Plant vs. marine n-3 fatty acids and cardiovascular outcomes: what is the verdict?

Tom Sanders
School of Medicine
King’s College London
tom.sanders@kcl.ac.uk
Plant vs marine sources of PUFA
Agenda

1. Do DHA and EPA have different effect from ALA on CHD risk factors?
2. At what level of intake do EPA and DHA influence CVD risk factors?
3. Can vegetarians convert ALA into EPA and DHA?
4. Do prospective cohort studies show differences in CVD risk between EPA+DHA and ALA with regard to risk?
5. Do vegetarians need to take preformed EPA and DHA to reduce risk of CHD or is ALA sufficient to meet needs?
Pharmacological effects of omega-3 fatty acids are only seen at high intakes.
Low DHA in vegetarians and vegans

Mean values with 95%CI

22:6n-3

RR of ALA intake and risk of total CVD stratified by dietary intake and biomarker concentration.

A Dietary ALA intake as the exposure

- Dolecek 1992 (13) Fatal CHD 0.71 (0.48, 1.03) 3.48
- Ascherio 1996 (14) Total MI 0.64 (0.69, 1.02) 4.82
- Pietinen 1997 (15) Total MI 0.97 (0.85, 1.11) 5.22
- Hu 1999 (16) Fatal IHD 0.63 (0.41, 0.95) 3.21
- Oomen 2001 (17) Total CAD 1.68 (0.86, 3.29) 1.91
- He 2002 (18) Stroke 0.98 (0.74, 1.29) 4.24
- Albert 2005 (19) Nonfatal MI 1.07 (0.94, 1.22) 5.23
- Laaksonen 2005 (37) Fatal CVD 0.63 (0.33, 1.21) 1.99
- Lopes 2007 (38) Nonfatal MI 0.66 (0.42, 1.04) 2.99
- Campos 2008 (39) Nonfatal MI 0.74 (0.58, 0.93) 4.58
- de Goede 2011 (20, CHD) Total CHD 1.01 (0.73, 1.40) 3.84
- de Goede 2011 (20, stroke) Stroke 0.71 (0.50, 1.03) 3.57
- Vedtofte 2011 (21, M) Total IHD 0.83 (0.56, 1.24) 3.32
- Vedtofte 2011 (21, F) Total IHD 1.04 (0.58, 1.86) 2.29
- Larsson 2012 (22) Stroke 1.07 (0.92, 1.25) 5.09

Subtotal (i-squared = 49.0%, p = 0.017) 0.90 (0.81, 0.99) 55.78

B ALA biomarker level as the exposure

- Simon 1995 (23) Total CHD 0.72 (0.37, 1.41) 1.91
- Simon 1995 (24) Stroke 0.49 (0.24, 1.00) 1.75
- Tornwall 1996 (25) Nonfatal MI 1.05 (0.66, 1.67) 2.92
- Gullar 1999 (26) Nonfatal MI 0.76 (0.41, 1.40) 2.14
- Pedersen 2000 (27) Nonfatal MI 1.84 (0.45, 7.41) 0.60
- Erkilla 2003 (28) Total CVD 0.61 (0.34, 1.13) 1.33
- Kark 2003 (29) Nonfatal MI 0.93 (0.53, 1.63) 2.39
- Lemaitre 2003 (30, fatal MI) Fatal MI 0.24 (0.05, 1.23) 0.45
- Lemaitre 2003 (30, nonfatal MI) Nonfatal MI 1.09 (0.56, 2.12) 1.94
- Wang 2003 (31) Total CHD 0.92 (0.61, 1.40) 3.22
- Laaksonen 2005 (37) Fatal CVD 1.19 (0.63, 2.26) 2.03
- Wiberg 2006 (32) Stroke 1.04 (0.64, 1.61) 4.63
- Lopes 2007 (38) Nonfatal MI 0.33 (0.09, 1.26) 0.65
- Campos 2008 (39) Nonfatal MI 0.57 (0.43, 0.77) 4.08
- Warenjo 2008 (33) Fatal CVD 1.23 (1.00, 1.52) 4.74
- Lemaitre 2009 (34) SCA 1.83 (1.16, 2.90) 2.94
- Shearer 2009 (35) ACS 0.08 (0.04, 0.17) 1.83
- Khaw 2012 (36) Total CHD 0.96 (0.77, 1.21) 4.67

Subtotal (i-squared = 79.8%, p = 0.000) 0.80 (0.63, 1.03) 44.22

Overall (i-squared = 71.3%, p = 0.000) 0.86 (0.77, 0.97) 100.00

An insufficient intake of linolenic acid could explain the relationship between trans fats and heart disease

• Partial hydrogenation of soy bean oil was specifically designed to selectively reduce the linolenic acid content of soybean oil to improve stability of the oils for deep fat frying.

• No plausible biological mechanism to explain why low intakes of trans increase CHD risk: the effect of low intakes of trans on the blood lipid profile trivial.

• High intakes of trans may really be reflecting a lack of linolenic acid.

• WARNING: plant breeders are producing new varieties of vegetable oils to be low in linolenic acid.
Estimates of risk of stroke according to long-chain n-3 intake

Relative risk of stroke

Biomarkers

Dietary intake

BMJ 2012; 345: e6698.
Relatives CVD risk reductions associated with linolenic acid vs long-chain n-3 PUFA from meta-analyses

Reduction in relative risk

Linolenic acid

Fish
Marine omega-3 and secondary prevention

Lack of clear benefit of long-chain n-3 fatty acids in secondary prevention of CHD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies</td>
<td>Events</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>17</td>
<td>6295</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>13</td>
<td>3480</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7</td>
<td>1030</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13</td>
<td>1755</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>1490</td>
</tr>
</tbody>
</table>

The alpha-omega trial

A Major Cardiovascular Events, EPA–DHA vs. Placebo and ALA Only

B Major Cardiovascular Events, ALA vs. Placebo and EPA–DHA Only

C Fatal Coronary Heart Disease, EPA–DHA vs. Placebo and ALA Only

D Fatal Coronary Heart Disease, ALA vs. Placebo and EPA–DHA only

Blood pressure and serum lipid as predictors of risk

Meta-analysis from the Prospective Triallist Collaboration

- A 20 mm difference in BP is associated with a doubling of risk
- BP is lower ~3.3 mm in vegetarians ie 15% lower risk

- A 1.33 increased in TC:HDL ratio is associated with a 30% increase in risk
- TC:HDL is about 0.19 units lower in vegetarians ie 4.3% lower risk

A 1.33 increased in TC:HDL ratio is associated with a 30% increase in risk

A 1.33 increased in TC:HDL ratio is associated with a 30% increase in risk

A 1.33 increased in TC:HDL ratio is associated with a 30% increase in risk
### Potential benefits

- Not established in vegetarians

### Potential harms

- Intakes as low as 0.8g/d of DHA from algal sources raise LDL-C by 8-11% (about the same as 6% energy from saturated fatty acids)


Algal DHA supplementation increases LDL-cholesterol even at low intakes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Effect Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>-0.32 (-1.02, 0.38)</td>
</tr>
<tr>
<td>19</td>
<td>0.27 (0.13, 0.41)</td>
</tr>
<tr>
<td>22</td>
<td>0.17 (-0.60, 0.94)</td>
</tr>
<tr>
<td>23</td>
<td>0.49 (0.00, 0.98)</td>
</tr>
<tr>
<td>26</td>
<td>0.23 (0.07, 0.39)</td>
</tr>
<tr>
<td>28</td>
<td>0.34 (0.14, 0.54)</td>
</tr>
<tr>
<td>29</td>
<td>0.56 (0.07, 1.05)</td>
</tr>
<tr>
<td>33</td>
<td>0.00 (-0.75, 0.75)</td>
</tr>
<tr>
<td>34</td>
<td>0.28 (0.10, 0.46)</td>
</tr>
<tr>
<td>35</td>
<td>-0.18 (-0.44, 0.08)</td>
</tr>
<tr>
<td>36</td>
<td>0.18 (-0.02, 0.38)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.23 (0.16, 0.30)</td>
</tr>
</tbody>
</table>

0.8g/d 1.5g/d 0.9g/d
Arterial stiffening

An index of arterial ageing

- Carotid to femoral pulse wave velocity (PWV) can be measured non-invasively to measure arterial stiffening.

- It is emerging as a strong predictor of future CVD events and is correlated with in vivo measures of atherosclerosis/arteriosclerosis measured by ultrasound.

- Important determinants of PWV are age and systolic BP.

- It has been suggested the long-chain n-3 PUFA favourable affect PWV.

We measured PWV in 165 vegan men and 165 omnivores.
Arterial stiffness in vegan vs omnivore men

<table>
<thead>
<tr>
<th></th>
<th>Vegans n=161</th>
<th>Omnivores n=164</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine SBP mm Hg</td>
<td>123 (120, 126)</td>
<td>126 (123, 128)</td>
</tr>
<tr>
<td>Supine DBP mm Hg</td>
<td>72 (71, 74)**</td>
<td>76 (75, 78)</td>
</tr>
<tr>
<td>TC:HDL-C</td>
<td>3.6 (3.4, 3.8)**</td>
<td>4.0 (3.8, 4.2)</td>
</tr>
<tr>
<td>Plasma- DHA wt %</td>
<td>0.96 (0.82, 1.10)**</td>
<td>2.68 (2.54, 2.81)</td>
</tr>
<tr>
<td>PWV&lt;sub&gt;c-f&lt;/sub&gt; m/sec</td>
<td>8.64 (8.34, 8.94)*</td>
<td>9.10 (8.81, 9.40)</td>
</tr>
</tbody>
</table>

Values are adjusted for age and BMI
* P<0.05 and **P<0.01 significantly lower in vegans than in omnivores
Regression analysis of components affecting arterial stiffness

![Graph showing predictor importance for PWV m/sec]

**Predictor Importance**

Target: PWV m/sec

- AGE
- SSBP
- BMI
- Diet

Least Important

Most Important
Lower CHD in vegetarians vs. omnivores

Crowe et al. 2013 doi: 10.3945/ajcn.112.04407

Omnivores  Vegetarians  32% difference

Crowe et al. 2013 doi: 10.3945/ajcn.112.04407
Summary

1. DHA and EPA have different pharmacological effects from ALA.

2. Prospective studies show no difference between ALA and EPA +DHA intakes and CVD risk.

3. EPA and DHA levels are lower in vegetarians but DHA supplementation increases LDL-C.

4. The hypothesis that a lack of EPA+DHA accelerates arterial increased CVD risk in vegetarians can be refuted.

5. Supplementation of vegetarians diet with EPA/DHA to prevent CHD is not justified by the published evidence and dietary requirements for n-3 PUFA are likely to be met by ALA.