Omega-3 fatty acids & health: Past, present & future

Philip C. Calder
Professor of Nutritional Immunology
University of Southampton
(pcc@soton.ac.uk)

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Today
NEWSPAPER OF THE YEAR
FRIDAY, SEPTEMBER 29, 1989 ★★★ DAILY SALE 612,060 (August daily sale) 22p (Republic of Ireland 35p)

FISH OILS CUT RISK OF HEART ATTACK

OFFICIAL

by CHRIS MIHILL

EATING oily fish twice a week can cut the risk of dying from a heart attack by almost a third.

The first proof that foods like mackerel and herring can save lives came in an official study of 2,000 male heart attack victims.

Half were advised to eat at least two portions of oily fish a week, while the others stuck to their normal diet.

After two years, there had been 29 per cent fewer deaths among those eating fish.

Researcher Dr Michael Burr said: "For those who have had a heart attack we can say with confidence that they would be well advised to eat oily fish at

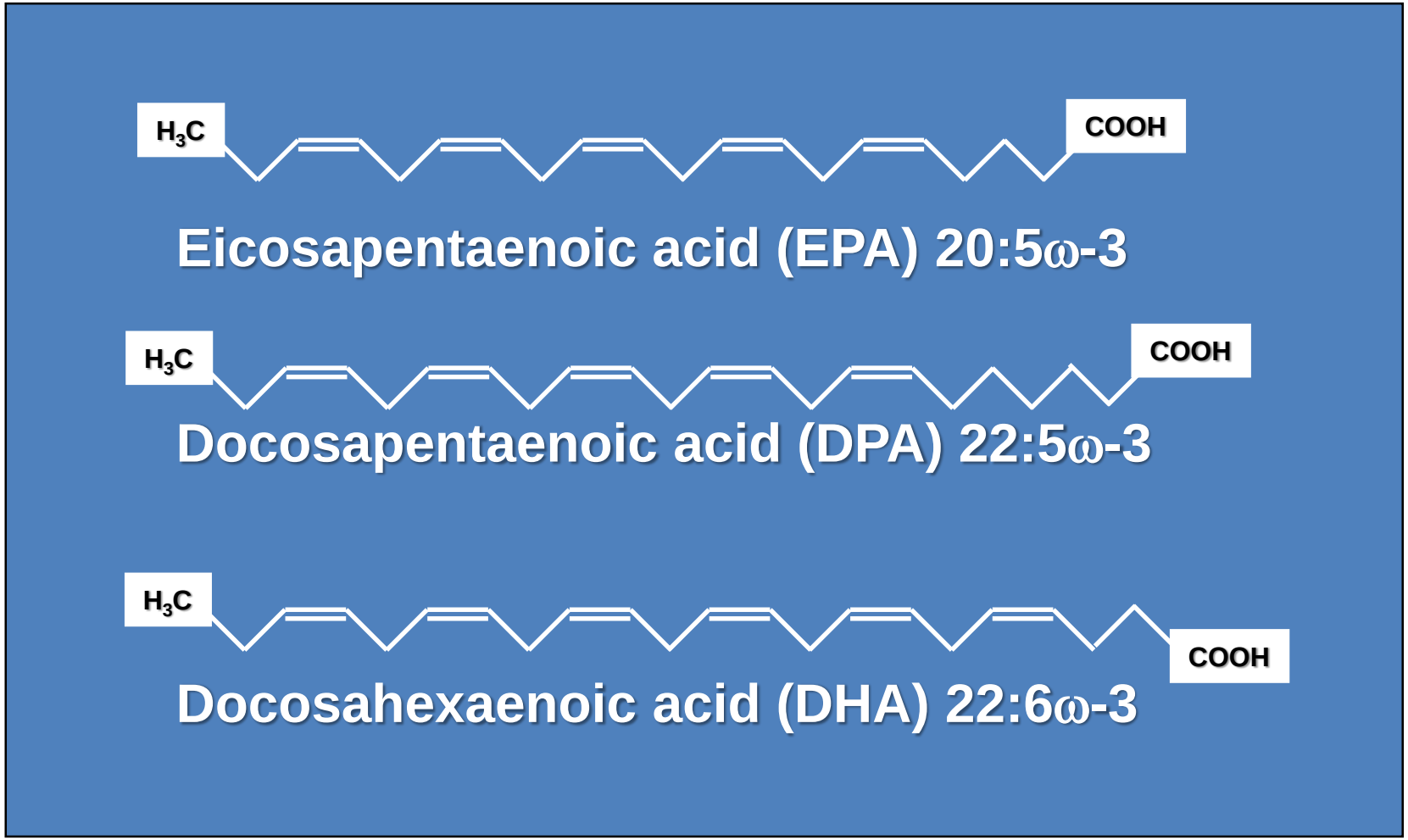
Turn To Page 5

Evening Standard Tuesday, 2 April 2002 31

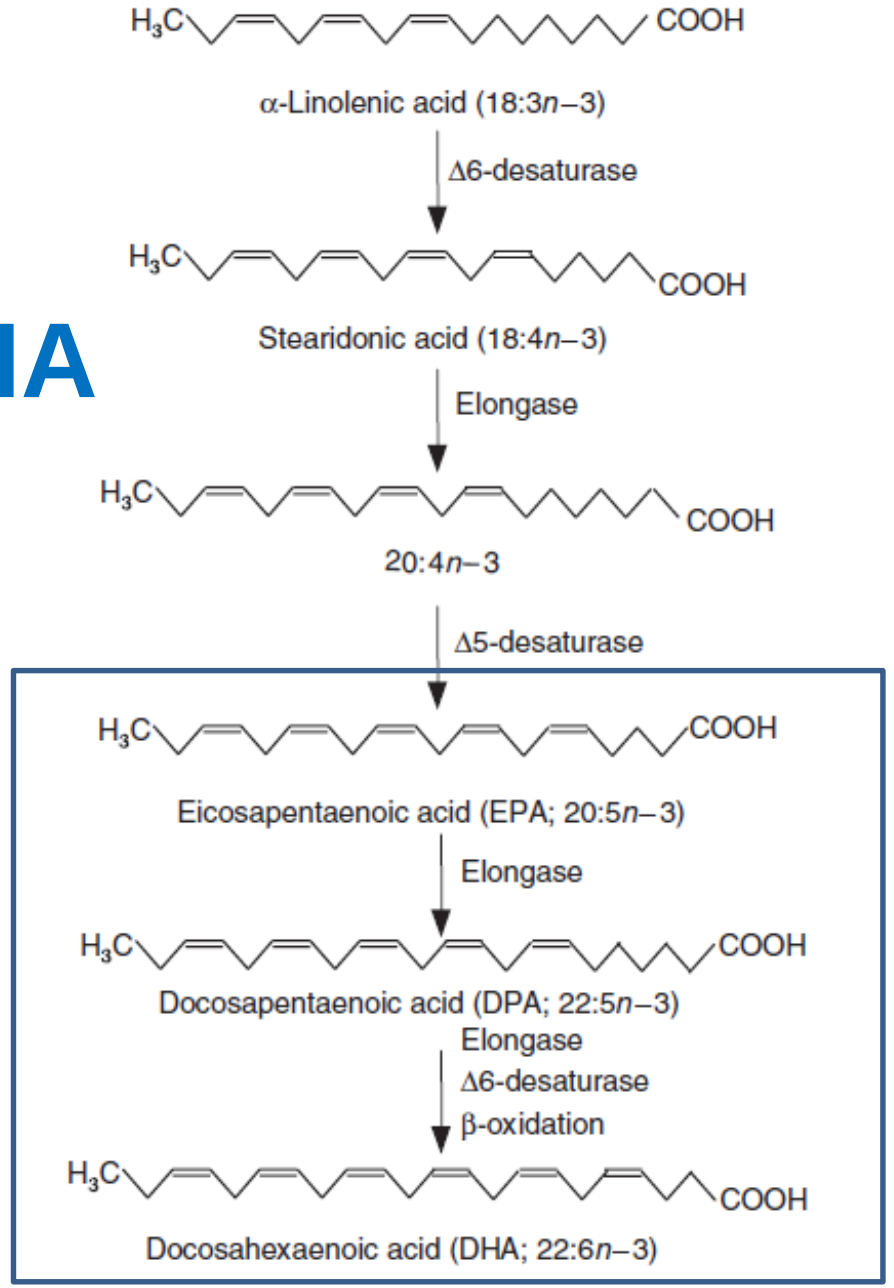
Health&Fitness

Fish oil saved my marriage

Very long chain (“marine”) ω-3 polyunsaturated fatty acids

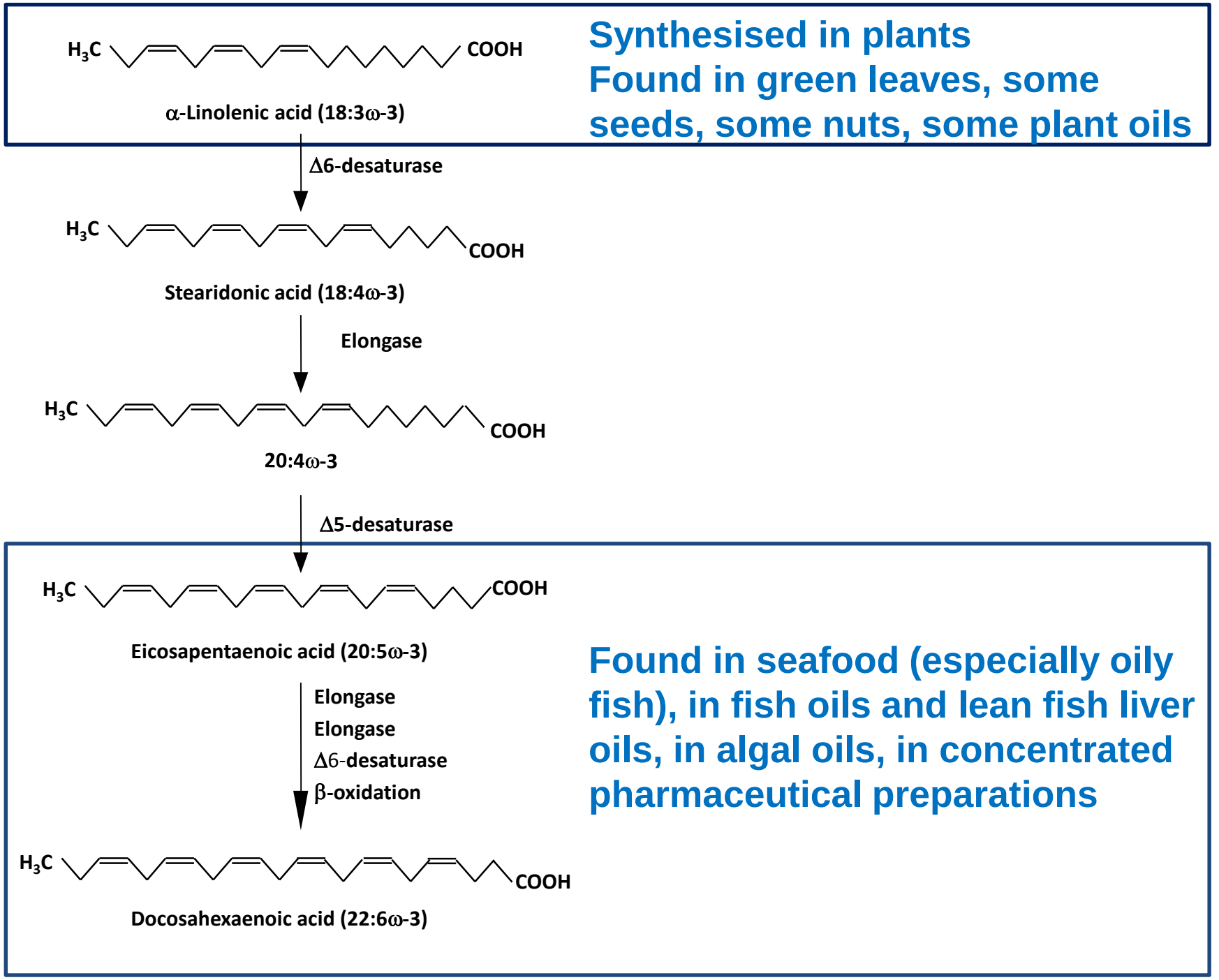


Pathway of biosynthesis of EPA, DPA and DHA



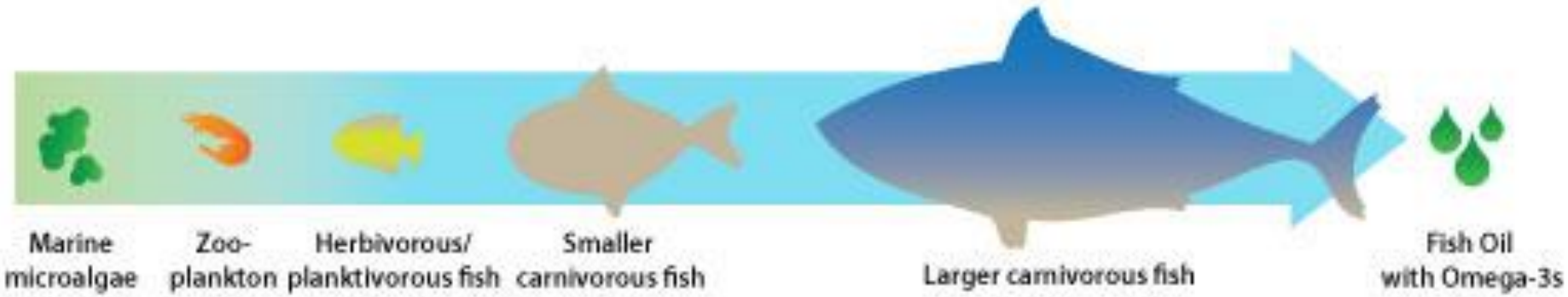
EPA, DPA and especially DHA are poorly synthesised in humans

-> dietary sources are important

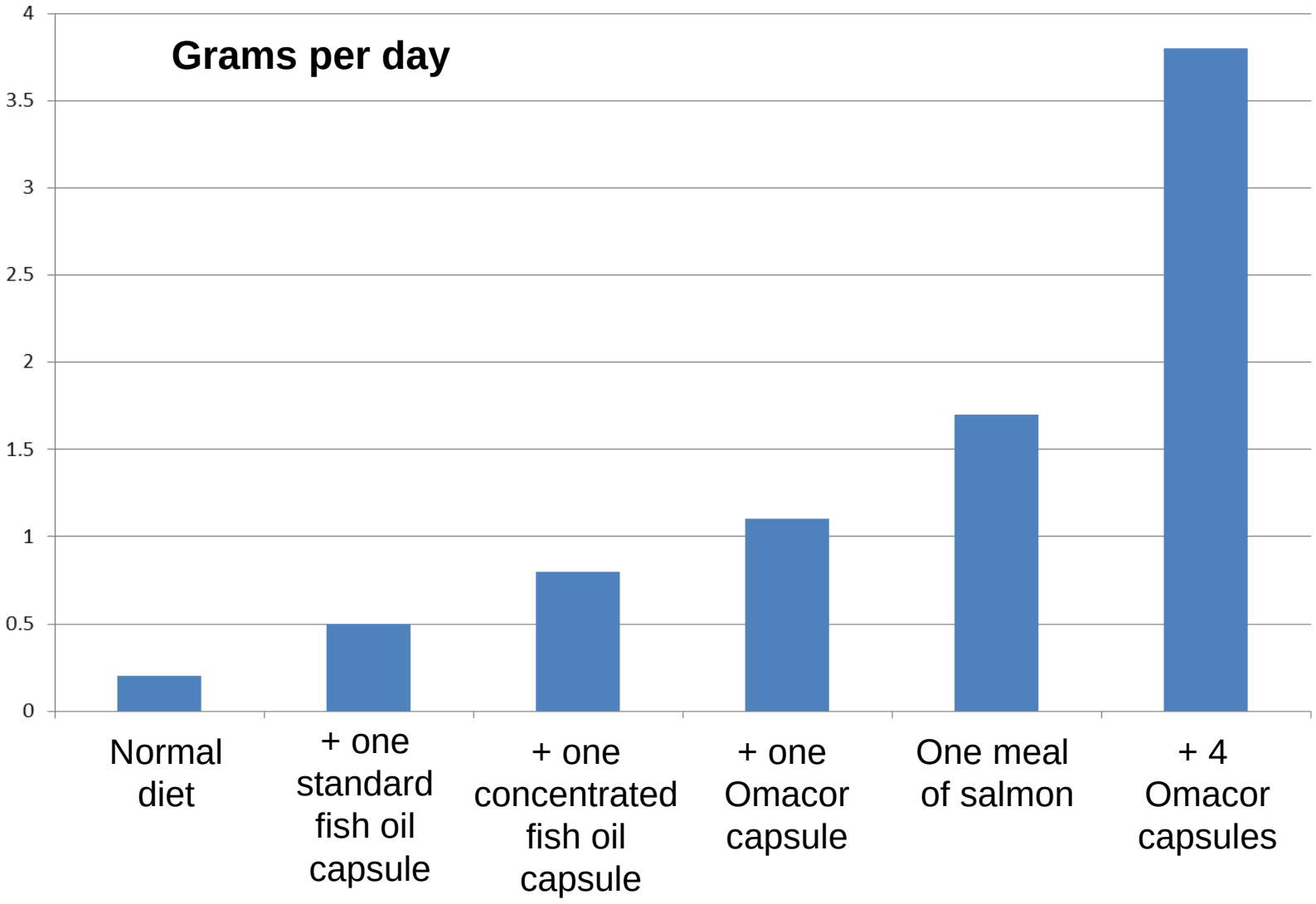

H3C
COOH
α-Linolenic acid (18:3ω-3)
Δ6-desaturase
H3C
COOH
Stearidonic acid (18:4ω-3)
Elongase
H3C
COOH
20:4ω-3
Δ5-desaturase
H3C
COOH
Eicosapentaenoic acid (20:5ω-3)
Elongase
Elongase
Δ6-desaturase
β-oxidation
H3C
COOH
Docosahexaenoic acid (22:6ω-3)
Synthesised in plants
Found in green leaves, some seeds, some nuts, some plant oils
Found in seafood (especially oily fish), in fish oils and lean fish liver oils, in algal oils, in concentrated pharmaceutical preparations

Long chain ω-3 PUFA content of fish

	EPA	DPA	DHA	Total
	(g/100 g food)			g/portion
Cod	0.08	0.01	0.16	0.30
Haddock	0.05	0.01	0.10	0.19
Herring	0.51	0.11	0.69	1.56
Mackerel	0.71	0.12	1.10	3.09
Salmon	0.55	0.14	0.86	1.55
Crab	0.47	0.08	0.45	0.85
Prawns	0.06	0.01	0.04	0.06


Marine microalgae
Zoo-plankton
Herbivorous/ planktivorous fish
Smaller carnivorous fish
Larger carnivorous fish
Fish Oil with Omega-3s

Effect on EPA + DHA intake by eating oily fish or taking supplements



In most cells and tissues the content of EPA and DHA is low (especially when compared with the content of ω-6 PUFAs)

ω-6 and ω-3 PUFA contents of phospholipids of human white (mononuclear) cells

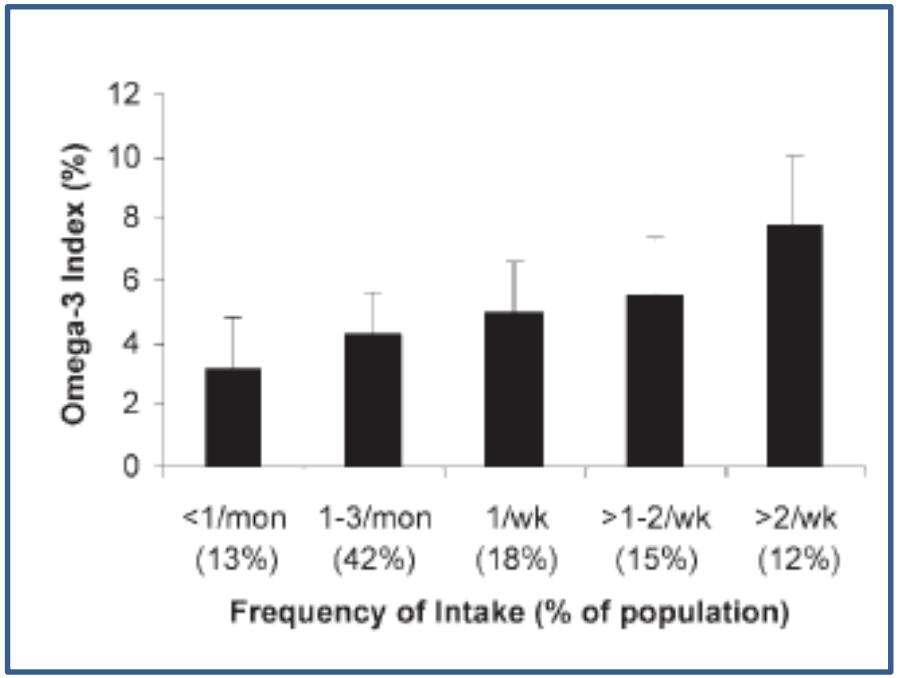
	% of total fatty acids
Linoleic acid (18:2ω-6)	10
DGLA (20:3ω-6)	1.5
Arachidonic acid (20:4ω-6)	20
α-Linolenic acid (18:3ω-3)	< 0.5
EPA	1.0
DHA	2.5

But increasing EPA+DHA intake increases the EPA and DHA content of blood lipids, blood cells, and many tissues including liver, heart & skeletal muscle – effect is dose, time and tissue dependent

Effect of fish consumption on EPA and DHA status

- Cross-sectional
- N = 163
- Male & female
- Aged 20 to 80 y
- Fish intake = Self reported tuna + nonfried fish
- Erythrocytes

  (Omega-3 index = EPA+DHA)



Sands et al. (2005) Lipids 40, 343-347

Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish[1–4]

Lucy M Browning, Celia G Walker, Adrian P Mander, Annette L West, Jackie Madden, Joanna M Gambell, Stephen Young, Laura Wang, Susan A Jebb, and Philip C Calder

Am J Clin Nutr 2012;96:748–58.

fish

the **fish** study

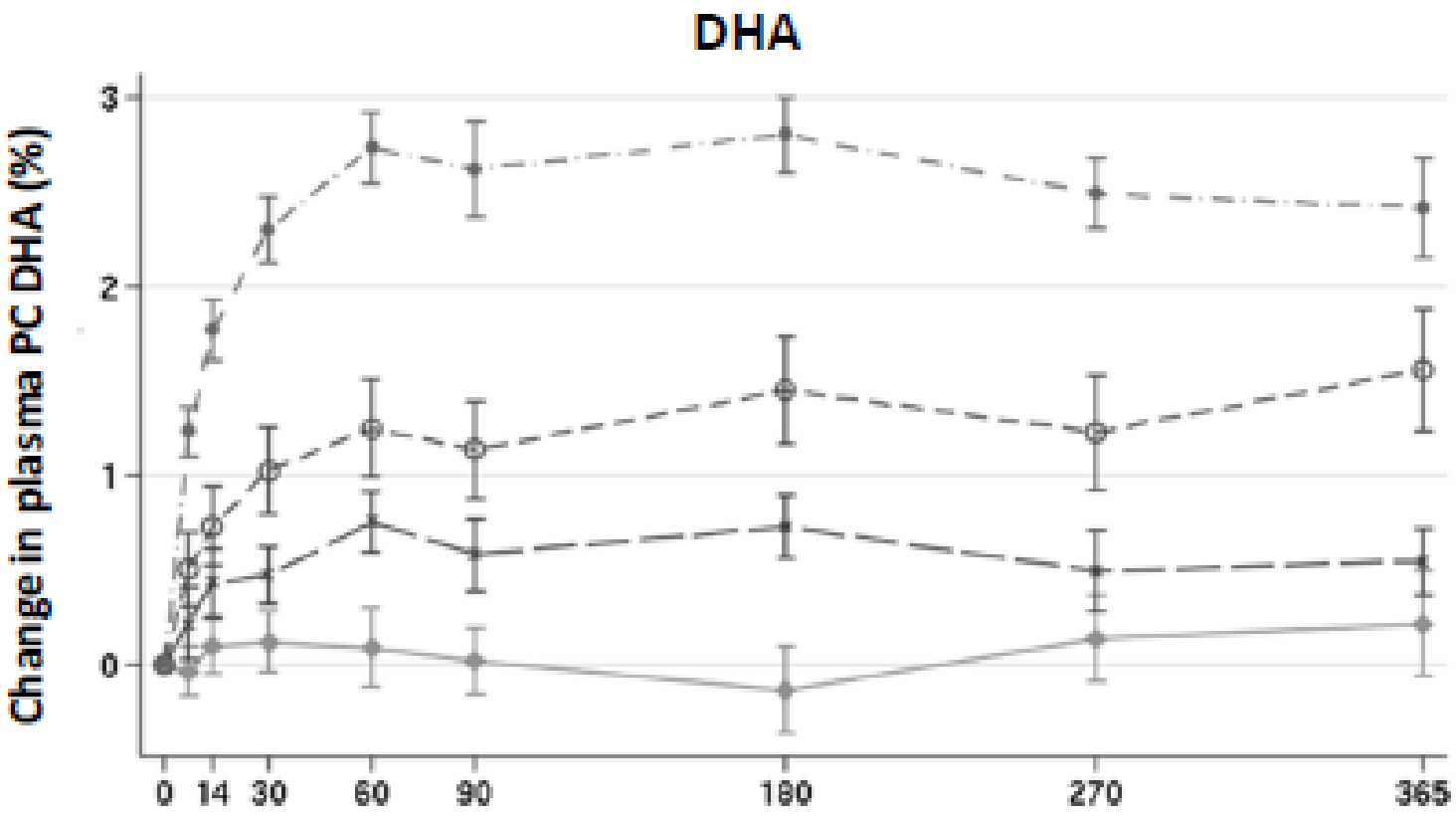
Analysed the fatty acid composition of:

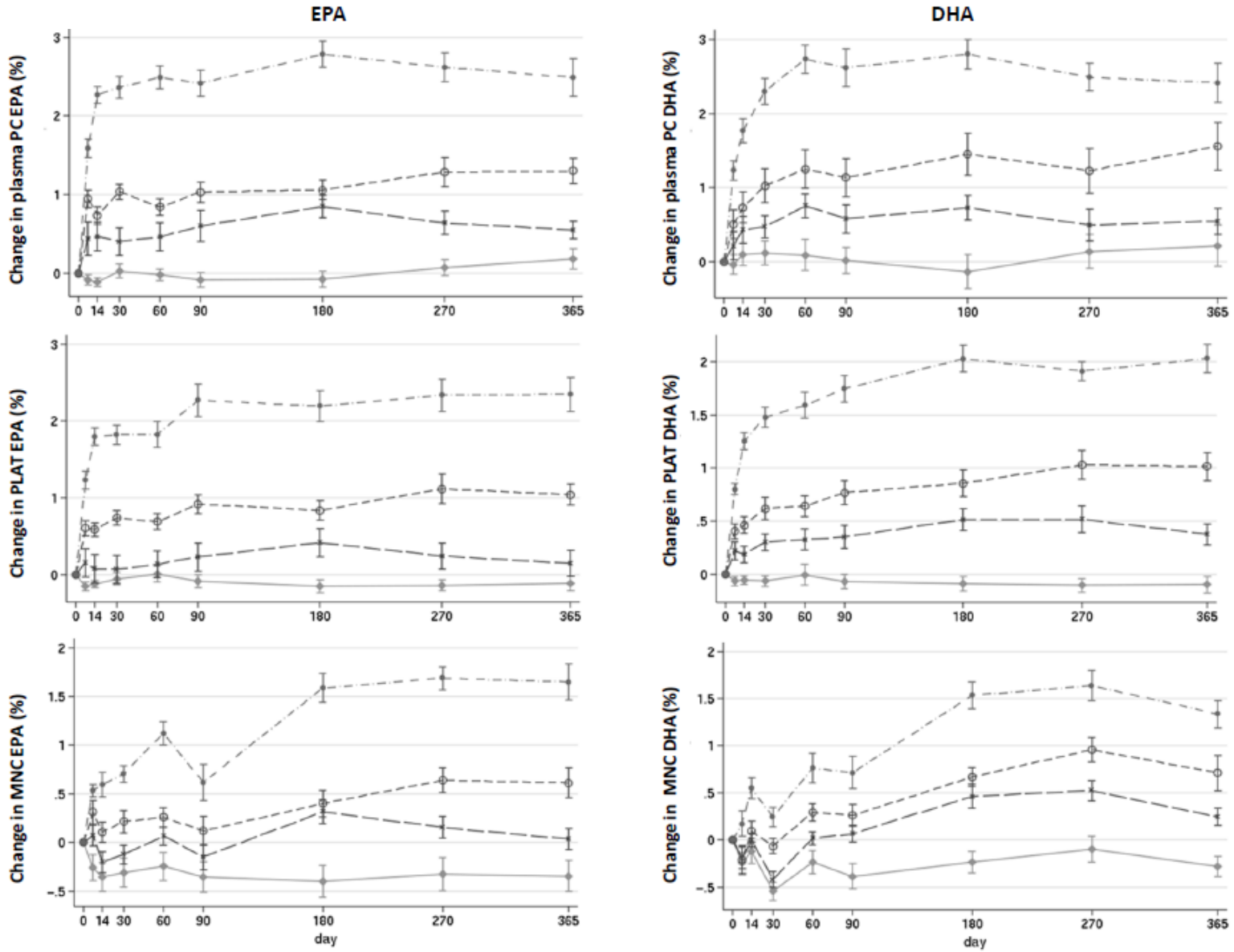
- **plasma PC, TAG, CE and NEFA**
- **platelets**
- **erythrocytes**
- **mononuclear cells**
- **buccal cells**

From 200 subjects at 9 time points over one year

- **adipose tissue**

From 200 subjects at three time points over one year


DHA
Change in plasma PC DHA (%)
3
2
1
0
0
14
30
60
90
180
270
365

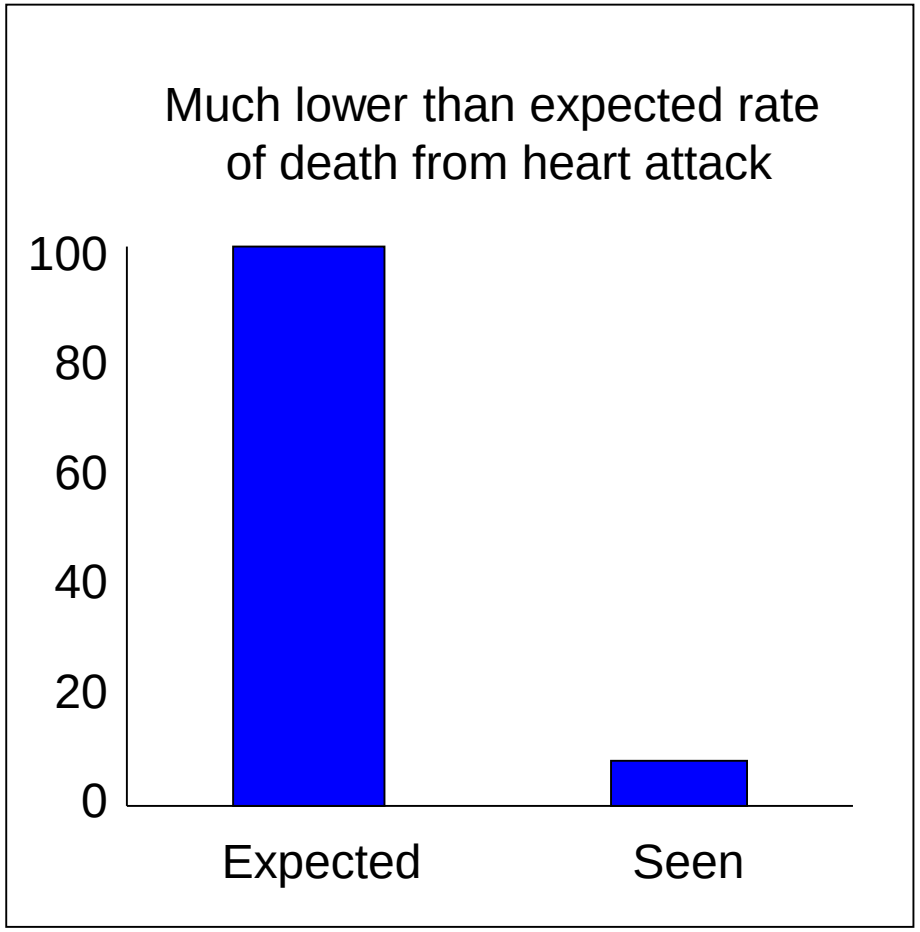

EPA
DHA
Change in plasma PC EPA (%)
Change in plasma PC DHA (%)
Change in PLAT EPA (%)
Change in PLAT DHA (%)
Change in MNC EPA (%)
Change in MNC DHA (%)
0 14 30 60 90 180 270 365
day

=> The amount of EPA and DHA being consumed is strongly reflected in the amounts of those fatty acids in blood, cell and tissue lipids

What is the health impact of increased intake (& status) of marine ω-3 PUFAs?

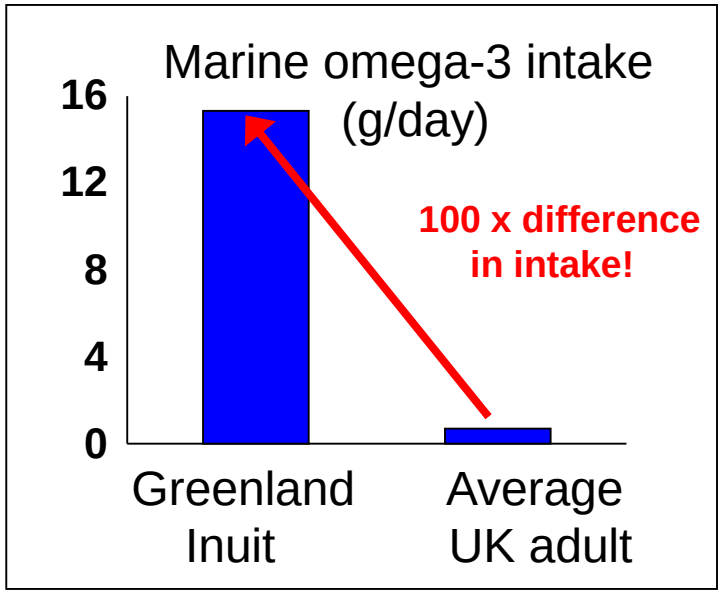

POLICE PUBLIC CALL BOX

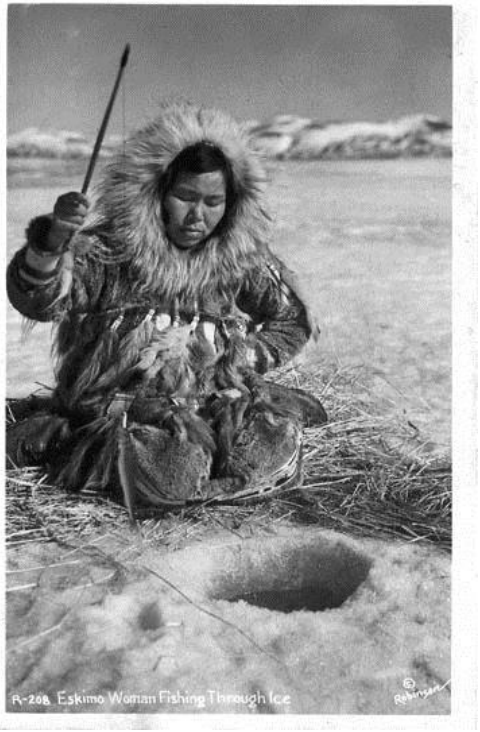
The Greenland Inuit (“Eskimo”)



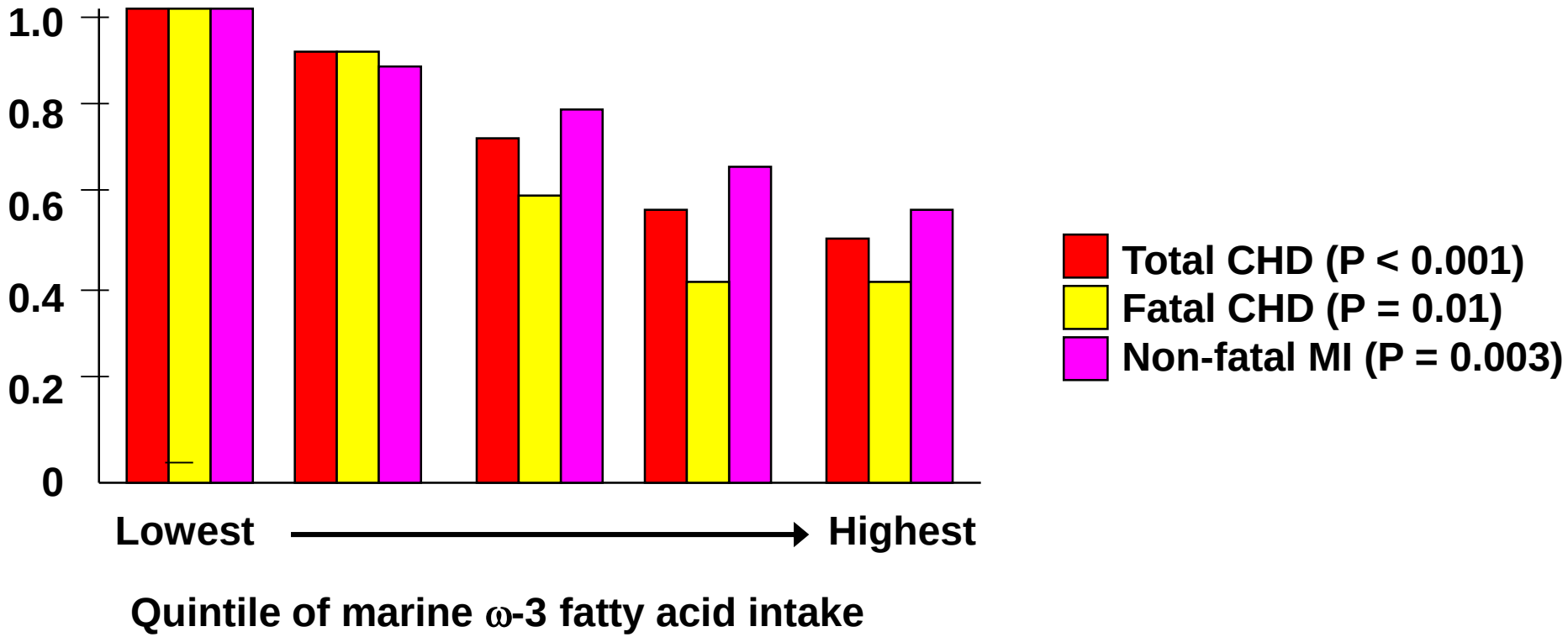
How could this be?
-> The Inuit diet??

- **Ate lots of seal meat, whale meat, whale blubber, fish**
- **-> Very high intake of ω-3 PUFAs**



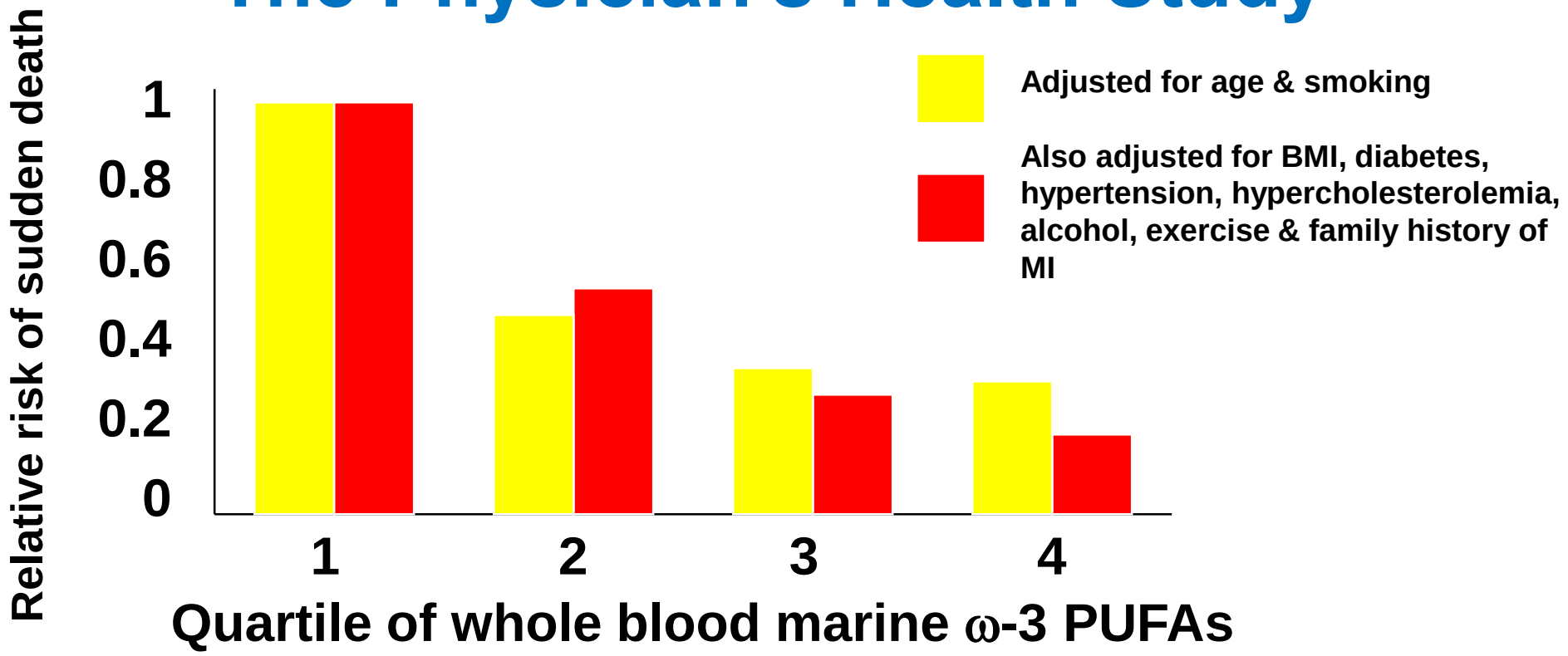


Prospective study of ω-3 PUFA intake and CHD outcomes: The Nurse's Health Study



Hu et al. (2002) J. Am. Med. Assoc. 287, 1815-1821

Prospective study of ω-3 PUFA status and sudden death: The Physician's Health Study



Albert et al. (2002) New Engl. J. Med. 346, 1113-1118

REVIEW | Annals of Internal Medicine

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk

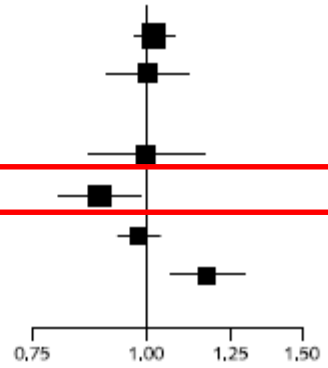
A Systematic Review and Meta-analysis

Rajiv Chowdhury, MD, PhD; Samantha Warnakula, MPhil*; Setor Kunutsor, MD, MSt*; Francesca Crowe, PhD; Heather A. Ward, PhD; Laura Johnson, PhD; Oscar H. Franco, MD, PhD; Adam S. Butterworth, PhD; Nita G. Forouhi, MRCP, PhD; Simon G. Thompson, FMedSci; Kay-Tee Khaw, FMedSci; Dariush Mozaffarian, MD, DrPH; John Danesh, FRCP*; and Emanuele DI Angelantonio, MD, PhD*

Ann Intern Med. 2014;160:398-406.

Figure 1. RRs for coronary outcomes in prospective cohort studies of dietary fatty acid intake.

Fatty Acid Intake	Studies, *n*	Participants, *n*	Events, *n*	RR (95% CI)*
Total saturated fatty acids	20	276 763	10 155	1.03 (0.98–1.07)
Total monounsaturated fatty acids	9	144 219	6031	1.00 (0.91–1.10)
Total ω-3 fatty acids				
α-Linolenic	7	157 258	7431	0,99 (0,86–1,14)
Total long-chain ω-3	16	422 786	9089	0,87 (0,78–0,97)
Total ω-6 fatty acids	8	206 376	8155	0,98 (0,90–1,06)
Total trans fatty acids	5	155 270	4662	1.16 (1.06–1.27)



RR (95% CI) Comparing Top vs. Bottom Thirds of Baseline Dietary Fatty Acid Intake

Figure 2. RRs for coronary outcomes in prospective cohort studies of circulating fatty acid composition.

Circulating Blood Fatty Acid Composition	Studies, *n*	Participants, *n*	Events, *n*	RR (95% CI)*
Total ϖ-3 polyunsaturated fatty acids				
18:3n-3, α-Linolenic	8	14 945	3426	0.93 (0.83–1.03)
Total long-chain ϖ-3	4	10 558	2753	0.84 (0.63–1.11)
20:5n-3, Eicosapentaenoic	13	23 065	4624	0.78 (0.65–0.94)
22:6n-3, Docosahexaenoic	13	23 065	4624	0.79 (0.67–0.93)
20:5n-3, Eicosapentaenoic + 22:6n-3, Docosahexaenoic	13	20 809	4073	0.75 (0.62–0.89)
22:5n-3, Docosapentaenoic (clupanodonic)	4	7155	2565	0.64 (0.47–0.89)

CVD : Classic and emerging risk factors

CLASSIC:

Age
Sex
Family history (genetics)

Smoking

High alcohol consumption
High blood pressure
Diabetes
Obesity
Lack of physical activity

High serum (LDL) cholesterol

EMERGING:

High serum triglycerides
Elevated post-prandial lipaemia
Endothelial dysfunction
Tendency towards thrombosis
Inflammation

Elevated plasma homocysteine

Poor antioxidant status

CVD : Classic and emerging risk factors

CLASSIC:

Age
Sex
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Smoking

High alcohol consumption
High blood pressure ✓
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High serum (LDL) cholesterol ✓

EMERGING:

High serum triglycerides ✓
Elevated post-prandial lipaemia ✓
Endothelial dysfunction ✓
Tendency towards thrombosis ✓
Inflammation ✓

Elevated plasma homocysteine

Poor antioxidant status

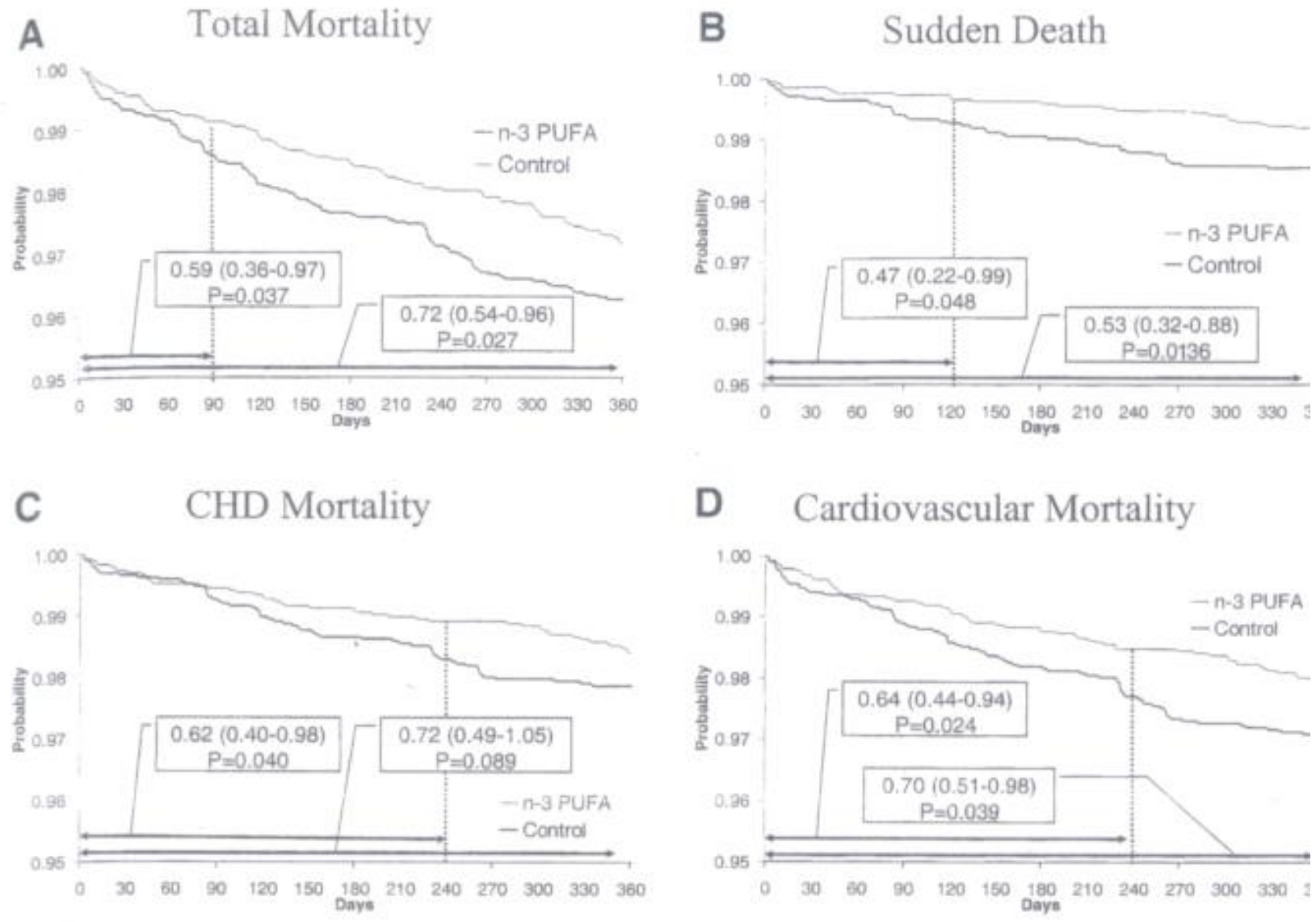
✓ = Improved by n-3 PUFAs

Marine ω-3 fatty acids most likely slow or limit atherosclerosis due to risk factor reduction …..

….. But marine ω-3 fatty acids also reduce risk of coronary events in people with advanced atherosclerosis

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial

GISSI Prevenzione Investigators (1999) Lancet 354, 447-455

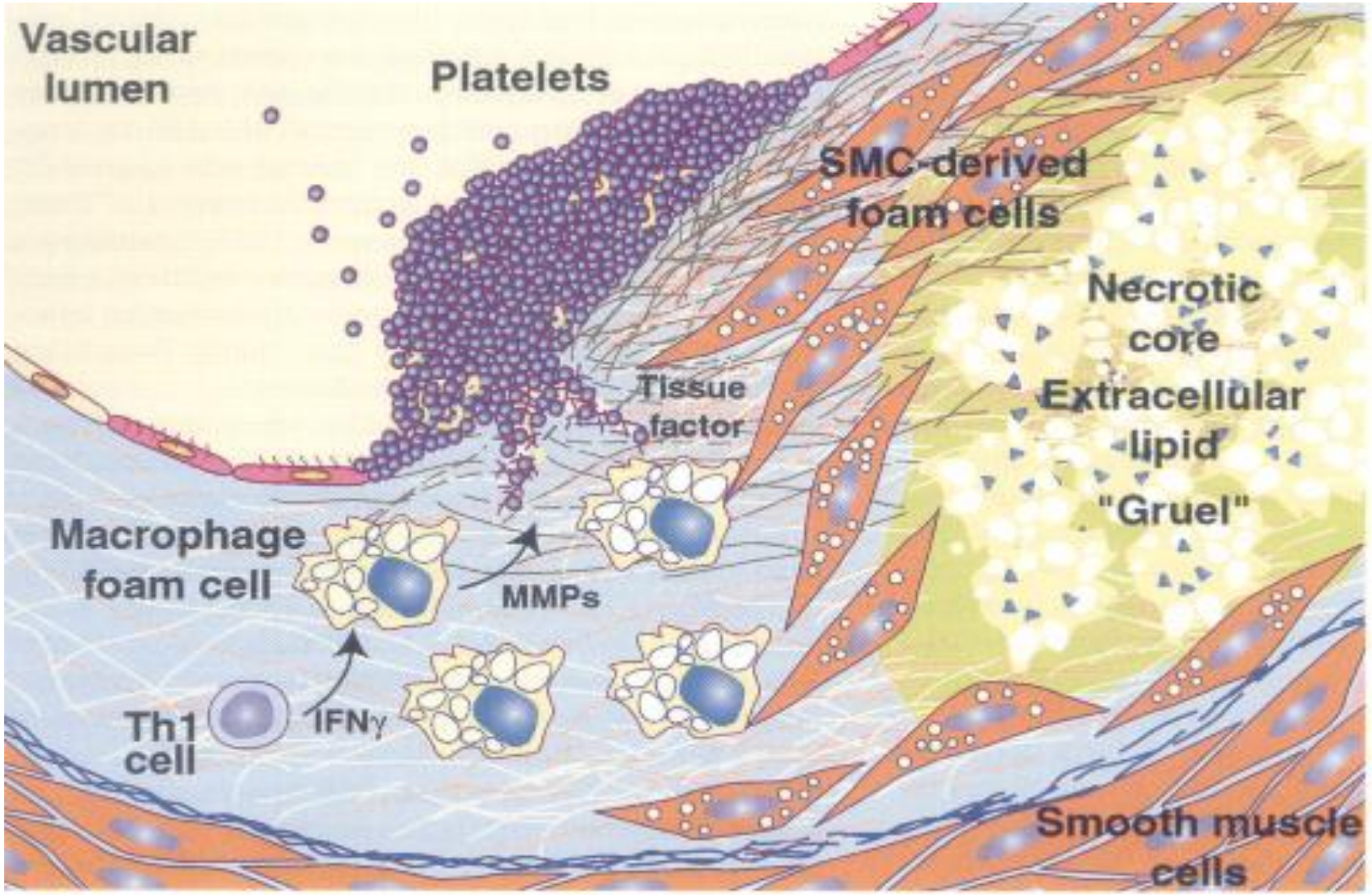


Marchioli et al. (2002) Circulation 105, 1897-1903

Possible mechanisms for prevention of non-fatal and fatal events with marine ω-3 fatty acids

1. Decreased cardiac arrhythmias
2. Decreased thrombosis
3. Decreased inflammation

Atherosclerotic plaque instability is driven by vessel wall inflammation

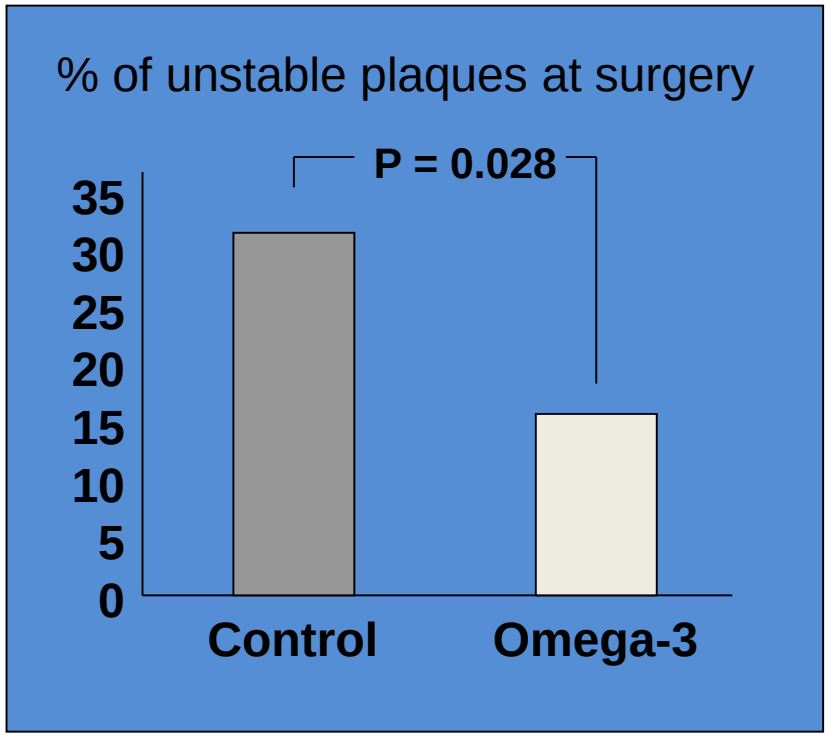


Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial

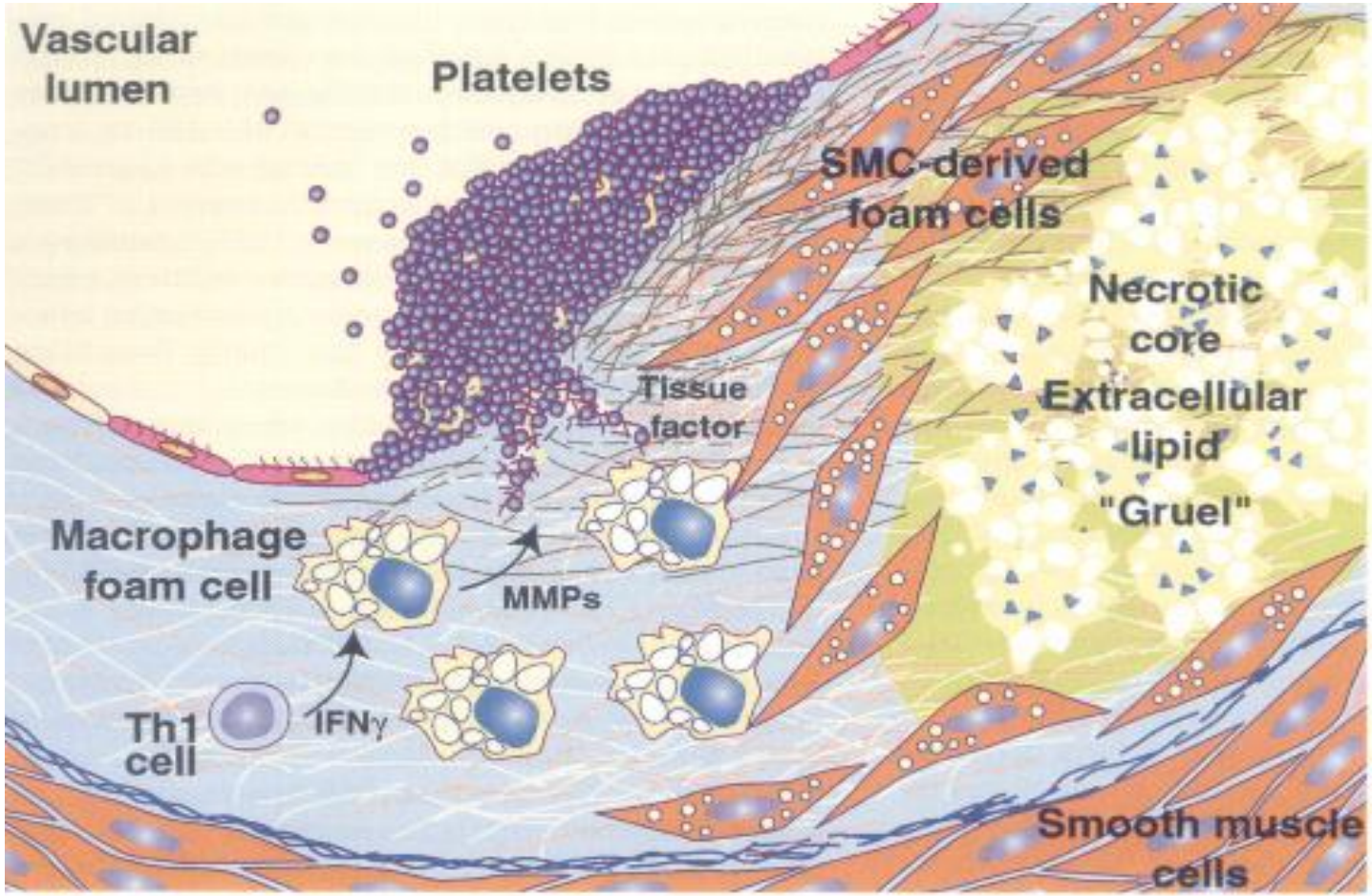
Frank Thies, Jennifer M C Garry, Parveen Yaqoob, Kittipan Rerkasem, Jennifer Williams, Cliff P Shearman, Patrick J Gallagher, Philip C Calder, Robert F Grimble

Lancet 2003; **361:** 477–85

- **RCT of ω-3 fatty acids (1.6 g EPA+DHA per day) in patients awaiting carotid endarterectomy (n = 180)**
- **Median time of treatment: 42 days**
- **Patients given ω-3 fatty acids have higher ω-3 fatty acid content in plaques**
- **Patients given ω-3 fatty acids have fewer macrophages within the plaque**



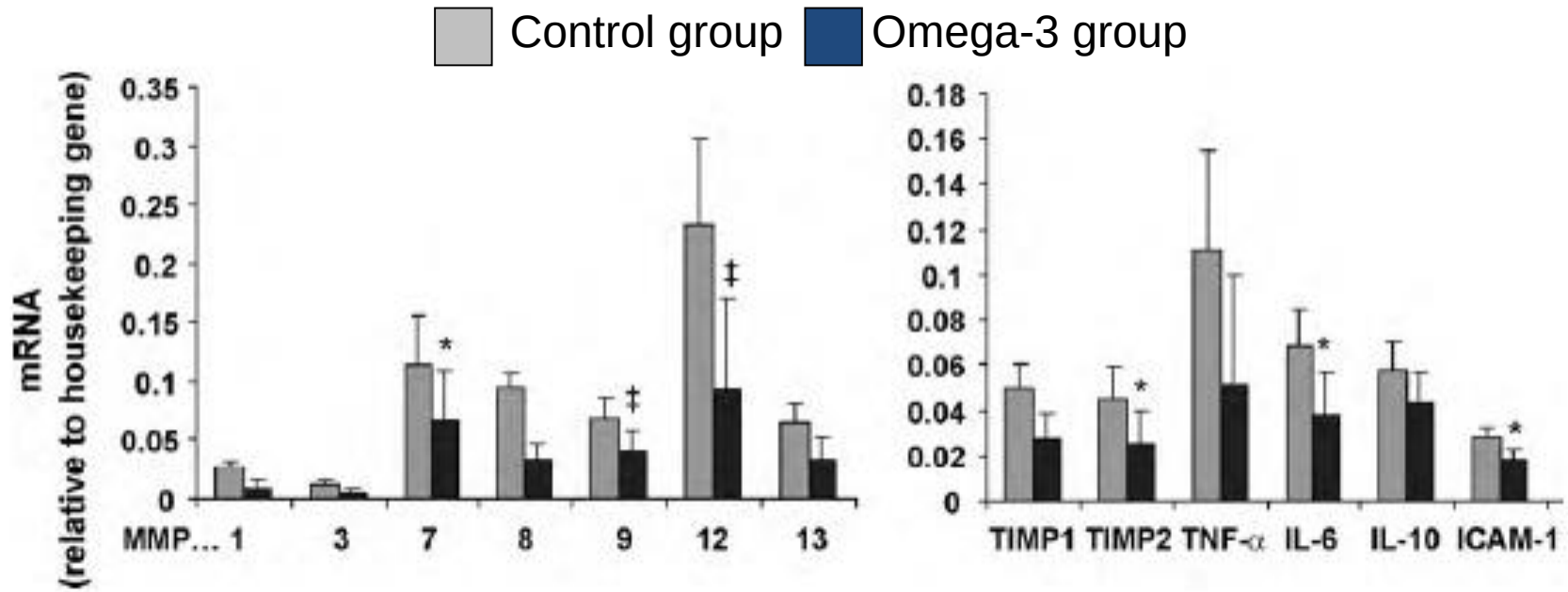
Matrix metalloproteinases (MMPs) released from macrophages, foam cells and smooth muscle cells degrade the plaque cap making it more vulnerable to rupture



Eicosapentaenoic acid (EPA) from highly concentrated $n-3$ fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability

Abbie L. Cawood[a], Ren Ding[a], Frances L. Napper[a], Ruth H. Young[a], Jennifer A. Williams[a], Matthew J.A. Ward[a], Ola Gudmundsen[b], Runar Vige[c], Simon P.K. Payne[d], Shu Ye[a], Ciff P. Shearman[a], Patrick J. Gallagher[a], Robert F. Grimble[a], Philip C. Calder[a,*]

Atherosclerosis 212 (2010) 252–259



N-3 Polyunsaturated Fatty Acids in Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials

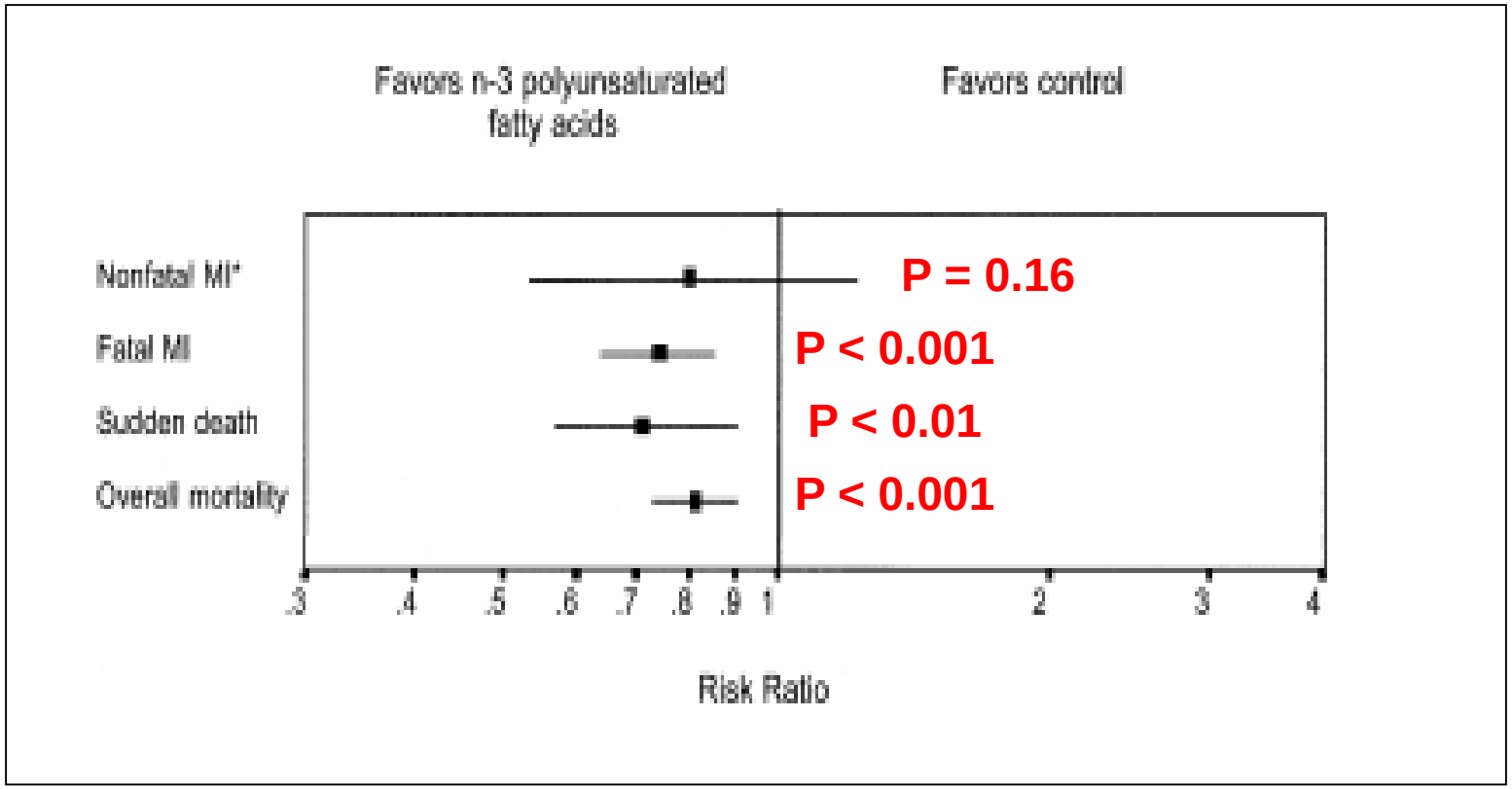
Heiner C. Bucher, MD, MPH, Peter Hengstler, MD, Christian Schindler, PhD, Gabriela Meier, MD

Am. J. Med. (2002) 112, 298-304

Considered: Eleven intervention trials with marine ω-3 PUFAs and with follow-up of at least 6 months (2 dietary studies; 9 supplementation studies)

N = 7835 in control group; 7951 in ω-3 PUFA group

Findings:
Risk of nonfatal MI = 0.8 (P = 0.16);
of fatal MI = 0.7 (P < 0.001);
of sudden death = 0.7 (P < 0.01);
of mortality = 0.8 (P < 0.001)



Conclusion: "dietary and non-dietary intake of ω-3 polyunsaturated fatty acids reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with coronary heart disease"

REVIEW ARTICLE

Effect of Different Antilipidemic Agents and Diets on Mortality

A Systematic Review

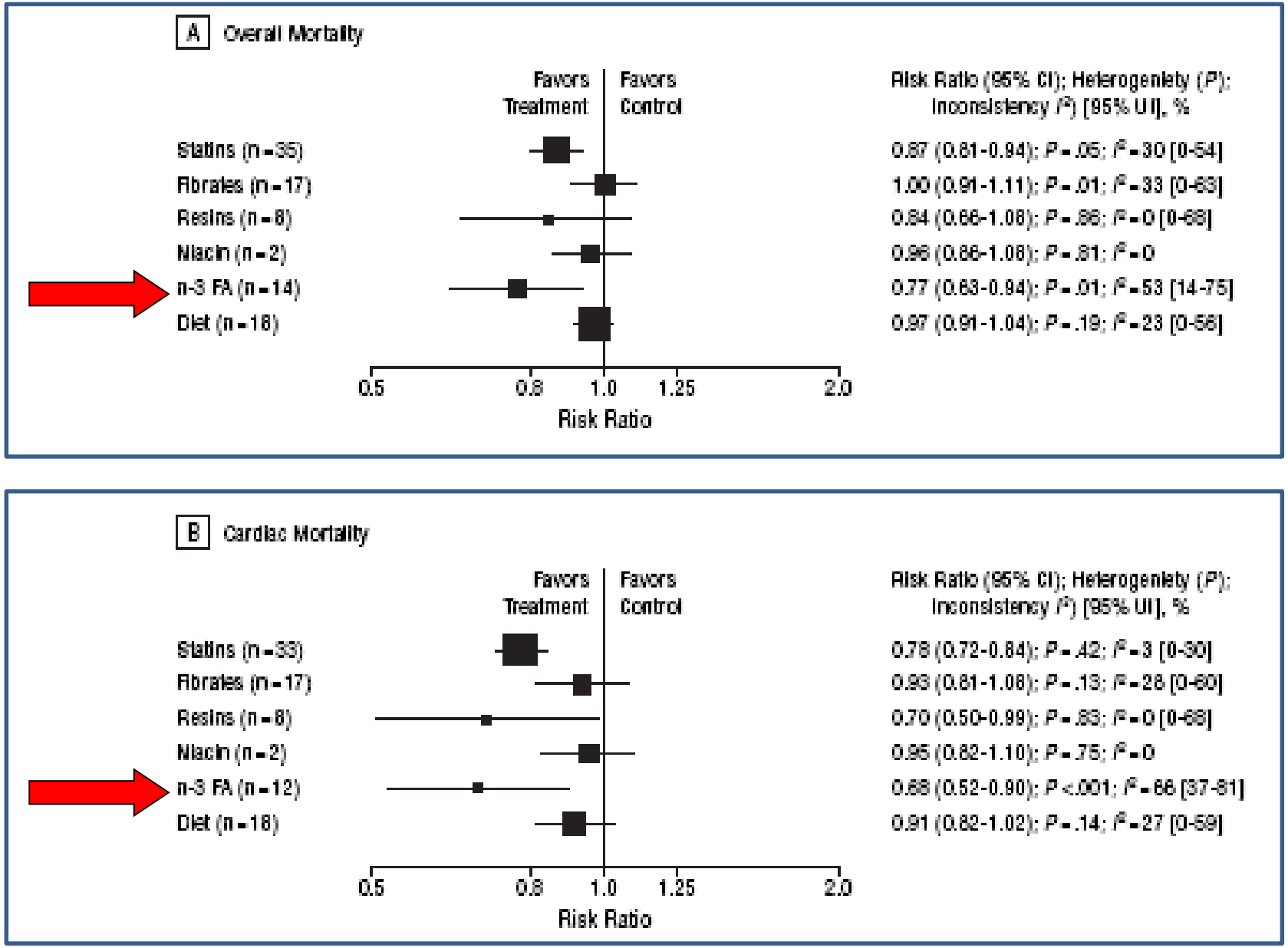
Marco Studer, MD; Matthias Briel, MD; Bernd Leimenstoll, MD; Tracy R. Glass, MSc; Heiner C. Bucher, MD, MPH

Arch. Int. Med. (2005) 165, 725-730

Considered: 97 intervention trials with lipid lowering strategies (incl. long chain ω-3 PUFAs) and with follow-up of at least 6 months (for ω-3 PUFAs considered 14 studies)

N = 10138 in control group; 10122 in ω-3 PUFA group

Findings for ω-3 PUFA:
Risk of cardiac mortality = 0.68 (P < 0.001);
of mortality = 0.77 (P = 0.01)



Conclusion "statins and ω-3 fatty acids are the most favourable lipid lowering interventions with reduced risks of overall and cardiac mortality"

But new studies published from 2010 onwards have challenged this view
(But these new studies have been criticised)

Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events

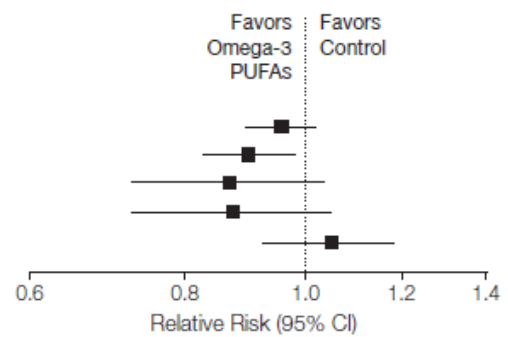
A Systematic Review and Meta-analysis

Evangelos C. Rizos, MD, PhD
Evangelia E. Ntzani, MD, PhD
Eftychia Bika, MD
Michael S. Kostapanos, MD
Moses S. Elisaf, MD, PhD, FASA, FRSH

JAMA. 2012;308(10):1024-1033

Figure 3. Efficacy of Omega-3 Polyunsaturated Fatty Acid Supplements Across Different Outcomes

Outcome	No. Studies	No. Events	No. Participants	RR (95% CI)
All-cause mortality	17	6295	63 279	0.96 (0.91-1.02)
Cardiac death	13	3480	56 407	0.91 (0.85-0.98)
Sudden death	7	1030	41 751	0.87 (0.75-1.01)
Myocardial infarction	13	1755	53 875	0.89 (0.76-1.04)
Stroke	9	1490	52 589	1.05 (0.93-1.18)



Error bars indicate 95% CIs; PUFAs, polyunsaturated fatty acids; RR, relative risk.

ELSEVIER

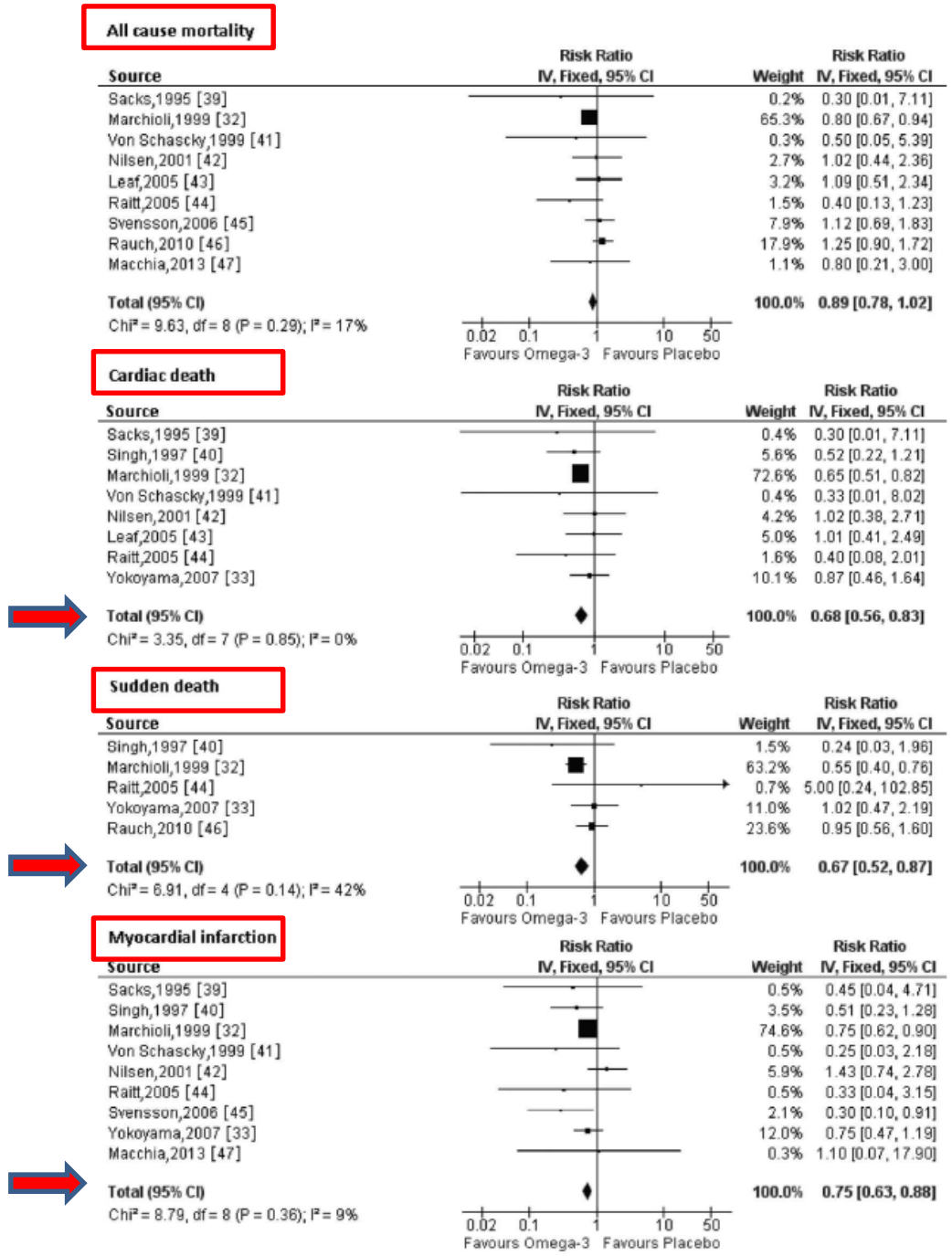
Atherosclerosis Supplements 14 (2013) 243–251

ATHEROSCLEROSIS
SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, double blind, placebo controlled trials

Manuela Casula[a,*], Davide Soranna[b], Alberico L. Catapano[a,c], Giovanni Corrao[b,*]



Cardiac death
32% reduction

Sudden death
33% reduction

MI
25% reduction

Clinical Therapeutics/Volume 35, Number 1, 2013

Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study

Chris D. Poole, PhD[1]; Julian P. Halcox, MD[2]; Sara Jenkins-Jones, MSc[3]; Emma S.M. Carr, PhD[4]; Mathias G. Schifflers, MD[4]; Kausik K. Ray, MD, MPhil[5]; and Craig J. Currie, PhD[1]

- **MI survivors**
- **1 g omega-3 ethyl ester per day**
- **N = 2466 real patients being treated as part of routine care**
- **Matched untreated controls (n = 9712)**
- **2002-2011**
- **Primary outcome: death**

Table III. Number of events and crude relative risk values for patients exposed and not exposed to omega-3 (*n*-3) fatty acids.

Parameter	Exposed	Nonexposed
All patients	2466	9712
No. of death events	243	1274
Total follow-up, y	6668	24,943
Deaths per 1000 person-years, no.	36.4	51.1
Crude relative risk (95% CI)	0.708 (0.602–0.833)	$P < 0.0001$
Patients with no previous diabetes	2140	8429
No. of death events	195	1016
Total follow-up, y	5882	22,066
Deaths per 1000 person-years, no.	33.2	46.0
Crude relative risk (95% CI)	0.724 (0.621–0.844)	$P < 0.0001$
Patients with previous type 2 diabetes	326	1283
No. of death events	48	258
Total follow-up, y	786	2878
Deaths per 1000 person-years, no.	61.1	89.7
Crude relative risk (95% CI)	0.686 (0.504–0.934)	$P = 0.0166$

The benefits of marine ω-3 PUFAs go beyond cardiovascular health

Marine ω-3 PUFAs are important in:

- membrane structure
- growth
- development and function of brain, neural tissue and eye

(-> VERY IMPORTANT IN EARLY LIFE)

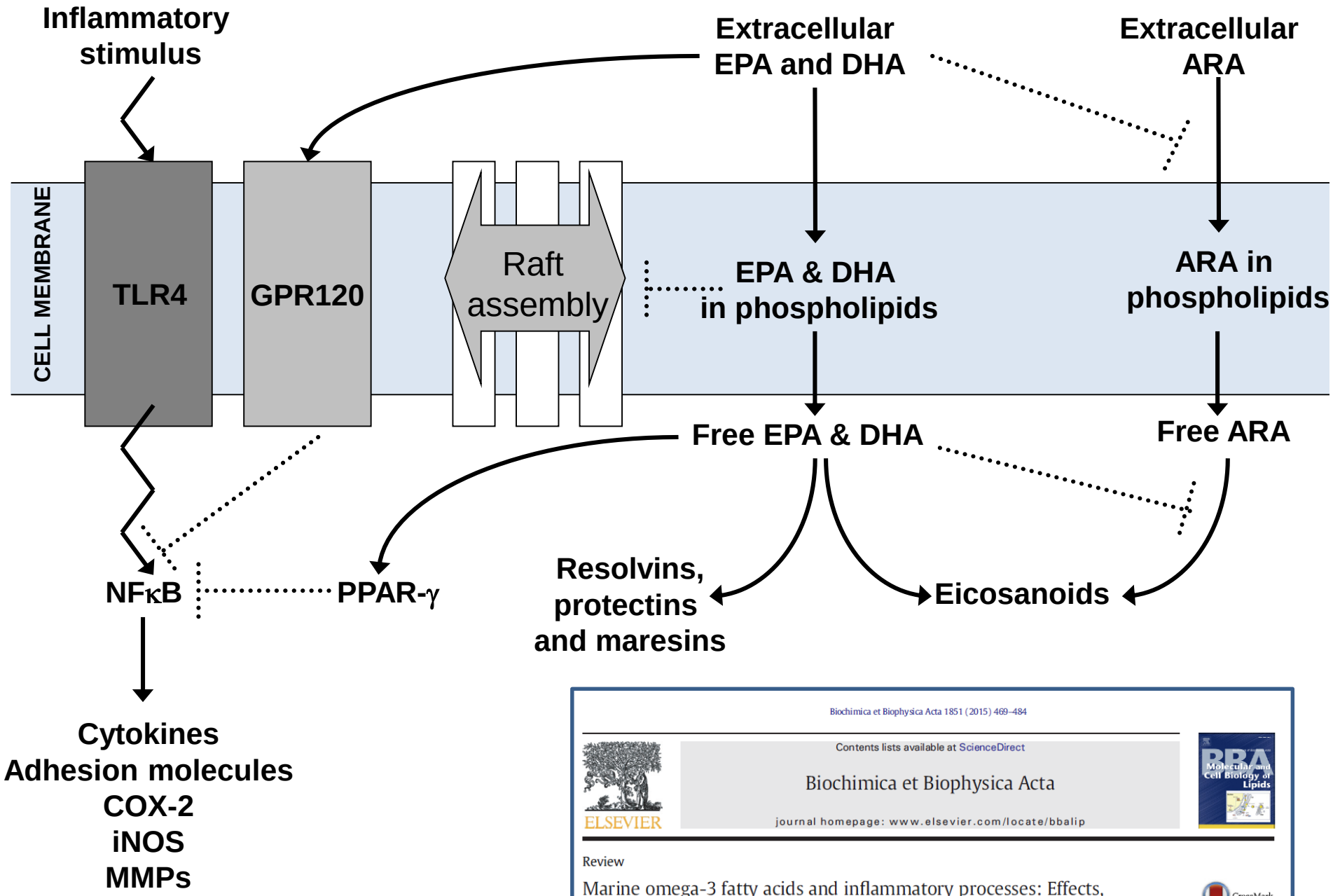
- regulation of
    - blood pressure
    - platelet function, thrombosis, fibrinolysis
    - blood lipid concentrations
    - vascular function
    - cardiac rhythm
    - inflammation
    - immune response
    - bone health
    - insulin sensitivity

Marine ω-3 PUFAs are or may be protective against:

- hypertension
- hypertriglyceridemia
- thrombosis
- vascular dysfunction
- cardiac arrhythmias
- cardiovascular disease
- inflammatory conditions
- allergic conditions
- immune dysfunction
- insulin resistance
- neurodegenerative diseases of ageing
- bone loss
- some cancers
- psychological and psychiatric disorders

Marine ω-3 PUFAs (ESPECIALLY DHA) promote:

- optimal brain growth & optimal visual and neural function



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Review

Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance☆

Philip C. Calder *

Summary of the past & present

- Typical intakes of marine ω-3 fatty acids are low in most people, resulting in low status
- Intake and status of marine ω-3 fatty acids can be markedly increased through intake of oily fish or supplements
- Much is known about patterns of incorporation of EPA and DHA in humans
- EPA and DHA act through multiple, increasingly understood, molecular and cellular mechanisms to affect cell and tissue function
- Through these actions marine ω-3 fatty acids act to promote and maintain health and to reduce disease risk
- Marine ω-3 fatty acids are important throughout the life course
- There is robust evidence that long-term intake of marine ω-3 fatty acids reduces risk of coronary heart disease – due to beneficial impacts on a range of risk factors – they have an important role in primary prevention of CHD/CVD
- There is strong evidence from studies conducted pre-2010 for a role for marine ω-3 fatty acids in secondary prevention of CHD – this role is challenged by some recent studies


The Future

There is still much to learn about:

- **Dose responses and fatty acid interactions**
- **Mechanisms**
- **Effects of the different marine ω-3 fatty acids (EPA vs DHA and don't forget DPA)**
- **The role of chemical formulation**
- **Differences among population subgroups (sex, age, genetics, disease, physiological state) with regard to ω-3 fatty acid handling, metabolism, and effectiveness**
- **Why some studies fail to show effects**
- **More sustainable sources of marine ω-3 fatty acids (algal oils, GMO plants, ….)**
- **Whether plant ω-3 fatty acids can have a role**