Optimum Health and Nutrition for our Ageing Population – The benefit of long chain omega-3 and CV health: The need for clear thinking

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Slides prepared by David Colquhoun & Jenni Shields
Disclosures of Author

- I have no stocks or shares in ANY company
- I have NEVER been offered nor received a bribe from ANY pharmaceutical company
- Honoraria I receive is far less than the AMA consulting rates and about one tenth of a neurosurgeon’s hourly rate in theatre.
- I follow the Rugby Super 14 Champions, am proud of Queensland and our winning State of Origin Team (7 in a row!) and I drink beer, wine and Mojitos and like chocolate soufflé.
- I admire Albert Einstein for his clear thinking and his view “I don’t need 200 NAZI scientists to say I’m wrong – just one to prove it”

If I offend someone I am sorry, but in the words of Ned Kelly (a distant relative) (before he was hung) in Melbourne –

**SUCH IS LIFE!**
The rapidly growing epidemic of non-communicable diseases (obesity, diabetes, vascular disease) already responsible for some 60% of world deaths, is clearly related to changes in global dietary patterns and increased consumption of industrially processed fatty, salty and sugary foods.
Misrepresentation of Randomized Trials in Press

Recent unnecessary confusion in public and health professionals regarding:

1) benefits of EPA/DHA for CV health
2) superiority of various preparations.

Due to

a) Recent poorly designed trials
b) Inadequate incorrect meta-analysis in JAMA and Ann I Med
c) Media advertising blitz of exaggerated claims based on 2 clinical trials from the same group in Canada – results NOT duplicated.
Misrepresentation of Randomized Trials in Press Release and News – “SPIN” Prevalence

“Spin” – specific reporting strategies (intentional or unintentional) of excessive emphasizing of the beneficial or possible deleterious effect of the experimental treatment.

Seen in 40% abstracts 47% press releases

Similar prevalence in prestigious journals e.g. NEJM

1) Over-emphasis on statistically insignificant results, sub-groups etc

2) Inadequate interpretation on non-significant differences as demonstrating equivalence or lack of differences in adverse effects

3) Adverse effects on animal or laboratory studies – no caveats about extrapolating to humans

**IMPORTANCE:**

Major impact on utilization of medical resources e.g. diagnostic testing demands.

Major impact on sales.

1) Yavchitz A, et al. PLOS Med 2012;9(9) e 1001308


3) Grilli R, Cochrane Database Sys Rev 2002 CD0000389
NURSES AND HEALTH PROFESSIONALS
HARVARD STUDIES

88,000 nurses studied over 14 years
51,000 males studied over 16 years

5 lifestyle factors

- Not smoking
- Moderate alcohol (5-30 grams/day)
- Exercise (30 minutes a day)
- BMI (Body Mass Index < 25)
- Healthy Diet
  (3 serves veges, 2.5 serves fruit, 0.5 serve nuts, 9gm cereal fibre, 2.5 serves chicken and fish for 1 serve of red meat).

Chuve, SE. McCullough ML, Sacks FM, Rimm EB. CIRC 2006;114:160-167
Nurses Health Study

• “82% of the coronary events in this cohort might be prevented if all women had been in the low risk group”

• “higher reductions in risk might be possible with these added preventive factors…nuts, ALA, Vitamin B6 and E”

Stampfer MJ et al NEJM 2000;343:10-22
Lifestyle & Sudden Death – Nurses Health Study

- Only 25% SCD in very high risk patients
- SCD very low survival of about 7%
- 81,722 nurses follow up 1984-2010
- 321 cases 26 year follow up
- Mean age nurses with SCD 72 years

Chiuve SE et al.  JAMA 2011;306:62-69
Now a healthy diet is called an “alternate Mediterranean diet” or “a Mediterranean style diet” and includes moderate alcohol consumption.

**Specifics:**

- High intake of vegetables, fruits, nuts, whole grains, legumes, fish.
- High ratio of MUFA:SFA.
- A moderate alcohol consumption (0.5-1 drink/day).
- Low intake red and processed meats.

## Nurses Health Study and SCD
### Lifestyle Factors

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.54</td>
</tr>
<tr>
<td>2</td>
<td>0.41</td>
</tr>
<tr>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
</tr>
</tbody>
</table>

92% lower SCD

Chiuve SE et al. JAMA 2011;306:62-69
## CORONARY HEART DISEASE MORTALITY and FISH INTAKE

2 meta-analyses of case-control or cohort studies over 200,000 individuals follow-up mean 12 years.

1 serve = 200gm fish

<table>
<thead>
<tr>
<th>Frequency</th>
<th>CHD Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>never or &lt;1/mth</td>
<td>comparator rate</td>
</tr>
<tr>
<td>1-3/mth</td>
<td>11% ↓</td>
</tr>
<tr>
<td>1/week</td>
<td>15% ↓</td>
</tr>
<tr>
<td>2-4/week</td>
<td>23% ↓</td>
</tr>
<tr>
<td>5/week *</td>
<td>38% ↓</td>
</tr>
</tbody>
</table>

* Equivalent to daily statin drug prescription Pravastatin 40mg, Simvastatin 20mg, Atorvastatin 10mg and probably Rosuvastatin 5mg

He K, Song Y et al. Circulation 2004;2705-2711
DHA  DocosaHexaenoic Acid (22:6w3): 
6 Unsaturated Bonds

EPA  EicosaPentaenoic Acid (20:5w3): 
5 Unsaturated Bonds

ALA  Alpha-Linolenic Acid (18:3w3): 
3 Unsaturated Bonds
Source of “fish oil” and ethyl esters of EPA/DHA

“A crustacean"

“The Beginning”
Microalgae

Krill eat plankton

Fish eat Krill

Capsule

Protective molecules are
Eicosapentaenoic acid (C20:5n-3 [EPA]) &
Docosahexaenoic acid (C22:6n-3 [DHA])
sunlight → phytoplankton, seaweed → Producers

Producers → fish, zooplankton

Producers → Decomposers

Decomposers → Inorganic Nutrients

Inorganic Nutrients: phosphorus, nitrogen

Producers → Consumers

Consumers → Decomposers

Decomposers: bacteria, Benthic organisms
Health professionals should advise adult Australians with documented CHD to:

1. Consume about 1000 mg per day of combined DHA and EPA through a combination of the following:
   - two or three serves (150 g serve) of oily fish per week
   - fish oil capsules or liquid
   - food and drinks enriched with marine n-3 PUFA.

2. Consume at least 2 g per day of ALA.

3. Follow government advice on fish consumption regarding local safety issues.

4. Discuss healthy eating and concerns about nutrition with an Accredited Practising Dietitian or a doctor.

Health professionals should advise adult Australians with elevated triglycerides (TG) to take fish oil capsules or liquid and marine n-3 PUFA enriched foods and drink as first-line therapy by:

- starting with a dose of 1200 mg per day of DHA and EPA; and if appropriate
- increasing the dose to 4000 mg per day of DHA and EPA and checking their patient’s response every 3 to 4 weeks when the dose is changed, until target TG levels are reached.
Polyunsaturated fatty acids (1000mg EPA/DHA) should be considered as a second-line agent for patients with CHF who remain symptomatic despite standard therapy.

Dietary recommendations for long-chain n-3 PUFA are based on the association of higher intakes with lower risk of cardiovascular disease. The European Food Safety Authority (EFSA, 2010a) suggests an intake of 0.25g long-chain n-3 PUFA per day.
<table>
<thead>
<tr>
<th>Form</th>
<th>Preparation</th>
<th>EPA/DHA Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Triglyceride form</td>
<td>Cod liver oil</td>
<td>10-20%</td>
</tr>
<tr>
<td></td>
<td>fish oil (and Maxepa)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Algal oil</td>
<td>30%</td>
</tr>
<tr>
<td>In Phospholipid form</td>
<td>Krill oil</td>
<td>30%</td>
</tr>
<tr>
<td>Re-constituted Triglyceride</td>
<td>“Omega”</td>
<td>60-70%</td>
</tr>
<tr>
<td>In Ethyl Ester form</td>
<td>“Omacor”</td>
<td>90%</td>
</tr>
</tbody>
</table>

(Prescription only TGA approved and on Repatriation Scheme and most health funds part subsidy for post AMI indication)
The FDA Panel reviewed composition of four fish oils. The predominant saturated fatty acids (myristic, palmitic and stearic acids) found in Krill oil are IDENTICAL to those found in fish oils. Krill oil is similar regarding total content of PUFA.

The FDA also considered the presence of vaccenic acid and astaxanthin esters which are found at higher levels than other food sources and found that they were safe.
KRILL OIL BIOAVAILABILITY

Krill Oil 1000mg  n=12 healthy males.
Identical dose of EPA/DHA taken with a standardised breakfast.
Krill oil (Neptune), triglyceride, EE and blood samples at 2,4,6,8,24,48 and 72 hours. (Only water during 1st 24 hours).

MEASUREMENT: Plasma phospholipid fatty acids

RESULTS: Similar in all three types (wide CI)
Possible trend better in Krill.

NOTE 20% FREE EPA/DHA in Krill oil.
Nil free EPA/DHA in triglyceride or ethyl ester forms.

Physiology of Triglyceride, Ethyl Ester, Phospholipid

- All forms are not fully absorbed and undergo hydrolysis to FF acids.
- The ESTER bond slows absorption kinetics in duodenum.
- Triglycerides rapidly digested by <Pancreatic lipase>, less active if they contain EPA/DHA (due to double bond position) by
- Phospholipids are more quickly and completely absorbed than triglycerides.
- After hydrolysis the free fatty acids EPA/DHA are taken up by enterocytes.
- All free fatty acids (EPA/DHA) must be reconverted into triglycerides for transport in blood.

Gissi-Prevenzione Trial

11,324 pts <3 months post AMI; 3.5 year follow-up

Open Label PROBE Design

TREATMENT: 1gm/d fish oil EPA+DHA=850mg 2:1 ratio or nil
[Vitamin E (synthetic) 300mg or placebo]

RESULT:
20% decrease total mortality (CI 6-33)
45% decrease sudden death (absolute RR 1.6%)
Drop out rate >25% further analysis of early protection

@ 3 month total mortality decreased 41%
@ 4 month sudden death decreased 53%

Rates of Total Mortality and Sudden Death According to left ventricular systolic function

Effect of n-3 PUFA treatment on total mortality and sudden death in patients with progressive impairment of left ventricular systolic function.

**SUDDEN DEATH**

<table>
<thead>
<tr>
<th>EF (%)</th>
<th>n-3 PUFA</th>
<th>Control</th>
<th>HR (95% CI)</th>
<th>2P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>38/2627</td>
<td>37/2679</td>
<td>0.89 (0.46-1.69)</td>
<td>0.7108</td>
</tr>
<tr>
<td>46-50</td>
<td>16/954</td>
<td>25/919</td>
<td>0.39 (0.15-1.02)</td>
<td>0.0546</td>
</tr>
<tr>
<td>41-45</td>
<td>6/563</td>
<td>24/568</td>
<td>0.19 (0.06-0.56)</td>
<td>0.0028</td>
</tr>
<tr>
<td>≤ 40</td>
<td>28/677</td>
<td>47/643</td>
<td>0.55 (0.29-1.04)</td>
<td>0.0666</td>
</tr>
<tr>
<td>Total</td>
<td>88/4821</td>
<td>133/4809</td>
<td>0.53 (0.36-0.76)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Test for Trend, 2P = 0.0170

(Adelaide Study) n-3 fatty acids and inducability of VT

Omega-3 index change
Supplement Group 3.7%→4.8% p=0.001
Control Group 3.6%→3.9% p=ns
HS-Omega-3 Index®

A measure of the amount of EPA+DHA in red blood cell membranes expressed as the percent of total fatty acids

There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

$\frac{3}{64} = 4.6\%$

HS-Omega-3 Index = 4.6%

"HS" stands for "Harris Schacky"
Omega-3 content in red blood cells is a strong predictor of cardiovascular disease.

**Physicians' Health Study**

Relative Risk:

- 1
- 0.8
- 0.6
- 0.4
- 0.2
- 0

Blood Omega-3 FA (%) by Quartile:

- 3.9%
- 5.1%
- 6.0%
- 7.3%

90% reduction in risk

$p$ for trend = 0.001

## JELIS Trial

Fatty acid levels and major coronary events.

### B) Control Group

<table>
<thead>
<tr>
<th>Fatty acids (μg/mL: mean)</th>
<th>Hazard ratio (95% CI)</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitic acid (736)</td>
<td>0.89 (0.60 – 1.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic acid (227)</td>
<td>0.73 (0.50 – 1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oleic acid (678)</td>
<td>1.18 (0.80 – 1.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linoleic acid (825)</td>
<td>1.33 (1.02 – 1.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arachidonic acid (168)</td>
<td>0.90 (0.69 – 1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA (95)</td>
<td>0.83 (0.62 – 1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHA (165)</td>
<td>1.22 (0.91 – 1.65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### C) EPA supplement group

<table>
<thead>
<tr>
<th>Fatty acids (μg/mL: mean)</th>
<th>Hazard ratio (95% CI)</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitic acid (710)</td>
<td>1.16 (0.72 – 1.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic acid (224)</td>
<td>0.74 (0.48 – 1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oleic acid (634)</td>
<td>0.88 (0.55 – 1.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linoleic acid (773)</td>
<td>1.12 (0.82 – 1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arachidonic acid (152)</td>
<td>0.86 (0.64 – 1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA (170)</td>
<td>0.71 (0.54 – 0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHA (154)</td>
<td>0.88 (0.64 – 1.20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case History: Mrs J.C. 18.4.18
1 Hour after 10,000 mg usual strength fish oil.
i.e. 3000mg EPA & DHA
## Recent Neutral Omega-3 Trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>DOSE EPA/DHA mg/day</th>
<th>MAJOR VASCULAR EVENTS</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRENCH SU.FOL.OM3 n=2501 4.7 years</td>
<td>600mg capsules</td>
<td>1.08 (P=0.64) &lt;CI 0.79-1.49&gt;</td>
<td>sub-therapeutic dose ? compliance</td>
</tr>
<tr>
<td>OMEGA n=3851 1 year</td>
<td>1 gm EE OMACOR</td>
<td>Mortality 1.12 (P=0.18) &lt;CI 0.9-1.72&gt;</td>
<td>Too short follow up SCD rate very low ? compliance</td>
</tr>
<tr>
<td>ALPHA-OMEGA n=4837 3 years</td>
<td>Margarines 400mg</td>
<td>1.01 (P=0.93) &lt;CI 0.87-1.17&gt;</td>
<td>Sub-therapeutic dose ? compliance</td>
</tr>
<tr>
<td>ORIGIN n=12,536 6.2 years</td>
<td>1 gram EE OMACOR</td>
<td>0.98 (P=0.72) &lt;CI 0.87-1.10&gt;</td>
<td>Too long follow up ? compliance</td>
</tr>
</tbody>
</table>

OMEGA-3 TRIAL

Chief author/investigator
Dr Jochen Serges

“The study was underpowered to show an effect because of the low rate of sudden cardiac death” Serges explained.

“It would be incorrect to say that omega-3 fatty acids are not effective”

Ref: ACC Scientific Sessions March 2009
www.theheart.org/article April 3, 2009
## Omega-3 Fatty Acid Outcome Trials – Comparison of Positive and Neutral Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>n=</th>
<th>Duration Years</th>
<th>Deaths</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-P 2 way analysis (1 gm EE Omega-3)</td>
<td>11,324</td>
<td>3.5</td>
<td>1017</td>
<td>0.86 (0.76-0.97)</td>
</tr>
<tr>
<td>4 Way Analysis</td>
<td>5,664</td>
<td>3.5</td>
<td>529</td>
<td>0.80 (0.67-0.94)</td>
</tr>
<tr>
<td>GISSI-HF (1 gm EE omega-3)</td>
<td>6,975</td>
<td>3.9</td>
<td>1969</td>
<td>0.91 (0.83-0.99)</td>
</tr>
<tr>
<td>OMEGA (1 gm EE omega-3)</td>
<td>3,851</td>
<td>1</td>
<td>158</td>
<td>1.25 (0.90-1.72)*</td>
</tr>
<tr>
<td>SU.FOL.OM (600mg omega-3 triglyceride)</td>
<td>2,501</td>
<td>4.7</td>
<td>117</td>
<td>1.03 (0.72-1.48)*</td>
</tr>
</tbody>
</table>

* The very large confidence intervals in the recent underpowered neutral trials
OMACOR high dose after Bypass
Improved Outcomes

- n=2,100 post coronary artery bypass
- The decision to prescribe OMACOR at discretion of cardiologist. Dose was 2 capsules/day. 44% were discharged on OMACOR.
- Primary end-point MORTALITY
- Secondary component CV EVENTS
- 3 year follow up

RESULTS:

- Omacor x 2 lowered mortality HR 0.51 (95% CI 0.36-0.73, P=0.0002)
- If EF < 40% mortality HR 0.38 (95% 0.17-0.77, P=0.007)
- Lower composite end point HR 0.56 (95% CI 0.56-0.8, P=0.001)

Marine n-3 Mechanisms

- Lower intake in food rich with SFA
- Lower heart rate and B.P
- Improved heart rate variability
- Elevation of VF threshold
- Improved endothelial function
- Decreased inflammation
- Anti platelet and thrombotic tendency
- Lower triglycerides
- Lower Non–HDL cholesterol
- Higher HDL-C
- Lower plasma leptin levels
- Improves depression

NHFA Website position statement 2008
Number Needed to Treat to Prevent CHD Event over 5 years

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annual Risk of CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.82</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>0.78</td>
</tr>
<tr>
<td>Statins</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoking Advice</td>
<td>0.68</td>
</tr>
<tr>
<td>Fish (+ fish oil)</td>
<td>0.65</td>
</tr>
<tr>
<td>Med Diet</td>
<td>0.24</td>
</tr>
</tbody>
</table>

(low fat diets OR = 0.96; 95% CI 0.89-1.04)

Ebrahim S et al. Effective Health Care 1998;4:1-16
10 Dietary Commandments

- No butter nor cream
- Extra virgin olive (or canola oils)
- Multigrain bread daily
- Fish at least weekly
- More & variety of fruit & vegetables
- Less meat (lean)
- Handful of nuts, tomatoes, onions most days
- Soy a few times/week
- Wine (or beer) daily
- Eat in a pleasant environment

Adapted from de Lorgeril
© D. Colquhoun 2002

D.Colquhoun@mailbox.uq.edu.au
“Nothing will benefit human health and increase the chances for survival of life on Earth as much as the evolution of a vegetarian diet” & the addition of fatty fish weekly for healthy adults and at least 1000mg EPA/DHA per day for those with CHD and 2000mg in heart failure – consider Ethyl Ester at night (The Quotable Colquhoun!)
The Quotable Einstein
How times have changed!
1949 TV Commercial

According to a recent Nationwide survey:
MORE DOCTORS SMOKE CAMELS
THAN ANY OTHER CIGARETTE
The End