Marine omega-3 fatty acids in clinical nutrition

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NHS
National Institute for Health Research

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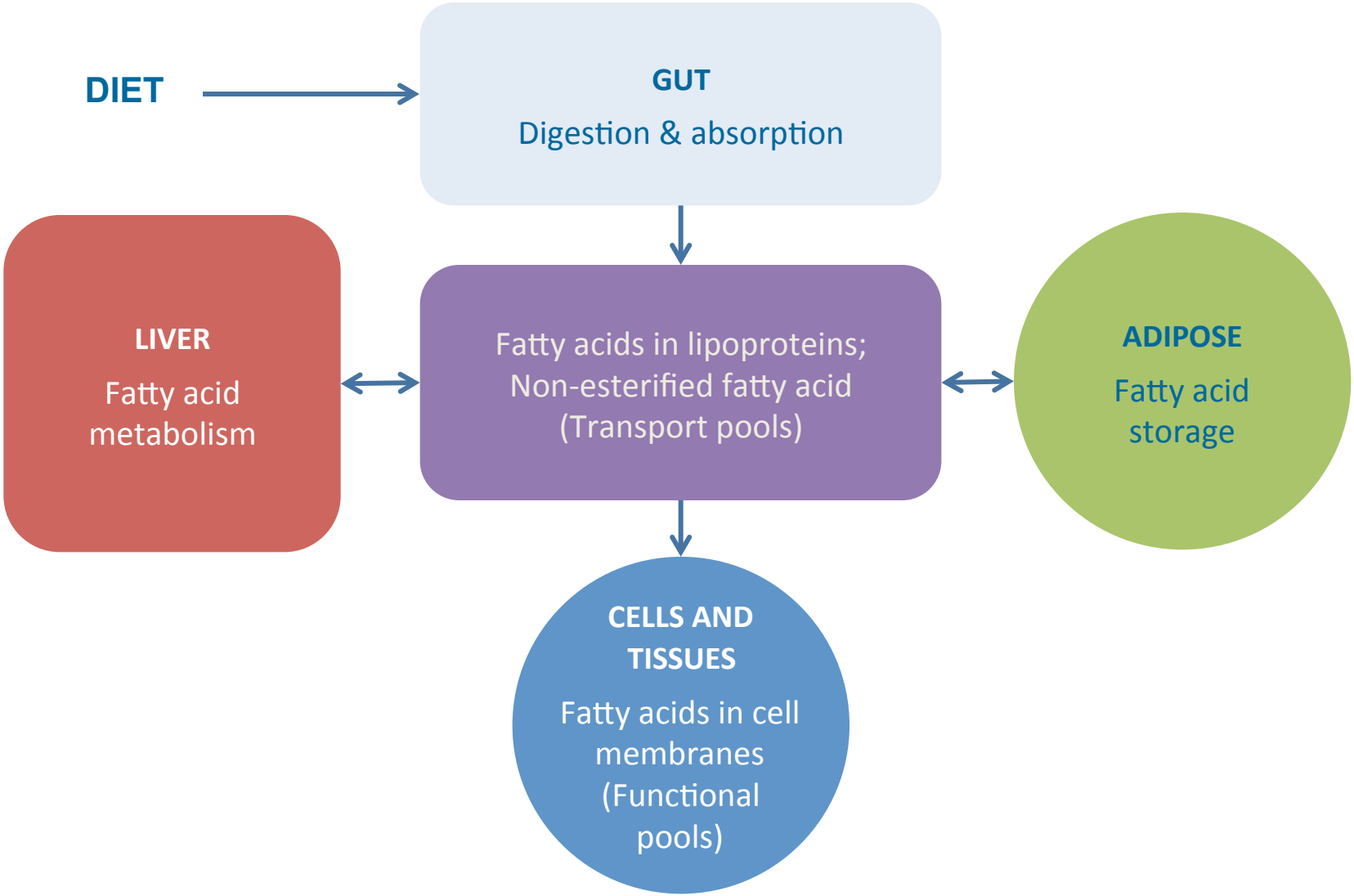
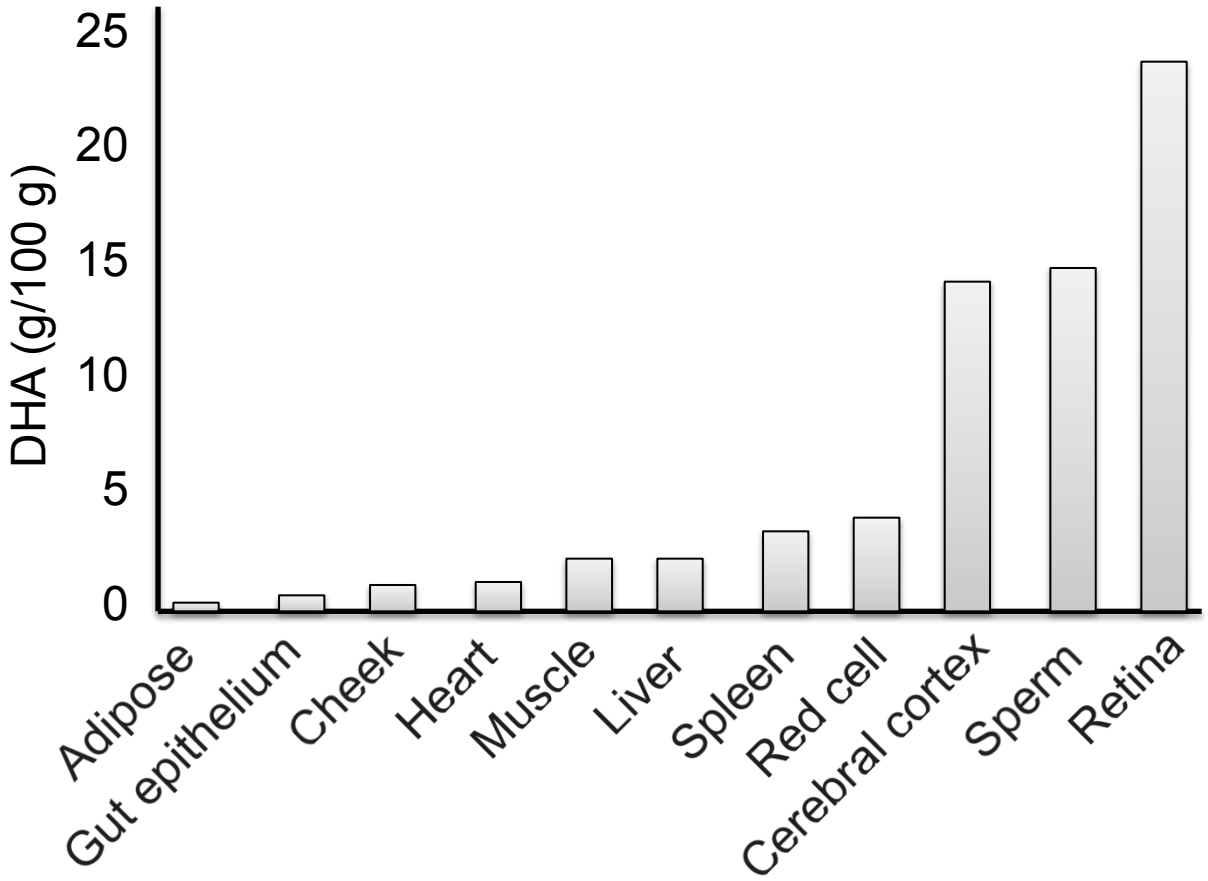
Fatty acids including EPA and DHA are normally found in esterified form

- In triglycerides:
  - Food (95% of fatty acids in the diet are in the TAG form)
  - Adipose tissue (stored as TAG)
  - Blood (lipoproteins)
  - Tissues (e.g. liver; muscle)
  - Intravenous lipid emulsions
- In phospholipids:
  - Food
  - Blood (lipoproteins)
  - Cell membranes
- In cholesteryl esters:
  - Blood (lipoproteins)

OVERVIEW OF WHOLE BODY FATTY ACID METABOLISM

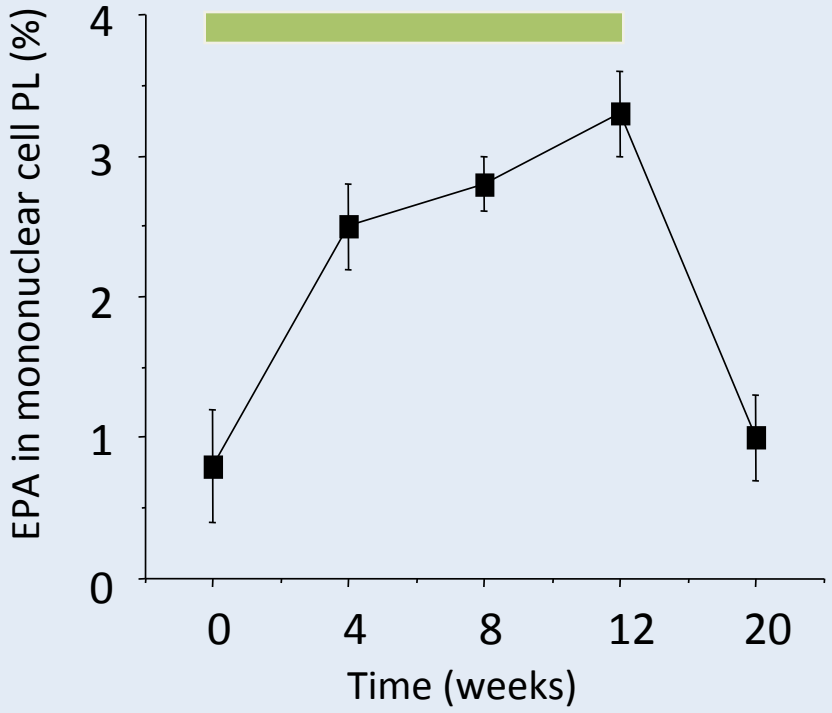


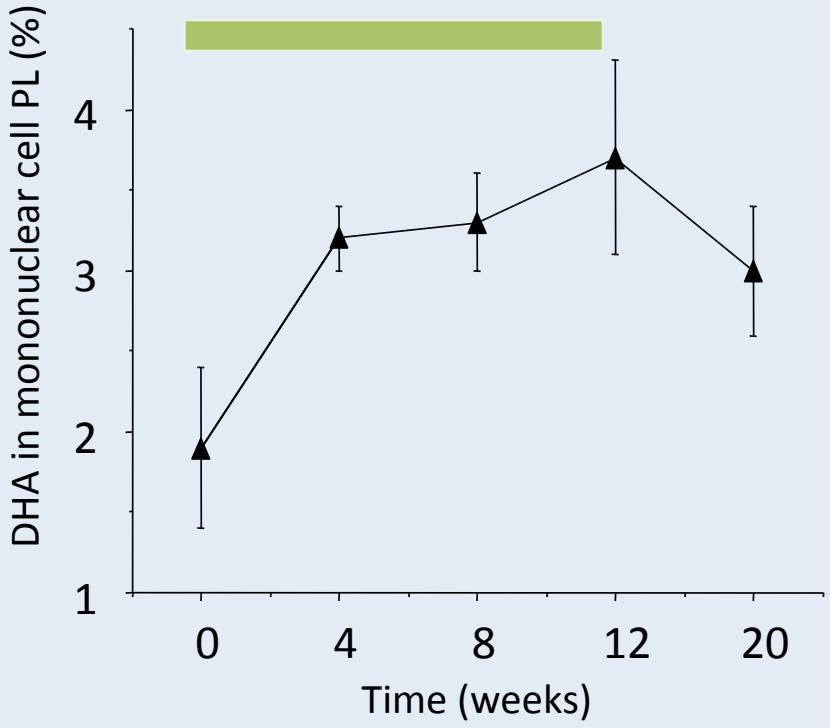
The fatty acid compositions of different pools are different



The amount of EPA and DHA in cells and tissues increases with intake

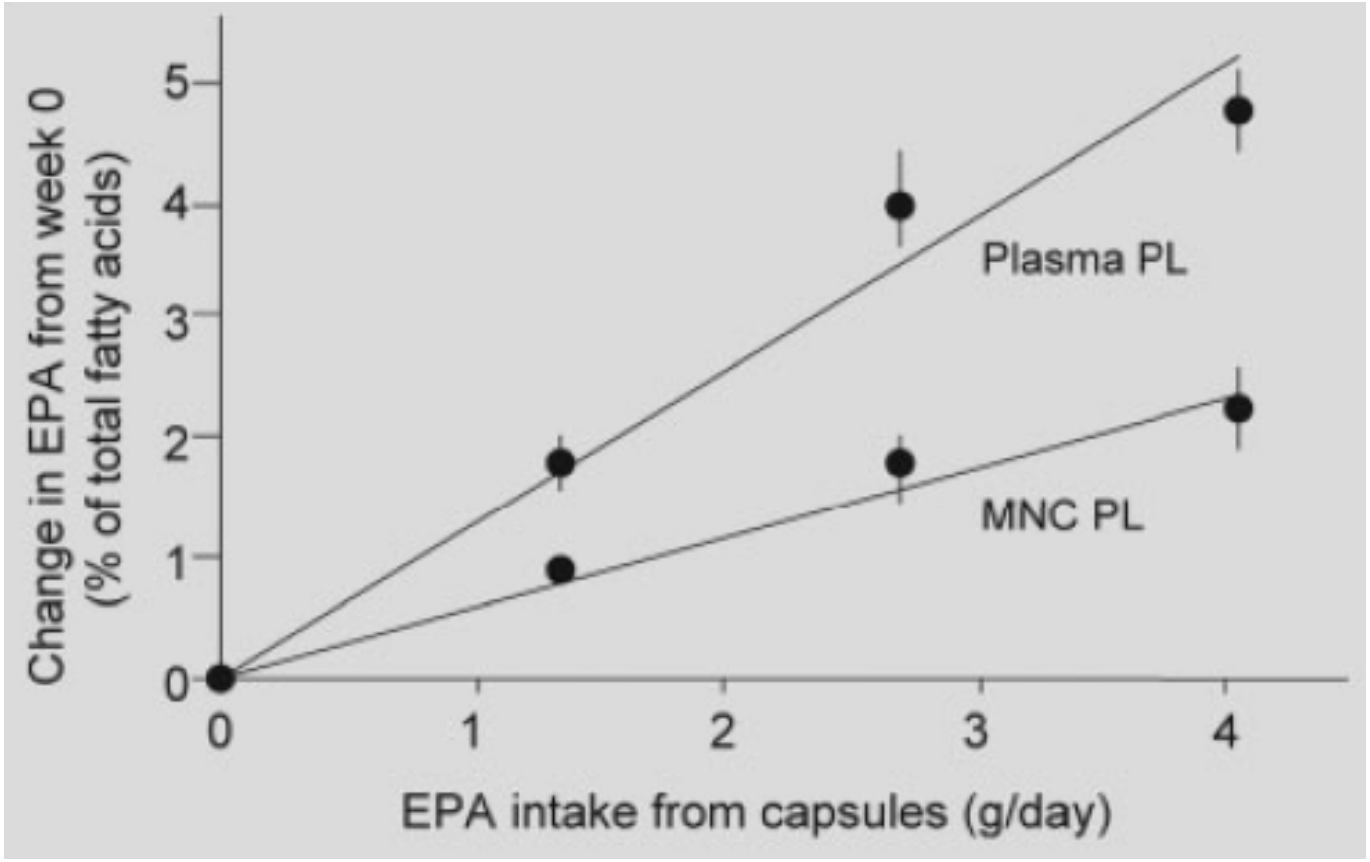
Healthy volunteers given fish oil (2.1 g EPA and 1.1 g DHA/day) for 12 weeks





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

Dose response of incorporation of EPA in humans



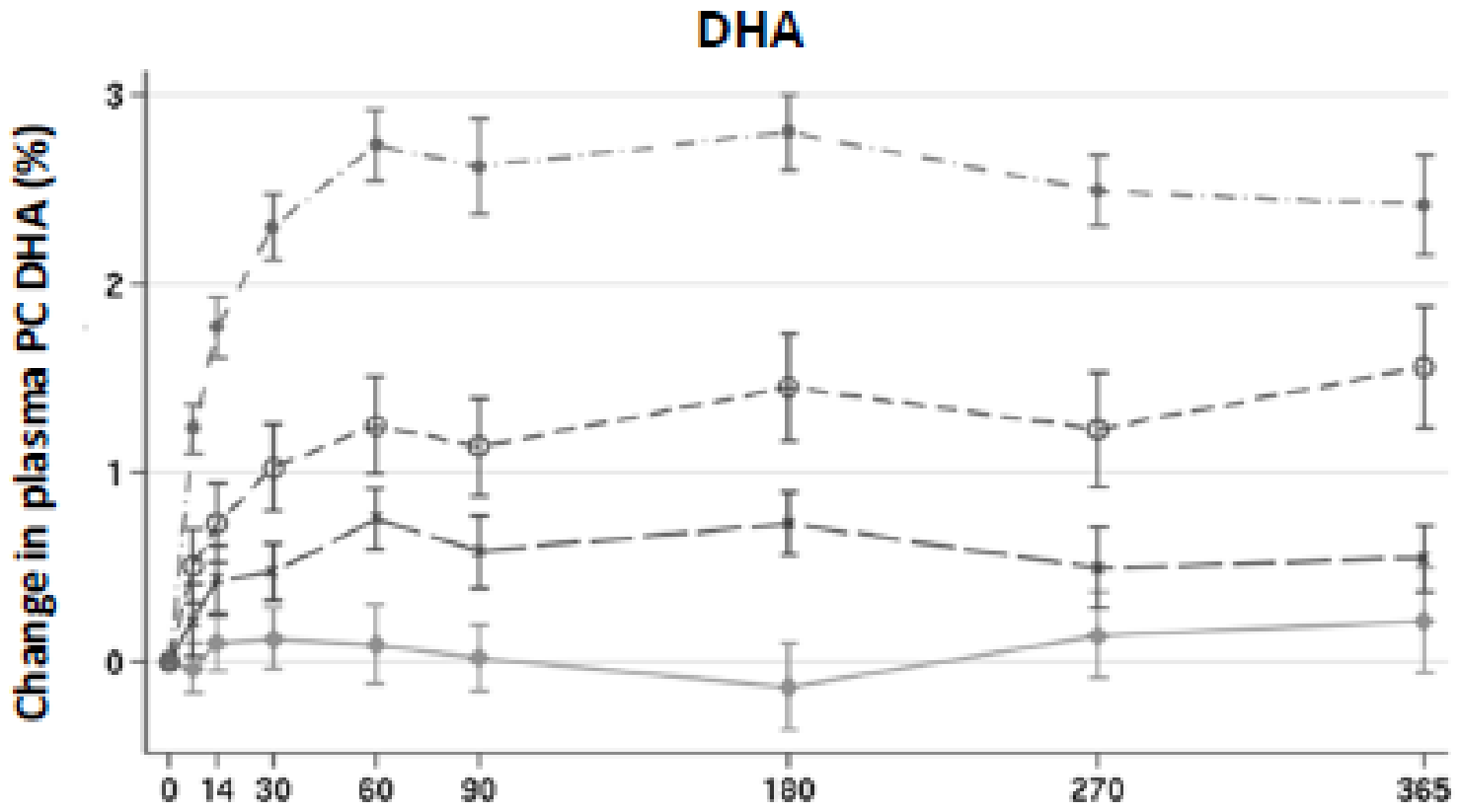
Rees et al. (2006) Am. J. Clin. Nutr. 83, 331-342

Increasing EPA+DHA availability (either orally or intravenously) increases the EPA and DHA content of blood lipids, blood cells, and tissues – effect is dose, time and tissue dependent

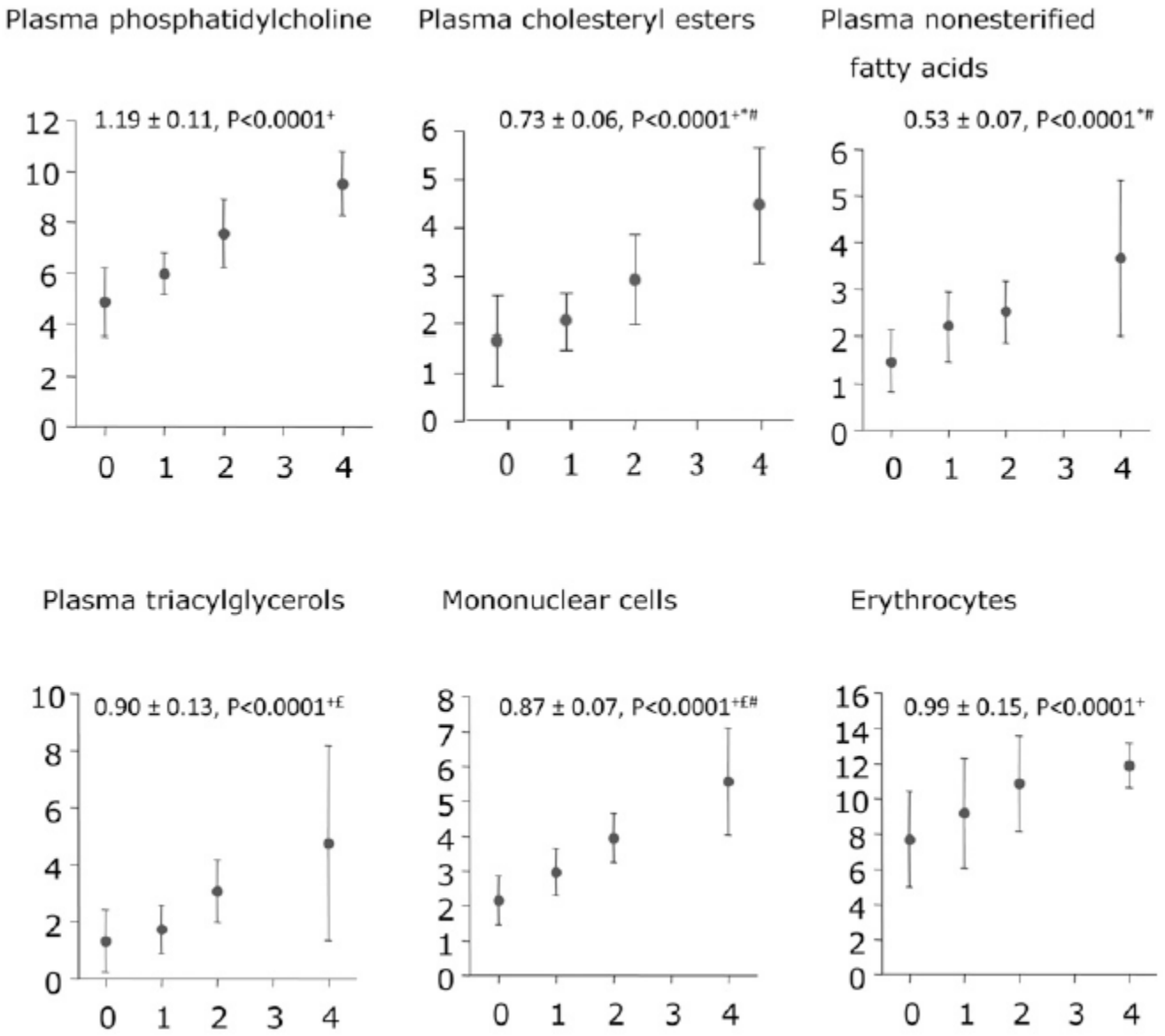
Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish[1–4]

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.


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

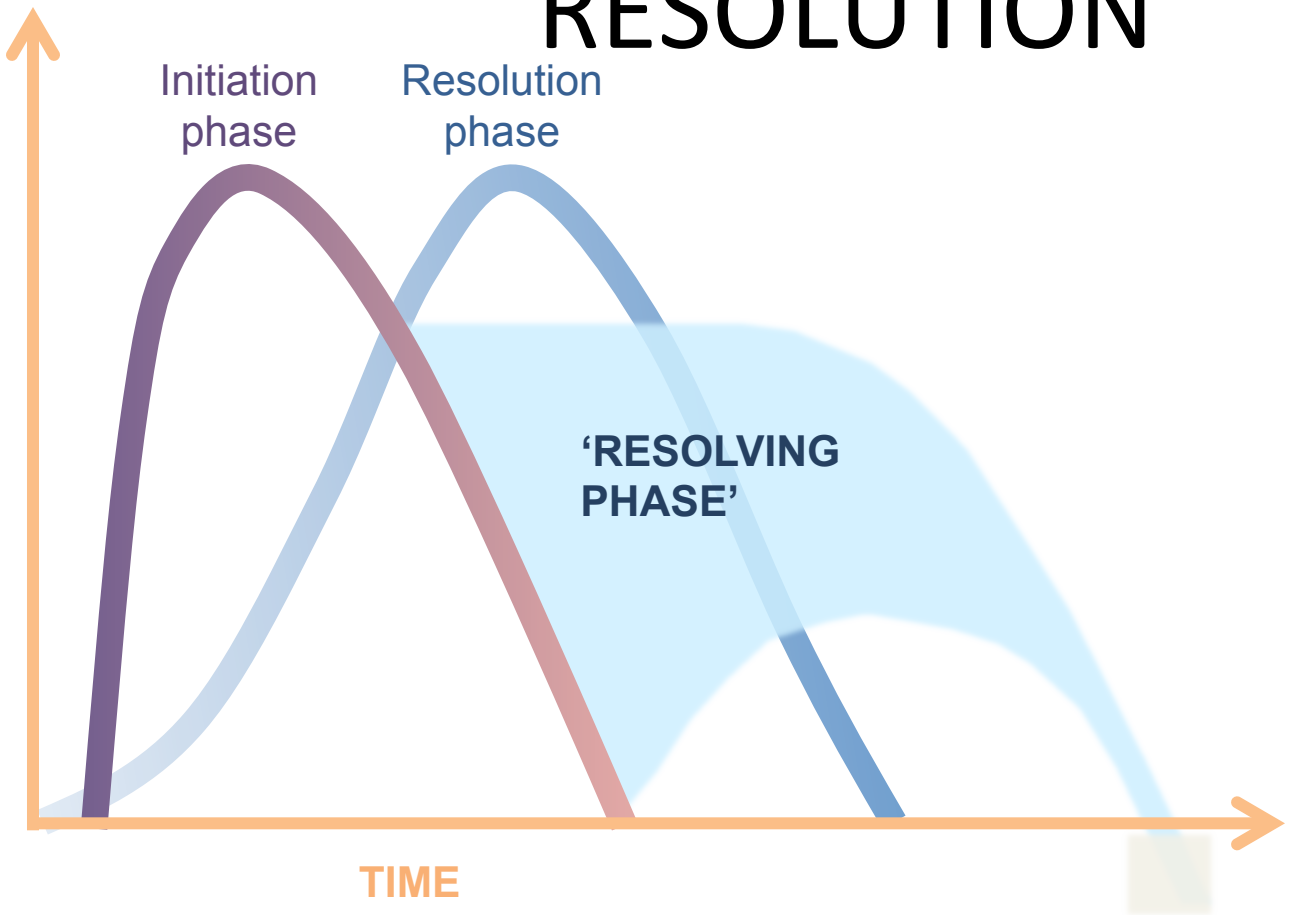
EPA + DHA


Plasma phosphatidylcholine
1.19 ± 0.11, P<0.0001+
Plasma cholesteryl esters
0.73 ± 0.06, P<0.0001+*#
Plasma nonesterified fatty acids
0.53 ± 0.07, P<0.0001*#
Plasma triacylglycerols
0.90 ± 0.13, P<0.0001+£
Mononuclear cells
0.87 ± 0.07, P<0.0001+£#
Erythrocytes
0.99 ± 0.15, P<0.0001+

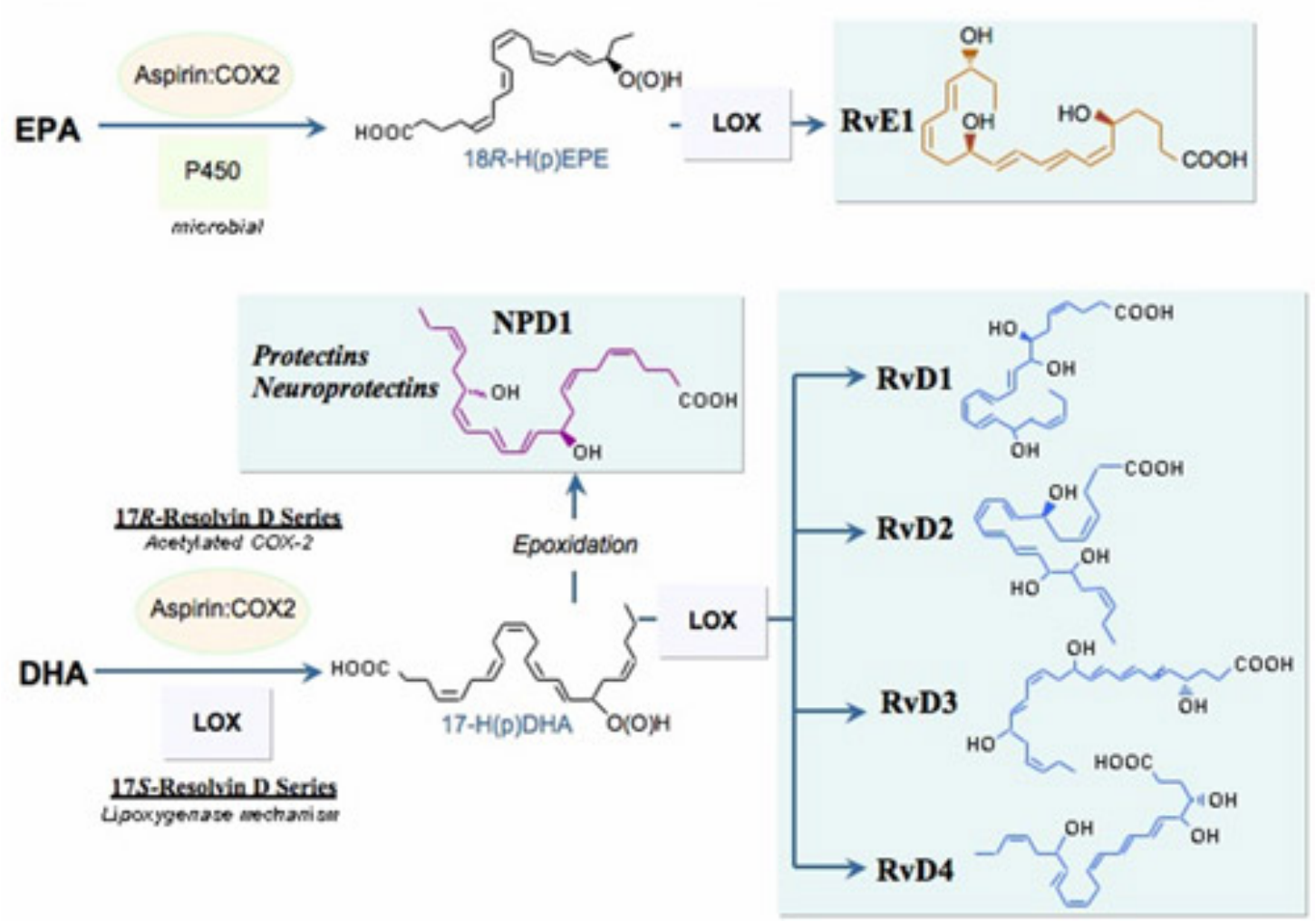
Special functions of ω-3 fatty acids

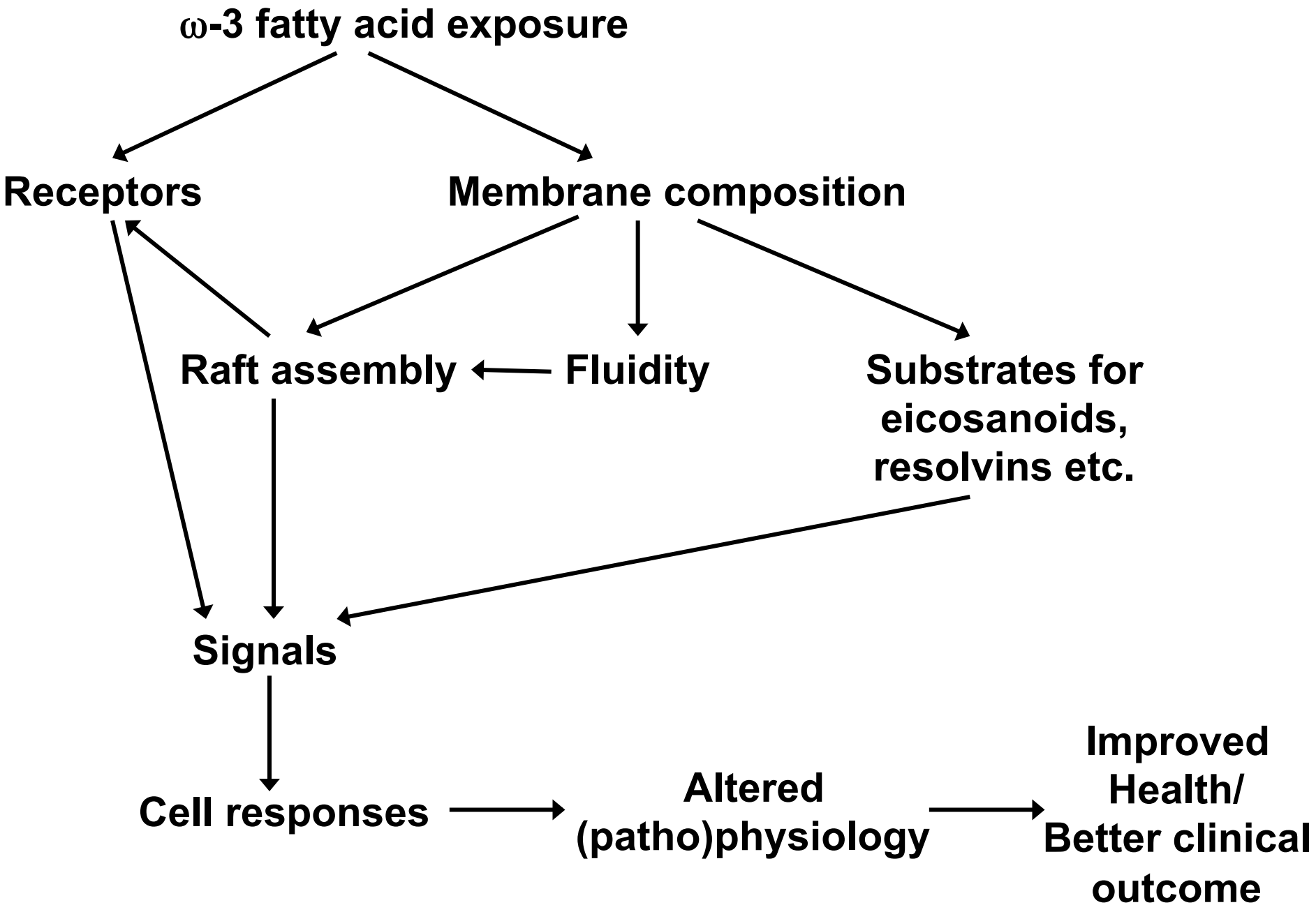
- Important components of cell membranes
  - Ensure membrane proteins function properly
- Contribute to cell membrane “fluidity”
  - Ensure formation of lipid rafts -> appropriate signal transduction
- Regulate production of bioactive lipid mediators (eicosanoids etc.)
  - Less inflammation, coagulation and vasoconstriction
  - Better immune function
- Act as cell signalling molecules
- Alter gene expression

INFLAMMATION HAS TWO PHASES: INITITATION AND RESOLUTION



EPA and DHA are precursors of pro-resolving lipid mediators



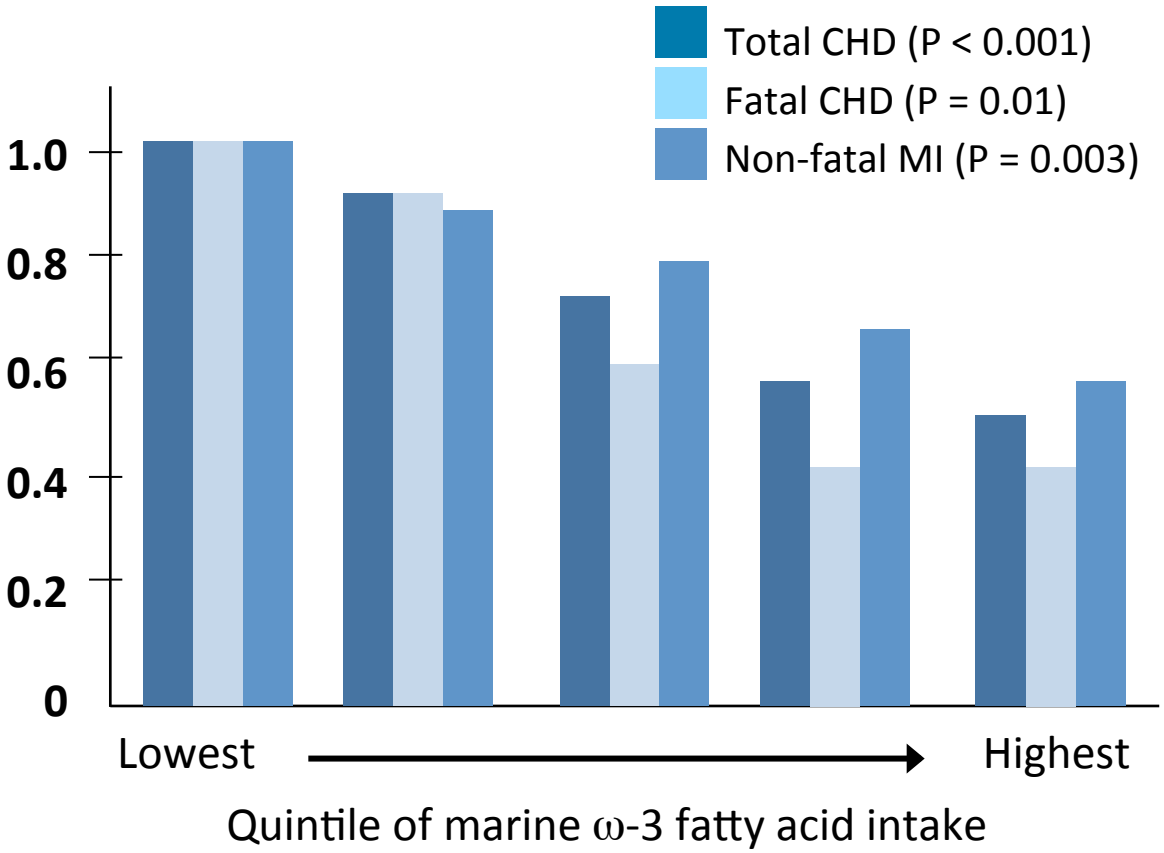

ω-3 fatty acid exposure
Receptors
Membrane composition
Raft assembly
Fluidity
Substrates for eicosanoids, resolvins etc.
Signals
Cell responses
Altered (patho)physiology
Improved Health/ Better clinical outcome

Oral ω-3 fatty acids have benefits in ….

- Hypertriglyceridemia
- Hypertension
- Thrombosis
- Cardiac arrhythmias
- Non-alcoholic fatty liver disease
- Rheumatoid arthritis
- Crohn's Disease
- Childhood asthma
- Chronic obstructive pulmonary disease
- Sarcopenia
- Cancer cachexia

Lowered risk of cardiovascular events and mortality

Extensive evidence from epidemiological and case-control studies shows that consumption of marine ω-3 fatty acids is associated with lowered risk of cardio-vascular events and mortality



Hu et al. (2002) JAMA 287, 1815-1821

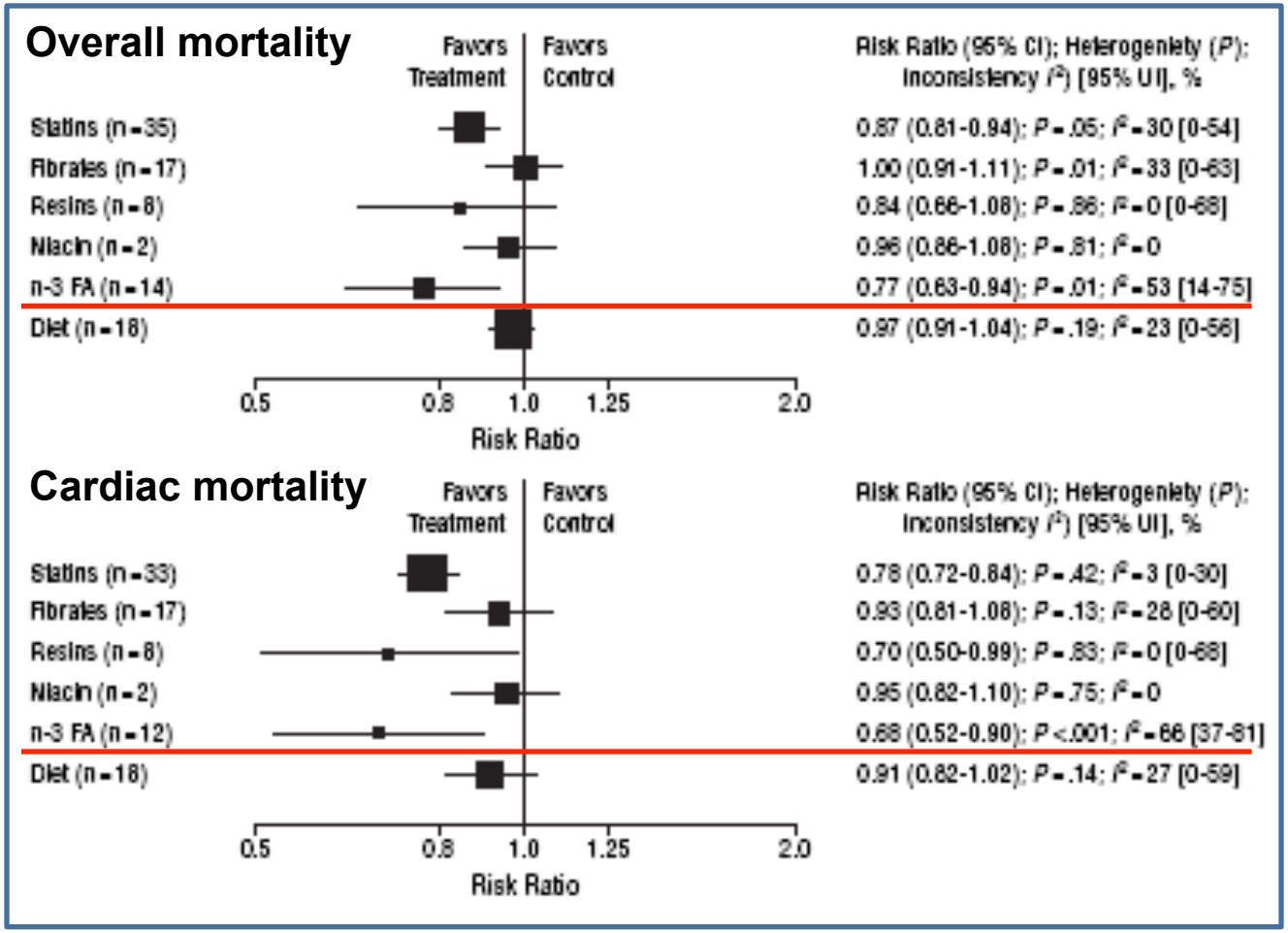
ω-3 fatty acids and CV mortality in post-MI patients

- **Patients with MI within the last 3 months assigned to ω-3 ethyl esters vs. placebo**
- **Follow up for 3.5 years**
- **356 deaths and non-fatal CV events in ω-3 group vs. 414 in placebo group**

Risk reduction in ω-3 group	
All fatal events	-20%
CV death	-30%
Coronary death	-35%
Sudden death	-45%

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

Statins and ω-3 are favourable interventions



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

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

AHA Scientific Statement

Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease

Penny M. Kris-Etherton, PhD, RD; William S. Harris, PhD; Lawrence J. Appel, MD, MPH; for the Nutrition Committee

Circulation. 2002;106:2747-2757

TABLE 5. Summary of Recommendations for Omega-3 Fatty Acid Intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)
Patients with documented CHD	Consume $\approx$1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician.
Patients needing triglyceride lowering	Two to four grams of EPA+DHA per day provided as capsules under a physician's care

INTERNATIONAL JOURNAL OF ONCOLOGY 28: 5-23, 2006

Enteral (oral or tube administration) nutritional support and eicosapentaenoic acid in patients with cancer: A systematic review

M. ELIA[1], M.A.E. VAN BOKHORST-DE VAN DER SCHUEREN[2], J. GARVEY[3], A. GOEDHART[3], K. LUNDHOLM[4], G. NITENBERG[5] and R.J. STRATTON[1]

Supplements providing EPA and DHA improve:

- **Energy intake**
- **Appetite**
- **Body weight**
- **Quality of Life**

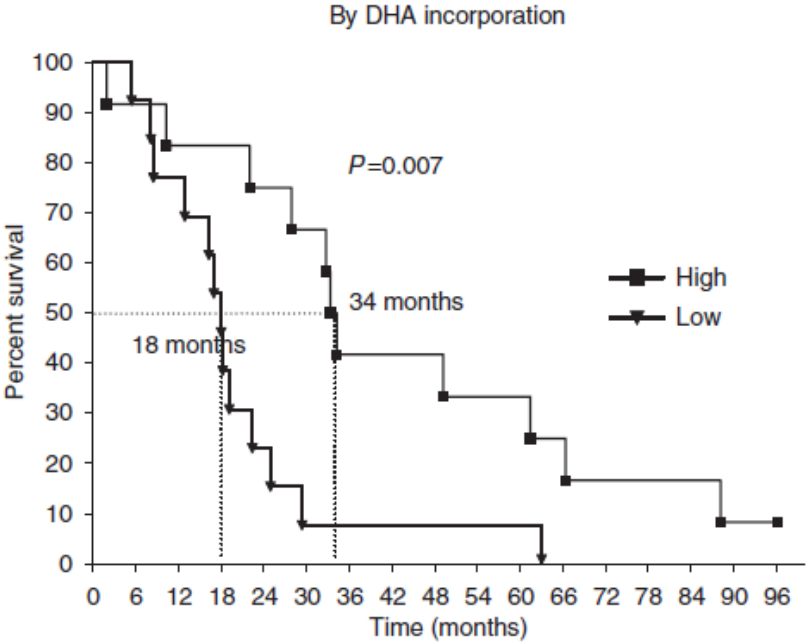
Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial

P Bougnoux*[,1,2], N Hajjaji[1,2], MN Ferrasson[1,2], B Giraudeau[3], C Couet[1,4] and O Le Floch[1,2]

[1]INSERM U921 'Nutrition, Croissance et Cancer', Tours, France; [2]Henry S. Kaplan Cancer Center, University Hospital Bretonneau, University François Rabelais, Tours, France; [3]INSERM CIC 202, University Hospital Bretonneau, University François Rabelais, Tours, France; [4]Nutrition Department, University Hospital Bretonneau, Tours, France

British Journal of Cancer (2009) 101, 1978 – 1985

- **25 patients with breast cancer receiving first line chemotherapy**
- **Open label (1.8 g DHA per day)**
- **From 7-10 days before initiating chemotherapy until 5 months of chemotherapy**
- **Patients split into high and low DHA incorporators into plasma phospholipid**
- **Patients with high DHA incorporation showed longer time to progression and better survival**



Supplementation With Fish Oil Increases First-Line Chemotherapy Efficacy in Patients With Advanced Nonsmall Cell Lung Cancer

Rachel A. Murphy, BSc[1]; Marina Mourtzakis, PhD[2]; Quincy S. C. Chu, MD[3]; Vickie E. Baracos, PhD[3]; Tony Reiman, MD, SM[4]; and Vera C. Mazurak, PhD[1]

Cancer 2011;117:3774–80.

- **46 patients with lung cancer receiving first line chemotherapy**
- **Randomised to standard of care (SOC; no intervention) vs fish oil capsules or liquid (2.2 g EPA + 0.25 g DHA per day)**

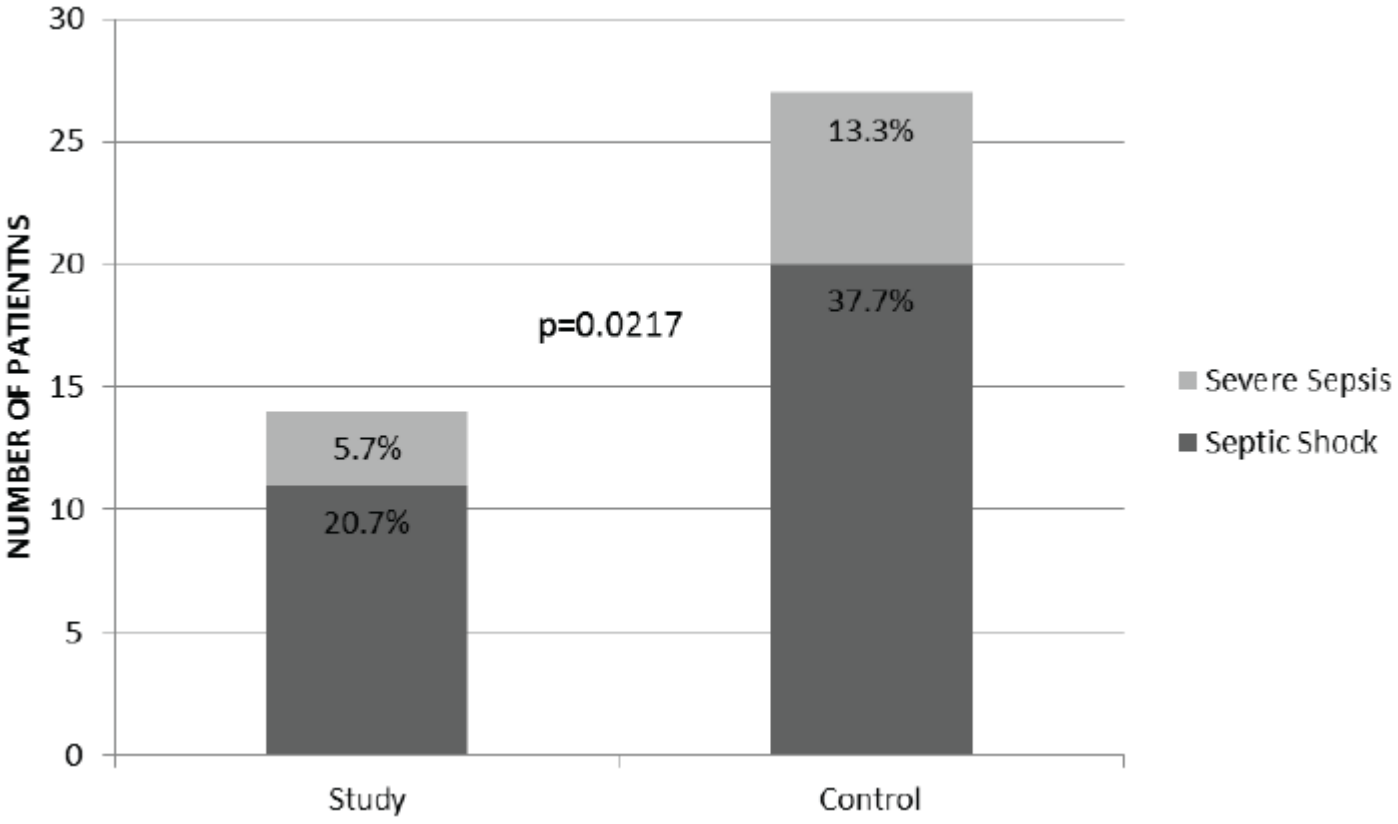
	SOC	Omega-3	P
Chemotherapy Response rate	26%	60%	0.008
Clinical benefit	42%	80%	0.02
Completed Chemotherapy	55%	87%	0.03
Cycles of Chemotherapy	3	3.9	0.02
One-year survival	39%	60%	0.15

Enteral ω-3 fatty acids in critically ill patients

- RCT in patients (n = 116) with early sepsis
- Tube feeding with high EPA formula for 7 days at 75% of basal energy expenditure x 1.3
- Primary outcome: progression to severe sepsis or septic shock
- Secondary outcomes: organ failure, ICU stay, hospital stay, ventilation need, 28-day mortality

Pontes-Arruda et al. (2011) Crit. Care 15, R144

Primary outcome



Secondary outcomes

- **Organ failure**
  - **Less cardiovascular failure (21% vs 36%)**
  - **Less respiratory failure (25% vs 40%)**
- **ICU stay**
  - **Shorter (7 days vs 13 days)**
- **Hospital stay**
  - **Shorter (9 days vs 19 days)**
- **Ventilation need**
  - **Required by fewer patients (17% vs 35%; NS)**
  - **Shorter duration (7 days vs 15 days)**
- **28-day mortality**
  - **Not different**

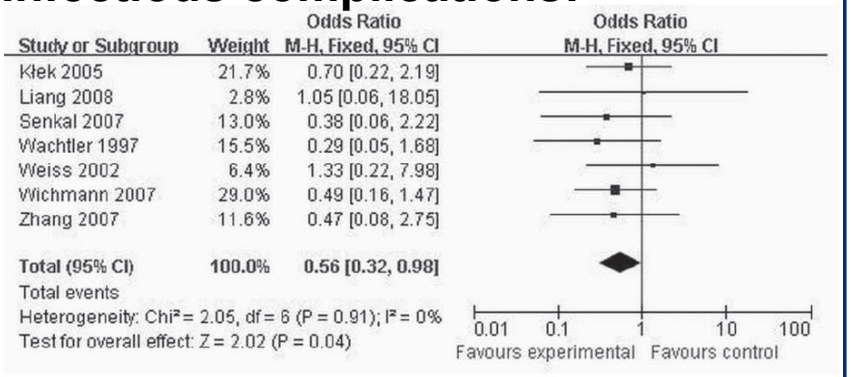
Intravenous ω-3 fatty acids have benefits in ….

- care following major surgery
- the intensive care unit
- critical illness
- head trauma
- Iv nutrition-induced liver disease
- situations where rapid delivery is required (e.g. post-MI)

Meta-analyses of iv ω-3 fatty acids in post-surgical patients

Chen et al. (2010) JPEN 34, 387-394

Infectious complications:



Also showed a reduction in length of ICU stay (-1.8 days, p = 0.004) and length of hospital stay (-2.98 days, p = 0.0005)

Wei et al. (2010) Nutrition 26, 474-481

Infectious complications:

Also showed a reduction in length of ICU stay (-2.1 days, p = 0.004)

Meta-analysis of iv ω-3 fatty acids in ICU patients and in elective surgery non-ICU patients

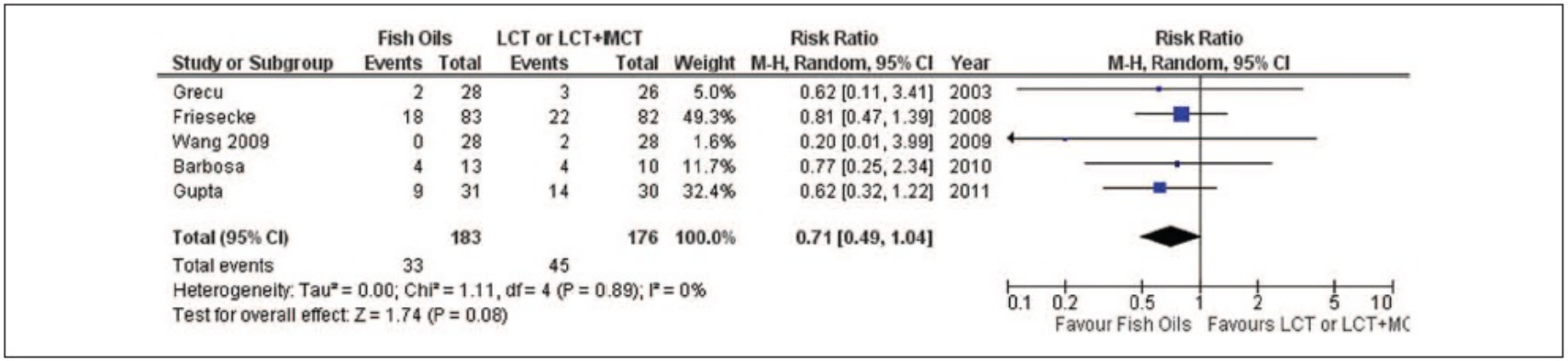
Table 3 n-3 PUFA-enriched versus standard parenteral lipid emulsions for parenteral nutrition: random effects meta-analysis

Outcome	Studies	Patients (n)	Effect estimate
Mortality, overall RR	10	847	0.89 (0.59, 1.33)
ICU patients	7	547	0.94 (0.61, 1.45)
Non-ICU patients	3	300	0.58 (0.18, 1.84)
Infection rate, overall RR	11	919	0.61 (0.45, 0.84)*
ICU patients	5	524	0.71 (0.45, 1.12)
Non-ICU patients	6	395	0.53 (0.34, 0.82)*
Hospital LOS, overall MD	15	1169	-3.29 (-5.13, -1.45)*
ICU patients	8	615	-5.17 (-8.35, -1.99)*
Non-ICU patients	7	554	-1.86 (-3.13, -0.59)*
ICU LOS, MD	8	615	-1.92 (-3.27, -0.58)*

Pradelli et al. (2012) Crit. Care 16, R184

Meta-analysis of iv ω-3 fatty acids in critically ill patients

Mortality:



Study or Subgroup	Fish Oils Events	Total	LCT or LCT+MCT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Grecu	2	28	3	26	5.0%	0.62 [0.11, 3.41]	2003
Friesecke	18	83	22	82	49.3%	0.81 [0.47, 1.39]	2008
Wang 2009	0	28	2	28	1.6%	0.20 [0.01, 3.99]	2009
Barbosa	4	13	4	10	11.7%	0.77 [0.25, 2.34]	2010
Gupta	9	31	14	30	32.4%	0.62 [0.32, 1.22]	2011
Total (95% CI)		**183**		**176**	**100.0%**	**0.71 [0.49, 1.04]**	
Total events	33		45				

Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)

No effect on length of ICU stay or infections

"Fish oil containing lipid emulsions may be able to decrease mortality and ventilation days in the critically ill."

Manzanres et al. (2013) JPEN, in press

Summary

- **Increased intake of EPA and DHA is reflected in increased content in blood, blood cells and tissues**
- **EPA and DHA have a number of physiological effects (membrane structure & function, cell signalling and gene expression, lipid mediator profile)**
- **Through their physiological effects EPA and DHA influence cell and tissue function, improving risk factor profiles and modifying pathological processes**
- **There are multiple applications of EPA and DHA in clinical nutrition (oral, enteral, parenteral routes all relevant) -> prevention of complications; treatment**
- **Clinical actions occur through plausible biological mechanisms**

Conclusion

Fish oil ω-3 fatty acids have a clear role in clinical nutrition