UNIVERSITY OF Southampton
School of Medicine

Future directions for nutritional and therapeutic research in omega-3 lipids

Philip Calder
Professor of Nutritional Immunology
University of Southampton

Aim …

- To review dietary sources and intakes of long chain ω-3 fatty acids
- To review ω-3 status in human blood and cells and how this may be altered
- To review the impact of ω-3 fatty acids on human health – mechanisms involved - cvd focus
- To highlight strategies to increase long chain ω-3 fatty acid status
- To highlight timely questions
  - EPA vs DHA
  - Plant ω-3 fatty acids (α-linolenic acid & stearidonic acid)
  - Genotype-specific responses

Eicosapentaenoic acid EPA 20:5ω-3

Docosahexaenoic acid DHA 22:6ω-3

Found in seafood, especially oily (fatty) fish, fish oils, liver oils, algal oils …

Long chain ω-3 PUFA content of fish (Typical values)

	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

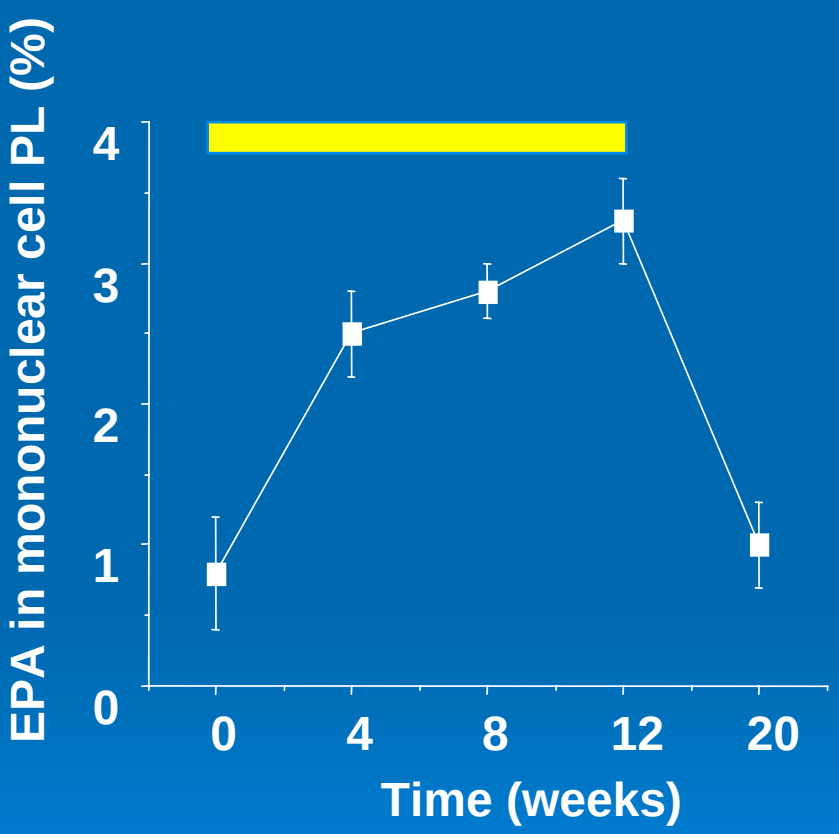
Typical intakes of long chain ω-3 PUFAs

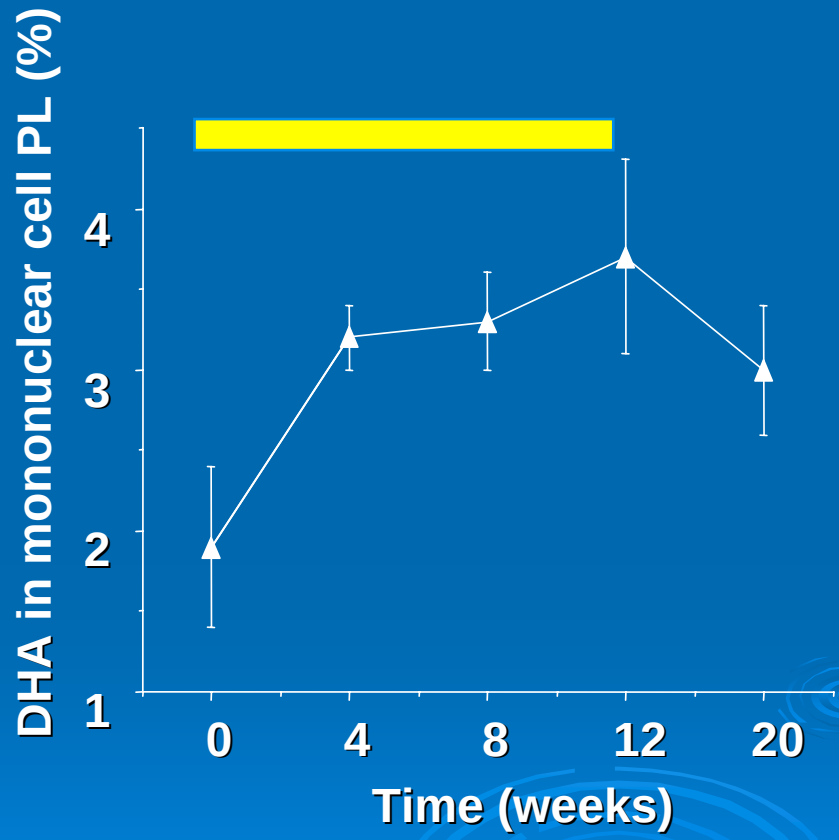
- Mean UK adult intake is about 0.2 g/day (but bimodal distribution since only 25% of the population consumes oily fish)
- Australian data (Meyer et al. (2003) Lipids 38, 391-398):
  - Mean daily intakes of EPA, DPA and DHA = 0.056, 0.026, and 0.106 g (Total = 0.188 g/d)
  - Median daily intakes of EPA, DPA and DHA = 0.008, 0.006, and 0.015 g DHA (Total = 0.029 g/d)

Typical contents of EPA and DHA in human blood, cells & tissues (% total fatty acids)

	EPA	DHA
Plasma PC	0.8	2.9
Plasma CE	0.8	0.5
Plasma TAG	0.8	0.5
Platelet PC	0.2	1.1
Platelet PE	0.6	6.3
Mononuclear cell PL	0.3	2.3
Neutrophil PL	0.6	1.3
Red cell PL	0.8	3.5
Brain grey matter PE	-	24.3
Brain grey matter PS	-	36.6
Brain grey matter PC	-	3.1
Brain white matter PE	-	3.4
Retina PC	-	22.2
Retina PE	-	18.5
Retina PS	-	4.6
Sperm PL	-	35.2
White adipose tissue	tr	0.1

Time course of incorporation of EPA and DHA into human mononuclear cell phospholipids

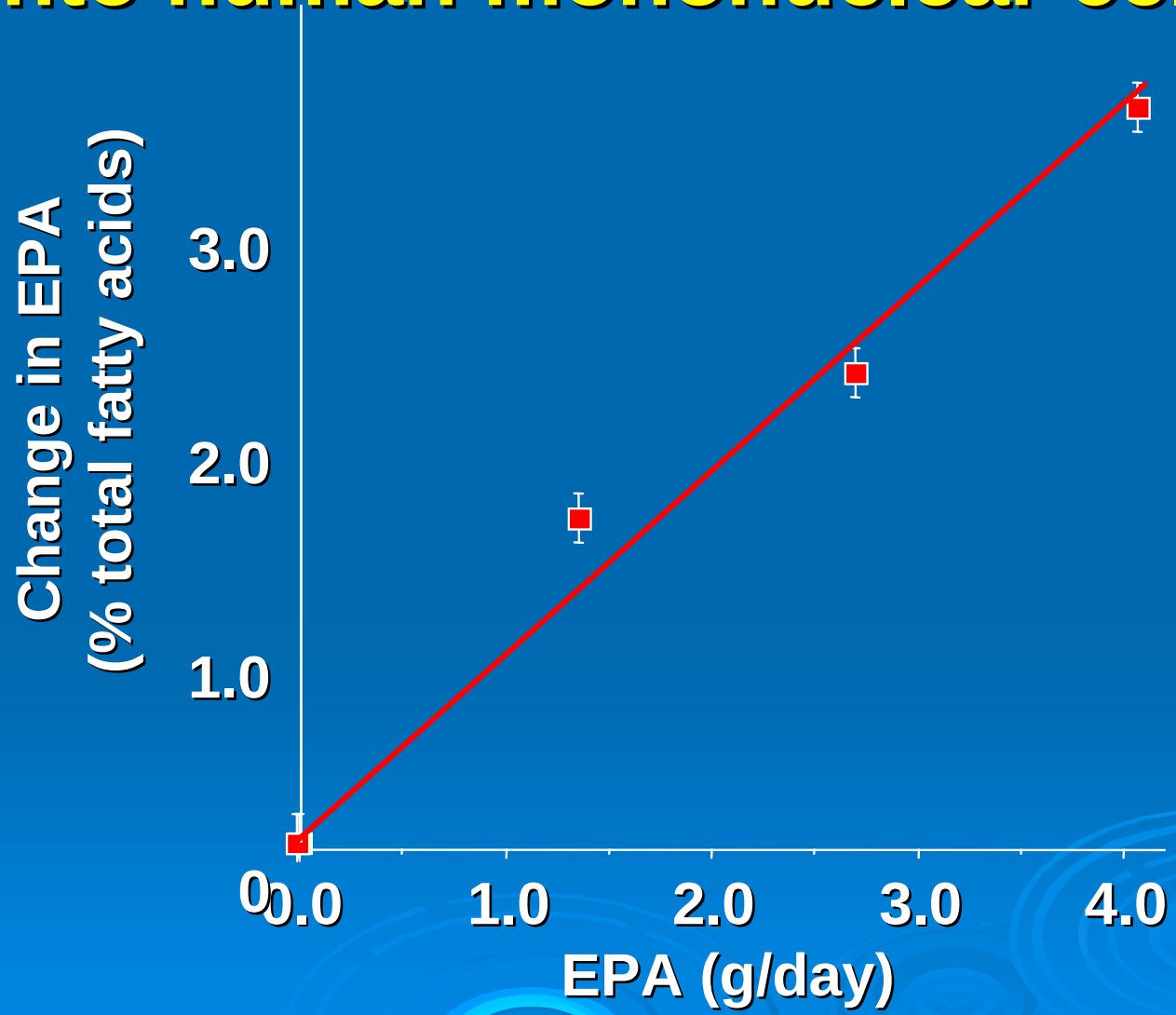




Healthy volunteers given fish oil (2.1 g EPA and 1.1 g DHA/day) for 12 weeks

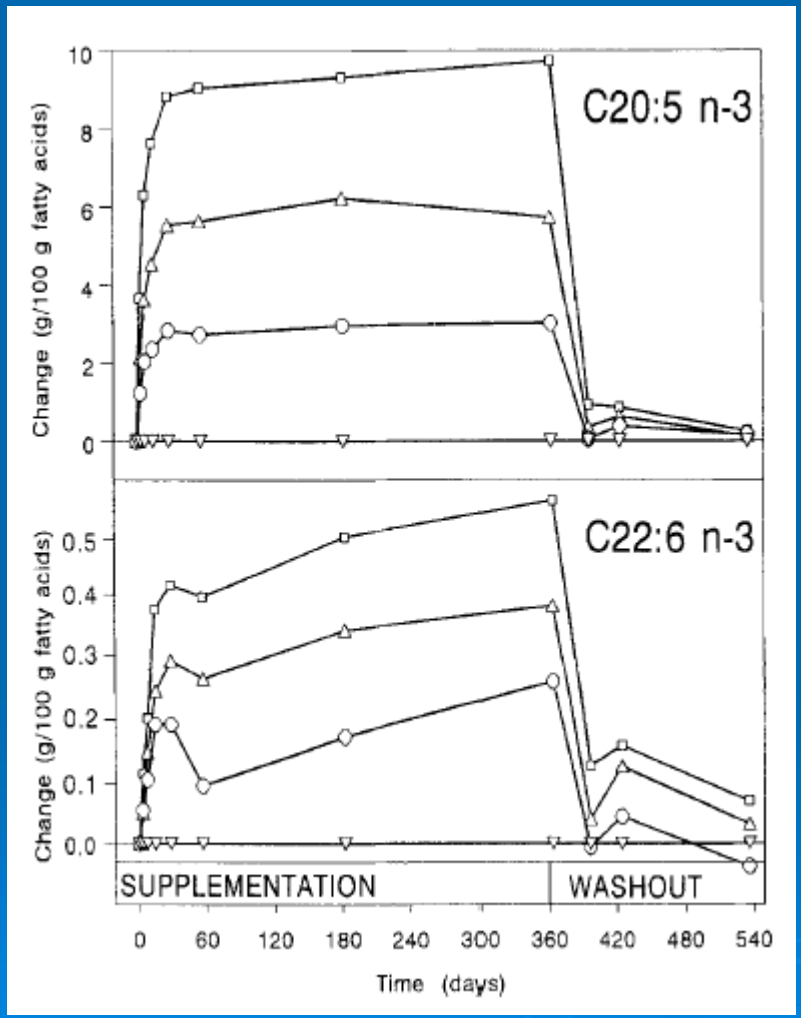
Yaqoob et al. (2000) Eur. J. Clin. Invest. 30, 260-274

Dose response of incorporation of EPA into human mononuclear cells

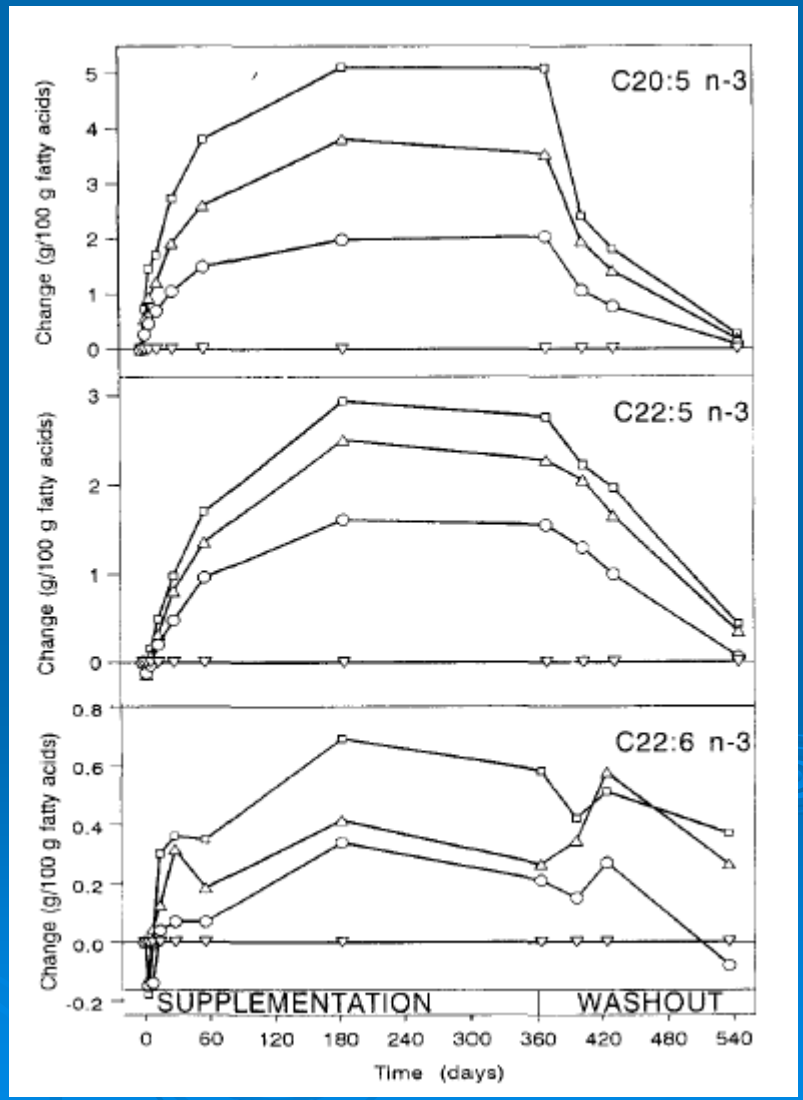


Rees et al. (2006) Am. J. Clin. Nutr. 83, 331-342

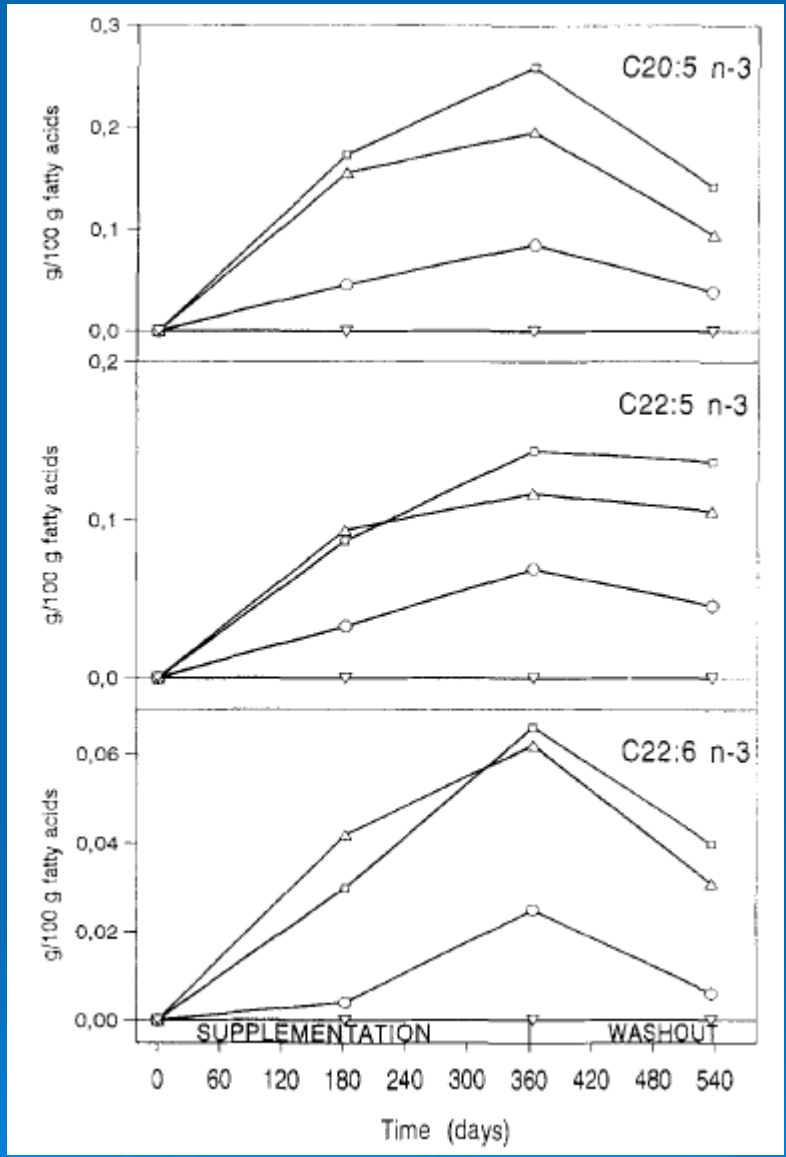
Data from Katan et al. (1997) J. Lipid Res. 38, 2012-2022



Serum CE



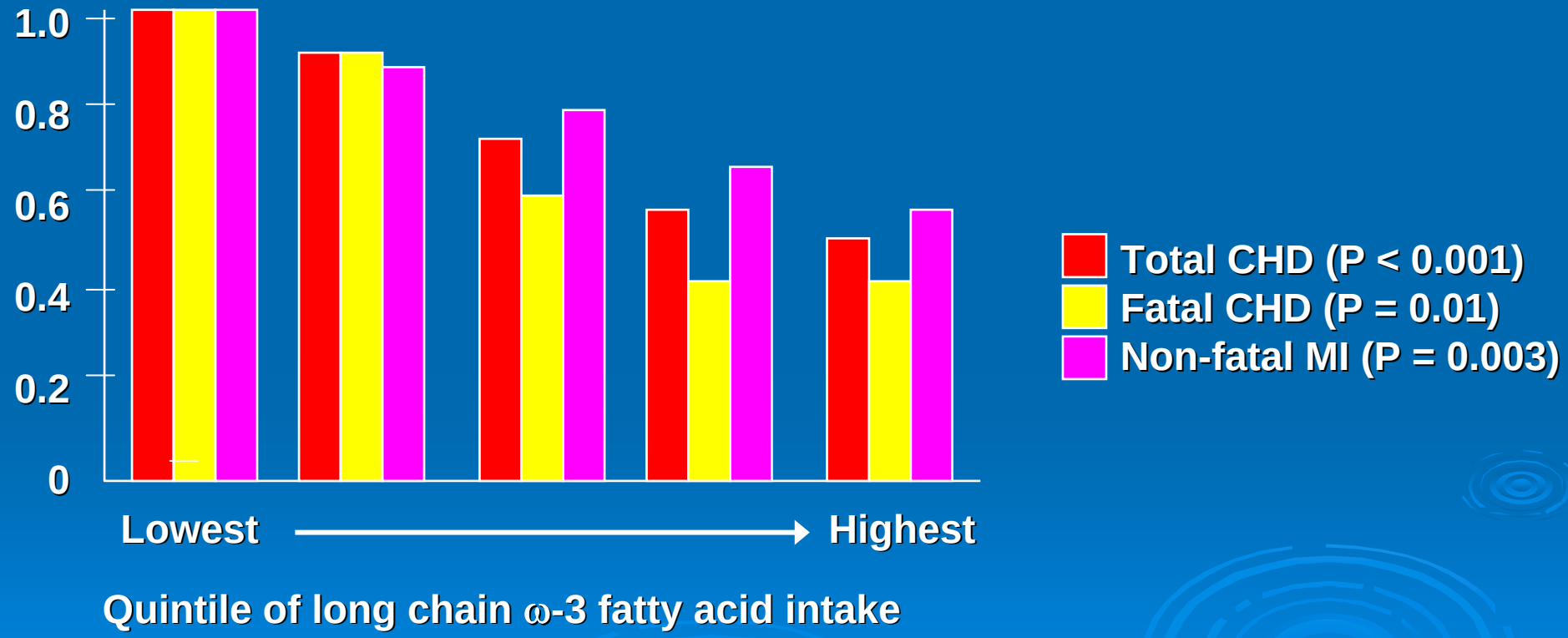
Red blood cells



Adipose tissue

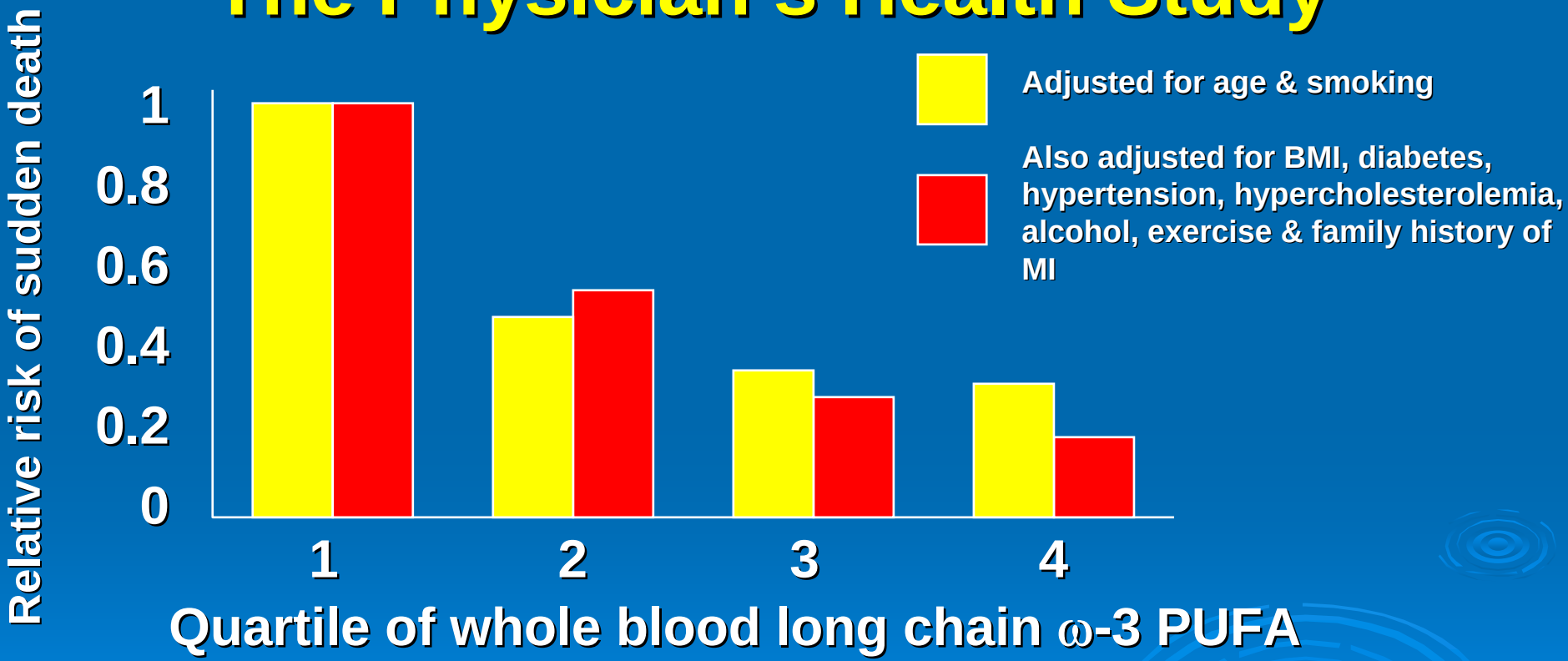
What is the health impact of increased intake (& status) of long chain ω-3 PUFAS?

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

CVD : Classic and emerging risk factors

CLASSIC:

Age
Gender
Family history (genetics)

Smoking

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

High serum 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

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Smoking

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EMERGING:

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

Elevated plasma homocysteine

Poor antioxidant status

✓ = Improved by ω-3 fatty acids

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

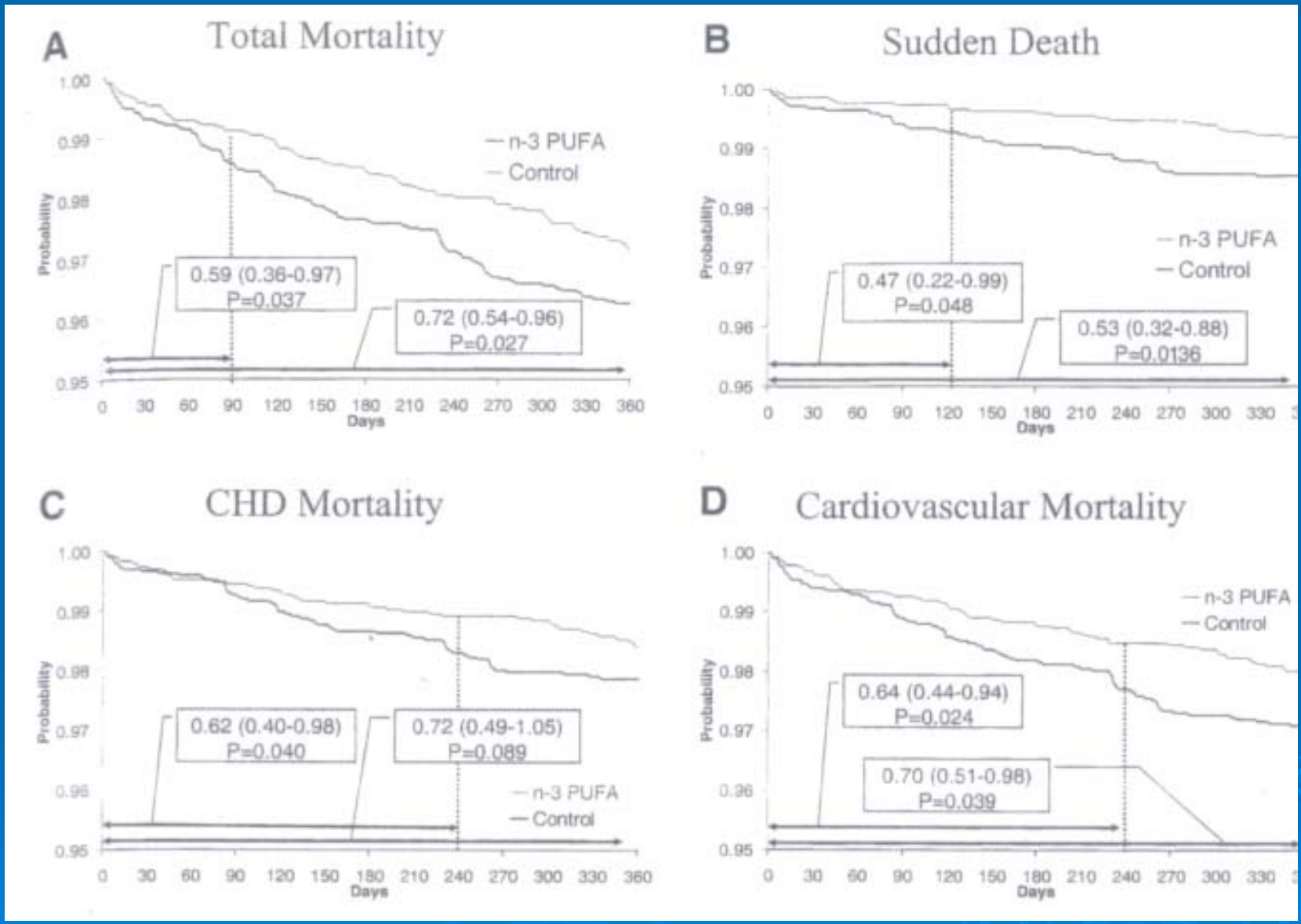
….. but ω-3 fatty acids also reduce risk of coronary events in people with advanced atherosclerosis

GISSI Prevenzione Study

- Patients with MI within the last 3 months assigned to ω-3 fatty acids (ca. 0.9 g/d) vs. placebo
- Follow up for 3.5 years
- 356 deaths and non-fatal CV events in ω-3 fatty acid group vs. 414 in placebo group

RRR in ω-3 fatty acid group	
All fatal events	-20%
CV death	-30%
Coronary death	-35%
Sudden death	-45%
Other deaths	-1%

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 ω-3 fatty acids

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

The benefits of long chain ω-3 PUFAs go beyond cardiovascular health

Long chain ω-3 PUFAs are important in:

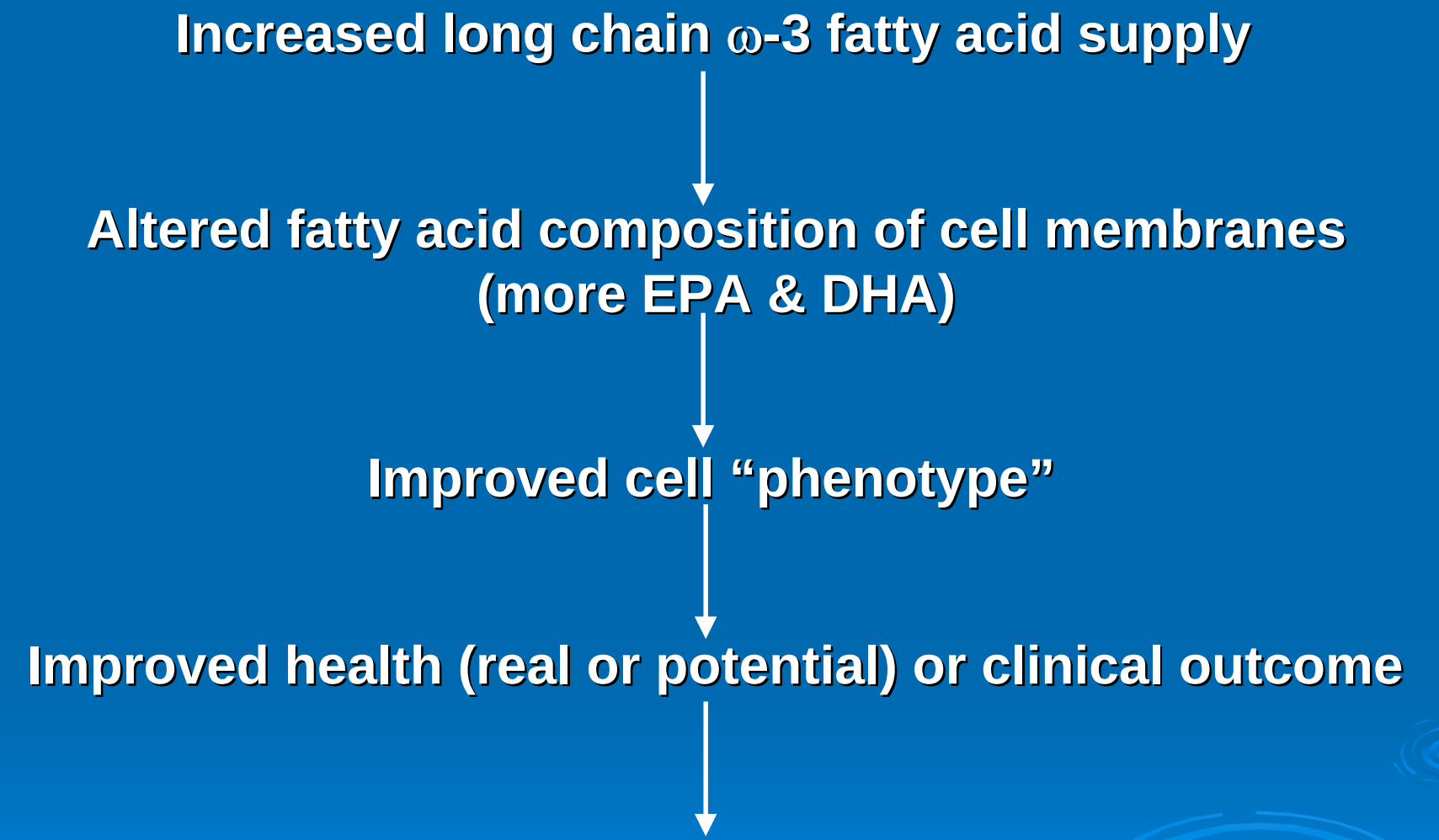
- membrane structure
- growth
- development and function of brain, neural tissue and eye
- regulation of
    - blood pressure
    - platelet function, thrombosis, fibrinolysis
    - blood lipid concentrations
    - vascular function
    - cardiac rhythmn
    - inflammation
    - immune response
    - bone health
    - insulin sensitivity

LC ω-3 PUFAs are 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

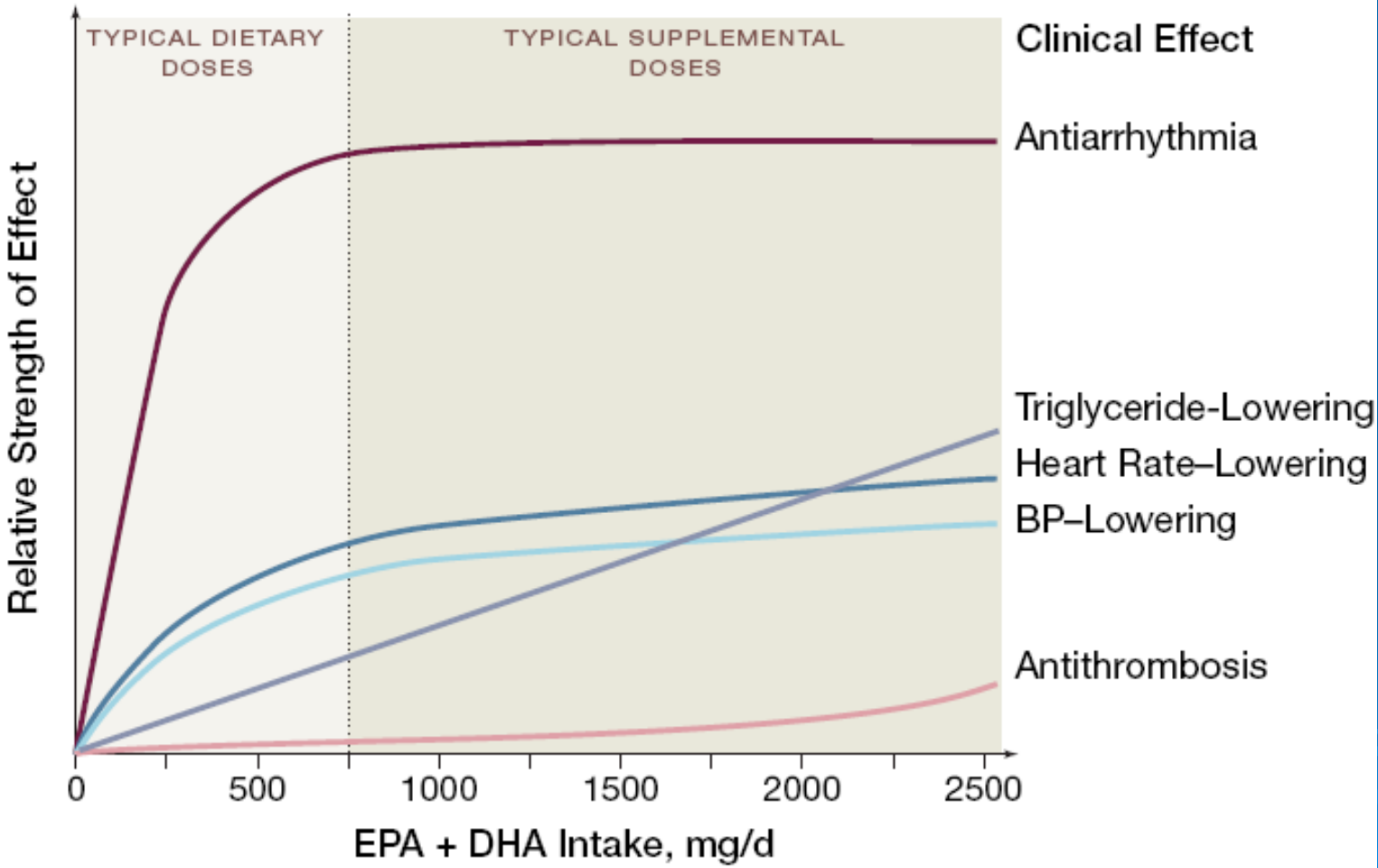
LC ω-3 PUFAs promote:

- optimal brain growth
- optimal visual and neural function


Increased long chain ω-3 fatty acid supply
Altered fatty acid composition of cell membranes (more EPA & DHA)
Improved cell “phenotype”
Improved health (real or potential) or clinical outcome
Dietary recommendations or new therapeutic potential

There is a clear need to increase intake and status of long chain ω-3 PUFAs

But … in many cases high intakes of ω-3 PUFAS are needed to elicit the desired effects



Mozaffarian et al. (2006) JAMA 296, 1885-1899

Implications of this for:

fish – one salmon or mackerel a day?

supplements – need to deliver > 1 g EPA+DHA (several capsules/day)

functional foods – how to deliver the desired amounts?

Murphy et al. (2007) Brit. J. Nutr. 97, 749-757

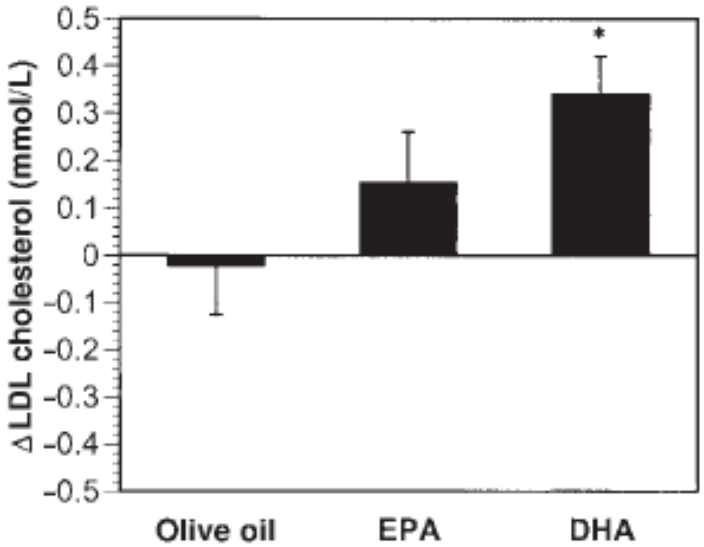
- Used long chain ω-3 PUFA enriched foods (biscuits, bread, cheese spread, chocolate, dips, eggs, margarine, milk, muesli, porridge, cakes, dressing, soups)
- Subjects consumed eight servings of enriched foods/day for 6 months
- Each serving would provide about 0.125 g EPA+DHA
- Mean intake of EPA+DHA increased from 0.2 to 1 g EPA+DHA/d
- EPA and DHA increased in red blood cells

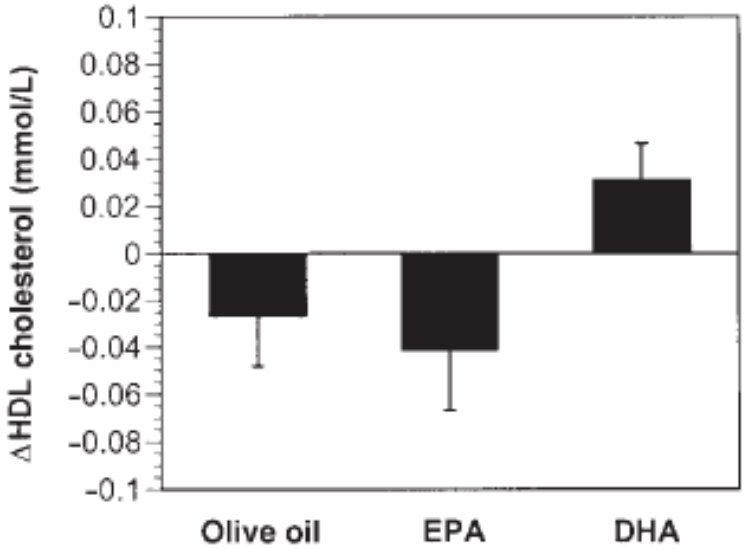
“There was no significant difference between omega-3 and control groups in the effects of the intervention for 3 or 6 months on the following parameters: systolic and diastolic blood pressure, compliance of small and large arteries, blood glucose, insulin, lipoprotein lipids (total, HDL and LDL cholesterol and TG), CRP or urinary 11-dehydro-TXB_2.”

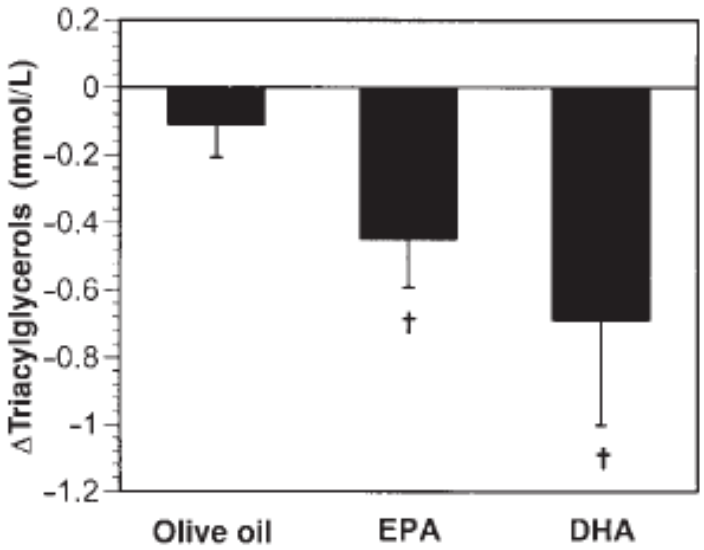
Achieving an effective intake (from fish, supplements or functional foods) may be difficult and is an important issue

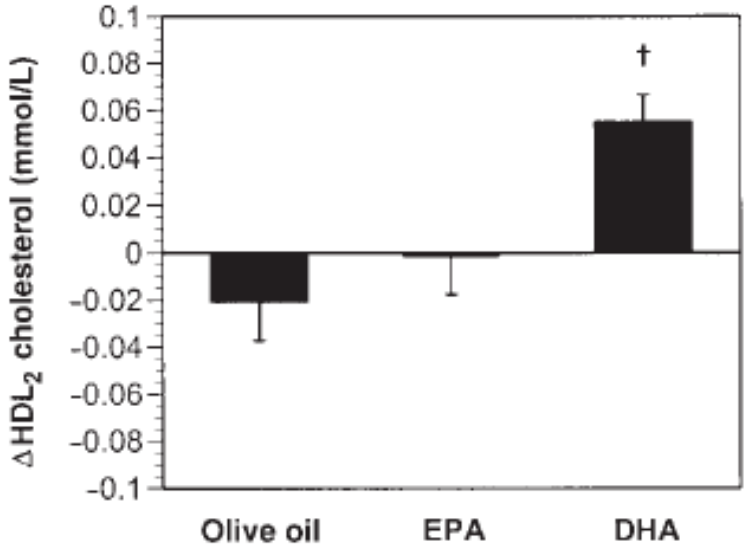
There are several other unresolved questions of importance

EPA or DHA?







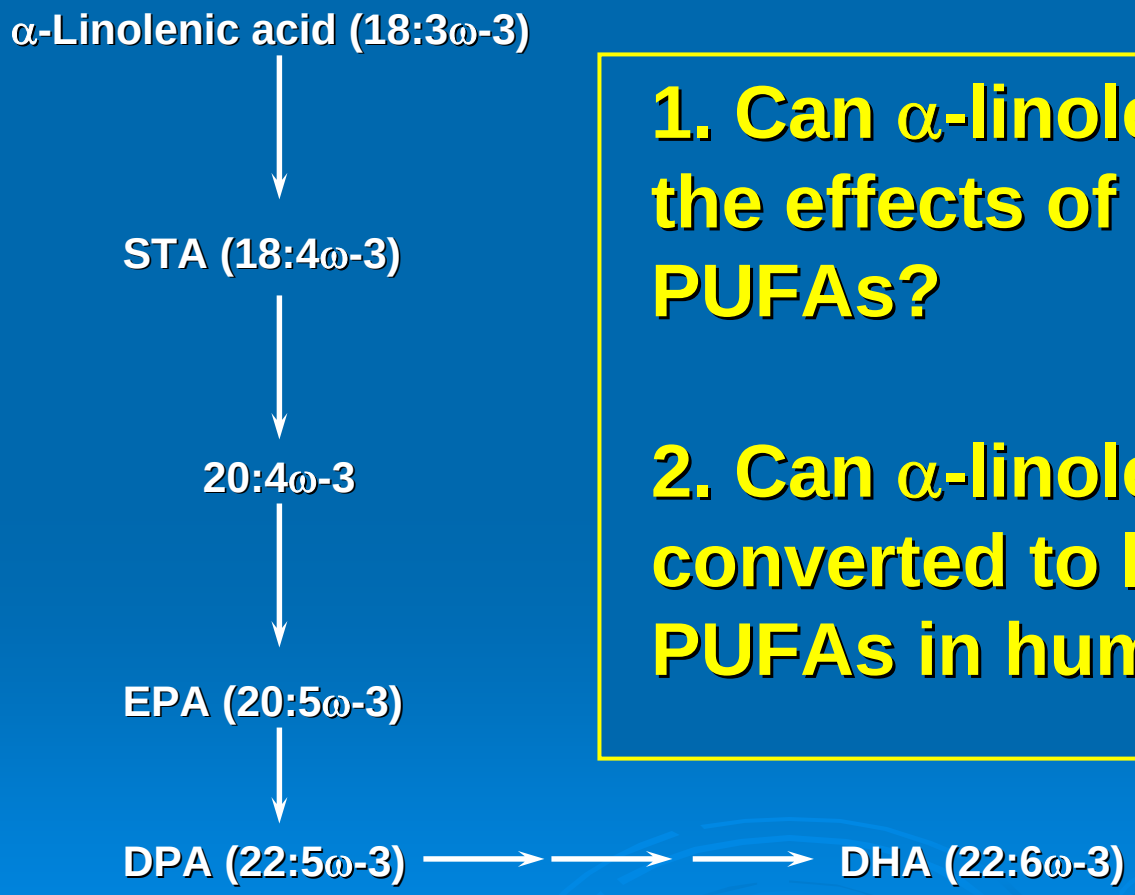


Mori et al. (2000) Am. J. Clin. Nutr. 71, 1085-1094

⇒ **EPA and DHA may have different effects and so cannot be regarded as equivalent**

What about α-linolenic acid?

Is α-linolenic acid an alternative ω-3 PUFAs?

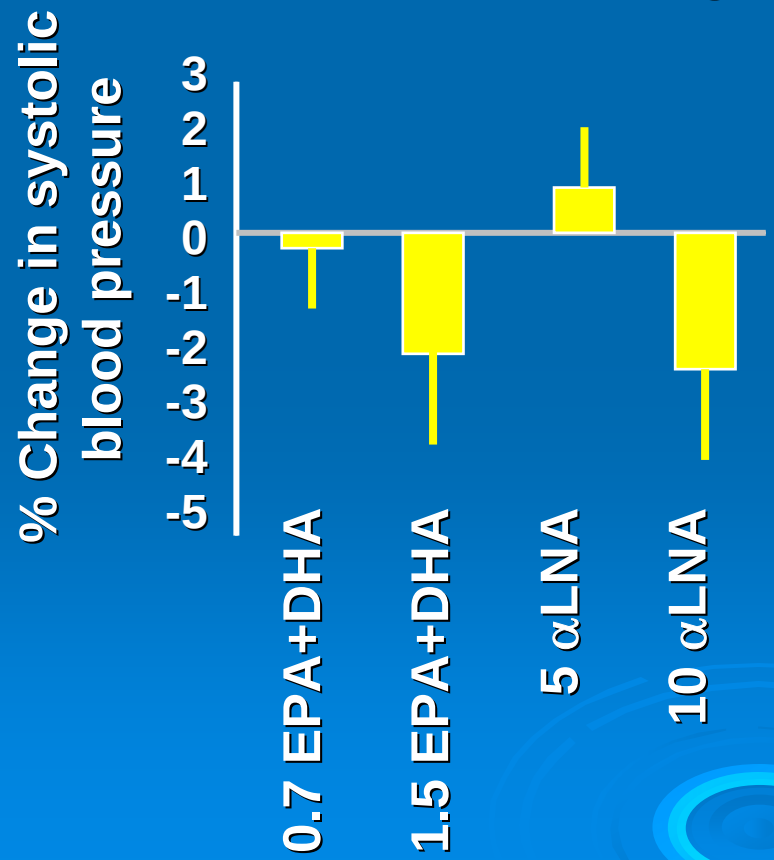


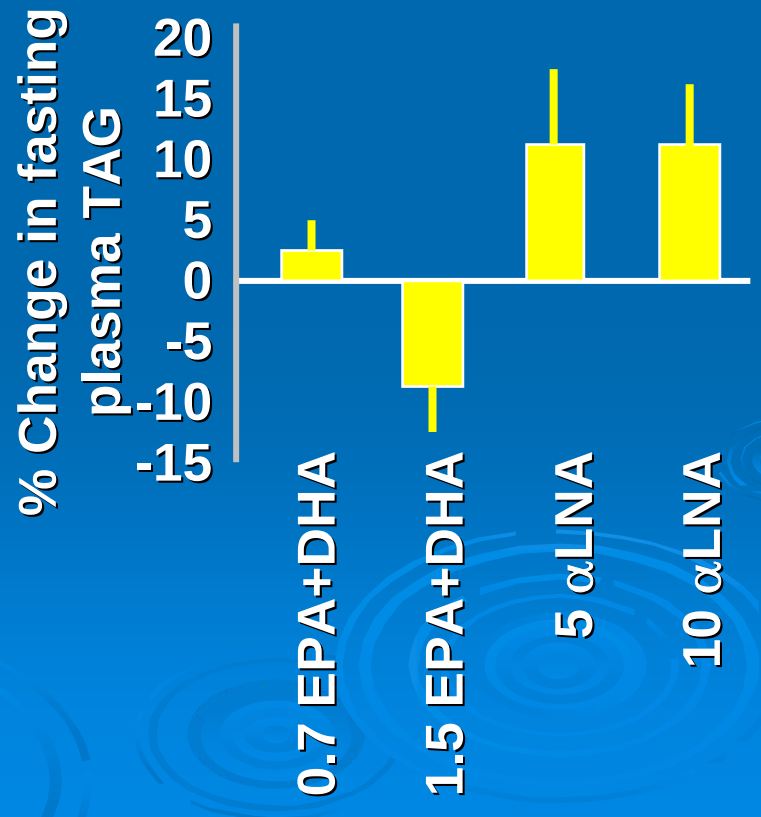
1. Can α-linolenic acid mimic the effects of long chain ω-3 PUFAs?

2. Can α-linolenic acid be converted to long chain ω-3 PUFAs in humans?

Finnegan et al. (2003)
Am. J. Clin. Nutr. 77, 783-795

Used margarines enriched in αLNA or EPA+DHA for 6 months





Functional effects of αLNA?

1. Relatively small increases in αLNA intake by subjects consuming typical amounts of αLNA (to give a total intake < 3.5 g/day) have little, if any, functional effect

2. Greater increases in αLNA intake (to give a total intake > 5 g/day) have some functional effects
- due to αLNA itself or
- due to conversion to EPA?

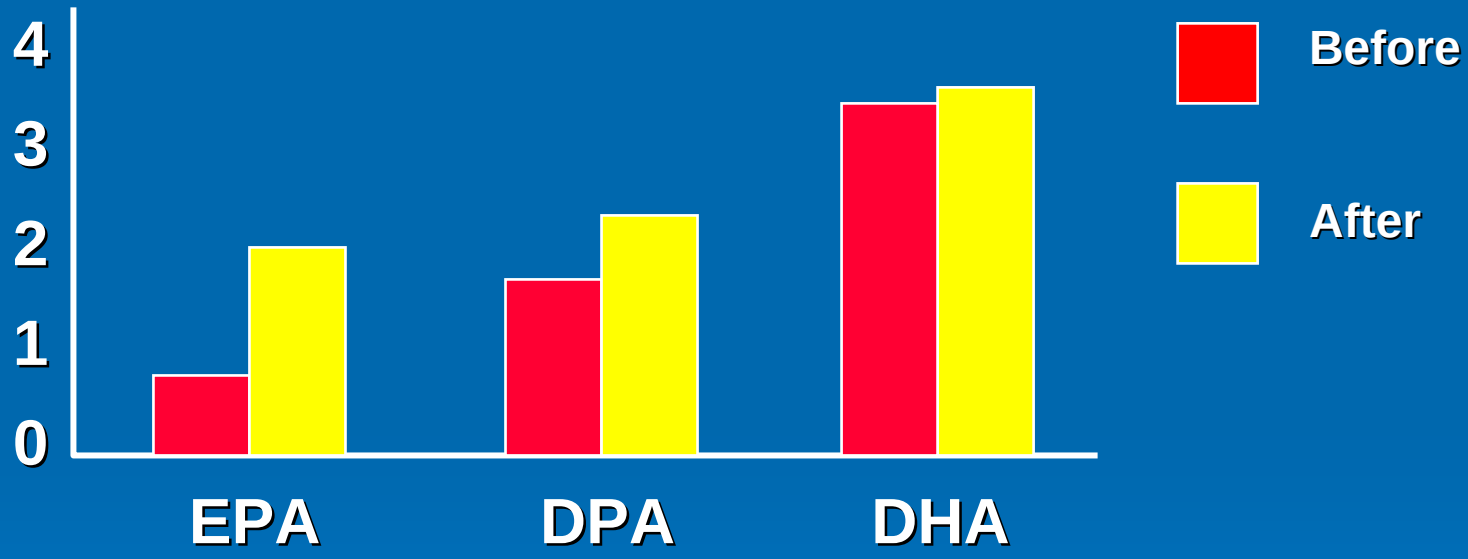
Is α-linolenic acid an adequate precursor for EPA and DHA in humans?

Two approaches have been used:

1. Increase intake of αLNA and look at alterations in fatty acid compositions

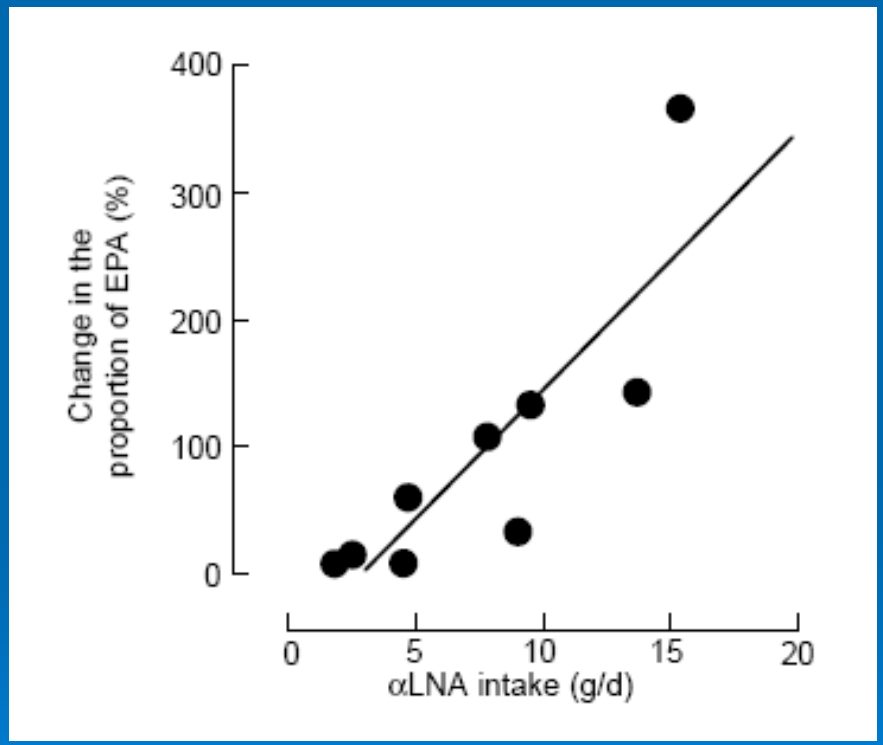
2. Stable isotope studies to trace αLNA metabolism

9.5 g αLNA/day Six months Plasma PL

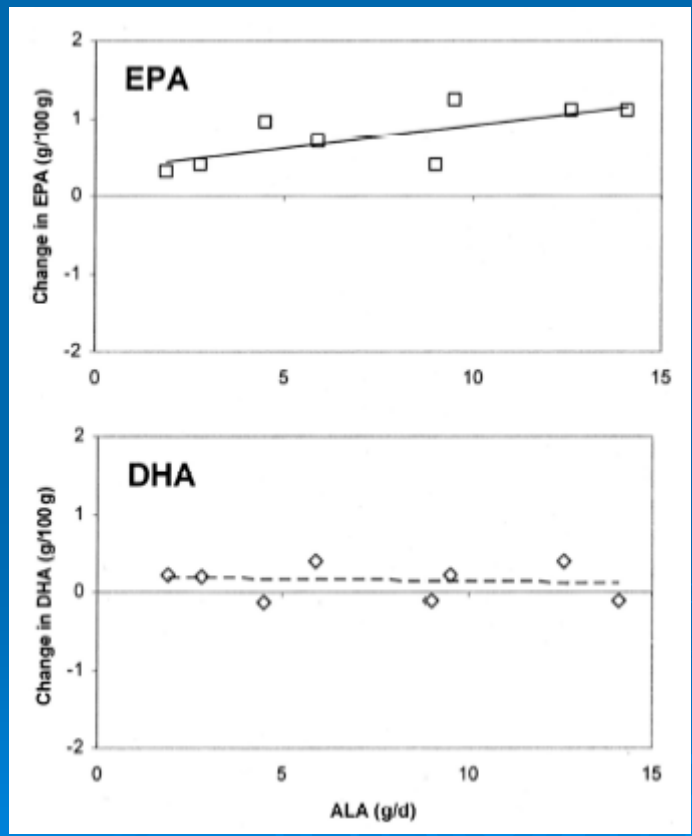


Finnegan et al. (2003) Am. J. Clin. Nutr. 77, 783-795

Effect of increasing αLNA on EPA and DHA content of plasma PL (human studies)

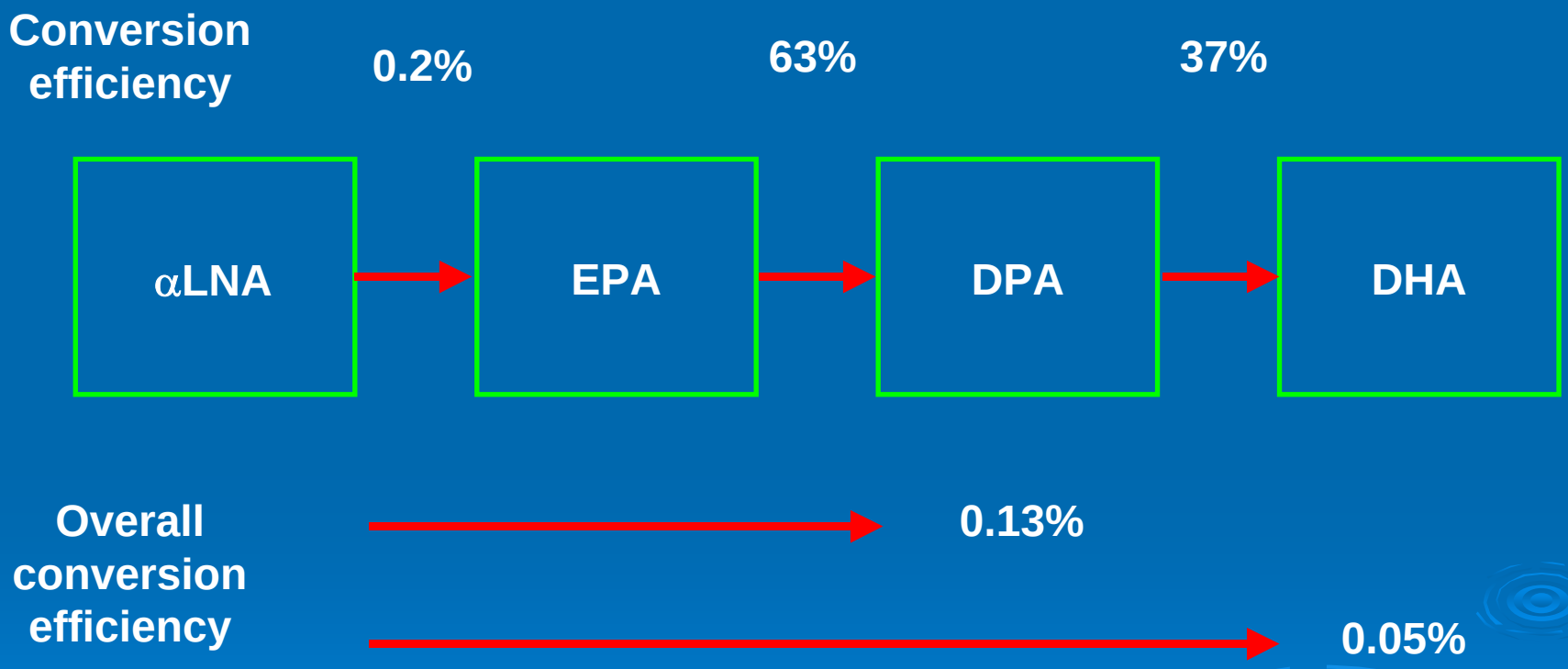


Burdge & Calder (2006) Nutr. Res. Rev. 19, 26-52



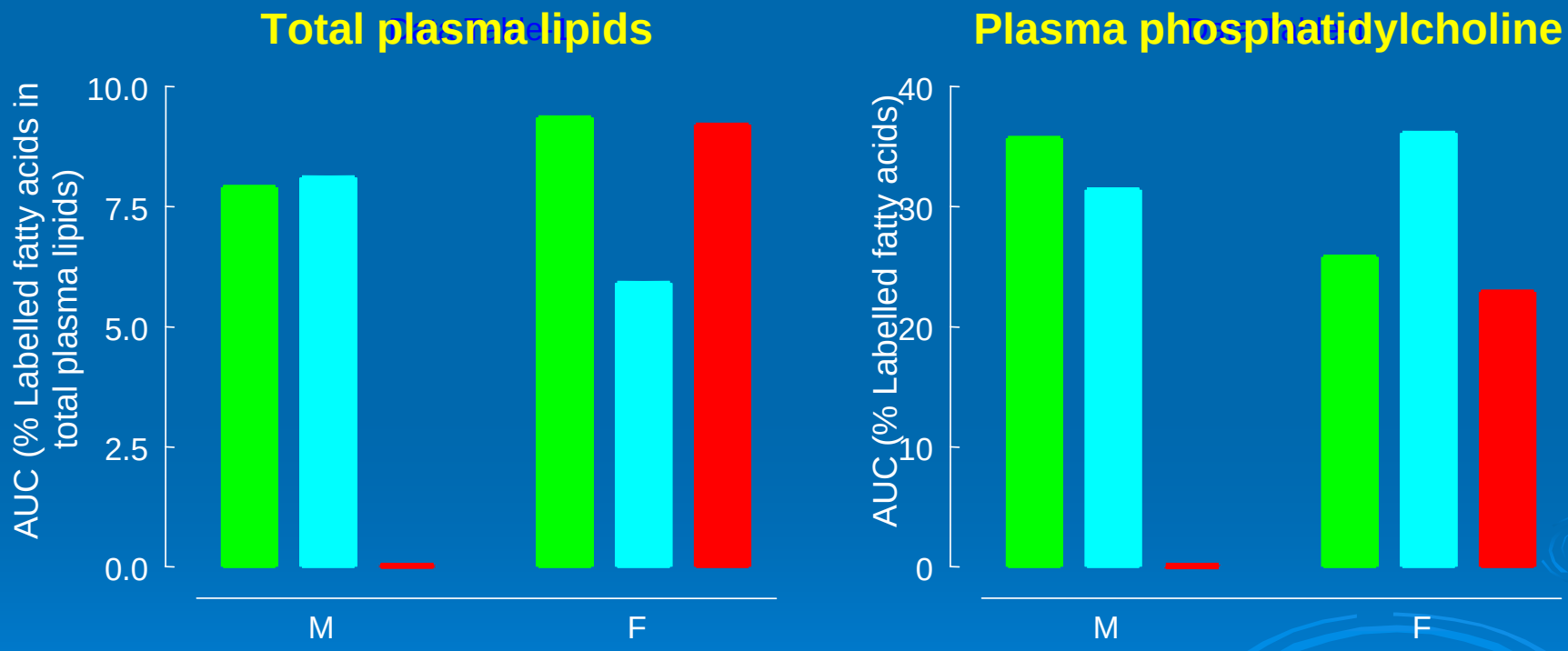
Arterburn et al. (2006) Am. J. Clin. Nutr. 83 (1467S-1476S

Estimated conversion efficiency based on kinetic modelling



Pawlosky et al. (2001) J. Lipid Res. 42, 1257-1265

Conversion of α-linolenic acid to longer-chain PUFA in men and women



Burdge et al. (2002) Brit. J. Nutr. 88, 355-363
Burdge & Wootton (2002) Brit. J. Nutr. 88, 411-420

Dietary studies show that αLNA is converted to EPA (and DPA), but not to DHA in humans

αLNA can mimic some effects of long chain ω-3 PUFAs but at a lower potency (ca. 10%)

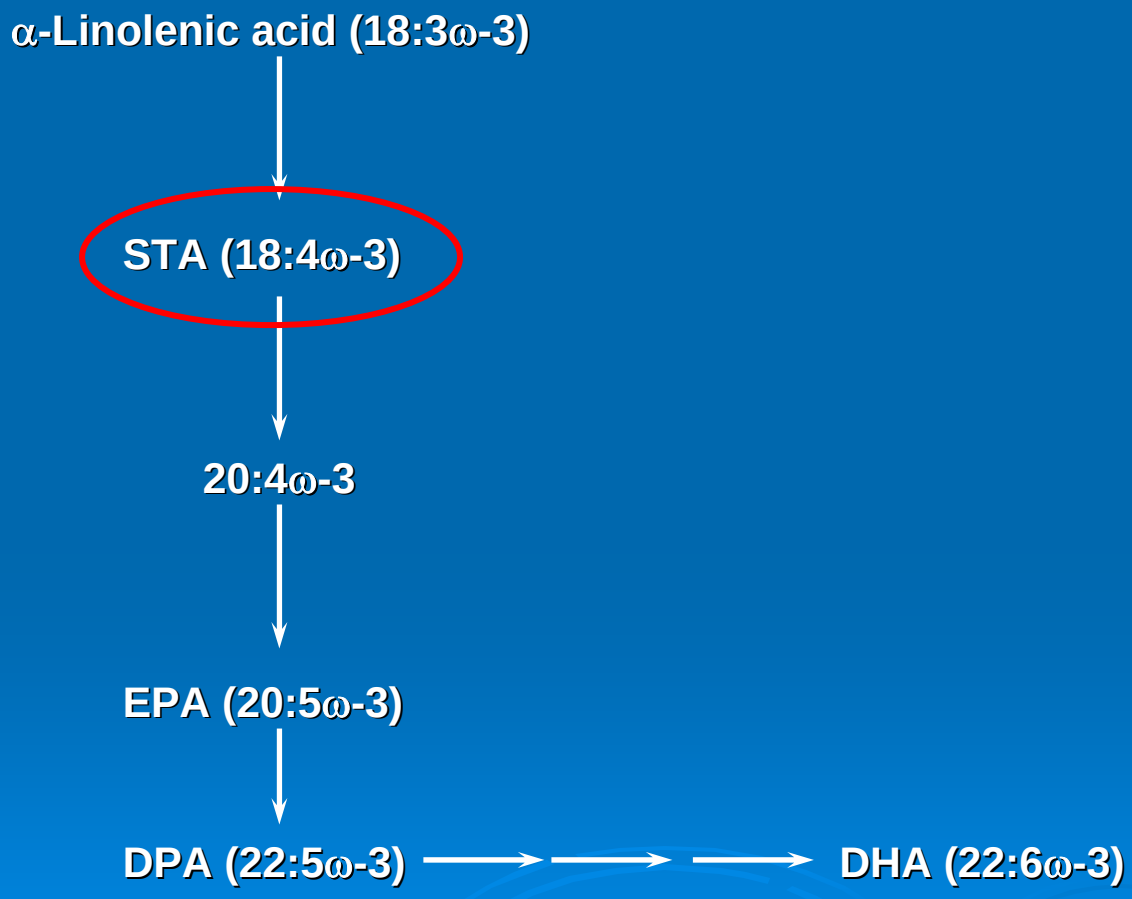
Stable isotope studies show that conversion of αLNA to long chain ω-3 PUFAs, especially to DHA, is limited

But conversion appears to be greater in females than males

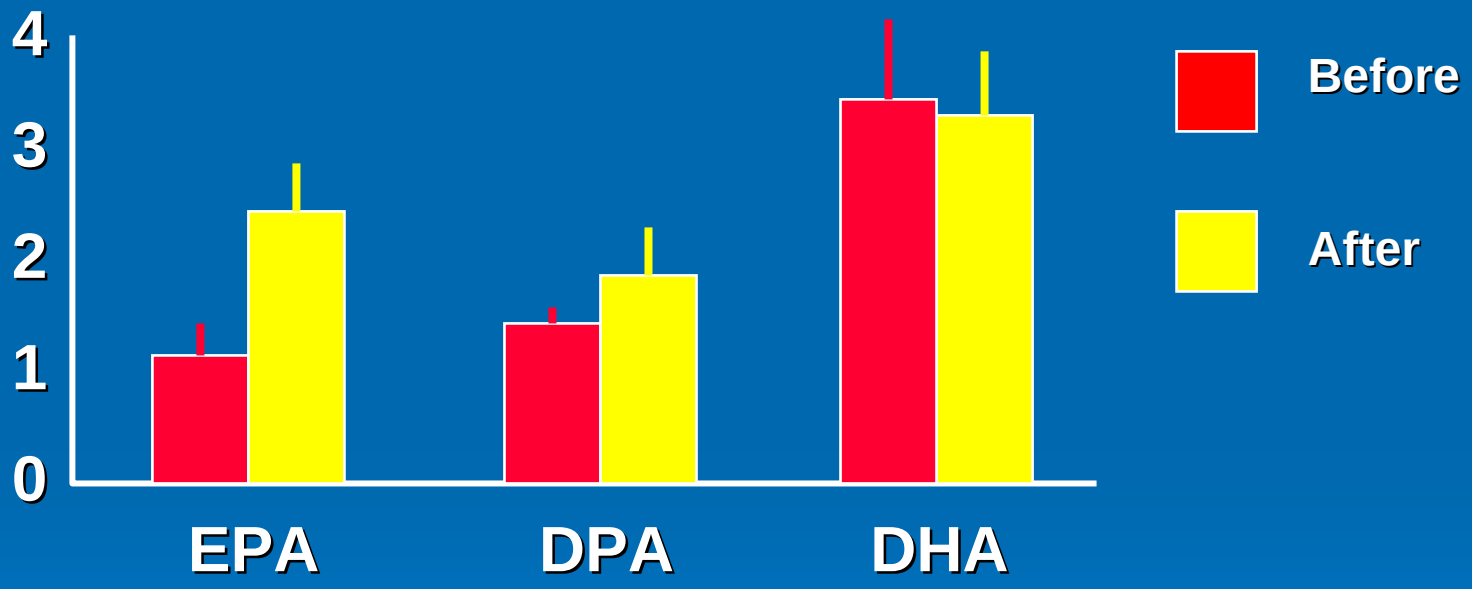
We do not know much about conversion in infants, adolescents, pregnant/lactating women, or the elderly

⇒ αLNA is NOT a replacement for preformed long chain ω-3 PUFAs

What about stearidonic acid?

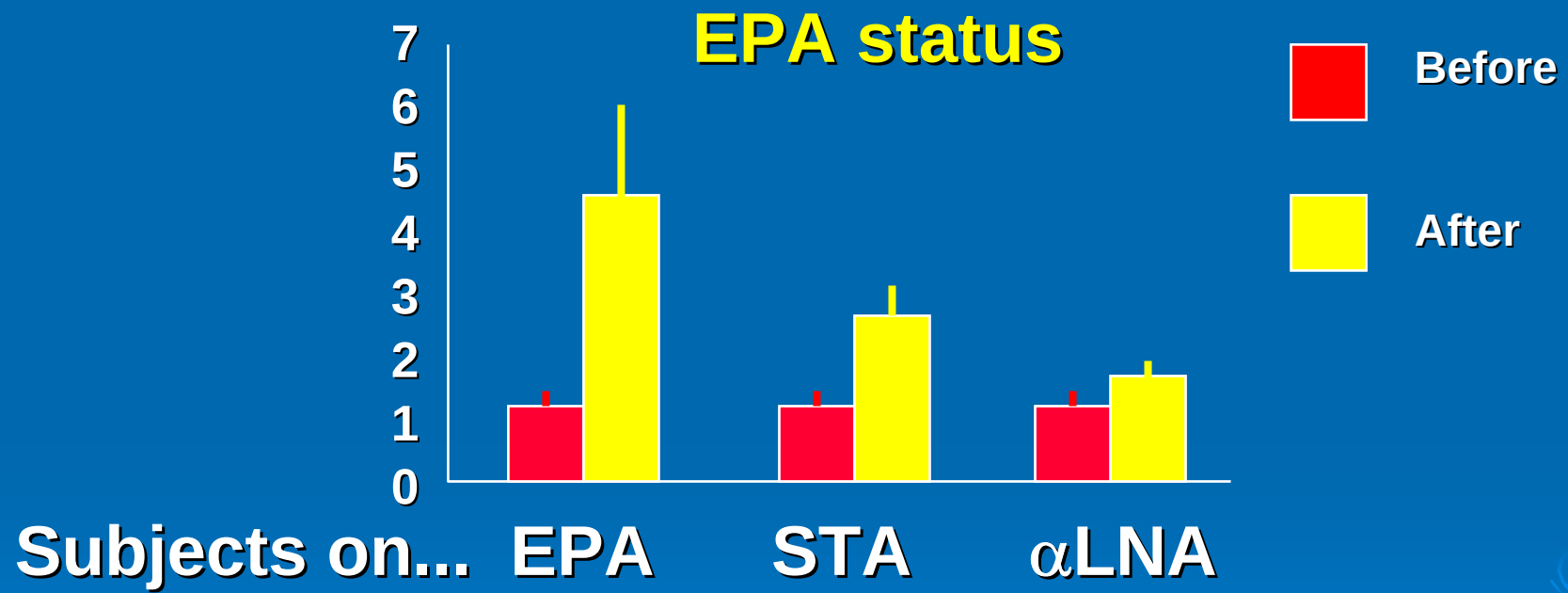


0.75 g STA/d 3 weeks then 1.5 g/d 3 weeks
Plasma PL



James et al. (2003) Am. J. Clin. Nutr. 77, 1140-1145

0.75 g EPA or STA or αLNA/d 3 weeks
then 1.5 g/d 3 weeks
Plasma PL



James et al. (2003) Am. J. Clin. Nutr. 77, 1140-1145

$\Rightarrow$ **Stearidonic acid produces more EPA than αLNA but is (also) not converted to DHA**

Potential strategies to increase long chain ω-3 PUFA status in humans

Metabolic	Dietary
Provide pre-formed long chain ω-3 PUFAs	Oily fish Fish oil capsules Fortified or enriched foods
Provide the precursor α-linolenic acid (18:3ω-3)	Vegetable oils (e.g. soybean, rapeseed) Flaxseed/Flaxseed oil Fortified or enriched foods
Provide the precursor stearidonic acid (18:4ω-3)	Unusual vegetable oils

Potential strategies to increase long chain ω-3 PUFA status in humans

Metabolic	Dietary	Comment
Provide pre-formed long chain ω-3 PUFAs	Oily fish	Good but may not be viable
	Fish oil capsules	Good but may not be desirable for populations (algal oils)
	Fortified or enriched foods	Good future potential but limited foods currently available
Provide precursor α-linolenic acid (or STA)	Vegetable oils	May be a viable way to increase EPA but requires high intake Does NOT increase DHA Need to decrease linoleic acid intake too (competition)
	Flaxseed/Flaxseed oil	
	Fortified or enriched foods	

These general statements assume that all individuals, irrespective of gender, age, physiological state, genetics etc. will respond to ω-3 PUFAs in the same way

This may not be the case

Certainly we now know that genotype may be important in determining the effect of long chain ω-3 PUFAs

TABLE 2. Impact of ApoE Genotype on Responsiveness of Lipid and Lipoprotein Fractions to Fish Oil Supplementation

	% Change				
Variable	All (n=50)	ApoE2 (n=8)	ApoE3 (n=22)	ApoE4 (n=20)	*P**
TG	−35.3±5.3†	−30.7±7.6	−34.9±7.0	−37.6±10.6	0.561
TG AUC	−23.3±3.0†	−32.5±4.6	−18.4±4.3	−24.8±5.2	0.136
TG IAUC	−7.9±5.6†	−27.7±7.0[a]	−2.7±10.0[b]	−5.5±8.2[b]	0.023
TC	−1.5±2.1	−1.1±3.8[a]	−6.3±2.8[a,b]	3.5±3.5[a,c]	0.014
HDL-C	−0.8±3.3	12.2±5.5	0.6±4.1	−7.4±6.3	0.806
LDL-C	7.1±3.2‡	3.1±5.4	0.6±4.5	15.9±4.0	0.120
% LDL-3	−26.0±8.3†	−31.0±40.3[a]	−17.2±8.8[a,b]	−35.7±13.6[a,c]	0.021
LPL	14.7±14.5§	47.2±29.7	2.1±9.7	17.3±33.9	0.177
NEFA	−7.8±4.8†	−22.1±5.9	−5.7±5.7	−4.1±9.9	0.616
NEFA AUC	−7.4±3.2†	−18.3±6.7	−4.8±4.7	−5.7±6.3	0.608

Minihane et al. (2000) ATVB 20, 1990-1997

Conclusions

- Intake of EPA and DHA is typically low
- Status of EPA and DHA is increased with increased intake (time, dose & pool dependent)
- Increased EPA and DHA intake leads to altered physiology and is associated with improved health
- But effects may require > 0.75 g/day
- EPA and DHA probably have different but overlapping effects
- α-LNA increases EPA but not DHA status
- α-LNA is less potent than EPA
- SDA increase EPA more than α-LNA does
- There are individual-specific responses to EPA and DHA that depend upon genotype -> a challenge and an opportunity