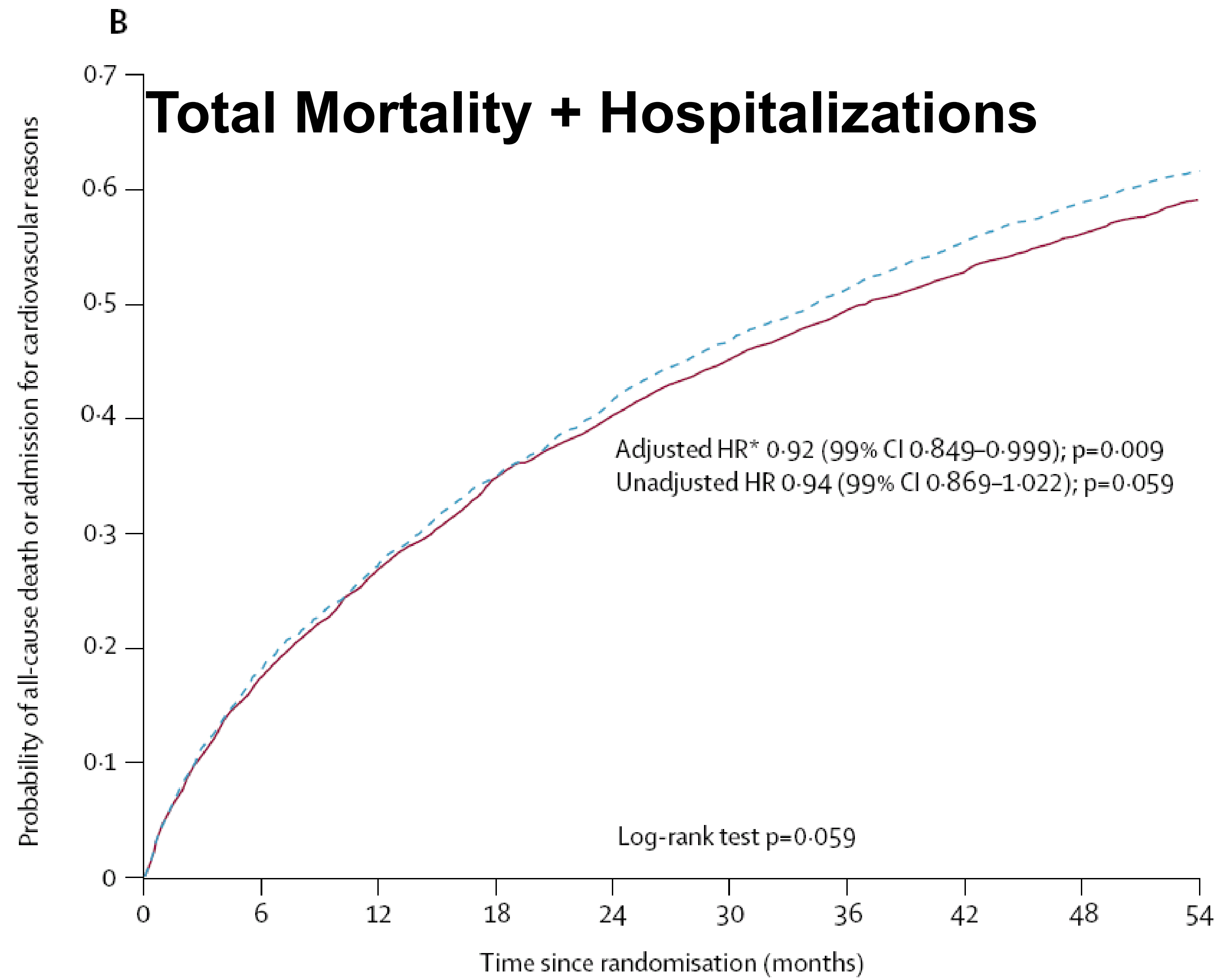
GISSI-HF: HS-Omega-3 Index

	Baseline	3 Months	
Placebo	4.73±1.70	4.81±1.49	
Verum	4.75±1.68	6.73±1.93	p<0.0001

Way below target range of 8 – 11%

Harris et al, Nutr Res 2016;36:989

GISSI-HF: Primary Endpoint



Patients at risk

n-3 PUFA	3494	2876	2543	2261	2066	1896	1718	1342	949	502
Placebo	3481	2846	2518	2251	1826	1826	1640	1254	876	446

GISSI-HF, Lancet 2008,372:1231

	n-3 PUFA (N=3494)	Placebo (N=3481)	p value
Patients permanently discontinuing study treatment	1004 (28·7%)	1029 (29·6%)	0·45
ADR	102	104	
Patients' decision	478	500	
Practitioners' decision	33	41	
Investigators' decision	266	257	
Open label	11	10	
Other	114	117	
Patients permanently discontinuing study treatment due to ADR	102 (2·9%)	104 (3·0%)	0·87
Gastrointestinal disorder	96	92	
Allergic reaction	3	9	
Liver dysfunction	1	1	
Lipid abnormality	0	1	
Hepatocellular jaundice	0	1	
Subdural haematoma	1	0	
Muscle-related symptoms	1	0	
Patients permanently discontinuing study treatment due to serious ADR	1 (<0·1%)	0	
Subdural haematoma	1	0	

PUFA=polyunsaturated fatty acids. ADR=adverse drug reaction.

***Table* 5: Permanent treatment discontinuations and adverse drug reactions**

GISSI-HF, Lancet 2008,372:1231

Summary EPA & DHA in CHF (HFrEF)

Epidemiology: low levels – later CHF

Low HS-Omega-3 Index in CHF

Mechanisms of Action, if HS-Omega-3 Index around 10%

- Heart Rate ↓
- Heart Rate Variability ↑
- LV-Function ↑
- Infarct Size ↓
- Fibrosis ↓
- Ejection Fraction ↑

Parameters of Physical Performance better

Comorbidities better: Depression, Cognition, Quality of Life, asf.

Endpoint Trial positive

Low HS-Omega-3 Index causal for HFrEF

Guidelines positive, no clear Recommendation of Dose

Intake ≠ Uptake

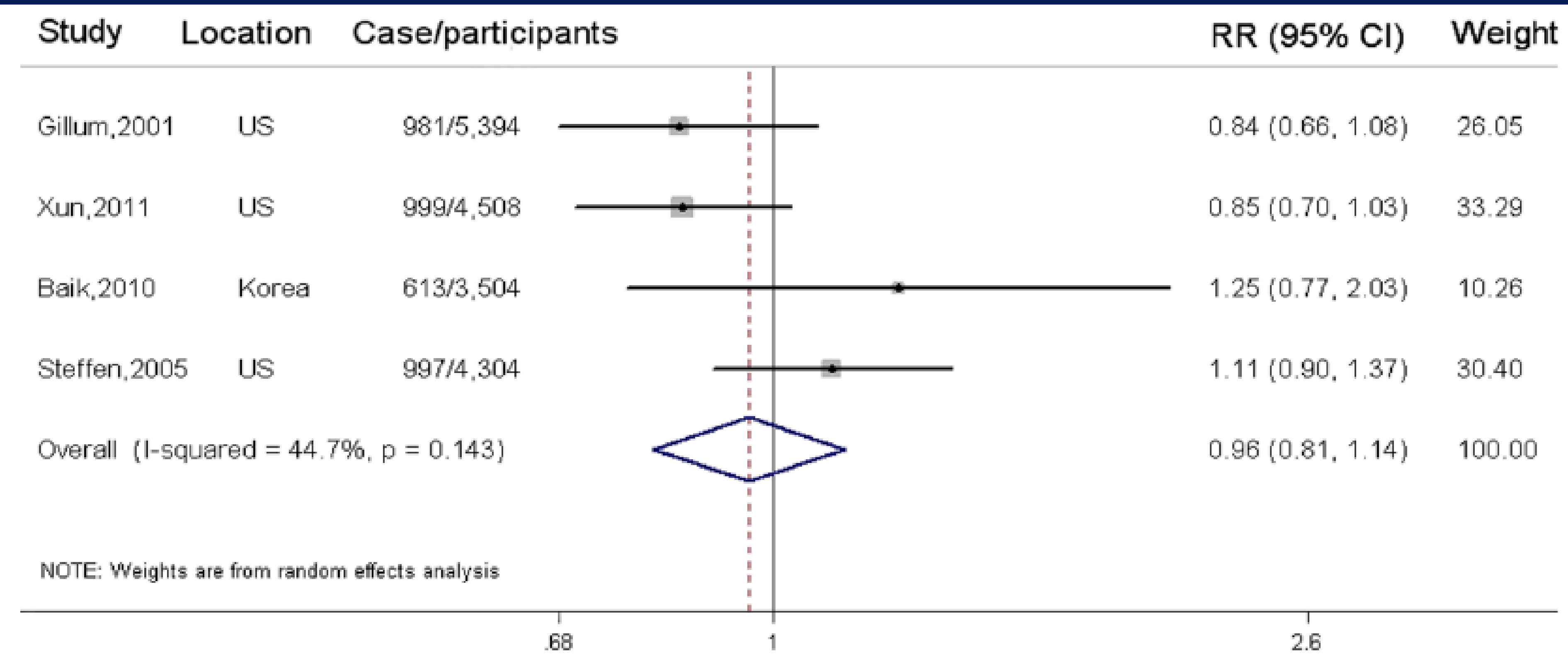
My Suggestion: Aim for HS-Omega-3 Index around 10%

Integrate Omega-3 Index into Clinical Analysis Platform

HFpEF as yet unclear

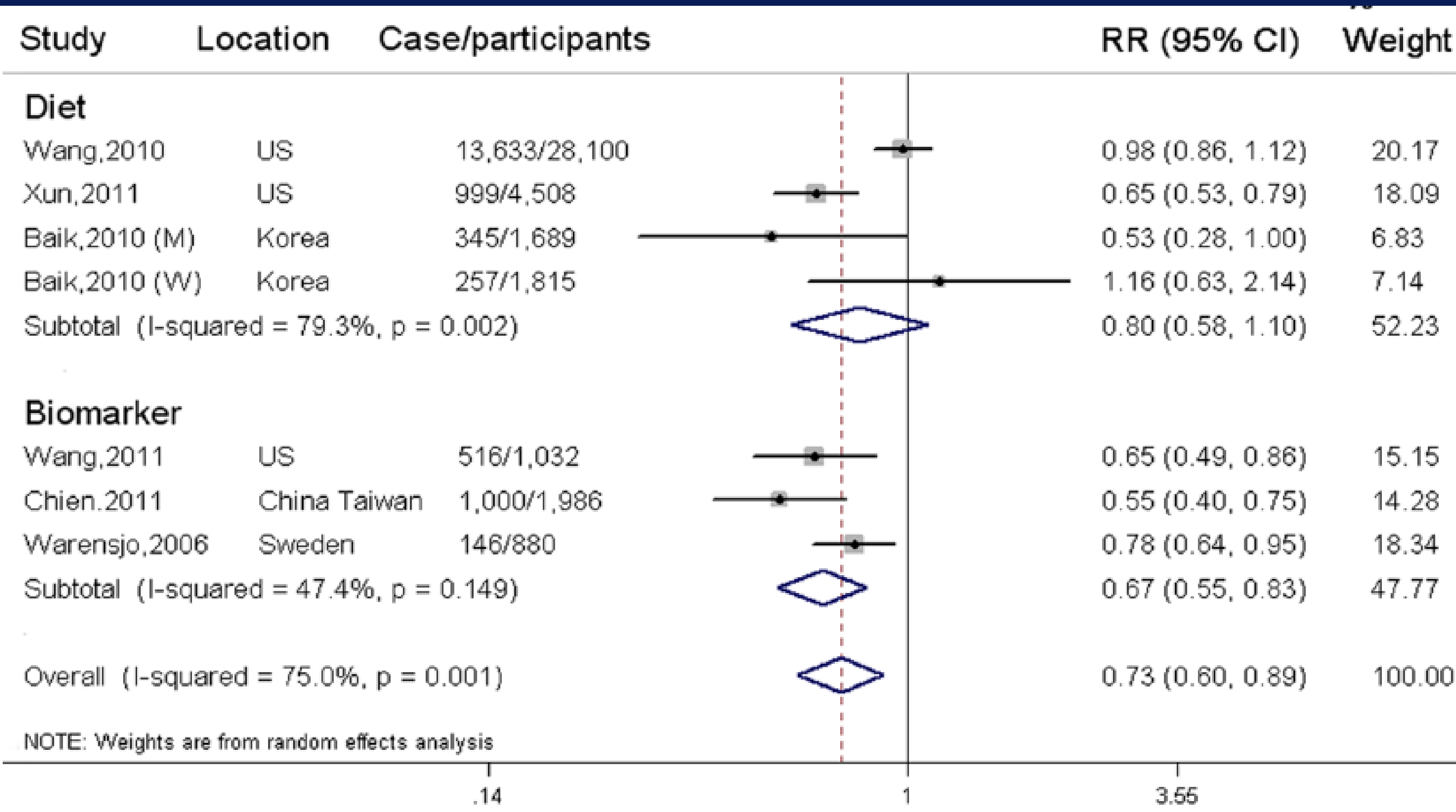
Omega-3 Index and Blood Pressure

No association between fish consumption and elevated blood pressure



Yang et al, Nutrients 2016; 8(1). pii: E58

No association between consumption of EPA and DHA and elevated blood pressure, But association with biomarkers for circulating levels of EPA and DHA



Yang et al, Nutrients 2016; 8(1). pii: E58

Whole blood omega-3 fatty acid concentrations are inversely associated with blood pressure in young, healthy adults

Mark G. Filipovic[a,b], Stefanie Aeschbacher[c], Martin F. Reiner[a,b], Simona Stivala[b], Sara Gobbato[b], Nicole Bonetti[b], Martin Risch[d,e], Lorenz Risch[d,f,g], Giovanni G. Camici[b], Thomas F. Luescher[h], Clemens von Schacky[i], David Conen[c,j], and Juerg H. Beer[a,b]

J Hypertens. 2018;36:1548

TABLE 2. Relationship between fatty acids and blood pressure indices

		Omega-3 Index	Docosahexaenoic acid	Eicosapentaenoic acid	Alpha-linolenic acid
SBP 24-h	Model 1	−3.97 (−6.11; −1.82), $P < 0.001$	−3.71 (−5.49; −1.92), $P < 0.0001$	−0.25 (−1.41; 0.90), $P = 0.66$	−0.21 (−1.38; 0.97), $P = 0.73$
	Model 2	−2.67 (−4.83; −0.51), $P = 0.02$	−2.49 (−4.28; −0.69), $P = 0.007$	−0.25 (−1.41; 0.91), $P = 0.67$	0.18 (−0.98; 1.34), $P = 0.76$
DBP 24-h	Model 1	−3.31 (−4.92; −1.70), $P < 0.0001$	−2.75 (−4.09; −1.41), $P < 0.0001$	−1.00 (−1.86; −0.13), $P = 0.02$	−0.18 (−1.06; 0.71), $P = 0.70$
	Model 2	−2.30 (−3.92; −0.68), $P = 0.005$	−1.90 (−3.25; −0.56), $P = 0.006$	−0.76 (−1.63; 0.11), $P = 0.09$	0.24 (−0.62; 1.11), $P = 0.58$
SBP day	Model 1	−4.02 (−6.25; −1.80), $P < 0.0001$	−3.87 (−5.72; −2.02), $P < 0.0001$	0.07 (−1.27; 1.13), $P = 0.91$	−0.01 (−1.24; 1.21), $P = 0.98$
	Model 2	−2.66 (−4.91; −0.41), $P = 0.02$	−2.57 (−4.44; −0.70), $P = 0.007$	−0.09 (−1.29; 1.12), $P = 0.89$	0.37 (−0.84; 1.57), $P = 0.55$
DBP day	Model 1	−3.38 (−5.09; −1.66), $P < 0.0001$	−2.84 (−4.27; −1.41), $P < 0.0001$	−0.97 (−1.89; −0.05), $P = 0.04$	−0.10 (−1.05; 0.84), $P = 0.83$
	Model 2	−2.22 (−3.95; −0.49), $P = 0.01$	−1.87 (−3.31; −0.43), $P = 0.01$	−0.70 (−1.63; 0.23), $P = 0.14$	0.35 (−0.58; 1.27), $P = 0.46$
SBP night	Model 1	−3.26 (−5.56; −0.96), $P = 0.005$	−2.69 (−4.61; −0.78), $P = 0.006$	−0.97 (−2.20; 0.27), $P = 0.12$	−0.64 (−1.90; 0.62), $P = 0.32$
	Model 2	−2.02 (−4.35; 0.31), $P = 0.09$	−1.64 (−3.58; 0.30), $P = 0.10$	−0.68 (−1.93; 0.57), $P = 0.29$	−0.23 (−1.47; 1.01), $P = 0.72$
DBP night	Model 1	−2.70 (−4.36; −1.04), $P = 0.001$	−2.12 (−3.50; −0.74), $P = 0.003$	−1.07 (−1.96; −0.18), $P = 0.02$	−0.28 (−1.19; 0.63), $P = 0.55$
	Model 2	−2.14 (−3.84; −0.45), $P = 0.01$	−1.71 (−3.11; −0.30), $P = 0.02$	−0.84 (−1.74; 0.07), $P = 0.07$	0.04 (−0.87; 0.94), $P = 0.93$
Systolic conventional BP	Model 1	−3.98 (−6.38; −1.58), $P = 0.001$	−3.47 (−5.47; −1.48), $P = 0.0007$	−0.81 (−2.10; 0.48), $P = 0.22$	0.63 (−0.69; 1.94), $P = 0.35$
	Model 2	−2.81 (−5.22; −0.40), $P = 0.02$	−2.46 (−4.46; −0.46), $P = 0.02$	−0.62 (−1.91; 0.67), $P = 0.34$	0.98 (−0.31; 2.26), $P = 0.14$
Diastolic conventional BP	Model 1	−2.78 (−4.58; −0.98), $P = 0.003$	−2.12 (−3.63; −0.62), $P = 0.006$	−1.07 (−2.04; −0.10), $P = 0.03$	0.26 (−0.72; 1.25), $P = 0.60$
	Model 2	−1.86 (−3.68; −0.04), $P = 0.05$	−1.41 (−2.93; 0.11), $P = 0.07$	−0.72 (−1.70; 0.25), $P = 0.15$	0.67 (−0.31; 1.64), $P = 0.18$

$n = 2036$; data are β-coefficients (95% confidence intervals). Fatty acid variables were used as a log-transformed variable. Model 1 was adjusted for age and sex; Model 2 was additionally adjusted for BMI, smoking status, glycated hemoglobin A1c, educational status, fruit/vegetable consumption, physical activity, estimated glomerular filtration rate, high-sensitivity C-reactive protein, alcohol consumption. BP, blood pressure.

Filipovic al, J Hypertens. 2018;36:1548

Meta-Analysis Intervention Trials on CV Risk Factors

Table 2 Pooled effects of eicosapentaenoic acid and/or docosahexaenoic acid supplementation on risk factors associated with cardiovascular disease

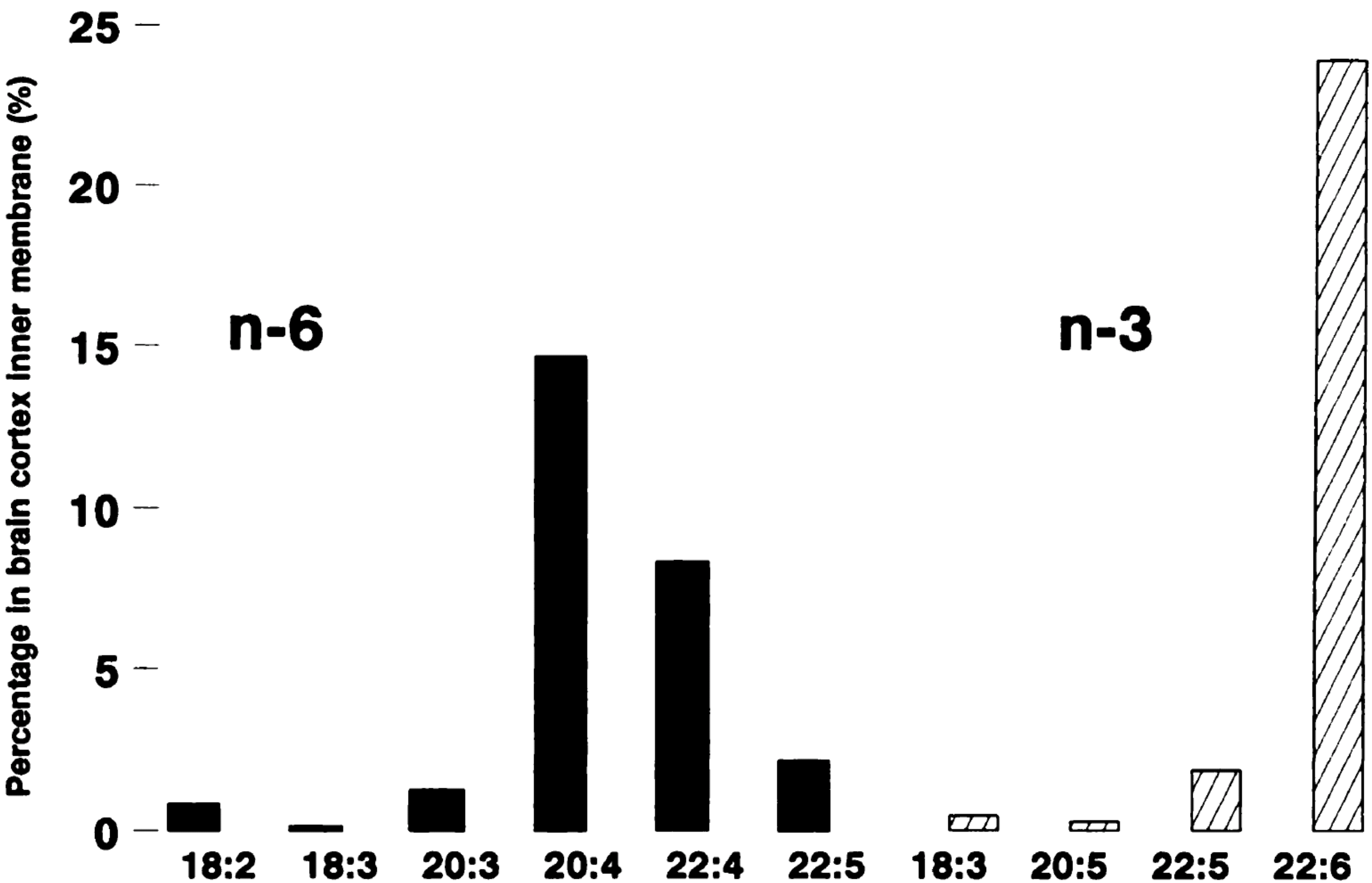
Outcome	Number of studies	Effect size (95% CI)	*P*-value*	Test of heterogeneity† *Q*-value	*P*-value	I^2
Total cholesterol (mmol L^{-1})	108	−0.051 (−0.166, 0.064)	0.387	1440.211	0.0001	92.57
LDL-cholesterol (mmol L^{-1})	100	0.150 (0.058, 0.243)	0.001	1270.903	0.0001	92.21
HDL-cholesterol (mmol L^{-1})	110	0.039 (0.024, 0.054)	0.0001	204.740	0.0001	46.76
Triglycerides (mmol L^{-1})	110	−0.368 (−0.427, −0.309)	0.0001	508.295	0.0001	80.34
Systolic blood pressure (mmHg)	50	−2.195 (−3.172, −1.217)	0.0001	109.009	0.0001	56.88
Diastolic blood pressure (mmHg)	50	−1.08 (−1.716, −0.444)	0.0001	123.045	0.0001	61.80
Heart rate (bpm)	26	−1.37 (−2.415, −0.325)	0.01	68.661	0.0001	63.58
C-reactive protein (mg L^{-1})	20	−0.343 (−0.454, −0.232)	0.0001	926.382	0.0001	97.95
Tumor necrosis factor α (pg mL^{-1})	11	−0.277 (−0.661, 0.108)	0.159	21.771	0.016	54.07
Fibrinogen (g L^{-1})	14	−0.032 (−0.146, 0.082)	0.584	21.229	0.069	38.76
Platelet count ($\times 10^3$)	9	−1.110 (−11.367, 9.146)	0.832	13.865	0.085	42.30
Soluble intercellular adhesion molecule-1 (ng mL^{-1})	9	−0.054 (−0.219, 0.108)	0.515	20.084	0.010	60.16
Soluble vascular cell adhesion molecule-1 (ng mL^{-1})	9	−8.112 (−23.507, 7.283)	0.302	10.449	0.235	23.44
Flow-mediated dilation (%)	6	1.460 (−0.475, 3.395)	0.139	28.657	0.0001	82.55

*For meta-analysis: $P < 0.05$ was considered statistically significant.
†For heterogeneity assessment: $P < 0.1$ for Q test or I^2 >50% was considered to indicate significant heterogeneity across the studies.
CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

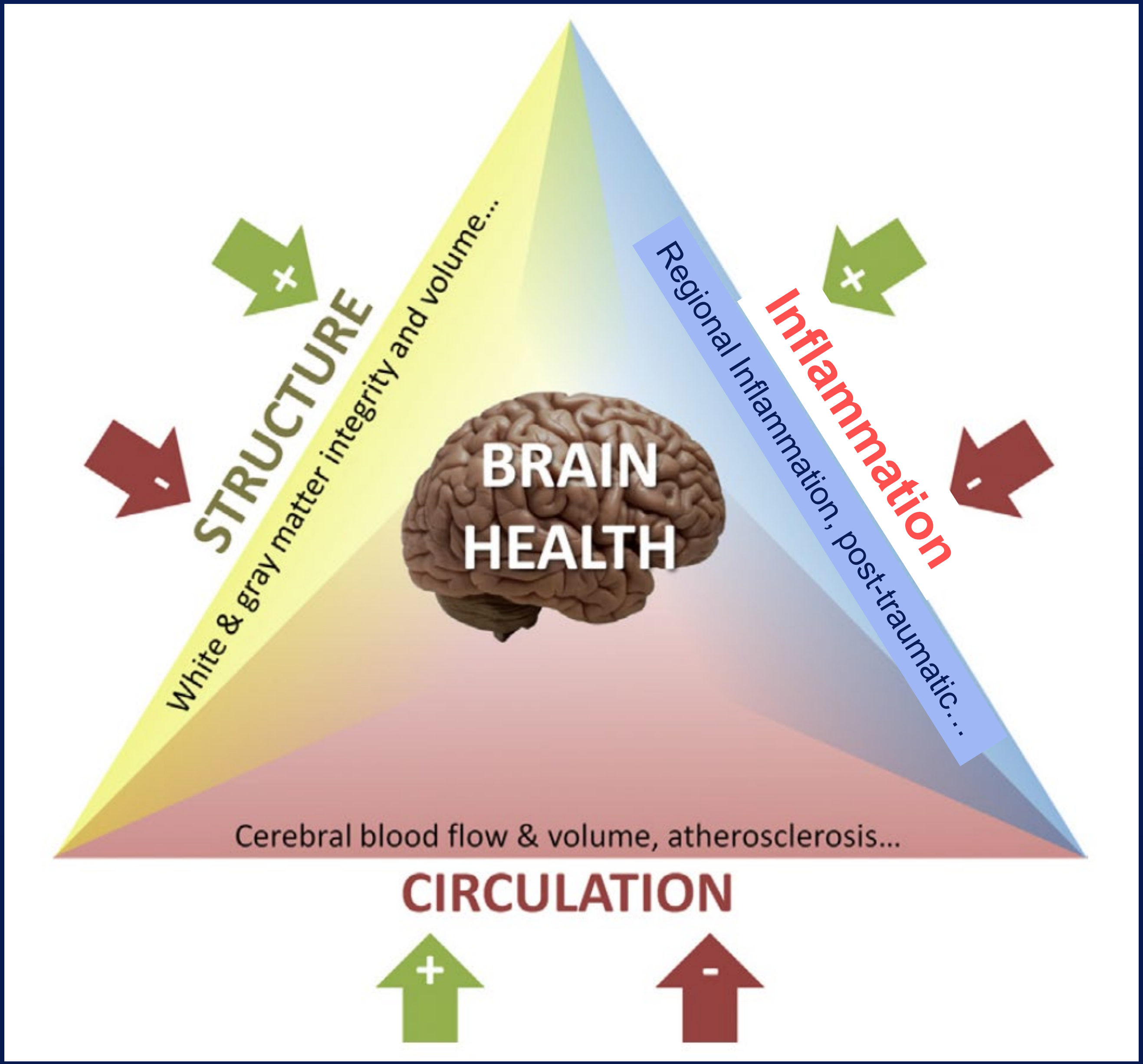
Abumweis et al J Human Nutr Diet 2018;31:67

Brain

Fatty Acids in Human Brain

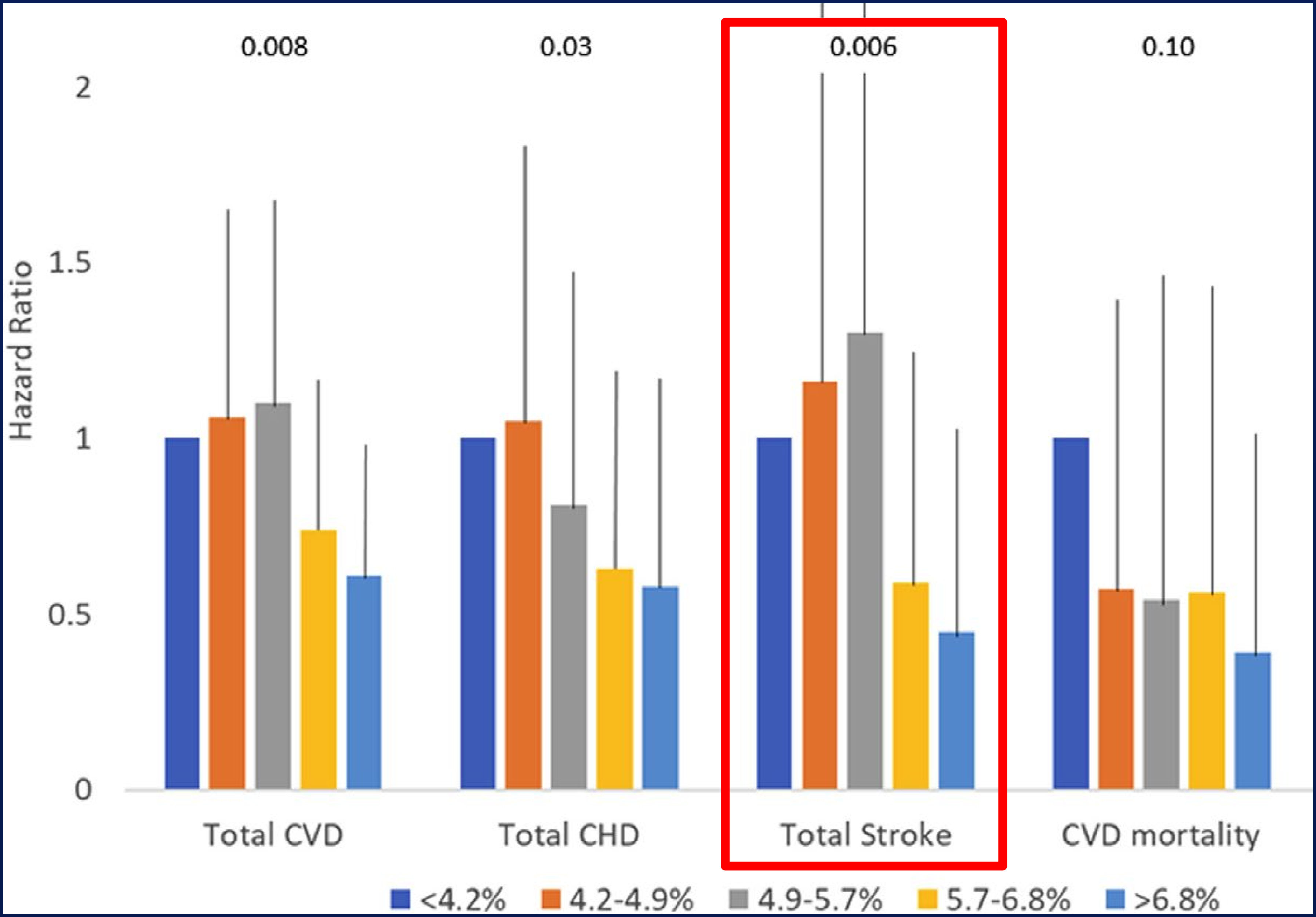


Crawford MA et al Am J Clin Nutr 1997:66:1032S-41S



Modified from Haast RA, PLEFA 2015;92C:3

Omega-3 Index and Cardiovascular Events in Framingham



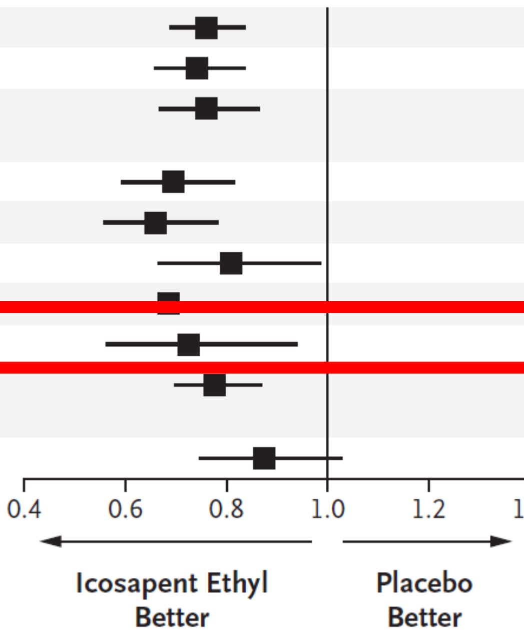
Harris et al, J Clin Lipidol. 2018;12:718

REDUCE-IT

RCT with 8179 Participants with CV Risiko, all on Statin

4 g EPA-Ethylester vs. Placebo, 4.9 Years mean Study Duration

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



28% Risk Reduction Stroke, p<0.01

Bhatt et al, N Engl J Med 2018, e-pub Nov 10

Cognition

HS-Omega-3 Index and Executive Function in 4-Year olds assessed as „Dimensional change card sort“

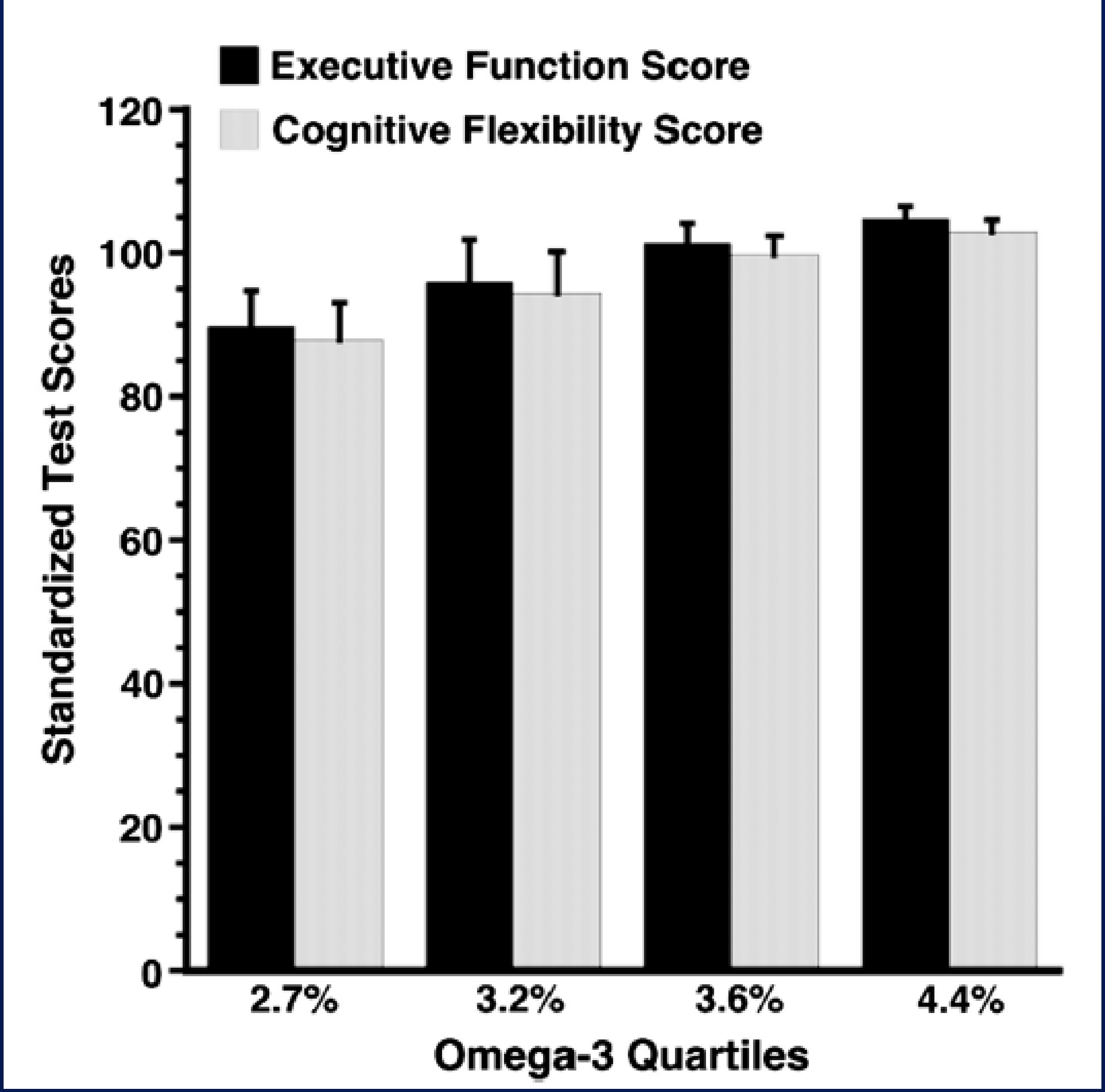
Regression results for performance on the dimensional change card sort test and selected fatty acids (FA). (Model: Total pass = Fatty acid of All Children + Age + BAZ + Hemoglobin)

Class	Fatty acid	Regression results for total pass (n=307)	
		B ± SE	*P*
	Alpha-linolenic	1.04±0.70	.14
	Eicosapentanoic	0.27±0.32	.40
n-3 FA	Docosahexaenoic	0.25±0.13	**.06**
	Omega-3 Index	0.17±0.09	**.07**
	Total n-3[b]	0.17±0.09	**.07**

Adjepong et al, J Nutr Biochem. 2018;57:287-293

Correlation HS-Omega-3 Index and Cognition

Mean Age
31.4+7.4 Jahre



Johnston et al Nutr Neurosci 2013;16:30

HS-Omega-3 Index, Brain Volume and Cognitive Function in Framingham

Quartile 1 vs. 2-4

Model	Covariates	Total Cerebral Brain Volume (%)	**Visual Memory**	**Executive Function**	**Abstract Thinking**
		Low Index = smaller Volume*	**Low Index = Worse 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 total cholesterol	**p=0.011**	p=0.079	p=0.108	**p=0.001**

n = 1575; Age = 67

*equivalent to approx. 2 years normal brain ageing

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

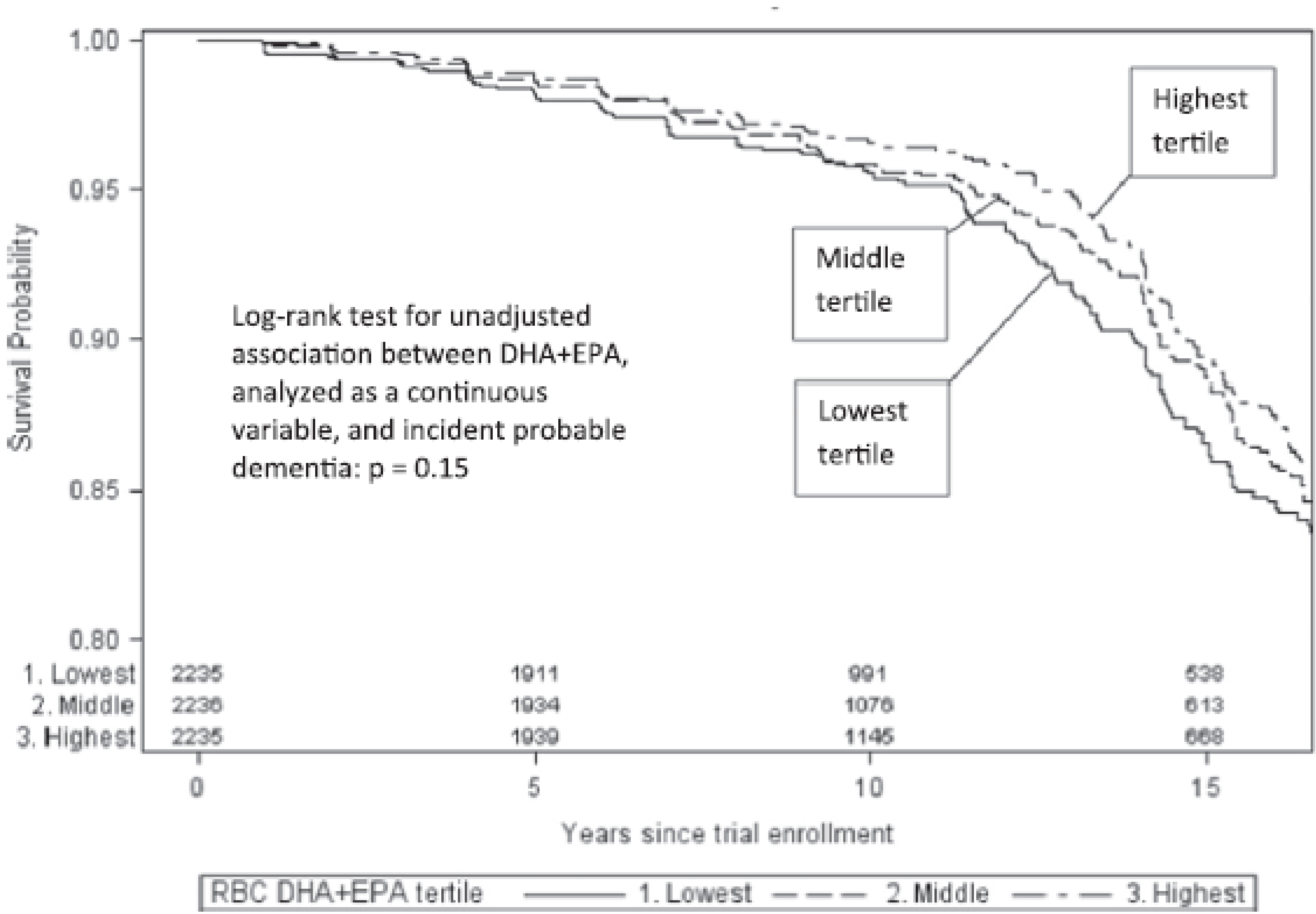
Risk for cognitive Impairment in the Elderly depends on Omega-3 Index
Data from KORA-Age-2 (95%CI)
Mean Omega-3 Index high Tertile: 8.09±1.02%

Omega-3 Index	Model 1	Model 2	Model 3	Model 4
Low	1.77 (1.15-2.73)*	1.77 (1.13-2.71)*	1.77 (1.14-2.75)*	1.77 (1.14-2.76)*
Mean	0.85 (0.53-1.38)	0.84 (0.52-1.36)	0.85 (0.52-1.39)	0.86 (0.53-1.40)
High	Ref.	Ref.	Ref.	Ref.
Age				
77-88	2.24 (1.51-3.32)**	2.25 (1.52-3.33)**	2.05 (1.36-3.07)*	2.05 (1.37-3.09)*
≥88	4.90 (2.59-9.25)**	4.85 (2.56-9.18)**	4.14 (2.15-7.98)**	4.15 (2.16-8.01)**

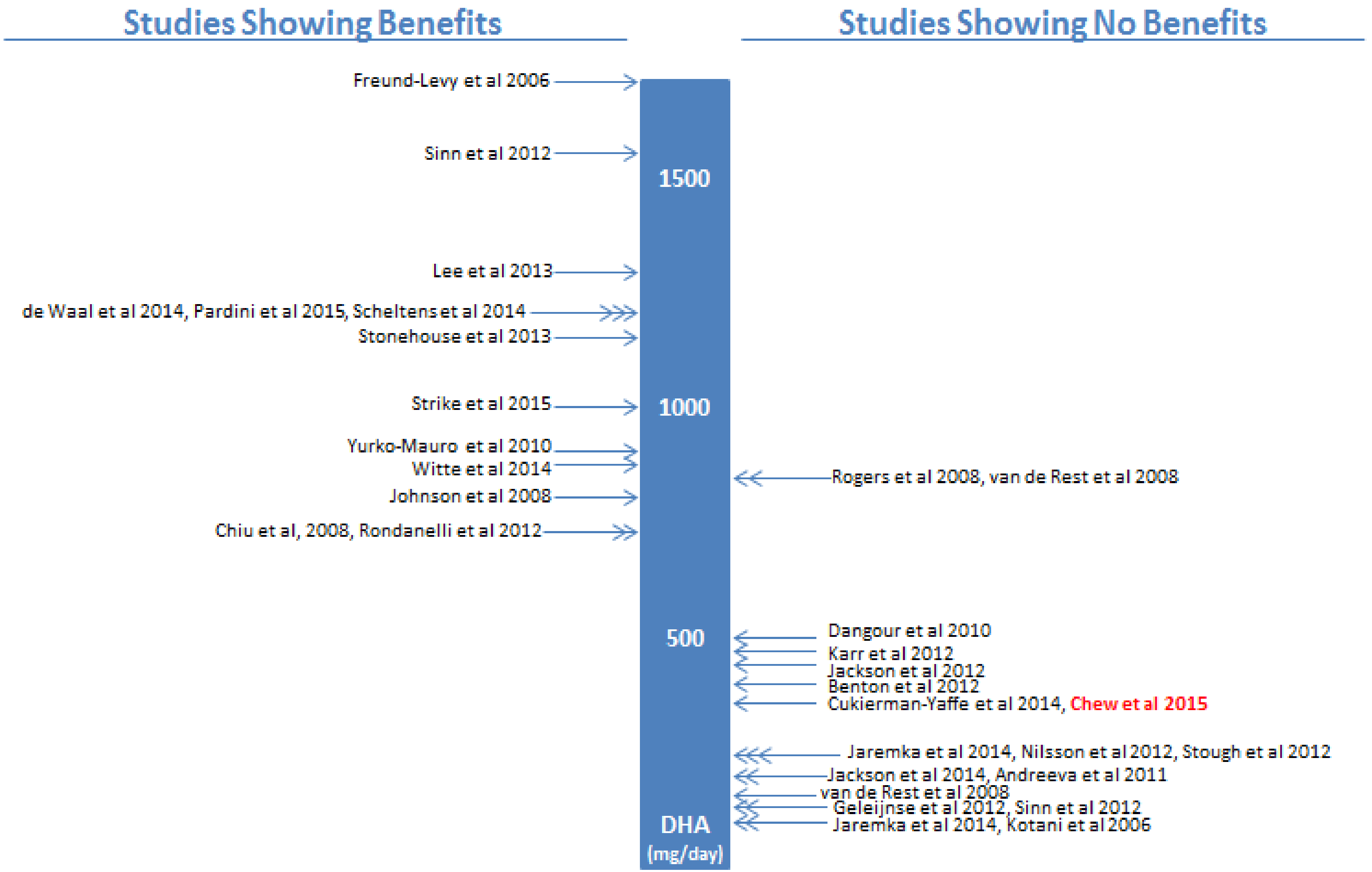
*$p<0.05$, ***$p<0,0001$. Model 1 was adjusted for age and sex, model 2 was additionally adjusted for education, model 3 additionally for metabolic risk factors (obesity, actual hypertension, hyper-cholesterolemia, smoking, physical inactivity) and model 4 additionally for depression and anxiety.

Lukaschek et al, Dementia Geriatr Cogn Dis 2016;42:236

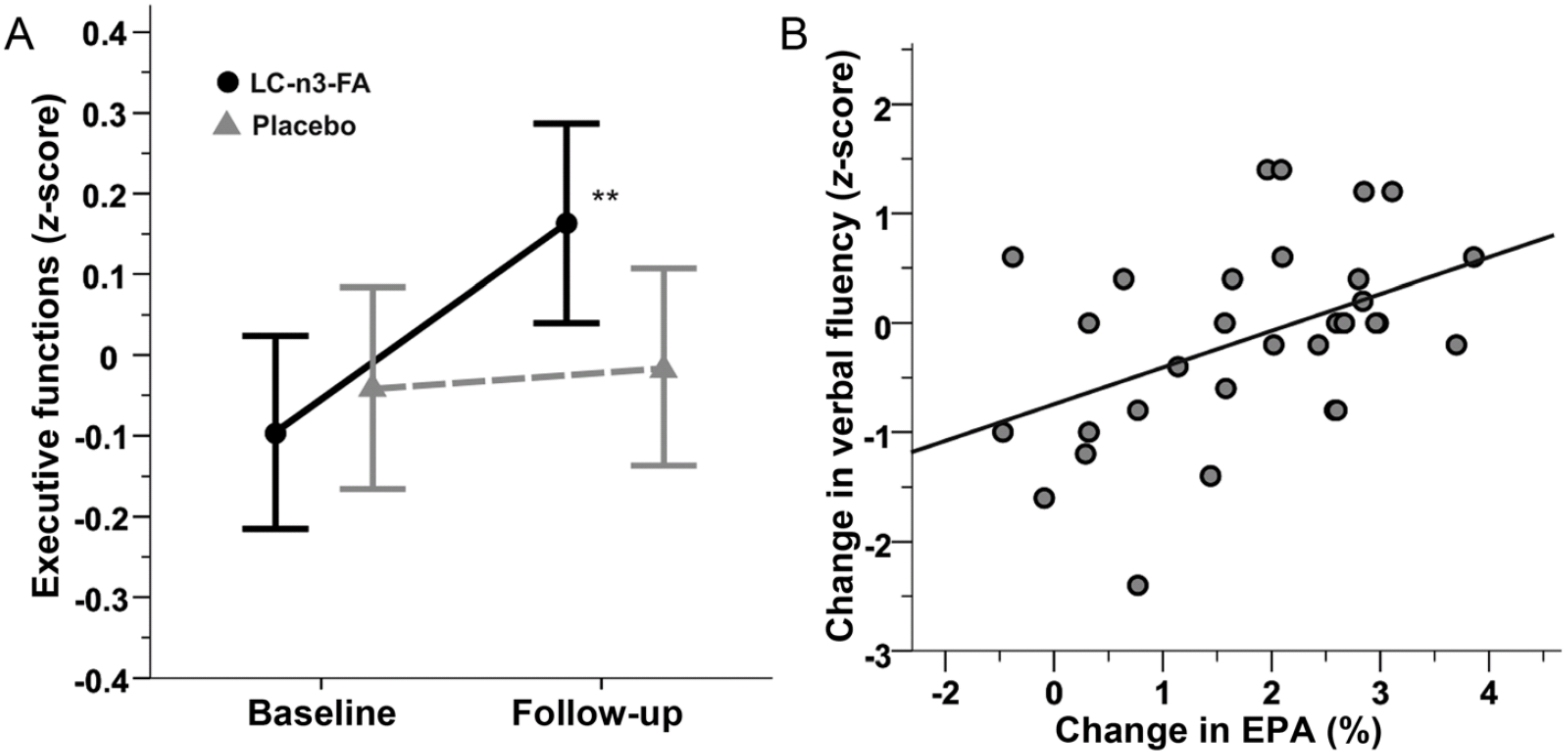
Women's Health Initiative Memory Study: 6706 Women >65, 10 J FU, 587 getting dementia



Omega-3 Cognitive Function Studies and Their Outcomes Sorted by DHA Dosage

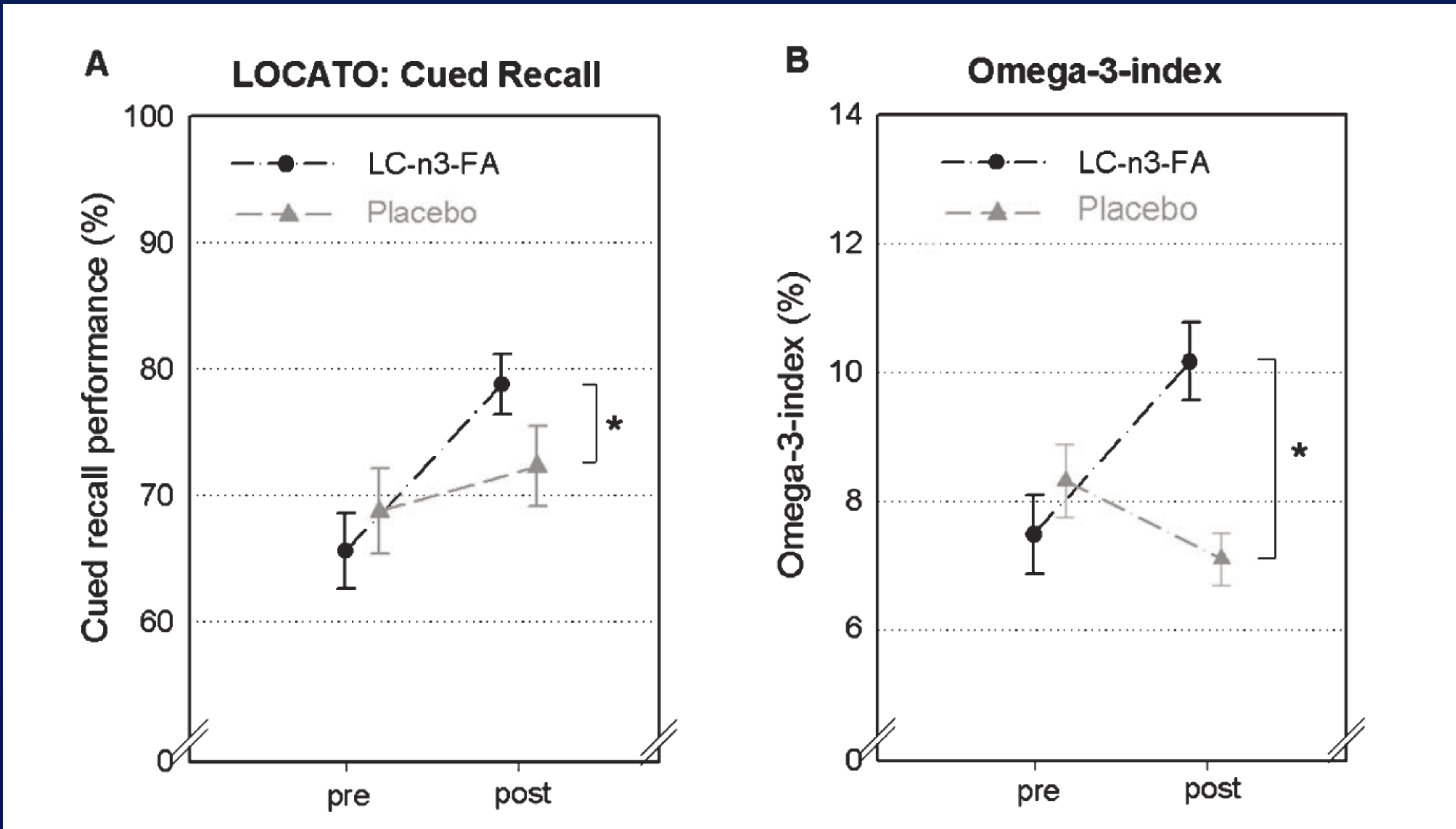


Correlation Improvement Executive Function and Omega-3 Index



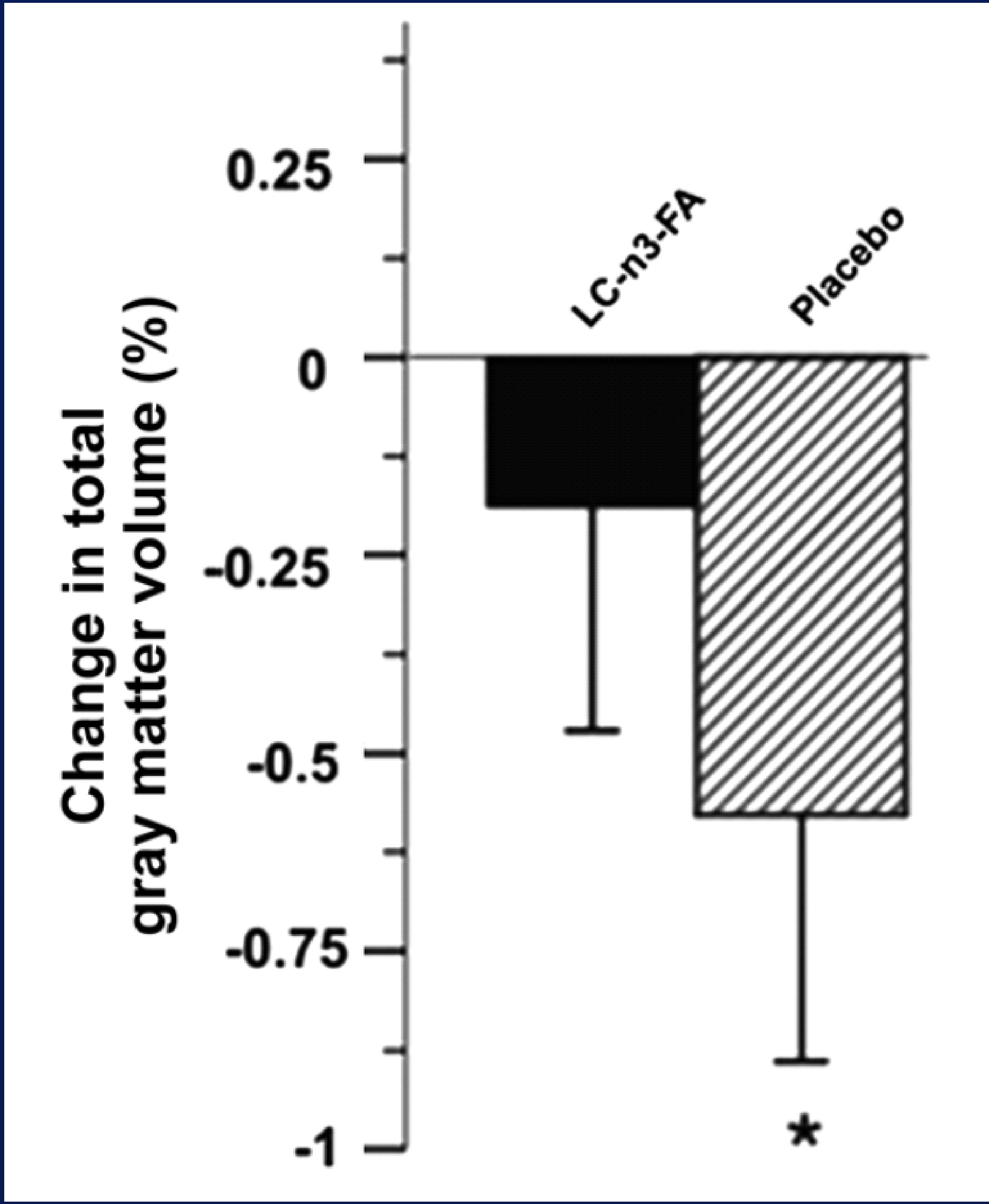
Witte et al, Cereb Cortex 2014;24:3059-68

Correlation Memory Improvement and Omega-3 Index



Külzow et al, J Alzheimers Dis 2016;51:713-25

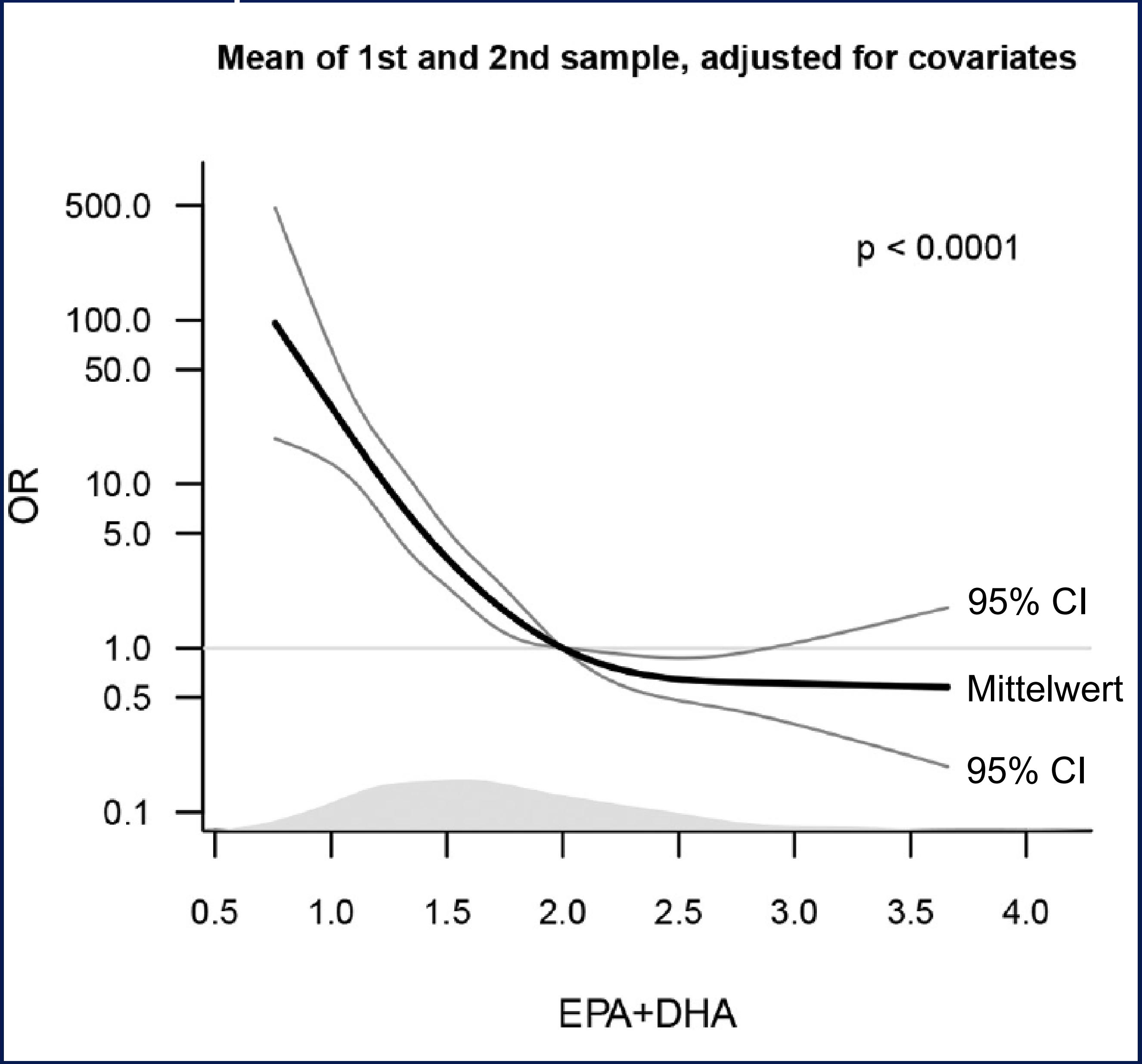
„Age-dependent“ Loss of Brain Structure



Witte et al, Cereb Cortex 2014;24:3059-68

Pregnancy

Likelihood Premature Birth <week 34
As dependent on Plasma EPA & DHA



Olsen et al, EBioMedicine 2018;35:325

Cochrane Meta-Analysis

Gestational Age	+1.67 days (95% CI 0.95 to 2.39)
	41 RCT’s, 12 517 pregnant Women
Low Birth Weight	15.6% vs. 14%; RR 0.90, (95% CI 0.82 btois 0.9
	15 RCT’s, 8 449 pregnant Women
Perinatal Death of Child	RR 0.75 (95% CI 0.54 to 1.03);
	10 RCT’s, 7 416 pregnant Women

Middleton et al, Cochrane Database Syst Rev. 2018 Nov 15;11:CD003402

Cochrane Meta-Analysis – Premature Birth

< Week 37	13.4% vs. 11.9% (RR 0.89 (95% CI 0.81 to 0.97)	
	26 RCT's, 10 304 pregnant Women;	
< Week 34	4.6% vs. 2.7% (RR 0.58, 95% CI 0.44 to 0.77)	
	9 RCT's, 5 204 pregnant Women	

Middleton et al, Cochrane Database Syst Rev. 2018 Nov 15;11:CD003402

Cochrane Meta-Analysis.

Practical Conclusion:

A universal Supplementation can make Sense,

Although, with better knowledge, it should be aimed

for women benefitting the most.

Middleton et al, Cochrane Database Syst Rev. 2018 Nov 15;11:CD003402

HS-Omega-3 Index in Pregnancy and Lactation representative Study in Germany

	Pregnant	Lactating	no Suppl.	with Suppl.
Omega-3 Index	6.62±1.39	5.57±1.39	6.04±1.39	7.73±1.28
Range	3.81-11.10	2.49-9.24	2.49-11.10	4.61-11.08
			85%	15%

Gellert et al, PLEFA 2016;109:22

Other Health Issues depending on Omega-3 Index

Perinatal Mortality
Perinatal Complications
Post-Partum Depression
Major Depression
Bipolar Depression
Suicide
Burn-out
PTSD
ADHD
Autism / ASD
Some chronic inflammatory diseases
Muscle
Age-related Muscle loss
NAFLD
others

Tolerability and Safety

	n-3 PUFA (N=3494)	Placebo (N=3481)	p value
Patients permanently discontinuing study treatment	1004 (28·7%)	1029 (29·6%)	0·45
ADR	102	104	
Patients' decision	478	500	
Practitioners' decision	33	41	
Investigators' decision	266	257	
Open label	11	10	
Other	114	117	
Patients permanently discontinuing study treatment due to ADR	102 (2·9%)	104 (3·0%)	0·87
Gastrointestinal disorder	96	92	
Allergic reaction	3	9	
Liver dysfunction	1	1	
Lipid abnormality	0	1	
Hepatocellular jaundice	0	1	
Subdural haematoma	1	0	
Muscle-related symptoms	1	0	
Patients permanently discontinuing study treatment due to serious ADR	1 (<0·1%)	0	
Subdural haematoma	1	0	

PUFA=polyunsaturated fatty acids. ADR=adverse drug reaction.

Table 5: **Permanent treatment discontinuations and adverse drug reactions**

GISSI-HF, Lancet 2008,372:1231

HS-Omega-3 Index can safely be increased

by increasing intake.

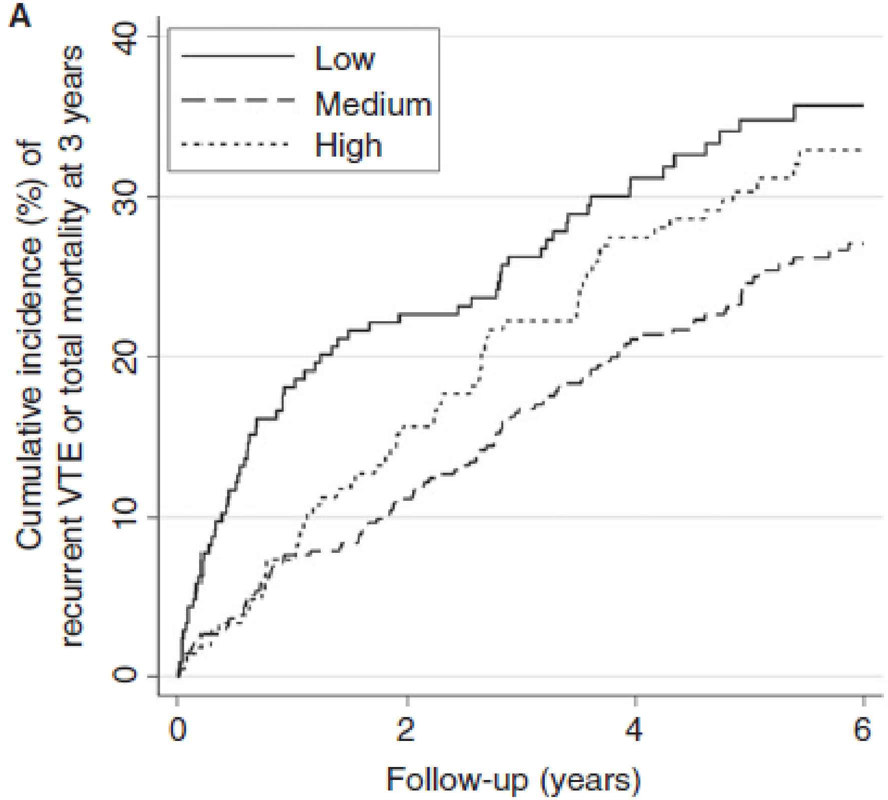
EFSA: up to 5 g / day EPA+DHA

FDA: up to 3 g / day safe.

Tolerability and Bioavailability maximized,

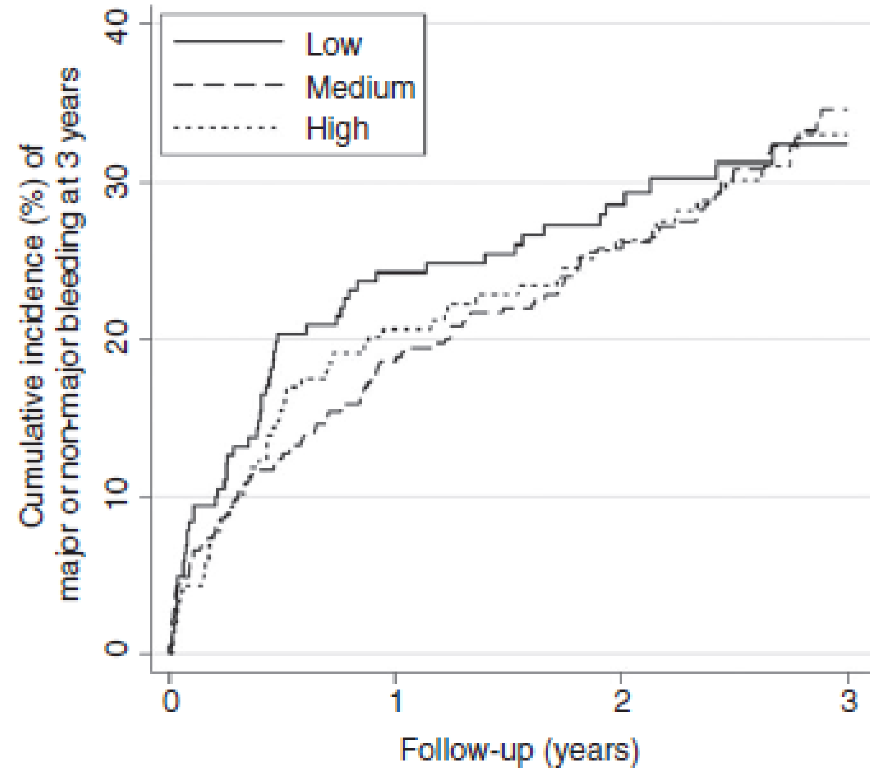
if taken with main meal.

Switco65+: 826 Patienten after Thromboembolic Event, all anticoagulated, 3 Years Observation



Number at risk

Low	207	152	102	54
Medium	412	350	265	124
High	207	171	129	47



Number at risk

Low	207	132	90	46
Medium	412	297	227	98
High	207	150	121	45

Reiner et al, J Thromb Haemostas 2017;17:47

JELIS: RCT in 19 466 Hyperlipidemics, ± cardiovasc. Disease, 9326 Participants 1,8 g / Tag EPA in Japan 9319 Controls, Mean Follow-up 4.6 Years.

	Control (n=9319)	EPA (n=9326)	p value
Common adverse experiences			
Pain (joint pain, lumbar pain, muscle pain)	180 (2·0%)	144 (1·6%)	0·04
Gastrointestinal disturbance (nausea, diarrhoea, epigastric discomfort)	155 (1·7%)	352 (3·8%)	<0·0001
Skin abnormality (eruption, itching, exanthema, eczema)	65 (0·7%)	160 (1·7%)	<0·0001
Haemorrhage (cerebral, fundal, epistaxis, subcutaneous)	60 (0·6%)	105 (1·1%)	0·0006

JELIS, Yokoyama et al 2007;369:1090

REDUCE-IT

RCT with 8 179 Participants with cardiovascular Risk, all on Statin
4 g EPA-Ethylester vs. Placebo
4.9 Years Study Duration

Supplementary Table 8. Assessment of Serious Bleeding Treatment-Emergent Adverse Events by Category and by Preferred Term.

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P Value[1]
Patients with Bleeding-Related Disorders[2]	111 (2.7%)	85 (2.1%)	0.06
By Category			
Gastrointestinal Bleeding[3]	62 (1.5%)	47 (1.1%)	0.15
Central Nervous System Bleeding[4]	14 (0.3%)	10 (0.2%)	0.42
Other Bleeding[5]	41 (1.0%)	30 (0.7%)	0.19

Bhatt et al, N Engl J Med 2018, e-pub Nov 10

Safety and Tolerability

Avoid daily Doses > 3 – 5 g say FDA - EFSA
Large interindividual variability in uptake
My suggestion: Avoid Omega-3 Index >16% - 17%
small bleeding risk
according to JELIS & REDUCE-It

European Food Safety Authority

Authorized Claims for Omega-3's

DHA and EPA contribute to the normal function of the heart

DHA and EPA contribute to the maintenance of normal blood pressure

DHA and EPA contribute to the maintenance of normal blood triglyceride levels

DHA contributes to maintenance of normal blood triglyceride levels efsa

European Food Safety Authority

Authorized Claims for Omega-3‘s

DHA contributes to maintenance of normal brain function

DHA contributes to the maintenance of normal vision

DHA maternal intake contributes to the normal brain development of the foetus and breastfed infants

DHA maternal intake contributes to the normal development of the eye of the foetus and breastfed infants

Summary

No human life without EPA&DHA
There is a world-wide deficit in EPA&DHA
can only be diagnosed with standardized Fatty Acid Analysis (HS-Omega-3 Index)
Deficit cannot be corrected with ALA, DHA must be ingested
Symptoms of a deficit are

- Reduced Life Expectancy
- Sudden Cardiac Death
- Cardiovascular Diseases
- Congestive Heart Failure
- Ischemic Stroke
- Impaired Cognition
- Major Depression
- Premature Birth and perinatal Complications
- Elevated Blood PRessure
- Many others

For Pregnancy, major Depression, cardiovascular Diseases, Congestive Heart Failure
Guidelines recommend EPA&DHA
Many Intervention Trials not positive for methodologic Reasons:
Bioavailability, Baseline Levels, inter-individual Variability in Uptake asf
Omega-3 Index up to 16% safe, small Bleeding Risk at higher levels (0,1%/Year)
Deficit in EPA&DHA, when Omega-3 Index <8%

Conclusion

A suboptimal HS-Omega-3 Index (<8%) identifies Individuals needing the Contribution of EPA&DHA to Health.

Safety and Tolerability of EPA&DHA make an optimal HS-Omega-3 Index (8 – 11%)
Safer than a lower HS-Omega-3 Index.

Some things we learned with the Omega-3 Index

Ankara, Dec 04, 2019

Prof. Dr. C. von Schacky, FESC
Preventive Cardiology
Med Clinic and Policlinic I
Ludwig Maximilians-University Munich
Clemens.vonSchacky@med.uni-muenchen.de
and Omegametrix, Martinsried
c.vonschacky@omegametrix.eu

Intake ≠ Uptake

Table 1 Recommen[illegible]ded intakes of EPA + DHA by cohort and organization

Cohort	Source	Daily recomme[illegible]on
General health		
Adults	[illegible]epartment of Agriculture	≥2[illegible]g
Adults	Europe[illegible]od Safety Agency	[illegible]250 mg
Adults	World Health [illegible]ization:	≥250 mg
Adults	Academy of Nutritio[illegible] Dietetics	≥500 mg
Adults without CHD	American Heart Association	~500 mg (fatty fish ≥ 2 times/week)
Adults	International Society for the Study [illegible]tty A[illegible]nd Lipids	≥500 mg
Pregnancy		
Pregnant/lactating	International Society for the St[illegible] Fatty Acid[illegible] Lipids	≥500 mg (≥300 mg DHA)
Pregnant/lactating	European Food Safety A[illegible]y	≥250 mg (100 to 200 mg DHA)
Heart disease and inflammatory disorders		
CHD	American [illegible] Association	~1 g
Patients with high TG	Am[illegible] Heart Association	[illegible] g
Generally viewed as safe upper limit[illegible]		
Population	US Food and Drug Administration	≤3 g EPA + D[illegible]
Population	European Safety Authority	5 g EPA + DHA

CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TG, triglyceride.

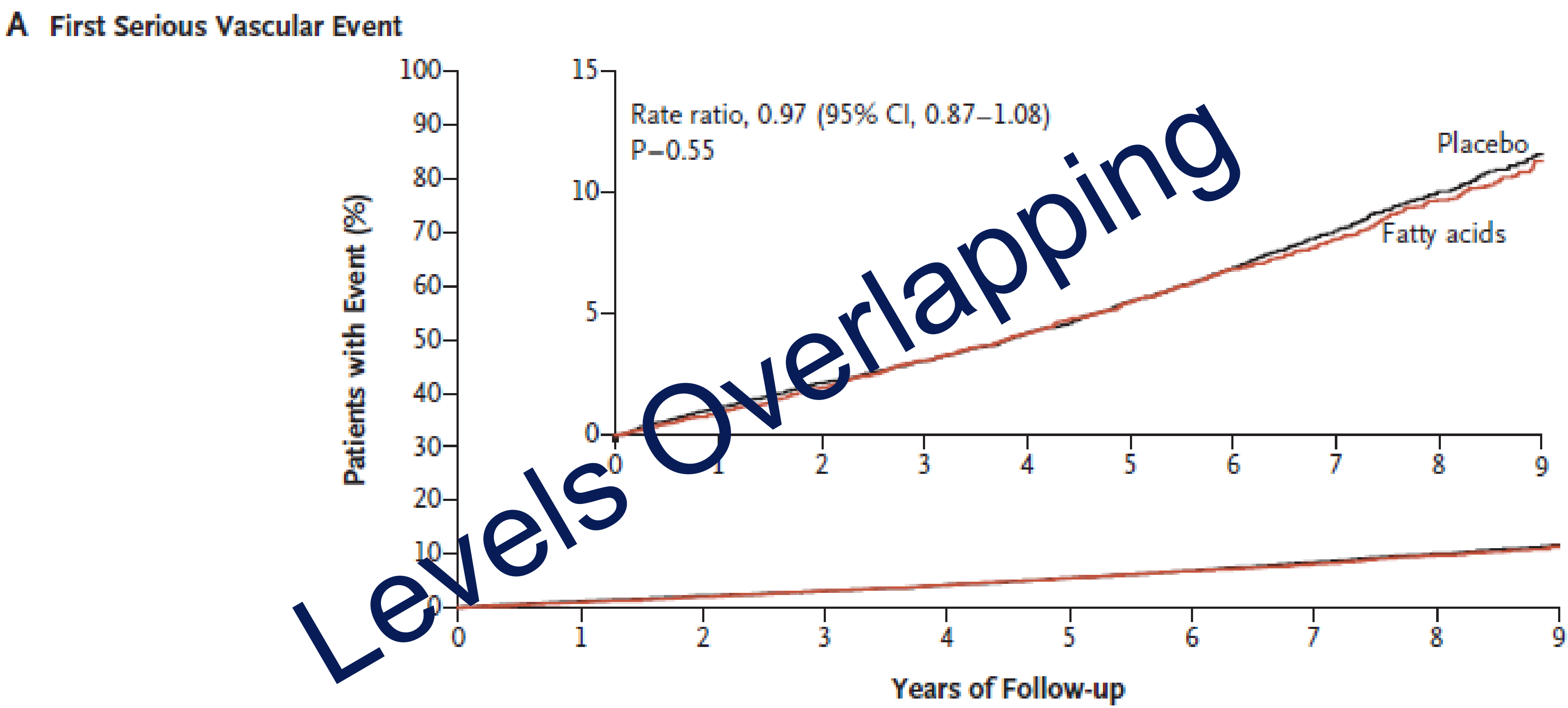
Fabian et al, Breast Canc Res 2015;17:62

ASCEND: RCT in 15480 Diabetics without cardiovascular Disease

Of them 7740 daily 410 mg EPA + 340 mg DHA –Ethylester in Capsule

7740 daily 1 g Olive Oil in Capsule

Mean Follow-up 7.4 Years



No. at Risk										
Placebo	7740	7627	7503	7377	7222	7047	5792	3934	2224	1428
Fatty acids	7740	7646	7519	7369	7218	7050	5804	3922	2198	1430

ASCEND N Engl J Med 2018, e-pub Aug 26

Vital

RCT with 25 871 Participants

460 mg EPA plus 380 mg DHA –Ethylester

vs. Placebo

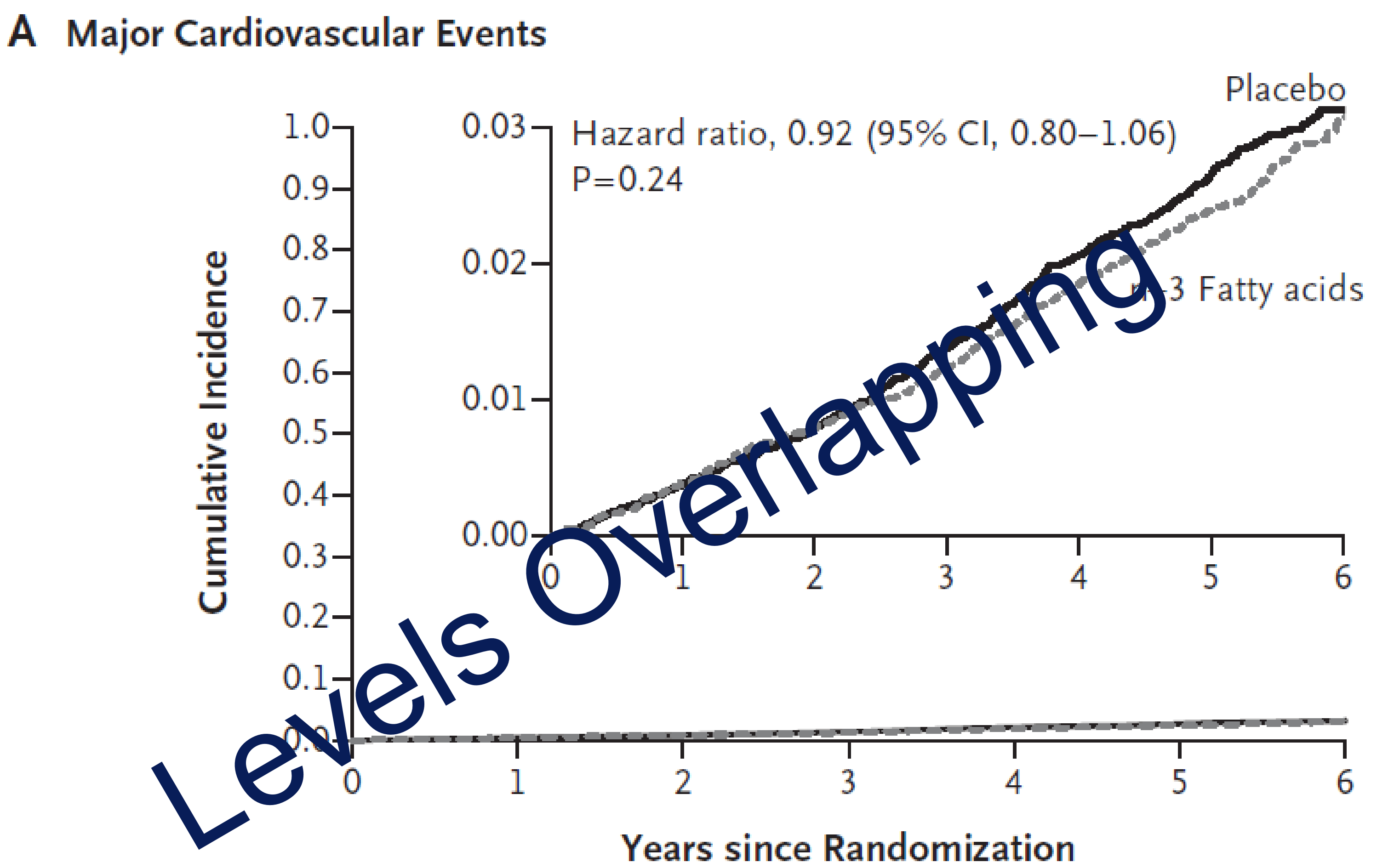
5.3 Years mean Trial Duration

Primary End Point: MACE

CV Death, Myocardial Infarction, Stroke

Manson et al, N Engl J Med 2018, e-pub Nov 10

Vital Results



No. at Risk

Placebo	12,938	12,862	12,745	12,592	12,281	9825	775
n–3 Fatty acids	12,933	12,842	12,725	12,594	12,322	9878	765

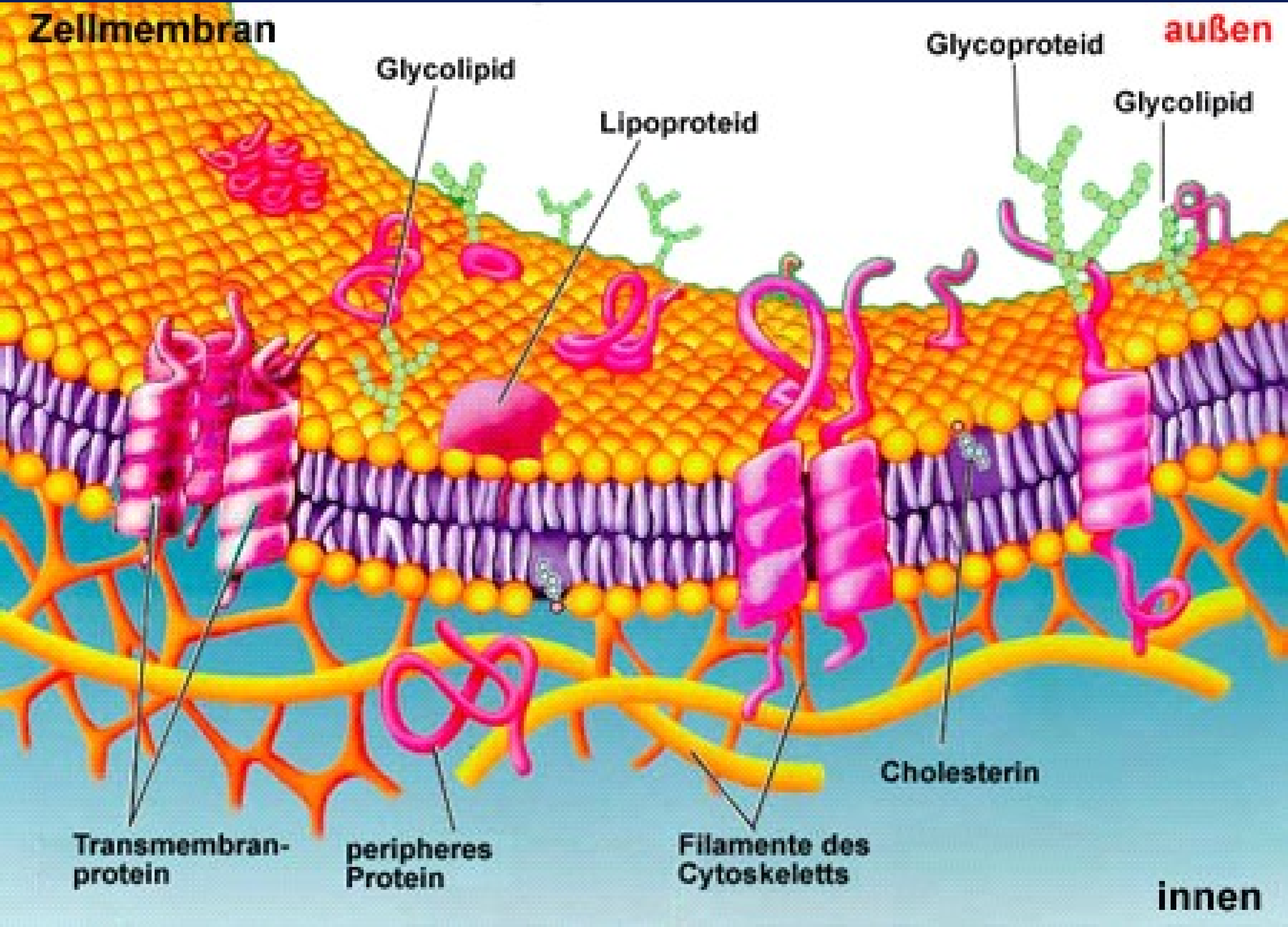
Manson et al, N Engl J Med 2018, e-pub Nov 10

Myth

Food supplements are generally not needed by healthy persons on a balanced diet. With a balanced diet the body obtains all nutrients needed.

Reality: Wrong with Omega-3 Deficit

http://www.bfr.bund.de/de/gesundheitliche_bewertung_von_nahrungsergaenzungsmitteln-945.html



Zellmembran
außen
Glycolipid
Glycoproteid
Glycolipid
Lipoproteid
Cholesterin
Transmembran-
protein
peripheres
Protein
Filamente des
Cytoskeletts
innen

Conventional Nomenclature of Fatty Acids

Conventional Method

in Nutritional Epidemiology:

Food Frequency Questionnaire

Approx. 50% Data plausible

Saturated

Mono-unsaturated

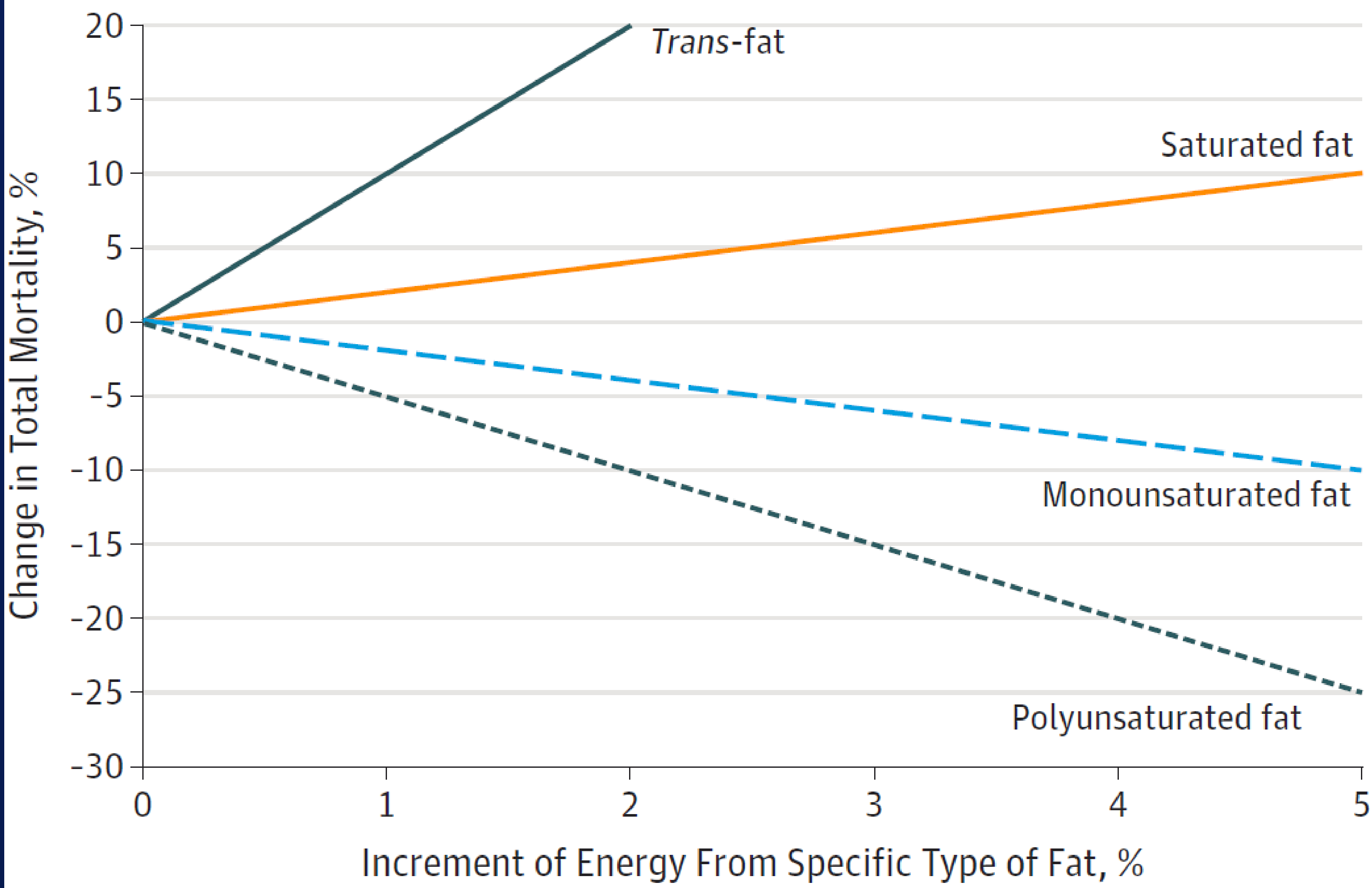
Poly-unsaturated

omega-6

omega-3

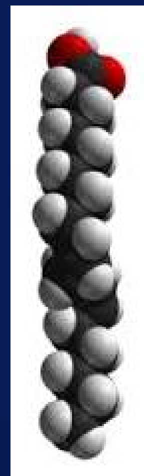
Trans Fatty Acids

Figure 1. Change in Total Mortality Associated With Increases in the Percentage of Energy From Specific Types of Fat

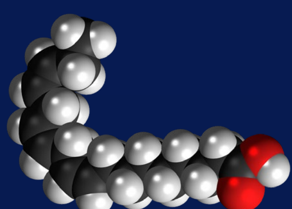


Wang et al JAMA Int Med 2016; e-pub Juli 5

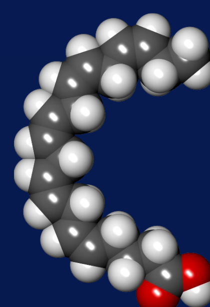
Linoleic Acid, C18:2ω-6



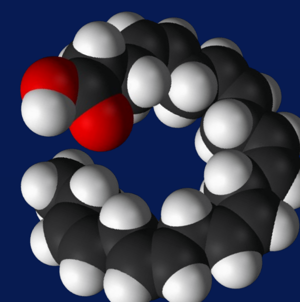
Arachidonic Acid, C20:4ω-6



Alpha-Linolenic Acid C18:3ω-3

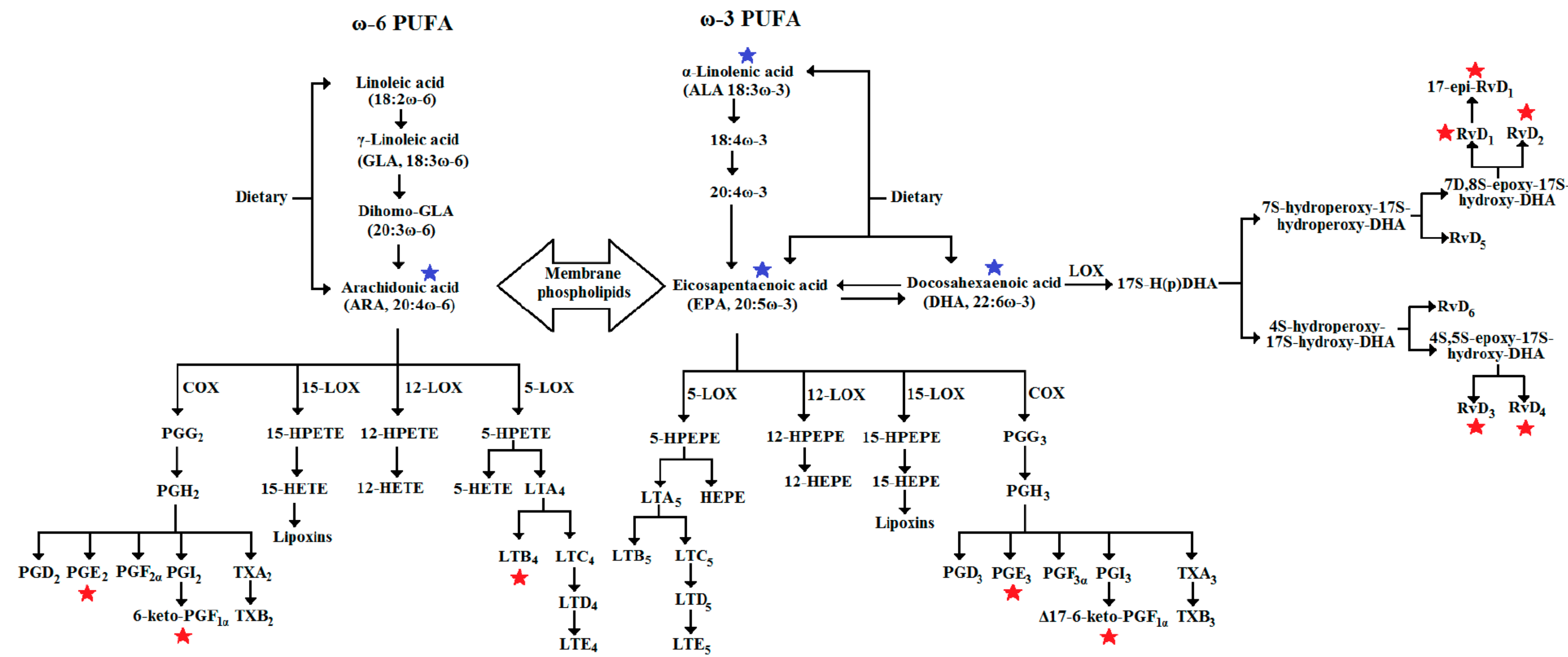


Eicosapentaenoic Acid C20:5ω-3



Docosahexaenoic Acid C22:6ω-3

A small Selection of biologically active Metabolites of AA, EPA und DHA



Alpha-Linolenic Acid: Energy Generation

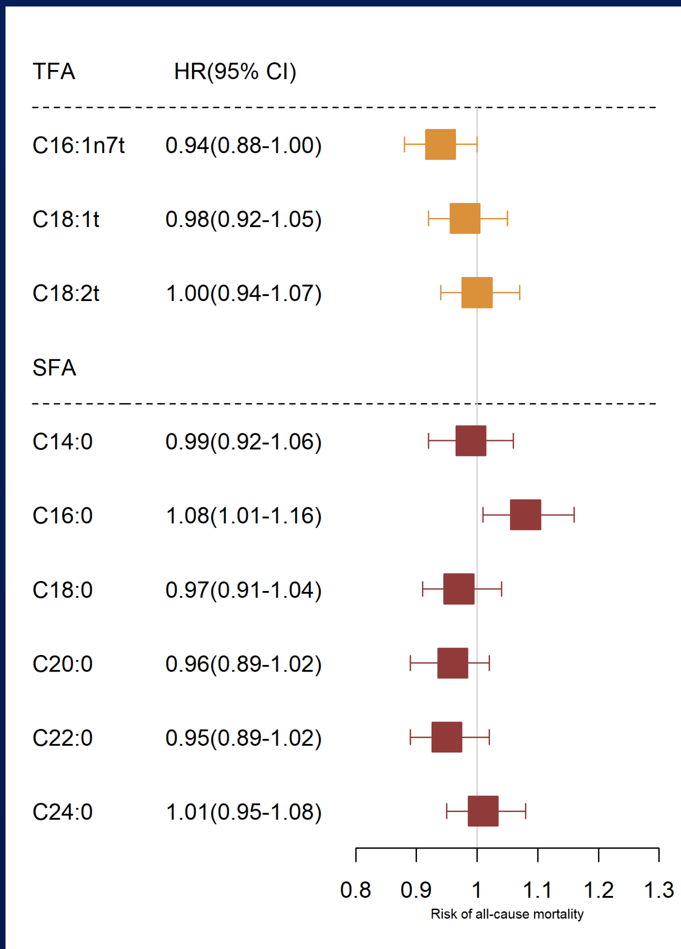
Araujo P et al Nutrients. 2019;11(5)

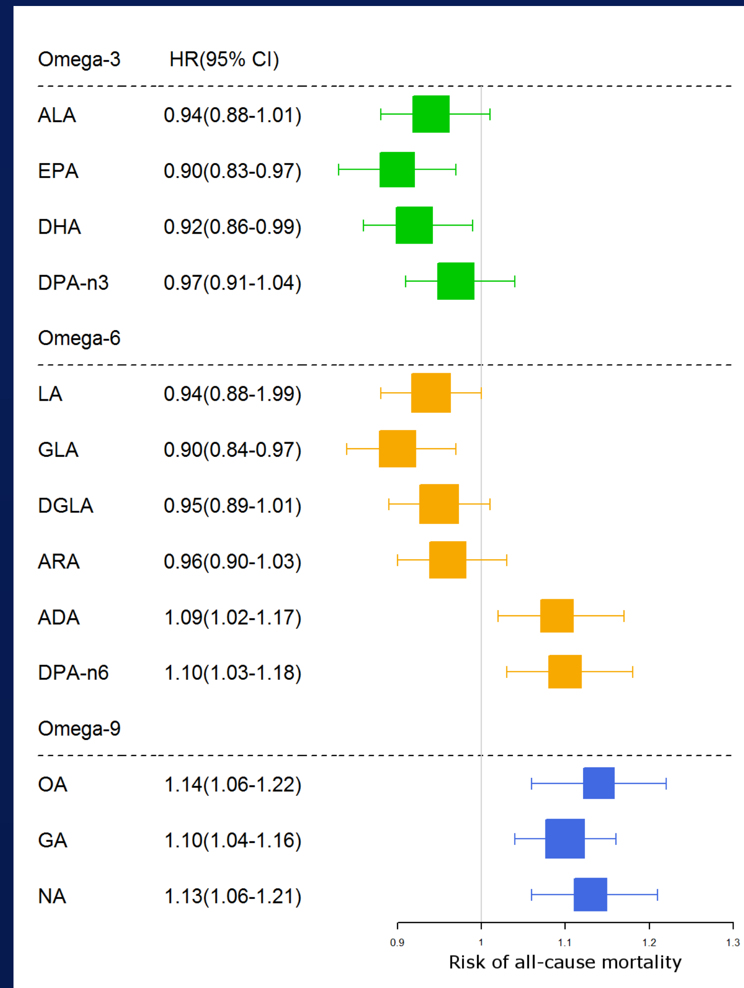
α-LNA, EPA, DHA

	α-LNA	EPA	DHA
Platelet Aggregation	-	⇩	⇩
Blood Pressure	-	⇩	⇩
Endothelial Function	-	⇧	⇧
Triglycerides	⇧	⇩	⇩
HDL(2) (29 %)	⇩	-	⇧
LDL (8%)	⇧	-	⇧

von Schacky JCI 1985, 76:2446 Mori TA et al Hypertension. 1999, 34:253
Mori TA et al . Circulation. 2000, 102:1264 Mori TA et al . Am J Clin Nutr 2000, 71:1085
Mori TA et al . Am J Clin Nutr. 2000, 71:1085 Finnegan YE et al Am J Clin Nutr 2003,77:783

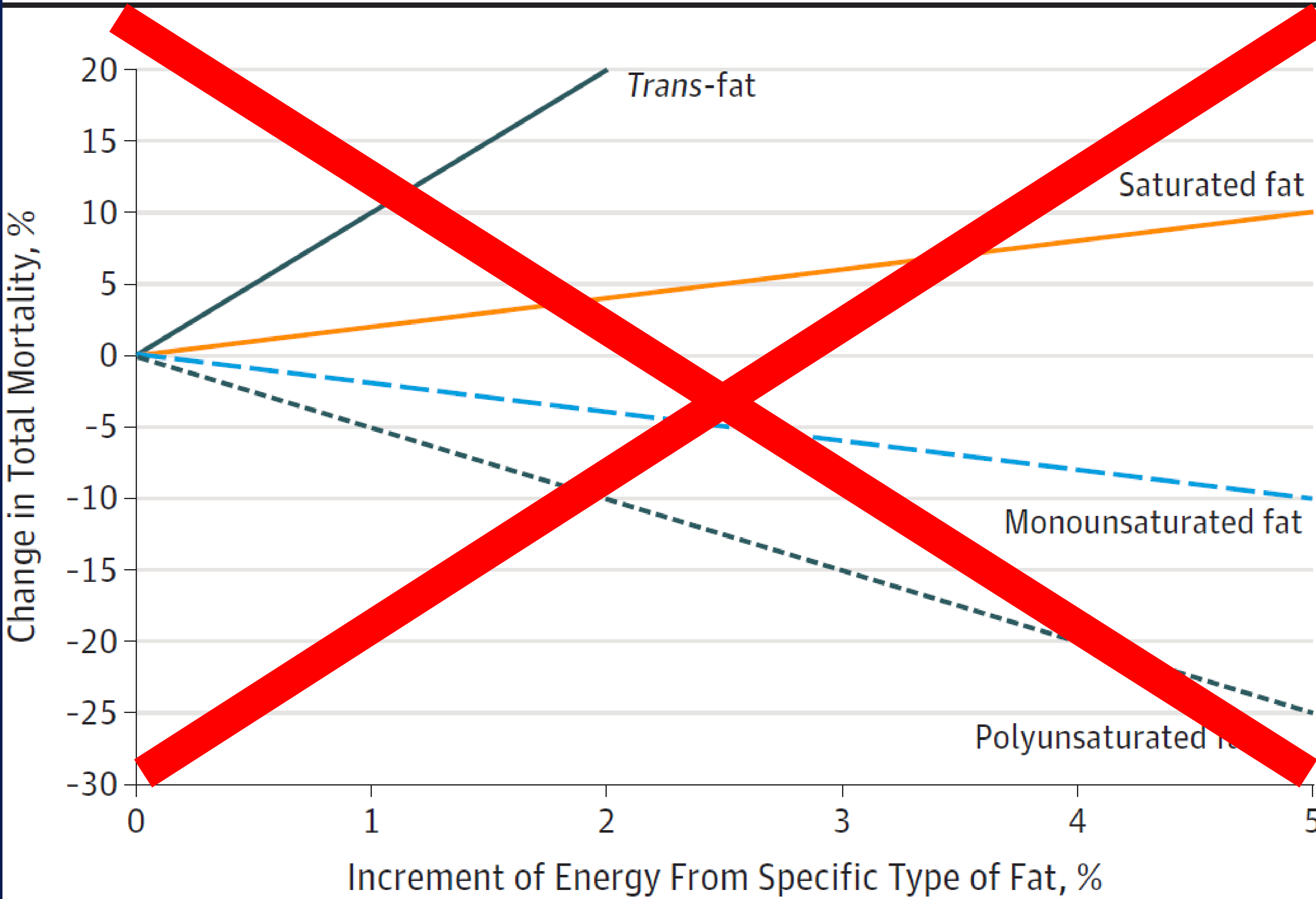
Associations of individual Fatty Acids with 10-year Total Mortality in LURIC





Kleber et al Eur Heart J 2016;37:1072-82; Kleber et al Atherosclerosis 2016;252:157-81
Delgado et al J Clin Lipidol 2017;11:126-35; Delgado et al Clin Lipidol, 2017;11:1082-90
Kleber et al J Clin Lipidol 2018;12:455-63

Figure 1. Change in Total Mortality Associated With Increases in the Percentage of Energy From Specific Types of Fat



Wang et al JAMA Int Med 2016; e-pub Juli 5