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Department of Epidemiology
Welch Center for Prevention, Epidemiology, and Clinical Research

The α and the ω

Nutritional benefits of fish consumption

Eliseo Guallar, MD, PhD
Johns Hopkins Medical Institutions
Baltimore, MD

eguallar@jhsph.edu

SEAFOOD CHOICES
BALANCING BENEFITS AND RISKS

Committee on Nutrient Relationships in Seafood:
Selections to Balance Benefits and Risks
Food and Nutrition Board

Malden C. Nesheim and Ann L. Yaktine, *Editors*

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Evidence Report/Technology Assessment
Number 94

Effects of Omega-3 Fatty Acids on Cardiovascular Disease

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Prepared by:
Tufts-New England Medical Center EPC, Boston, Massachusetts

Investigators
Chenchen Wang MD, MSc
Mei Chung, MPH, Research Associate
Ethan Balk, MD, MPH, Project Leader
Bruce Kupelnick, BA, Research Associate
Deirdre DeVine, MLitt, Project Manager
Amy Lawrence, BA, Research Assistant
Alice Lichtenstein, DSc, Primary Technical Expert
Joseph Lau, MD, Principal Investigator

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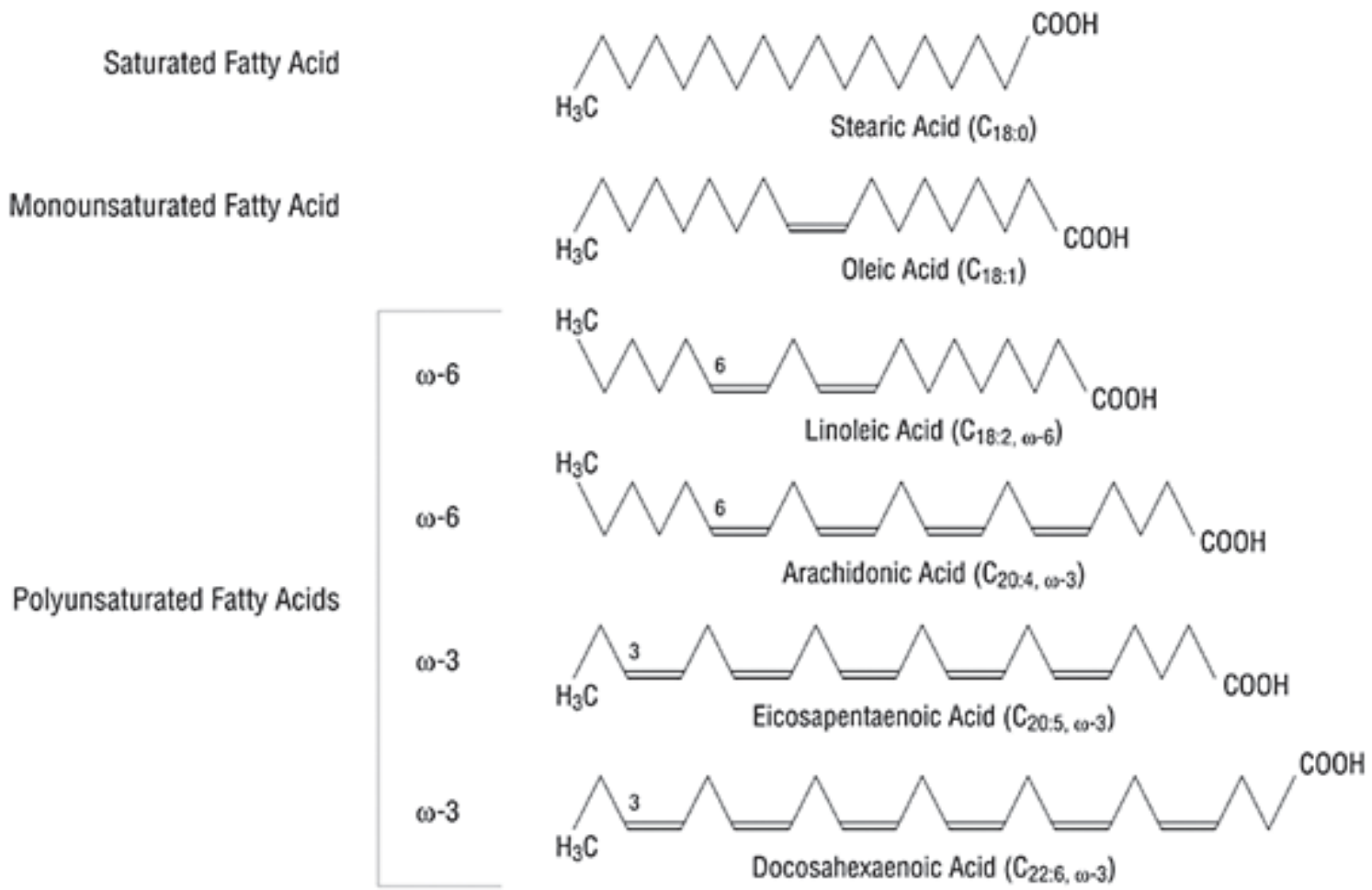
http://dietary-supplements.info.nih.gov/Headlines/Omega-3_AHRQ_Reports.aspx

Structure of fatty acids



Harper CR, Jacobson TA. Arch Intern Med 2001;161:2185-2192

US consumption of fishery products

	2004	
Rank	**Fish**	**PPC**
1	Shrimp	4.2
2	Canned tuna	3.3
3	Salmon	2.2
4	Pollock	1.3
5	Catfish	1.1
6	Tilapia	0.7
7	Crab	0.6
8	Cod	0.6
9	Clams	0.5
10	Flatfish[a]	0.3

Institute of Medicine. Seafood Choices, 2007:31-32

Fish consumption among subjects > 1 y old – NHANES 1999 – 2002

Percent of persons using in 1 day	15.9
Quantity consumed in 1 day, by users (1 ounce = 28 g)	
Mean	89.2
SEM	2.6
Average quantity consumed per person per day	
Mean	14.2
SEM	0.7

Institute of Medicine. Seafood Choices, 2007:36

Nutritional properties of fish

- **Gropued with meats, poultry, eggs, nuts, legumes, and seeds**
  - *Major contributors of protein, niacin, zinc and vit B6*
  - *Substantial contributor of vits E and B12, thiamin, riboflavin, P, Mg, Fe, Cu, K, linoleic acid*
- **Relative to comparable foods, fish are**
  - *main source of EPA / DHA*
  - *rich in selenium*
  - *low in saturated fats and in calories*

ω–3 fatty content of selected fish

Fish	ALA	EPA	DHA
Mackerel	0.1	0.9	1.6
Atlantic herring	0.1	0.7	0.9
Albacore tuna	0.2	0.3	1.0
Chinook salmon	0.1	0.8	0.6
Anchovy	Trace	0.5	0.9
Coho salmon	0.2	0.3	0.5
Greenland halibut	Trace	0.5	0.4
Rainbow trout	0.1	0.1	0.4
Atlantic cod	Trace	0.1	0.4
Atlantic white shrimp	Trace	0.2	0.2
Catfish	Trace	0.1	0.2
Northern lobster	0	0.1	0.1
Flounder	Trace	0.1	0.1

*Given as grams of fatty acid per 100 g of raw material. ALA indicates α linolenic acid; EPA, eicosapentaenoic acid; and DHA, docosahexaenoic acid.

Harper CR, Jacobson TA. Arch Intern Med 2001;161:2185-2192

Potential mechanisms of ω–3 fatty acids to reduce CVD risk

- Reduce susceptibility of the heart to ventricular arrhythmia
- Antithrombogenic
- Hypotriglyceridemic (fasting and postprandial)
- Retard growth of atherosclerotic plaque
  - Reduce adhesion molecule expression
  - Reduce platelet-derived growth factor
  - Antiinflammatory
- Promote nitric oxide-induced endothelial relaxation
- Mildly hypotensive

Kris-Etherton PM, et al. Circulation 2002;106:2747-2757

ω–3 fatty acids: Concerns

- Oxidative stress
- Hemorrhagic events
- Contaminants of fish / fish oils
- Side effects of fish oil supplements

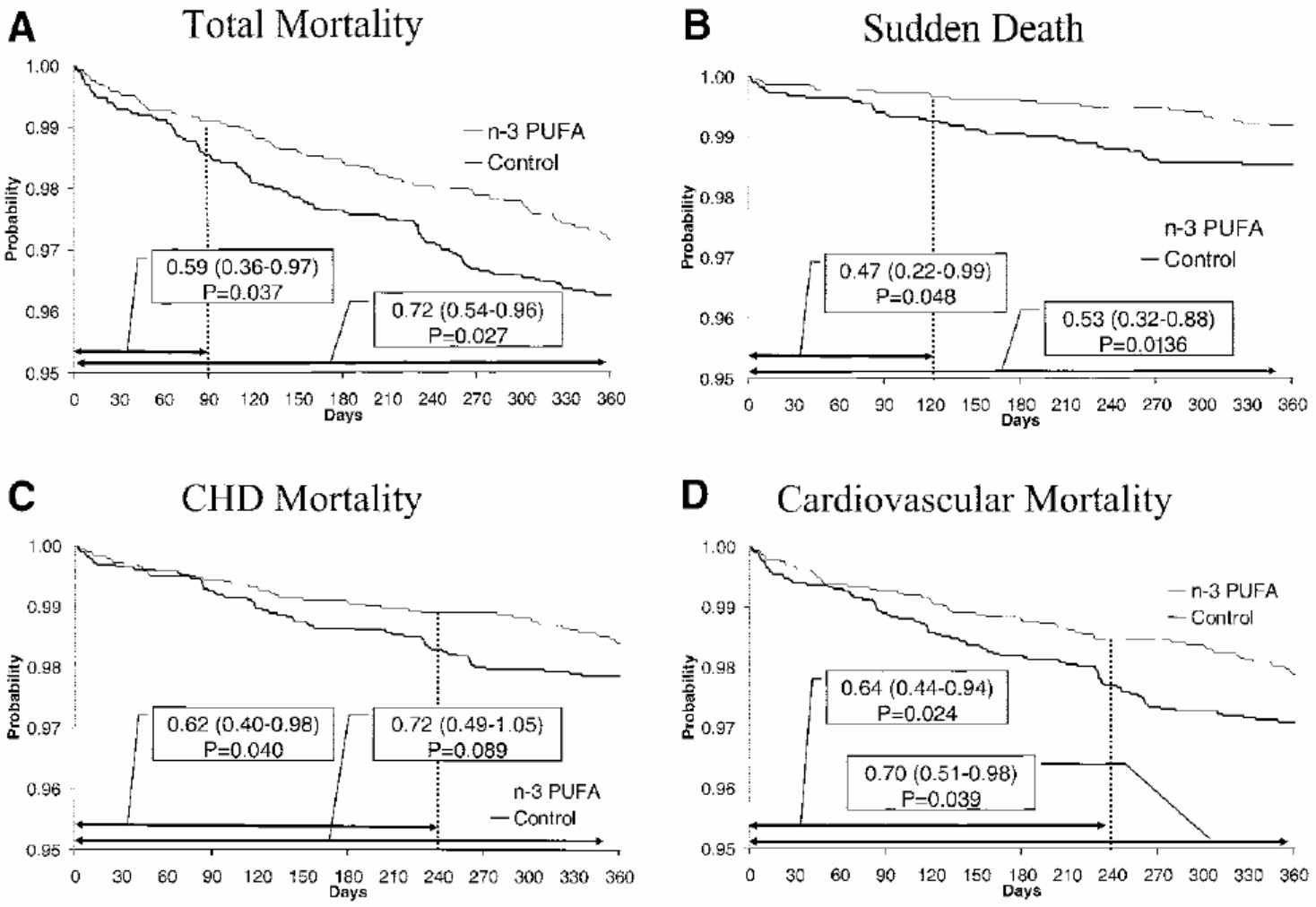
- Generally recognized as safe dose of fish oils – up to 3 g/d

GISSI-Prevenzione Trial – efficacy of ω–3 supplements on main endpoints

	Two-way analysis		
	n-3 PUFA (n=5666)	Control (n=5668)	Relative risk (95% CI)
Main endpoints			
Death, non-fatal MI, and non-fatal stroke	715 (12·6%)	785 (13·9%)	0·90 (0·82–0·99)
Cardiovascular death, non-fatal MI, and non-fatal stroke	547 (9·7%)	608 (10·8%)	0·89 (0·80–1·01)
Secondary analyses			
All fatal events	472 (8·3%)	545 (9·6%)	0·86 (0·76–0·97)
Cardiovascular deaths	291 (5·1%)	348 (6·2%)	0·83 (0·71–0·97)
Cardiac death	228 (4·0%)	292 (5·2%)	0·78 (0·65–0·92)
Coronary death	214 (3·8%)	265 (4·7%)	0·80 (0·67–0·96)
Sudden death	122 (2·2%)	164 (2·9%)	0·74 (0·58–0·93)
Other deaths	181 (3·2%)	197 (3·5%)	0·91 (0·74–1·11)
Non-fatal cardiovascular events	287 (5·1%)	291 (5·1%)	0·98 (0·83–1·15)
Other analyses			
CHD death and non-fatal MI	424 (7·5%)	485 (8·6%)	0·87 (0·76–0·99)
Fatal and non-fatal stroke	98 (1·7%)	80 (1·4%)	1·21 (0·91–1·63)

GISSI-Prevenzione Investigators. Lancet 1999;354:447-455

GISSI-Prevenzione Trial – time-course of efficacy of ω–3 supplements



Marchioli R, et al. Circulation 2002;105:1897-903

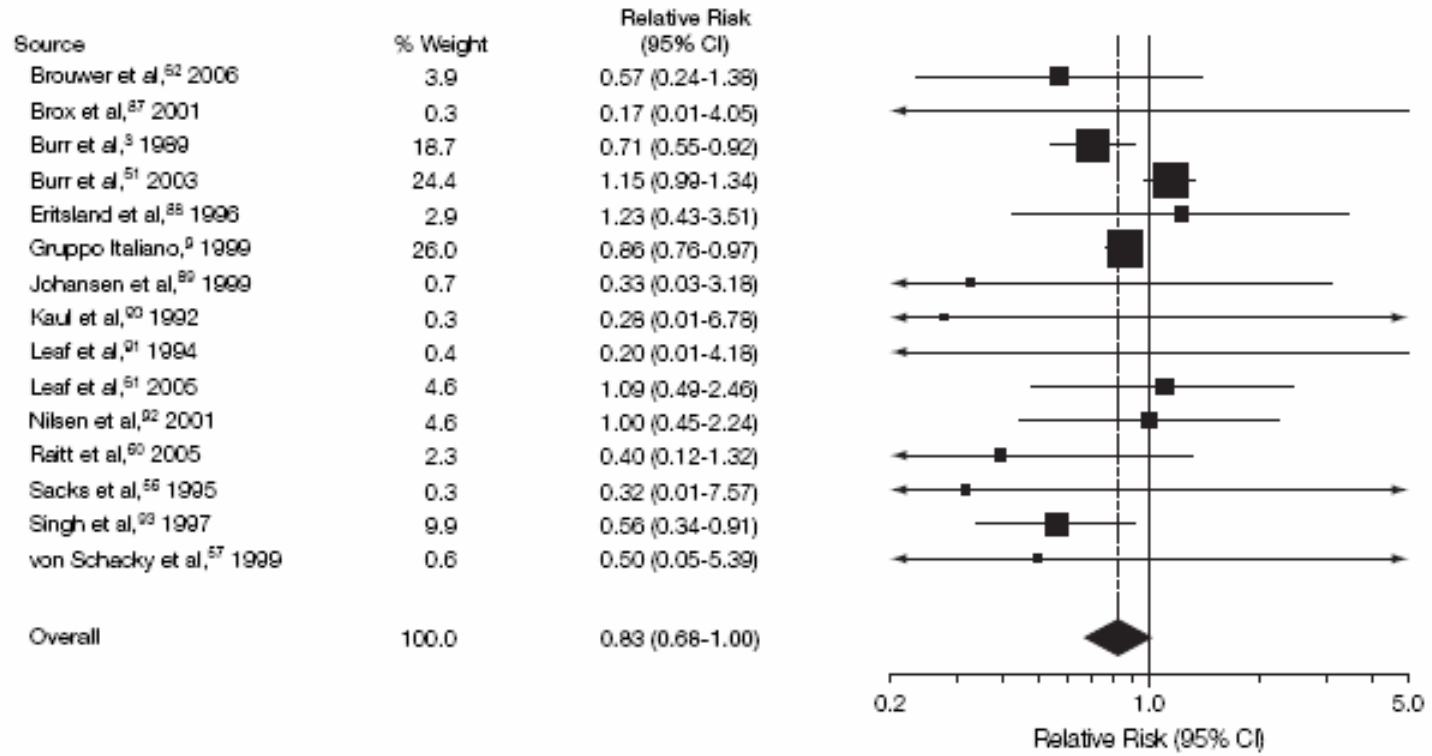
Table 7 Mortality of subjects advised about fish and fruit: adjusted hazard ratios (HR)[a] relative to subjects not so advised

	Fish advice		*Fruit advice*	
	HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*
All deaths	1.15 (0.96, 1.36)	0.13	1.12 (0.94, 1.34)	0.20
Cardiac deaths	1.26 (1.00, 1.58)	0.047	1.00 (0.80, 1.25)	1.0
Sudden deaths	1.54 (1.06, 2.23)	0.025	1.01 (0.70, 1.46)	0.94

[a]Hazard ratios adjusted for age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication (see text), and fruit advice (for fish) or fish advice (for fruit).

Burr ML, et al. Eur J Clin Nutr 2003;57:193–200

Figure 4. Risk of Total Mortality Due to Intake of Fish or Fish Oil in Randomized Clinical Trials



The size of the shaded squares indicates each trial's contribution (inverse-variance weight) to the pooled estimate (dotted line) and 95% confidence interval (CI; diamond), determined by random effects meta-analysis.[37] Intake of fish or fish oil reduced total mortality by 17% ($P=.046$), with evidence for heterogeneity between trials ($P=.04$ for heterogeneity). If 2 trials with methodologic concerns[51,93] were excluded, the pooled relative risk was 0.83 (95% CI, 0.74-0.92; $P<.001$) with little evidence for heterogeneity ($P=.75$). A recently reported trial of fish oil among Japanese individuals[17] was not included in the primary analysis due to very high fish intake in the reference group (estimated eicosapentaenoic acid + docosahexaenoic acid intake, 900 mg/d) which would obviate mortality benefits of additional fish oil intake. When this trial was added to the secondary analysis, the pooled relative risk was 0.87 (95% CI, 0.76-0.99; $P=.048$; $P=.29$ for heterogeneity).

Mozaffarian D, et al. JAMA 2006;296:1885-1899

Reasons for conflicting epidemiological findings

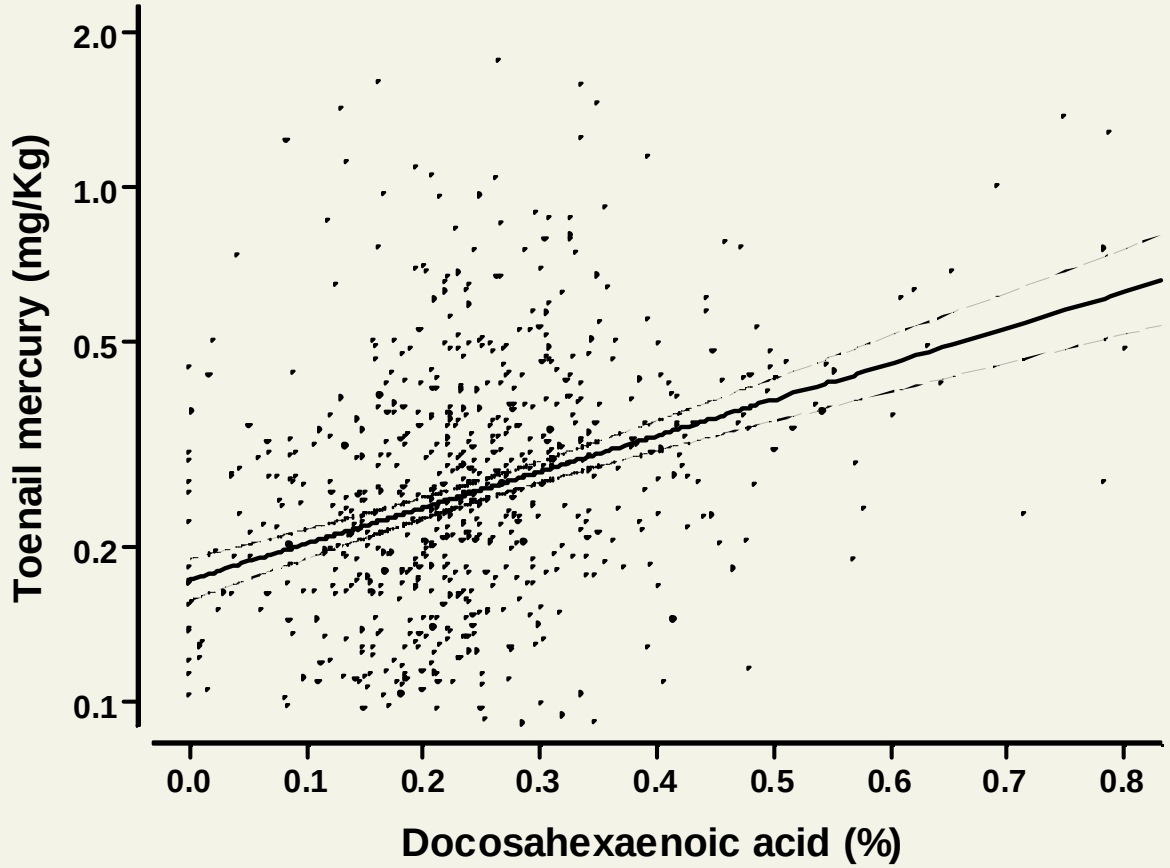
- Differences in endpoint definitions
- Differences in estimation of fish intake
- Variability in fish intake in reference group
- Differences in fish intake across populations
- Risk status of population studied
- Differences in effects of foods that substitute for fish
- Confounding effects of other foods
- Effects of other contaminants in fish

Methylmercury levels in selected commercial fish species

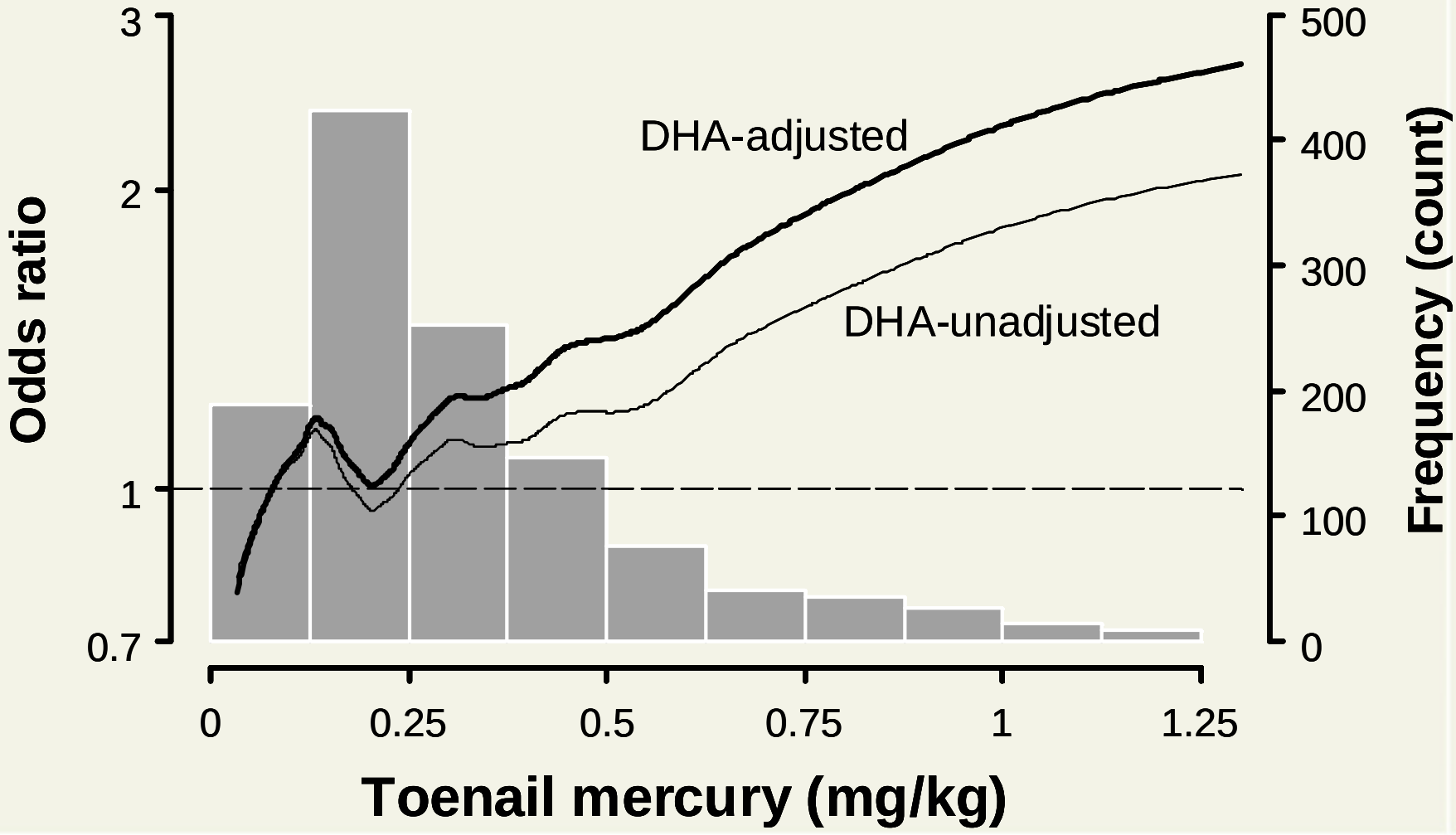
Species	Methylmercury Concentration (ppm)	
	MEAN	RANGE
Tilefish	1.45	0.65–3.73
Swordfish	1.00	0.65–3.73
King mackerel	1.00	0.10–1.67
Shark	0.96	0.05–4.54
Tuna (fresh and frozen)	0.32	ND–1.3
Pollack	0.20	ND–0.78
Tuna (canned)	0.17	ND–0.75
Catfish	0.07	ND–0.31
Salmon (fresh and canned)	ND	ND–0.18
Shrimp	ND	ND

Bolger PM, Schwetz BA. N Engl J Med 2002;347:1735-1736

EURAMIC Study – Association between Hg and DHA among controls



EURAMIC Study – Non-parametric odds ratios of MI by level of toenail Hg



Guallar E, et al. N Engl J Med 2002;347:1747-1754

HPFU Study – Relative risks of CHD by quintile of toenail Hg

Measure*	Quintile of Mercury Level					P for Trend†
	1	2	3	4	5	
Mercury level in toenails — μg/g						
Median	0.15	0.28	0.45	0.67	1.34	
Range	0.03–0.21	0.22–0.35	0.36–0.54	0.55–0.86	0.87–14.56	
No. of patients (n=470)	101	93	90	90	96	
No. of controls (n=464)	85	94	97	97	91	
Age- and smoking-adjusted RR (95% CI)‡§	1.00	0.83 (0.55–1.25)	0.77 (0.51–1.16)	0.77 (0.51–1.16)	0.87 (0.57–1.31)	0.83
Multivariate RR (95% CI)‡¶	1.00	0.92 (0.60–1.41)	0.80 (0.52–1.24)	0.92 (0.60–1.41)	0.97 (0.63–1.50)	0.78
Multivariate RR (95% CI)‡‖	1.00	0.93 (0.60–1.43)	0.83 (0.53–1.30)	0.96 (0.62–1.51)	1.03 (0.65–1.65)	0.55

*RR denotes relative risk, and CI confidence interval.

†The P value was calculated from a test for trend across quintiles.

‡The lowest quintile of toenail mercury level served as the reference category.

§Values have been adjusted for age (six categories: ≤50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, and >70 years) and smoking status (four categories: never smoked, former smoker, 1–24 cigarettes daily, and >24 cigarettes daily).

¶Values have been adjusted for age (six categories: ≤50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, and >70 years), smoking status (four categories: never smoked, former smoker, 1 to 24 cigarettes daily, and >24 cigarettes daily), alcohol intake (four categories: 0, 1.0 to 5.0, 5.1 to 30.0, and >30.0 g per day), family history of coronary heart disease (binary), high blood pressure (binary), hypercholesterolemia (binary,) diabetes (binary), body-mass index (five categories) at the 1986 base line, and quintile of toenail sample weight.

‖Values have been adjusted for the covariates listed above and also for quintiles of intake of n−3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid).

Yoshizawa K, et al. N Engl J Med 2002;347:1755-1760

TABLE 3-2 Level of Evidence for Benefits of Increasing Seafood or EPA/DHA Intake in the General Population[a] and Specific Subgroups Reviewed

Level of Evidence[b]		Higher Seafood Intake	Increase in EPA/DHA Intake
1a	Meta-analyses of randomized controlled trials		• Blood pressure • Triglyceride levels • Infant neurological development
1b	Randomized controlled trial(s)		• Gestational duration • Mortality and cardiovascular events in people with a history of MI • Infant neurological development
2a/3a	Meta-analyses of observational studies	• Cardiovascular mortality and events	
2b	Cohort study(ies)	• Fetal neurological development • Gestational duration • Postpartum depression in women	
3b	Case-control study(ies)		
	Cross-sectional study(ies)		
	Contradictory evidence or insufficient evidence on which to base recommendations	• Blood pressure • Stroke • Allergy and asthma • Cancer • Alzheimer's disease • Glycemic control in type II diabetes	• Cardiovascular mortality and events • Arrhythmia • Cancer • Alzheimer's disease • Glycemic control in type II diabetes • Allergy and asthma • Preeclampsia • Postpartum depression • HDL, LDL, Lp(a) levels

See corresponding editorial on page 1.

n−3 Fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review[1–3]

Chenchen Wang, William S Harris, Mei Chung, Alice H Lichtenstein, Ethan M Balk, Bruce Kupelnick, Harmon S Jordan, and Joseph Lau

ABSTRACT

Studies on the relation between dietary n−3 fatty acids (FAs) and cardiovascular disease vary in quality, and the results are inconsistent. A systematic review of the literature on the effects of n−3 FAs (consumed as fish or fish oils rich in eicosapentaenoic acid and docosahexaenoic acid or as α-linolenic acid) on cardiovascular disease outcomes and adverse events was conducted. Studies from MEDLINE and other sources that were of ≥1 y in duration and that reported estimates of fish or n−3 FA intakes and cardiovascular disease outcomes were included. Secondary prevention was addressed in 14 randomized controlled trials (RCTs) of fish-oil supplements or of diets high in n−3 FAs and in 1 prospective cohort study. Most trials reported that fish oil significantly reduced all-cause mortality, myocardial infarction, cardiac and sudden death, or stroke. Primary prevention of cardiovascular disease was reported in 1 RCT, in 25 prospective cohort studies, and in 7 case-control studies. No significant effect on overall deaths was reported in 3 RCTs that evaluated the effects of fish oil in patients with implantable cardioverter defibrillators. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes. The effects on stroke were inconsistent. Evidence suggests that increased consumption of n−3 FAs from fish or fish-oil supplements, but not of α-linolenic acid, reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke. The evidence for the benefits of fish oil is stronger in secondary- than in primary-prevention settings. Adverse effects appear to be minor. *Am J Clin Nutr* 2006;84:5–17.

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

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

Kris-Etherton PM, et al. Circulation 2002;106:2747-2757

U.S. Department of Health and Human Services
and
U.S. Environmental Protection Agency

March 2004 EPA-823-R-04-005

What You Need to Know About Mercury in Fish and Shellfish

2004 EPA and FDA Advice For:
Women Who Might Become Pregnant
Women Who are Pregnant
Nursing Mothers
Young Children

By following these 3 recommendations for selecting and eating fish or shellfish, women and young children will receive the benefits of eating fish and shellfish and be confident that they have reduced their exposure to the harmful effects of mercury.

1. Do not eat Shark, Swordfish, King Mackerel, or Tilefish because they contain high levels of mercury.

2. Eat up to 12 ounces (2 average meals) a week of a variety of fish and shellfish that are lower in mercury.

    - Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.
    - Another commonly eaten fish, albacore ("white") tuna has more mercury than canned light tuna. So, when choosing your two meals of fish and shellfish, you may eat up to 6 ounces (one average meal) of albacore tuna per week.

3. Check local advisories about the safety of fish caught by family and friends in your local lakes, rivers, and coastal areas. If no advice is available, eat up to 6 ounces (one average meal) per week of fish you catch from local waters, but don't consume any other fish during that week.

Follow these same recommendations when feeding fish and shellfish to your young child, but serve smaller portions.

http://www.cfsan.fda.gov/~dms/admehg3.html