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

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FISH OILS CUT RISK OF HEART ATTACK

Health & Fitness

Fish oil saved my marriage
Very long chain ("marine") ω-3 polyunsaturated fatty acids

Eicosapentaenoic acid (EPA) 20:5ω-3

Docosapentaenoic acid (DPA) 22:5ω-3

Docosahexaenoic acid (DHA) 22:6ω-3
Pathway of biosynthesis of EPA, DPA and DHA
EPA, DPA and especially DHA are poorly synthesised in humans

-> dietary sources are important
α-Linolenic acid (18:3\(\omega-3\))

\[ \Delta6\text{-desaturase} \]

Stearidonic acid (18:4\(\omega-3\))

\[ \text{Elongase} \]

20:4\(\omega-3\)

\[ \Delta5\text{-desaturase} \]

Eicosapentaenoic acid (20:5\(\omega-3\))

\[ \text{Elongase} \]
\[ \text{Elongase} \]
\[ \Delta6\text{-desaturase} \]
\[ \beta\text{-oxidation} \]

Docosahexaenoic acid (22:6\(\omega-3\))

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

<table>
<thead>
<tr>
<th></th>
<th>EPA (g/100 g food)</th>
<th>DPA (g/100 g food)</th>
<th>DHA (g/100 g food)</th>
<th>Total g/portion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod</td>
<td>0.08</td>
<td>0.01</td>
<td>0.16</td>
<td>0.30</td>
</tr>
<tr>
<td>Haddock</td>
<td>0.05</td>
<td>0.01</td>
<td>0.10</td>
<td>0.19</td>
</tr>
<tr>
<td>Herring</td>
<td>0.51</td>
<td>0.11</td>
<td>0.69</td>
<td>1.56</td>
</tr>
<tr>
<td>Mackerel</td>
<td>0.71</td>
<td>0.12</td>
<td>1.10</td>
<td>3.09</td>
</tr>
<tr>
<td>Salmon</td>
<td>0.55</td>
<td>0.14</td>
<td>0.86</td>
<td>1.55</td>
</tr>
<tr>
<td>Crab</td>
<td>0.47</td>
<td>0.08</td>
<td>0.45</td>
<td>0.85</td>
</tr>
<tr>
<td>Prawns</td>
<td>0.06</td>
<td>0.01</td>
<td>0.04</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Effect on EPA + DHA intake by eating oily fish or taking supplements

Grams per day

- Normal diet
- + one standard fish oil capsule
- + one concentrated fish oil capsule
- + one Omacor capsule
- One meal of salmon
- + 4 Omacor capsules
In most cells and tissues the content of EPA and DHA is low (especially when compared with the content of ω-6 PUFAs).
$\omega$-6 and $\omega$-3 PUFA contents of phospholipids of human white (mononuclear) cells

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>% of total fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid (18:2$\omega$-6)</td>
<td>10</td>
</tr>
<tr>
<td>DGLA (20:3$\omega$-6)</td>
<td>1.5</td>
</tr>
<tr>
<td>Arachidonic acid (20:4$\omega$-6)</td>
<td>20</td>
</tr>
<tr>
<td>$\alpha$-Linolenic acid (18:3$\omega$-3)</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>EPA</td>
<td>1.0</td>
</tr>
<tr>
<td>DHA</td>
<td>2.5</td>
</tr>
</tbody>
</table>
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\textsuperscript{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*

Analysed the fatty acid composition of:
- plasma PC, TAG, CE and NEFA
- platelets
- erythrocytes
- mononuclear cells
- buccal cells
- adipose tissue

From 200 subjects at 9 time points over one year

From 200 subjects at three time points over one year
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 $\omega$-3 PUFAs?
The Greenland Inuit ("Eskimo")

Much lower than expected rate of death from heart attack
How could this be?
-> The Inuit diet??

- Ate lots of seal meat, whale meat, whale blubber, fish
- -> Very high intake of $\omega$-3 PUFAs

<table>
<thead>
<tr>
<th>Marine omega-3 intake (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenland Inuit</td>
</tr>
<tr>
<td>Average UK adult</td>
</tr>
</tbody>
</table>

100 x difference in intake!
Prospective study of $\omega$-3 PUFA intake and CHD outcomes: The Nurse’s Health Study

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

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk
A Systematic Review and Meta-analysis

Rajiv Chowdhury, MD, PhD; Samantha Warmakula, 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*
Figure 1. RR for coronary outcomes in prospective cohort studies of dietary fatty acid intake.

<table>
<thead>
<tr>
<th>Fatty Acid Intake</th>
<th>Studies, n</th>
<th>Participants, n</th>
<th>Events, n</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total saturated fatty acids</td>
<td>20</td>
<td>276,763</td>
<td>10,155</td>
<td>1.03 (0.98-1.07)</td>
</tr>
<tr>
<td>Total monounsaturated fatty acids</td>
<td>9</td>
<td>144,219</td>
<td>6031</td>
<td>1.00 (0.91-1.10)</td>
</tr>
<tr>
<td>Total ω-3 fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Linolenic</td>
<td>7</td>
<td>157,258</td>
<td>7431</td>
<td>0.99 (0.86-1.14)</td>
</tr>
<tr>
<td>Total long-chain ω-3</td>
<td>16</td>
<td>422,786</td>
<td>9089</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>Total ω-6 fatty acids</td>
<td>8</td>
<td>206,376</td>
<td>8155</td>
<td>0.98 (0.90-1.06)</td>
</tr>
<tr>
<td>Total trans fatty acids</td>
<td>5</td>
<td>155,270</td>
<td>4662</td>
<td>1.16 (1.06-1.27)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Circulating Blood Fatty Acid Composition</th>
<th>Studies, n</th>
<th>Participants, n</th>
<th>Events, n</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ω-3 polyunsaturated fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:3n-3, α-Linolenic</td>
<td>8</td>
<td>14,945</td>
<td>3426</td>
<td>0.93 (0.83-1.03)</td>
</tr>
<tr>
<td>Total long-chain ω-3</td>
<td>4</td>
<td>10,558</td>
<td>2753</td>
<td>0.84 (0.63-1.11)</td>
</tr>
<tr>
<td>20:5n-3, Eicosapentaenoic</td>
<td>12</td>
<td>23,065</td>
<td>4624</td>
<td>0.78 (0.65-0.94)</td>
</tr>
<tr>
<td>22:6n-3, Docosahexaenoic</td>
<td>13</td>
<td>23,065</td>
<td>4624</td>
<td>0.79 (0.67-0.93)</td>
</tr>
<tr>
<td>20:5n-3, Eicosapentaenoic + 22:6n-3, Docosahexaenoic</td>
<td>13</td>
<td>20,809</td>
<td>4073</td>
<td>0.75 (0.62-0.89)</td>
</tr>
<tr>
<td>22:5n-3, Docosapentaenoic (clupanodonic)</td>
<td>4</td>
<td>7155</td>
<td>2565</td>
<td>0.64 (0.47-0.89)</td>
</tr>
</tbody>
</table>
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
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**EMERGING:**
- High serum triglycerides
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- Endothelial dysfunction
- Tendency towards thrombosis
- Inflammation
- Elevated plasma homocysteine
- Poor antioxidant status

= Improved by n-3 PUFAs
Marine $\omega$-3 fatty acids most likely slow or limit atherosclerosis due to risk factor reduction ….

….. But marine $\omega$-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

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

% of unstable plaques at surgery

Control

Omega-3

P = 0.028
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


Atherosclerosis 212 (2010) 252–259
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”
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. Nizani, MD, PhD
Eftychia Bika, MD
Michael S. Kostapanos, MD
Moses S. Eliaf, MD, PhD, FASA, FRSH

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>17</td>
<td>0.96 (0.91-1.02)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>13</td>
<td>0.91 (0.85-0.98)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7</td>
<td>0.87 (0.75-1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13</td>
<td>0.89 (0.76-1.04)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>1.05 (0.83-1.32)</td>
</tr>
</tbody>
</table>

Error bars indicate 95% CIs; PUFAs, polyunsaturated fatty acids; RR, relative risk.
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\textsuperscript{a,\#}, Davide Soranna\textsuperscript{b}, Alberico L. Catapano\textsuperscript{a,c}, Giovanni Corrao\textsuperscript{b,\*}
Cardiac death
32% reduction

Sudden death
33% reduction

MI
25% reduction
• 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>
<thead>
<tr>
<th>Parameter</th>
<th>Exposed</th>
<th>Nonexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2466</td>
<td>9712</td>
</tr>
<tr>
<td>No. of death events</td>
<td>243</td>
<td>1274</td>
</tr>
<tr>
<td>Total follow-up, y</td>
<td>6668</td>
<td>24,943</td>
</tr>
<tr>
<td>Deaths per 1000 person-years, no.</td>
<td>36.4</td>
<td>51.1</td>
</tr>
<tr>
<td><strong>Crude relative risk (95% CI)</strong></td>
<td>0.708 (0.602-0.833)</td>
<td><em>P</em> &lt; 0.0001</td>
</tr>
<tr>
<td>Patients with no previous diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of death events</td>
<td>195</td>
<td>1016</td>
</tr>
<tr>
<td>Total follow-up, y</td>
<td>5882</td>
<td>22,066</td>
</tr>
<tr>
<td>Deaths per 1000 person-years, no.</td>
<td>33.2</td>
<td>46.0</td>
</tr>
<tr>
<td><strong>Crude relative risk (95% CI)</strong></td>
<td>0.724 (0.621-0.844)</td>
<td><em>P</em> &lt; 0.0001</td>
</tr>
<tr>
<td>Patients with previous type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of death events</td>
<td>48</td>
<td>258</td>
</tr>
<tr>
<td>Total follow-up, y</td>
<td>786</td>
<td>2878</td>
</tr>
<tr>
<td>Deaths per 1000 person-years, no.</td>
<td>61.1</td>
<td>89.7</td>
</tr>
<tr>
<td><strong>Crude relative risk (95% CI)</strong></td>
<td>0.686 (0.504-0.934)</td>
<td><em>P</em> = 0.0166</td>
</tr>
</tbody>
</table>
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
ARA in phospholipids

Eicosanoids

Resolvins, protectins and maresins

Inflammatory stimulus

Extracellular EPA and DHA

EPA & DHA in phospholipids

ARA in phospholipids

Extracellular ARA

CELL MEMBRANE

TLR4

GPR120

Raft assembly

Free EPA & DHA

Free ARA

Resolvins, protectins and maresins

NFκB

PPAR-γ

Cytokines

Adhesion molecules

COX-2

iNOS

MMPs

Eicosanoids

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
There is still much to learn about:
- Dose responses and fatty acid interactions
- Mechanisms
- Effects of the different marine $\omega$-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 $\omega$-3 fatty acid handling, metabolism, and effectiveness
- Why some studies fail to show effects
- More sustainable sources of marine $\omega$-3 fatty acids (algal oils, GMO plants, ....)
- Whether plant $\omega$-3 fatty acids can have a role