Omega-3 Fatty Acids 101
Rationale for Selecting a Target Intake of EPA+DHA in Healthy US Adults

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LSRO
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Essential Fatty Acid Families

**ω-6 family**
- **C18:2 ω-6**
  - Linoleic
  - Corn Oil
  - Safflower Oil
  - Sunflower Oil
- **C20:4 ω-6**
  - Arachidonic

*More thrombotic and inflammatory metabolites*

**ω-3 family**
- **C18:3 ω-3**
  - α-Linolenic
  - Flaxseed Oil
  - Canola Oil
  - Soybean Oil
- **C20:5 ω-3**
  - Eicosapentaenoic (EPA)
  - Oily Fish
  - Fish Oil Capsules
- **C22:6 ω-3**
  - Docosahexaenoic (DHA)

*Less thrombotic and inflammatory metabolites*
GISSI-Prevenzione: *Time Course of Clinical Events*

>11,300 post-MI patients were given usual care with or without **850 mg** EPA+DHA (1 cap/d omega-3 acid ethyl esters) for 3.5 years

**Total mortality reduced by 28%**

(p=0.027)

**Sudden death reduced by 47%**

(p=0.0136)

Japan EPA Lipid Intervention Study - JELIS
(Yokoyama et al. Lancet 2007;369:1090-98)

Entire Cohort N=18,645
1a Prevention=14,981
2a Prevention=3,664

Figure 2: Kaplan-Meier estimates of incidence of coronary events in the total study population (panel A), the primary prevention arm (panel B) and the secondary prevention arm (panel C).

18,645 Japanese (70% women, 61 yrs) randomized to statin alone or statin+EPA (1.8 g/d) and followed for 5 years.
Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels - *Physicians’ Health Study*


90% reduction in risk

p for trend = 0.001
Risk for Primary Cardiac Arrest and Red Blood Cell EPA+DHA Level

Adapted from Siscovick DS et al. *JAMA* 1995;274:1363-1367.

Mean RBC EPA+DHA by Quartile

- 3.3%
- 4.3%
- 5.0%
- 6.5%

Odds Ratio

- 90% reduction in risk

*p<0.05 vs Q1*
The Benefits of Omega-3 FA are Not Mediated through Classic or Emerging CHD Risk Factors

Lipids (LDL, HDL, TG)
Blood Pressure
Inflammatory Markers (e.g., CRP)

MEMBRANE EFFECTS
Heart rate or HR variability (?)
Anti-Platelet (?)
Anti-arrhythmic (?)
Omega-3 Index – A new CHD risk factor?

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

\[
\frac{3}{64} = 4.6\%
\]

Omega-3 Index = 4.6%

Omega-3 Index: Estimating Targets

Greatest Protection

GISSI-P: ~9–10%
CHS: 8.8%
DART: ~8–9%
SCIMO: 8.3%
5 epi studies: ~8%
PHS: 7.3%
Seattle: 6.5%

Least Protection

PHS: 3.9%
SCIMO: 3.4%
Seattle: 3.3%

Proposed Omega-3 Index Risk Zones: Relative Risk for Death from CHD

- Undesirable
- Intermediate
- Desirable

Percent of EPA + DHA in RBC

RBC Omega-3 Fatty Acids and Acute Coronary Syndromes (768 case-control pairs)

Multivariable logistic regression model including: age; race; gender; history of diabetes mellitus, hypertension, hyperlipidemia and/or myocardial infarction; a family history of coronary artery disease; and LDL-C, HDL-C, and triglycerides.

Criteria for Diet-Disease Relationships

- Strength of association
- Dose-response relationship
- Temporally correct association
- Consistency of association
- Specificity of association
- Biological plausibility

Hill, 1971
A PROPOSED U.S. TARGET INTAKE FOR EPA+DHA FOR HEALTHY ADULTS
# American Heart Association Omega-3 FA Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Patients without documented CHD</td>
<td>Eat a variety of (preferably oily) fish at least twice a week.</td>
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<tr>
<td>Patients with documented CHD</td>
<td>Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician</td>
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<tr>
<td>Patients needing triglyceride lowering</td>
<td>2–4 grams of EPA+DHA per day provided as capsules under a physician’s care</td>
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<tr>
<th>Organization</th>
<th>Yr</th>
<th>EPA+DHA Recommendation</th>
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<tbody>
<tr>
<td>Eurodiet Conference, University of Crete</td>
<td>2000</td>
<td>200 mg/d</td>
</tr>
<tr>
<td>France: AFFSA, CNERNA &amp; CNRS</td>
<td>2001</td>
<td>500 mg/d</td>
</tr>
<tr>
<td>US National Academy of Sciences Institute of Medicine</td>
<td>2002</td>
<td>None (10% of ALA AI can be provided by EPA+DHA)</td>
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<tr>
<td>UK Scientific Advisory Committee on Nutrition (SACN)</td>
<td>2004</td>
<td>Fish twice/wk, one of which should be oily, minimum intake EPA+DHA (≈ 450 mg/d)</td>
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<tr>
<td>ISSFAL</td>
<td>2004</td>
<td>500 mg/d</td>
</tr>
<tr>
<td>Australia and New Zealand Government Recommendations*</td>
<td>2005</td>
<td>442 mg/d for men, 318 mg/d for women*</td>
</tr>
<tr>
<td>Dutch Health Council</td>
<td>2006</td>
<td>Fish twice/wk, one of which should be oily, to achieve the dietary reference intake of 450 mg/d</td>
</tr>
<tr>
<td>Superior Health Council of Belgium</td>
<td>2006</td>
<td>Minimum of 0.3 en% for adults (≈ 667 mg/d)</td>
</tr>
<tr>
<td>American Dietetics Assn / Dietitians of Canada</td>
<td>2007</td>
<td>500 mg/d</td>
</tr>
</tbody>
</table>

Harris W. J Cardiovasc Med 2007;8:S50

*Not including DPA; Howe P. Nutr Diet 2007;64:S135-139
Examine US epidemiological studies to determine the intakes of EPA+DHA that were associated with the lowest risk for death from CHD

Estimate the amount of EPA+DHA that one would consume by following the AHA advice to eat “at least 2 (preferably oily) fish meals per week”
APPROACH: Epidemiologic Studies

Characteristics

1. population was from the US
2. population was free of known CHD at baseline
3. risk for CHD death, primary cardiac arrest, and/or sudden cardiac death were reported
4. risk was assessed as a function of the estimated EPA+DHA intake by quintile
5. multivariate analysis was used to calculate relative risk
Studies Fulfilling the Inclusion Criteria

**Hu**: Nurses’ Health Study  *(JAMA 287:1815, 2002)*

**Albert**: US Physicians’ Health Study  *(JAMA. 279:23, 1998)*

**Dolecek**: MRFIT  *(PSEBM 200:177, 1992)*

**Siscovick**: Seattle Case-Control Study  *(Am J Clin Nutr 71:208S, 2000)*

**Mozaffarian**: Cardiovascular Health Study  *(Circulation.107:1372, 2003)*

**Ascherio**: Health Professional’s Study  *(NEJM 332:977, 1995)*
Relative Risk of CHD Death According to Estimated n-3 FA Intakes

Nurses’ Health Study

P-value for trend <0.001

(Subanalysis with diabetic nurses gave same results)

Hu, et al. JAMA, 2002
Relative Risk of CHD Death According to Estimated n-3 FA Intakes

Physicians’ Health Study

P-value for trend = 0.2; * p<0.05

Relative Risk of CHD Death According to Estimated n-3 FA Intakes

MRFIT

P-value for trend <0.05

Dolecek. PSEBM, 1992
Relative Risk of Primary Cardiac Arrest According to Estimated n-3 FA Intakes

Seattle Case-Control Study

P-value for trend <0.001

Siscovick, et al. AJCN, 2002
Relative Risk of IHD Death According to Estimated n-3 FA Intakes

*Tuna/non-fried fish; P-value for trend <0.002

Relative Risk of CHD Death According to Estimated n-3 FA Intakes

Health Professionals’ Study

P-value for trend = NS  
Ascherio, et al. NEJM, 1995

Mean long-chain n-3 intake (mg/d)

NOT INCLUDED IN ANALYSIS SINCE NO EFFECT SEEN
EPA and DHA *Intakes* Associated with Lowest Risk for Fatal CHD in US Epidemiology Studies

- **Albert**: 100 mg/d
- **Siscovick**: 200 mg/d
- **Dolocek**: 400 mg/d
- **Hu**: 600 mg/d
- **Mozaffarian**: 800 mg/d

The EPA+DHA intake associated with the lowest risk for fatal CHD is 496 mg/d.
Eliminating the extremes still produces an estimated beneficial intake of about 500 mg/d.
Meta analysis of US Epidemiological Studies Relating Estimated EPA+DHA Intakes with Risk for CHD Death

![Graph showing relative risk for different EPA+DHA intakes](image)

- **All Studies (n=6)**
  - 25 (34)
  - 78 (56)
  - 159 (85)
  - 290 (146)
  - 566 (224)

- **Studies with >6 yrs of follow-up (n=5)**
  - 15 (29)
  - 64 (49)
  - 143 (84)
  - 280 (161)
  - 564 (250)

EPA+DHA Intake (mg/d)
The average, estimated EPA+DHA intake in the five US epidemiological studies in which fish intake was associated with reduced CHD risk was 496 mg/d. The reduction in risk for CHD mortality (relative to the lowest intake group) was 37-50% in these studies. This is about 0.22% en (based on a 2000 kcal diet).
“Eat a variety of (preferably oily) fish at least twice a week.”

How much EPA+DHA is in a typical serving of oily fish?

What is an oily fish?

What is a serving?
What is a “Serving” of Fish?

Although the standard serving is traditionally considered to be 3 oz. (85 g), data from the USDA* indicate that the typical serving size for finfish in the US is 110 g, or about 4 oz. The variability in serving size is tacitly acknowledged by the FDA in their recommendations** regarding mercury from fish where they note that “a typical serving size of fish is from 3 to 6 ounces.”


**http://www.fda.gov/oc/opacom/mehgadvisory1208.html
Seafoods Ranked by Omega-3 Content

(mg n-3 FA/3-oz serving - USDA)

1. Orange roughy
2. Tilapia
3. Mahi-Mahi (dolphin fish)
4. Cod
5. Catfish Farmed
6. Catfish Wild
7. Tuna Chunk light canned (in water)
8. Tuna Yellowfin
9. Clams, dry heat
10. Shrimp Cooked mixed
11. Tuna Skipjack
12. Scallops, cooked, steamed
13. Oyster, farmed, raw
14. Crab Dungeness
15. Walleye
16. Crab King
17. Halibut
18. Crab Blue
19. Flat fish (Flounder/sole)
20. Pollock
21. Sea Bass
22. Swordfish
23. Shark (raw)
24. Tuna White canned (in water)
25. Sardines (canned in oil)
26. Salmon Coho wild
27. Rainbow Trout farmed
28. Salmon Chum (canned)
29. Mackerel (canned)
30. Salmon Sockeye
31. Salmon Coho farmed
32. Salmon Pink
33. Tuna Bluefin
34. Salmon Atlantic wild
35. Herring Atlantic
36. Herring Pacific
37. Salmon Atlantic farmed

Assume an ‘oily fish’ contains at least 500 mg EPA+DHA per 3 oz serving.

EPA+DHA per 3 oz
= 1.115 g
= 2.975 g/8 oz
= 425 mg/day
Is an intake of 500 mg/d of EPA+DHA Safe?

- FDA has ruled that up to 3 g of EPA+DHA from all sources can be incorporated into the American food supply.
- Stroke incidence is either reduced or not affected by intakes of fish that would provide about 500 mg E+D*.
- Methylmercury intake can easily be kept below the FDA guidelines, and the 500 mg target can be met (even for pregnant women) by consumption of 8-9 oz of oily fish per week.

* He et al. Circulation 2004;35:1538-1546
CONCLUSIONS

An intake of about 500 mg/d of EPA+DHA

- has been associated with significantly reduced risk for death from CHD in several major epidemiologic studies in the US
- is evidence-based and objectively derived
- is obtainable by diet alone (about 8 oz per wk)
- is half of the AHA recommended intake for secondary prevention
- Is safe and can be obtained within FDA mercury guidelines
- Is in harmony with other agencies and countries