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Proceedings of the 2007 National Forum on Contaminants in Fish

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Section II-E
Health Benefits of Fish Consumption

Moderator:

Judy Sheeshka, University of Guelph

Omega-3 Fatty Acid Deficiency among Pregnant Women: Biochemical and Dietary Approaches to Identifying Women at Risk and Implications for Infant Development

Sheila Innis, University of British Columbia

Fish, n-3 Fatty Acids and Dementia

Martha Clare Morris, Rush University Medical Center

Fish Consumption and Cardiovascular Risk

Dariush Mozaffarian, Harvard School of Public Health

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Omega-3 Fatty Acid Deficiency among Pregnant Women: Biochemical and Dietary Approaches to Identifying Women at Risk and Implications for Infant Development

Sheila Innis, University of British Columbia

Biosketch

Dr. Sheila Innis is a Professor in the Department of Pediatrics and Director of the Nutrition and Metabolism Research Program at the Child and Family Research Institute, Oak Street campus, University of British Columbia. The nutrition and metabolism research program is one of the major research programs at the Child and Family Research Institute and was established in 2003 with the award of $5.5 million in funding from the Canadian Foundation for Innovation and from Provincial funding to establish a program of research, training, and education addressing the biological basis for how dietary components promote health during early development. Dr. Innis has been a faculty member at the University of British Columbia since 1983. Her research program spans basic research and preclinical and clinical studies, as well as community-based studies in infants, children, and pregnant women, and it ranges from physiological measures to studies on the effects of dietary components on measures of growth and development, as well as gene expression, proteins targets and metabolite profiles, and later consequences through epigenetic mechanisms.

Dr. Innis is currently involved in clinical studies focusing on omega-3 and omega-6 fatty acids and methyl donors, and she has considerable experience in preclinical and clinical trials, as well as community studies.

Dr. Innis has attracted more than $25 million in research funding over 20 years of scholarly activities, has given more than 300 invited presentations world wide at major national and international functions on numerous topics related to children's diet and health, and has organized and chaired many such events. Her record of peer-reviewed original communications exceeds 180. She is also recognized for her participation in expert panels establishing dietary recommendations, in national and provincial task forces addressing diet and health, and in working with regulatory authorities in Canada and the United States.

Abstract

The importance of the n-3 fatty acid docosahexaenoic acid (DHA) (22:6n-3) is one of the most intensely studied areas relating nutrition to central nervous system (CNS) development. Particular focus has been given to DHA and the CNS because DHA is a major fatty acid in the ethanolamine phosphoglycerides (EPG) and phosphatidylserine of brain grey matter and the visual elements of the retina. Inadequate DHA during early development decreases DHA in the brain and retina, impairs neurogenesis and visual function, and results in long-term deficits in neurotransmitter metabolism and visual function in animals. Intervention studies to show that dietary DHA increases visual, mental, and motor skill development in some preterm and term infants fed formula provides evidence that DHA is also important in human development. Although a general dogma has been present that n-6 and n-3 fatty acids are preferentially transferred across the placenta and that human milk is the gold standard for infant feeding, it is clear that the maternal dietary DHA intake determines the DHA transfer across the placenta and secretion in human milk. Thus, attention has turned to consider whether low DHA intakes among pregnant and lactating women could contribute to poor infant CNS development. However, the following information is not known: the extent of DHA deficiency, if present; biochemical cut-offs for circulating DHA; dietary intakes; or infant visual or other developmental scores indicative of inadequate maternal DHA status to support optimal infant development.

Alpha-linolenic acid (ALA) (18:3n-3), not DHA, is currently considered the essential dietary n-3 fatty acid because humans lack a delta15 desaturase, but it can desaturate ALA via eicosapentaenoic acid (EPA) (20:5n-3) to DHA. However, stable isotope tracer studies have shown that conversion of ALA to DHA is low in humans, and interventions to increase ALA intake during pregnancy and lactation do not increase DHA in maternal or fetal circulating lipids or in human milk. However, although circulating levels of DHA increase with increasing DHA intake, enhanced DHA intake is not expected to benefit individuals with a DHA status above their physiological need. Neither the DHA status that meets the needs for CNS function, nor who or how many individuals are able to benefit from enhanced DHA nutrition is known. Adding complexity, infant development has a distribution in which the developmental potential of individual infants is unknown. We are conducting an intervention with DHA designed to determine if DHA deficiency is present among pregnant women. This session will illustrate the approach, using the measures of infant visual acuity at 60 days of age, and will provide evidence of deficiency sufficient to delay infant development in the population.

Omega-3 Fatty Acids Deficiency Among Pregnant Women:

Approaches to identifying risk and implications for infant development.

Sheila M. Innis
Nutrition Research Program
University of British Columbia

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- Omega (n)-3 fatty acids
  - essential dietary nutrients
  - specifically concentrated in select membranes, brain, retina, heart
  - specific functions poorly understood, but do involve
    - regulation of gene expression (lipogenesis/lipolysis, cytokines)
    - precursors for eicosanoids & docosanoids
    - protein interactions, *incl.* rhodopsin

High intake associated with reduced risk of many diseases

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Essential fatty acid supply

Vegetable oils nuts, seeds → **18:2n-6** **linoleic** *(14 g/d)*

Some vegetable oils,nuts, seeds → **18:3n-3** **α linolenic** ***(1.5 g/d)***

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Essential fatty acid supply

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Δ 6 desaturase
Δ 5 desaturase

20:4n-6 **arachidonic**

20:5n-3 **eicosapentaenoic**

Δ 6 desaturase

22:6n-3 **docosahexaenoic**

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Essential fatty acid supply

Vegetable oils nuts, seeds → **18:2n-6** **linoleic** *(14 g/d)*

Some vegetable oils,nuts, seeds → **18:3n-3** **α linolenic** ***(1.5 g/d)***

meat, eggs ← **Δ 6 desaturase** **Δ 5 desaturase** → ***fish***

20:4n-6 *(100 mg/d)* **arachidonic**

20:5n-3 *(80mg/d)* **eicosapentaenoic**

Δ 6 desaturase

<1% conversion

fish,eggs. meat

22:6n-3 *(100 mg/d)* **docosahexaenoic**

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Background:

- Retina rod & cones outer & brain grey matter are high in the long chain n-3 fatty acid docosahexaenoic acid (DHA, 22:6*n*-3).
- In animals, feeding an *n*-3 fatty acid deficient diet reduces retina & brain DHA, visual function & "cognitive" function
- In humans, *n*-3 fatty acid requirements are uncertain:
  DHA can be formed from α linolenic acid (ALA, 18:3n-3)
  but, conversion of ALA to DHA appears low & variable
- *and,* low blood lipid DHA is associated with decreased visual acuity maturation, cognitive & motor development in formula-fed infants, several behavioral, cognitive and visual problems in adults, and poorer behavioral, attentional and 'cognitive" ability in children

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Background:

- DHA is critical for neurogenesis,
  in humans, neurogenesis occurs between 3 & 6 mths gestation
- visual function is sensitive to n-3 fatty acid deficiency
  retina levels of DHA are attained by 36-40wk gestation

❖ *The prenatal period may be particularly sensitive for "DHA deficiency"*

- mean intakes of DHA among pregnant women is about 120mg/day, but intakes vary widely.
  with a range of 10-600 mg/ day among 'non" vegans
  deficiency & "toxicity" occur at the extremes of the intake distribution

❖ Is n-3 fatty acid nutrition adequate among pregnant women ?

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Prelude to the problem:

- Infant/ child development has a distribution, not a single value
- The developmental potential of an individual infant or child is not known

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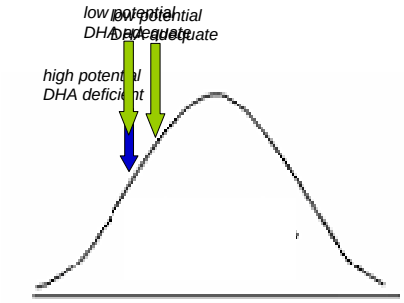

Distribution of function (cognitive potential)

Cognition has a distribution; many factors influence this

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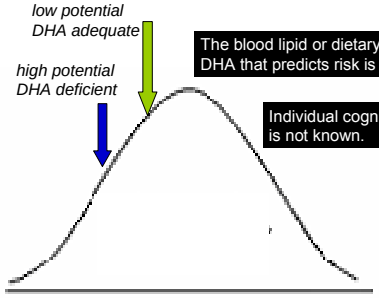

The blood lipid or dietary intake of DHA that predicts risk is not known.

Individual cognitive potential is not known.

Distribution of function (cognitive potential)

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Prelude to the problem:

- Infant/ child development has a distribution, not a single value
- The developmental potential of an individual infant or child is not known
- The relationship between nutrient intake and functions dependent on that nutrient are "non-linear"
- Only deficient individuals can benefit from intervention if other key nutrients are limiting, intervention will have no benefit.

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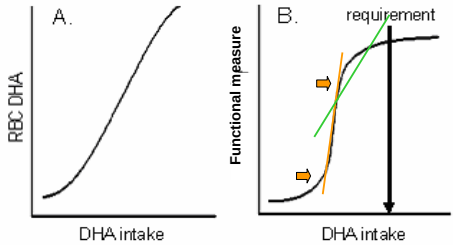
Addressing nutrient needs



- The relationship between DHA intake & blood DHA is linear
- The relationship between intake of a nutrient & functions dependent on that nutrient are non-linear (unless all in the group are deficient

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Prelude to the problem:

- Infant/ child development has a distribution, not a single value
- The developmental potential of an individual infant or child is not known
- The relationship between nutrient intake and functions dependent on that nutrient are "non-linear"
- Only deficient individuals can benefit from intervention if other key nutrients are limiting, intervention will have no benefit.
- Many things influence infant and child development the "effect-size" of DHA is not known,

➢ *choose outcome measures for which environmental or other dietary variables are likely to have minimal influence*

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addressing to the problem:

- Biochemical markers of poor DHA status/ deficiency are not identified
  what blood levels of DHA indicates deficiency ?
- Functional measures of DHA deficiency are not established.
  what IQ, behavior or visual acuity indicates DHA deficiency ?
- The developmental potential of individual infants is not known.
  how "smart" can the individual be?

➢ If maternal n-3 fatty acid nutrition in our community is adequate to support optimal transfer of DHA to the developing infant,

then

intervention to enhance maternal DHA nutrition will have no effect on the distribution of infant development test scores for measures sensitive to low retina and/or brain DHA

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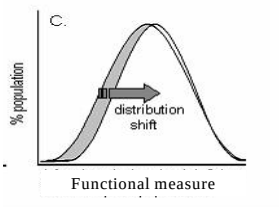
Results of intervention to enhance DHA nutrition in a mixed group of deficient & adequate group:



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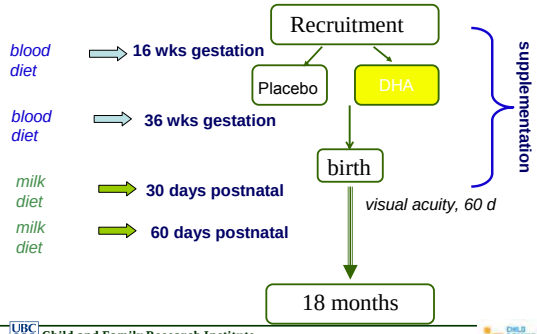
Design: placebo controlled: double –double blind



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Supplements

400 mg/day DHA from single cell oil, no EPA
500 mg/LA +40 mg ALA from corn+soybean oil
trivial compared to usual diet

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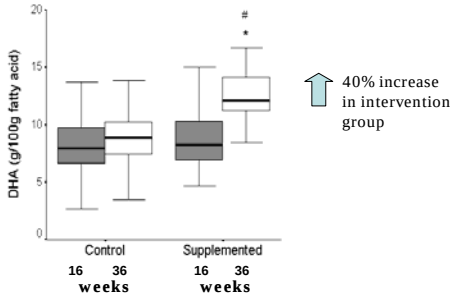
Biochemical measures: RBC inner membrane PE

Avoids problems of varying plasma lipid



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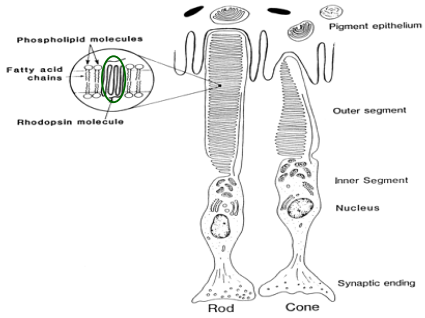

Photoreceptors cells contain hundreds of stacked membrane disks
Each molecule of visual pigment is surrounded by ~ 60 phospholipids

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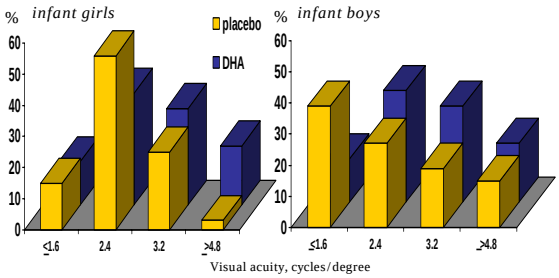
Visual acuity in term infant girls & boys of mothers assigned to DHA or placebo in gestation



- **In multivariate analysis, the OR for an acuity score below the group mean in the placebo group was 3.37. The results provide functional evidence to suggest the DHA status of some pregnant women is inadequate.**

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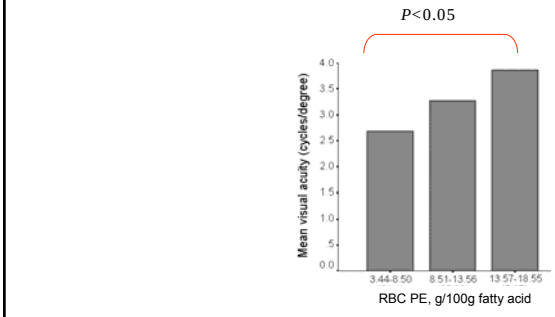
Placebo group: visual acuity scores by maternal DHA status



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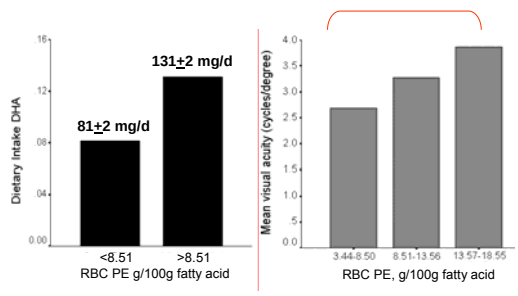
Placebo group: Maternal dietary DHA by maternal DHA status



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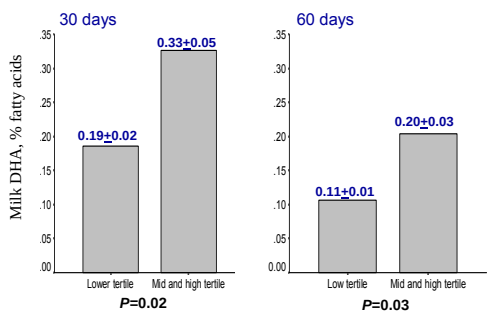

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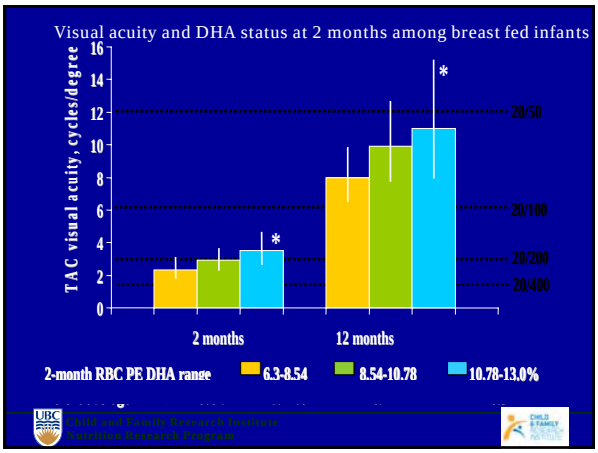

Summary

We provide evidence that poor DHA status is present & related to lower performance on early tests of infant neural development,

Women who consume < 80 mg DHA/day (& 0.9 gm ALA day), appear to be at risk, this is about 40% of our study population

Women with a low DHA status in gestation also have lower DHA in their milk, levels of <0.2 % DHA indicate risk.

This study does not address requirements, only deficiency, or whether ALA vs DHA is needed.. these studies require a different design.

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Nutrition Research Program

Sheila M. Innis and Russell W. Freisen
Nutrition Research Program
University of British Columbia

Funded by Canadian Institutes of Health Research

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Questions and Answers

Q. Do you know of any biomonitoring implemented for DHA [Docosahexaenoic acid]? Are nutritionists addressing this issue? (Frohmberg)

A. DHA levels on approximately 1,000 people analyzed by the same lab, person, and machine have been collected over the course of this study. Dietary and blood levels found in this study do reflect those found in other studies with other groups done in other areas and universities. The types of people who participate in this large trial, however, are not representative. Many communities, especially those that have members who have recently immigrated, are fearful of blood sampling.

Q. Can you speculate what increased or decreased visual acuity during infancy means to a more developed child of 14 or 15?

A. It is unclear if the developmental benefits vary over time; however, other studies on children show that decreased acuity in infancy can be recovered. Many people have measured visual acuity as it is an extension of the nervous system. We do study the reading levels, and they are higher in young children with increased DHA.

Q. Have you looked at other developmental domains, and which is the most sensitive to DHA? (Mahaffey)

A. Language appears to be the most sensitive, but no conclusive or comprehensive study exists.

Q. Dietary efficiencies do not generally occur in isolation. Is this a chemical that is relatively available and cheap enough to increase health benefits of developing individuals?

A. We work with well-nourished, well-cared-for individuals, where the probability is low that other deficiencies exist. We can show an effect here (e.g., they do take vitamins but just don't like fish). I am hesitant to say that it would be helpful in situations where other deficiencies exist and one cannot isolate DHA as an independent solution.

Fish, n-3 Fatty Acids and Dementia

Martha Clare Morris, Rush University Medical Center

Biosketch

Dr. Martha Clare Morris (Sc.D.) is an Associate Professor in the Department of Internal Medicine and the Rush Institute for Healthy Aging, and she is Assistant Provost for Community Research at Rush University Medical Center. She received her bachelors and master of science degrees in Sociology at the University of Iowa and her doctorate in Epidemiology at the Harvard School of Public Health in 1992. She is the Epidemiologist of a large population-based study of risk factors for the development of Alzheimer's disease, cognitive decline, and other problems of older persons. The ongoing study, which is called the Chicago Health and Aging Project, began in 1993 and includes more than 9,000 residents aged 65 years and older living on the south side of Chicago. Since 1996, she has been funded by the National Institute on Aging to investigate dietary risk factors for Alzheimer's disease and cognitive decline. The study has generated numerous findings of dietary associations, including lower risk of Alzheimer's disease and slower rate of cognitive decline with high intake of vitamin E in food, consumption of fish and n-3 fatty acids, and dietary fat composition that is low in saturated and transunsaturated fats and high in vegetable fats.

Abstract

The n-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA) (22:6 n-3), is the primary component of membrane phospholipids in the brain, and it is particularly abundant in the more metabolically active areas of the cerebral cortex, mitochondria, synaptosomes, and synaptic vesicles. DHA is consumed directly from fish, but smaller amounts can be synthesized endogenously through a process of desaturation and elongation of its precursor n-3 fatty acids, alpha-linolenic acid (ALA) (18:3n-3) and eicosapentaenoic acid (EPA) (20:5n-3). In laboratory studies, in comparison to animals fed control diets, animals fed diets enriched with n-3 polyunsaturated fatty acids had better regulation of neuronal membrane excitability, increased neurotransmission and hippocampal nerve growth, greater fluidity of synaptic membranes, less oxidative damage to neurons, and superior learning acquisition and memory performance. There is growing evidence that fish and n-3 fatty acids protect against dementia and cognitive decline. A number of prospective studies found that fish consumption was inversely associated with risk of incident Alzheimer's disease. In the Chicago Health and Aging Project (CHAP) study, persons who consumed fish at least weekly had a 60% reduction in 4-year risk of Alzheimer's disease compared with persons who rarely or never ate fish. The CHAP study also examined risk of disease according to intake of the n-3 fatty acids, including DHA, EPA, and ALA. Those persons in the highest fifth of DHA intake had an 80% reduction in risk compared with persons in the lowest fifth, whereas intake of EPA was not associated. DHA is found in most types of fish. High consumption of ALA was associated with lower risk of disease only among persons with the APOE-epsilon4 allele.

FISH, n-3 FATTY ACIDS and DEMENTIA

2007 EPA National Forum on Contaminants in Fish

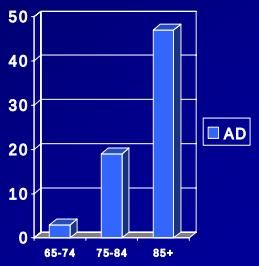
Martha Clare Morris, Sc.D.
Rush University Medical Center

There is growing evidence that fish and n-3 fatty acids are important risk factors in the development of Alzheimer's disease and cognitive decline with age.

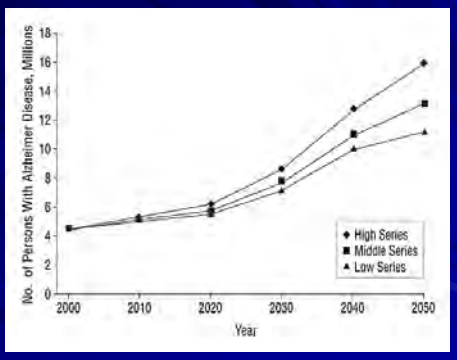
1. **Background on Alzheimer's Disease**
2. **Biologic properties of n-3 fatty acids and importance for brain function**
3. **Animal models**
4. **Epidemiologic studies**
   - **Chicago Health & Aging Project**

Alzheimer's Disease Prevalence

- Exponential increase with age
- Oldest age categories are fastest growing
- No cure
- Ineffective treatment
- Limited knowledge of preventable risk factors



Prevalence of Alzheimer's Disease in U.S.



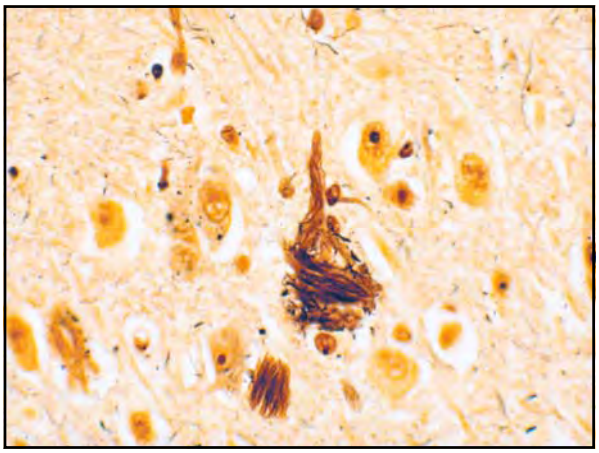
Hebert LE, et al. *Arch Neurol* 2003;60:1119-1122.

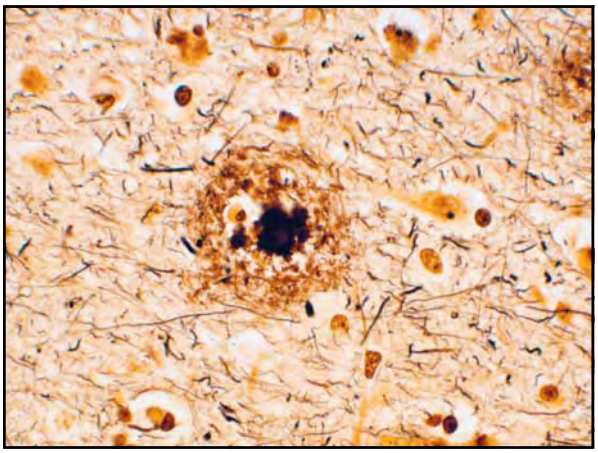
Alzheimer's Disease

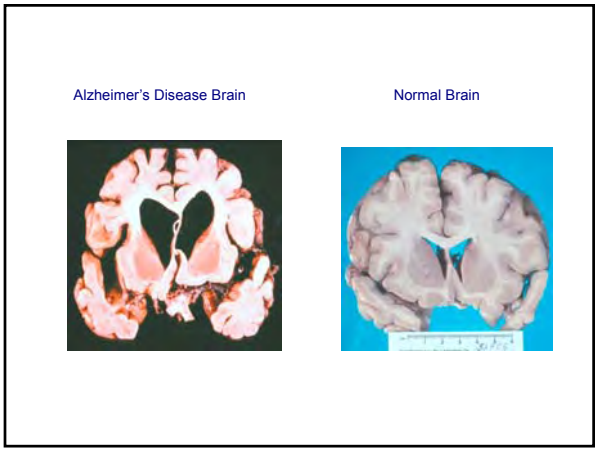
- Gradual decline in memory and other cognitive abilities
- Neuropathology linked to oxidative damage and inflammation:
  - ➢Aβ plaques
  - ➢Neurofibrillary tangles
  - ➢Neuron loss
  - ➢Synapse loss

Alzheimer's Disease: Diagnosis

- **Onset: 40+ years**
- **Deficits in memory and at least one other area of cognition**
- **Progressive loss in cognitive function**
- **Absence of diseases and disorders that could account for the dementia**
- **Associated symptoms**
  - **depression**
  - **insomnia**
  - **incontinence**
  - **delusions**
  - **illusions**
  - **hallucinations**
  - **outbursts**
  - **weight loss**







Risk Factors for Late Onset Alzheimer's Disease

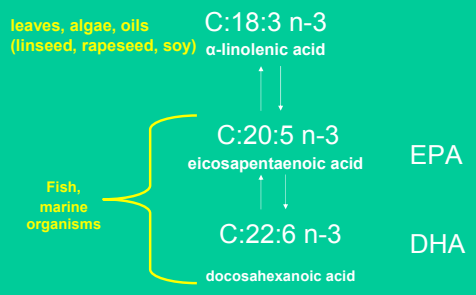
Established
- Age
- Education
- APOE-ε4

Possible
- CVD risk factors
- Dietary Factors
- Exercise

Possible (continued)
- Obesity
- Head Injury
- Anti-inflammatory agents
- Cholesterol/Statins
- Cognitive Activities
- Depression, neuroticism

n-3 fatty acids and the brain

n-3 Polyunsaturated Fatty Acids



α-linolenic acid (18:3n-3)

Wheat Germ

Black current oil
Canola oil
Mustard seed oils
Soybean oil
Walnut oil
Wheat germ oil

Soybeans, walnuts

Human milk

Fish: Brain Food

50% to 60% Lipid

Fish: Brain Food

50% to 60% Lipid

DHA

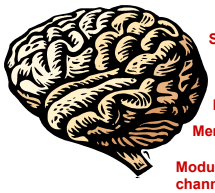
cerebral cortex
synaptosomes
mitochondria

Fish: Brain Food

50% to 60% Lipid

DHA

cerebral cortex
synaptosomes
mitochondria



Function

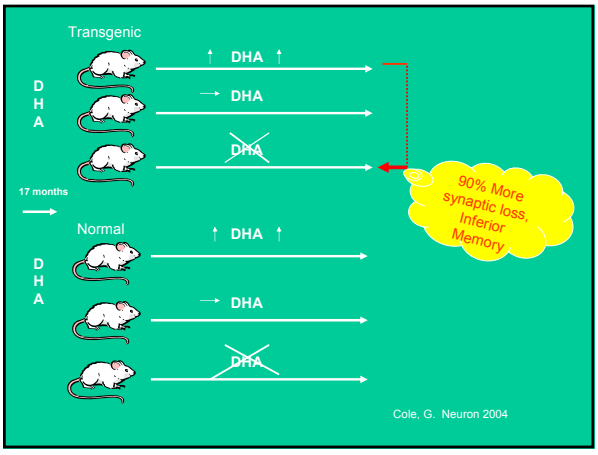
Structural and functional maintenance of neuronal membranes
Neurotransmission
Membrane fluidity
Modulation of ion channels, receptors, ATPase

DHA and Brain Aging

DHA composition in brain decreases with age
Dietary DHA increases brain levels

- ↑ hippocampal nerve growth
- ↑ fluidity of synaptic membranes
- ↑ antioxidant enzymes
- ↑ transcription of transthyretin (amyloid protein scavenger)

- ↓ oxidation of lipid membranes
- ↓ ischemic damage to neurons
- ↓ inflammation
- ↓ amyloid burden



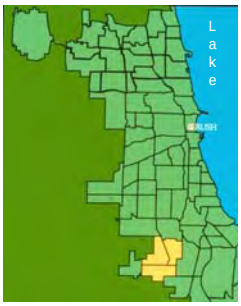
CHICAGO HEALTH AND AGING PROJECT

CHAP: Chicago Health and Aging Project

- **Door-to-door census**
- **Home interviews:**
  6,158 persons 65+yrs
  (79% of all eligible residents)

  Successive Cohorts and expansion of study community to 9,000+
- **Validated Food Frequency Questionnaire**
- **Clinical Evaluations for AD on stratified random samples**

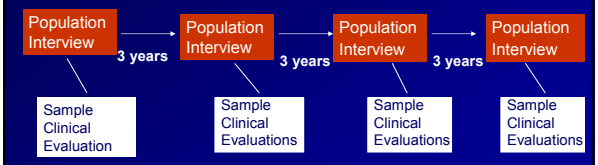
Map of Chicago



CHAP POPULATION CHARACTERISTICS

- 65 to 104 years of age
- 62% Black, 38% non-Hispanic White
- Mean education: 12 years
  - socio-economically diverse in both races

CHAP DESIGN



Population Interview

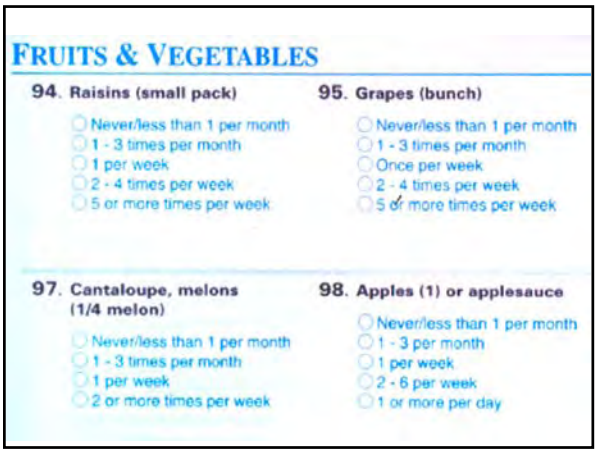
- **Structured Questions**
  - **Demographic**
  - **Health history & meds**
  - **Health habits (smoking, alcohol, exercise)**
  - **Functional status (Katz, Rosow, Nagi)**
  - **Family history and childhood experiences**
  - **Social support**
  - **Personality/depressive symptoms/anxiety**
- **Direct Measurements**
  - Cognitive performance (4 tests)
  - Physical performance
  - Anthropometric measurements
  - Blood pressure

Clinical Evaluations

- **Home evaluations by a neurologic team**
  - **Medical history and psychiatric evaluation**
  - **Structured neurological evaluation**
  - **Cognitive function testing (CERAD)**
  - **Laboratory testing & MRI's**
  - **Informant interview**
- **AD diagnosis: NINCDS-ADRDA criteria (National Institute of Neurological Disorders and Stroke and Alzheimer's disease and Related Dementia Association)**

CHAP FFQ

- **Content**
  - 139 food items
  - vitamin supplements
  - questions on brands, fat content
- **Administration**
  - primarily self-administered
  - distribution & return by mail
  - in-person follow-up



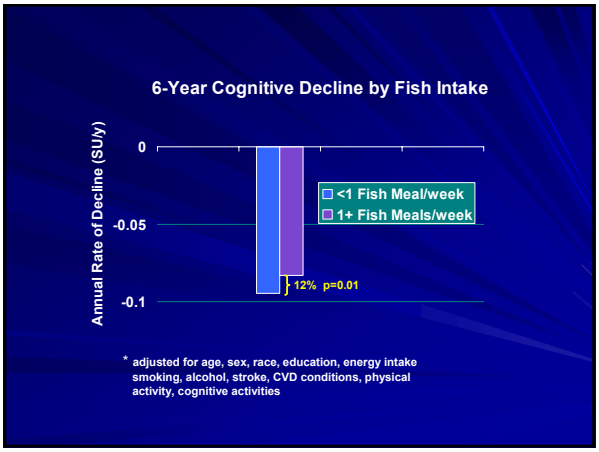
FRUITS & VEGETABLES

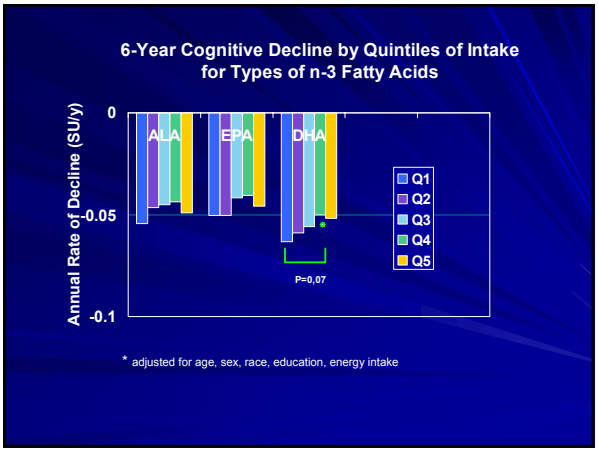
94. Raisins (small pack)
- Never/less than 1 per month
- 1 - 3 times per month
- 1 per week
- 2 - 4 times per week
- 5 or more times per week

95. Grapes (bunch)
- Never/less than 1 per month
- 1 - 3 times per month
- Once per week
- 2 - 4 times per week
- 5 or more times per week

97. Cantaloupe, melons (1/4 melon)
- Never/less than 1 per month
- 1 - 3 times per month
- 1 per week
- 2 or more times per week

98. Apples (1) or applesauce
- Never/less than 1 per month
- 1 - 3 per month
- 1 per week
- 2 - 6 per week
- 1 or more per day





Relative Risk

Relative Risk = Risk of AD in Q5 / Risk of AD in Q1

RR = 1.0 no association

RR < 1.0 protective association

CHAP: Fish Intake and 4-Year Incidence of AD

	FISH INTAKE			
	Never	1-3/month	1/week	2+/week
RR	1.0	0.6	0.4*	0.4*
(95% CI)		(0.3-1.3)	(0.2-0.9)	(0.2-0.9)

* adjusted for age, sex, race, education, total energy intake, APOE4

Morris, MC. Arch Neurol 2003

Relative Risks of Alzheimer's Disease by Quintile of n-3 Fatty Acid Intake

Quintile	Total n-3	DHA	EPA
1	1.0	1.0	1.0
2	1.2	0.8	1.0
3	0.6	0.4*	1.1
4	0.7	0.2*	0.5
5	0.4*	0.3*	0.9

Adjusted for age, sex, race, apoE-4, education, time of observation

Conclusions on Fish, n-3 FA

- Fish consumption of 1 meal per week may reduce cognitive decline in old age
- Fish and n-3 fatty acids, DHA, total, reduced risk of AD
  - 1+ fish meals/week associated with 60% reduction in risk
  - DHA associated with 70% reduction in risk

Epidemiologic Studies of AD

Rotterdam Study 2-year follow-up
RR=0.3 (0.1-0.9) fish intake 18 g/d vs. <3 g/d
6-year follow-up
RR=1.07 (0.9-1.3) per SD n-3 fatty acid intake

PAQUID Study 7-year follow-up AD n=135
RR=0.7 (0.5-1.0) 1 fish meal/week vs never

Cardiovascular Health Study
RR=0.60 (0.4, 0.9) 2+ fish/wk vs. <1/mo

Framingham Study
RR=0.67 (p<0.05) DHA PC in upper half

Epidemiologic Studies of AD and Cognitive Decline

- Canadian Study Health and Aging
  - N-3 FA in plasma associated with increased risk of AD (n=79)
- Zutphen Study
  - Kalmijn 1997 OR=0.45 for drop in cognitive score in 2yrs with 18 mg/d fish
  - Van Gelder 2007 Less 5-year decline in score with n-3 FA of 380 mg/d
- EVA
  - OR=0.59 for drop in cognitive score over 4 years with 1 SD increase in erythrocyte n-3 fatty acids

Co-Investigators

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Julia Bienias, ScD Paul Scherr, ScD, PhD
Neelum Aggarwal, MD Robert Wilson, PhD
David Bennett, MD Julie Schneider MD
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**Over 100 interviewers and data collectors and programmers

Supported by the National Institute on Aging
AG11101 AG13170 AG021972

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Fish Consumption and Cardiovascular Risk

Dariush Mozaffarian, Harvard School of Public Health

Biosketch

Dr. Dariush Mozaffarian (Ph.D.) is an Assistant Professor of Medicine in the Division of Cardiovascular Medicine at Brigham and Women's Hospital and Harvard Medical School, and he is Assistant Professor of Epidemiology at the Harvard School of Public Health. His research focuses on the effects of dietary habits on cardiovascular health and disease.

Dr. Mozaffarian has written more than 50 publications and research studies, including the 2006 studies, Medical Progress: Trans Fatty Acids and Cardiovascular Disease, which appeared in the *New England Journal of Medicine* (April 2006), and Fish Intake, Contaminants, and Human Health: Evaluating the Risks and Benefits, which appeared in the *Journal of the American Medical Association* (October 2006).

A Fellow of the American College of Cardiology and a Fellow of the American Heart Association, Dr. Mozaffarian graduated with Honors from Stanford University and received his M.D. from Columbia College of Physicians and Surgeons. He also holds an M.P.H. from the University of Washington and a Doctorate of Public Health in Epidemiology from Harvard School of Public Health.

Abstract

There is uncertainty among the public and scientific communities about the role of fish intake for preventing cardiovascular disease. Substantial evidence suggests that fatty fish intake reduces the risk of fatal coronary heart disease and sudden cardiac death, which is the leading cause of death in industrialized and also most developing nations. This benefit appears to be related to anti-arrhythmic effects, which may be direct or indirect, and occurs at a remarkably low level of intake: ~250 mg (2 calories) of eicosapentaenoic acid plus docosahexaenoic acid (EPA+DHA) per day. Fish intake may also reduce the risk of other cardiovascular outcomes, such as ischemic stroke, atrial fibrillation, and congestive heart failure, which are possibly related to the effects of marine n-3 fatty acids on cardiac and vascular hemodynamics, endothelial function, and systemic inflammation. Molecular mechanisms require further elucidation, but they are to likely include effects on cell membrane fluidity and receptor function and fatty acid-ligand mediated effects on gene transcription. The current evidence for effects of fish intake on cardiovascular health are reviewed, including potential mechanisms of effect. Current uncertainties and answered questions are also discussed.

Fish Consumption and Cardiovascular Risk

Dariush Mozaffarian, MD DrPH

Harvard Medical School
Harvard School of Public Health

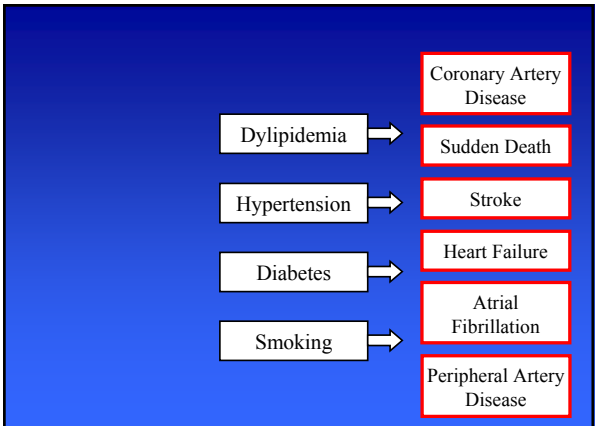
EPA National Forum on Contaminants in Fish
July 24, 2007

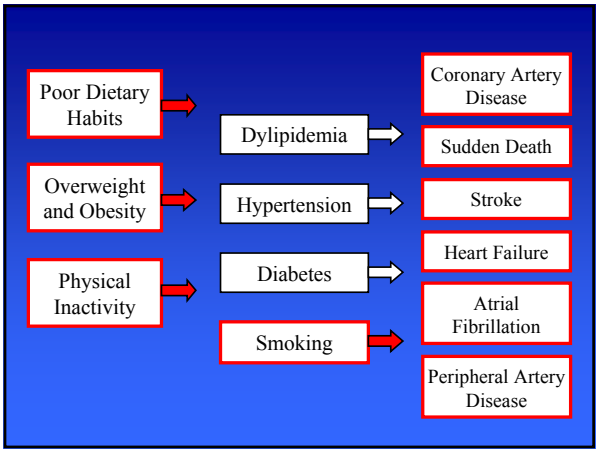
Disclosures

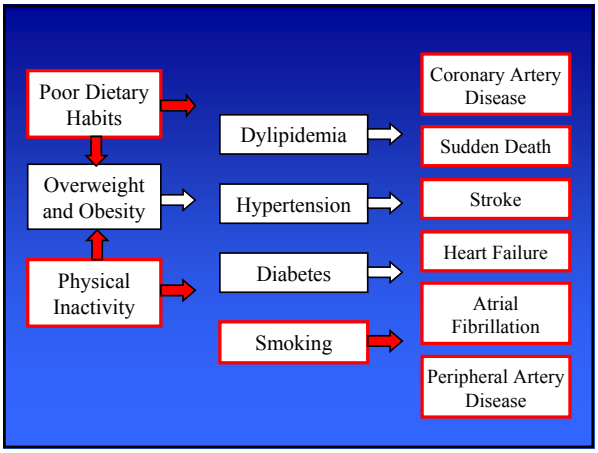
No commercial interests or financial disclosures.
No conflicts of interest.

Risk Factors

- Dylipidemia
- Hypertension
- Diabetes
- Smoking







The Traditional Diet-Heart Paradigm

Total Fat, Saturated Fat → Serum Total and LDL Cholesterol → Coronary Heart Disease

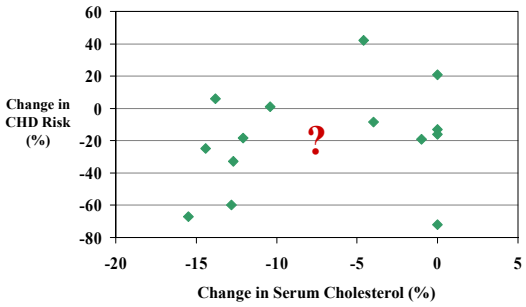
Ecologic Studies (across countries or populations) / Biochemical & Metabolic Pathways

Hypothesis Generation

Randomized Controlled Trials

Observational Studies (Individuals) ⇄ Experimental Studies

Serum Cholesterol and CHD: Diet Trials

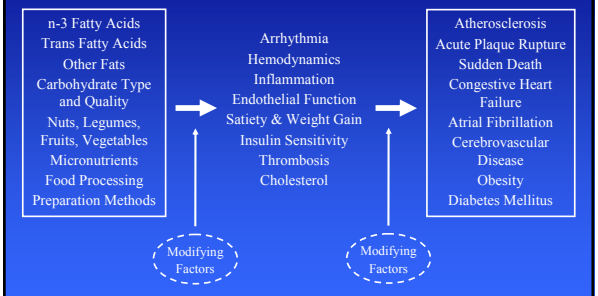


12 RCTs: Research Committee, MRC Low Fat, Finnish Mental Hospital, Los Angeles VA, Oslo Diet-Heart, Sydney Diet-Heart, MRC Soy Oil, Minnesota Coronary Survey, Lyon Diet-Heart, DART, GISSI, JELIS.

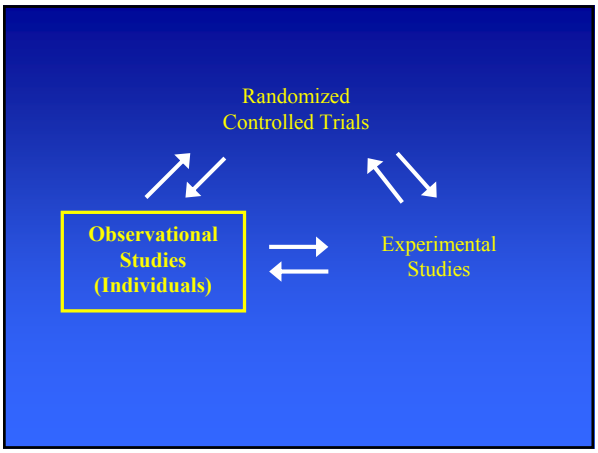
The Traditional Diet-Heart Paradigm

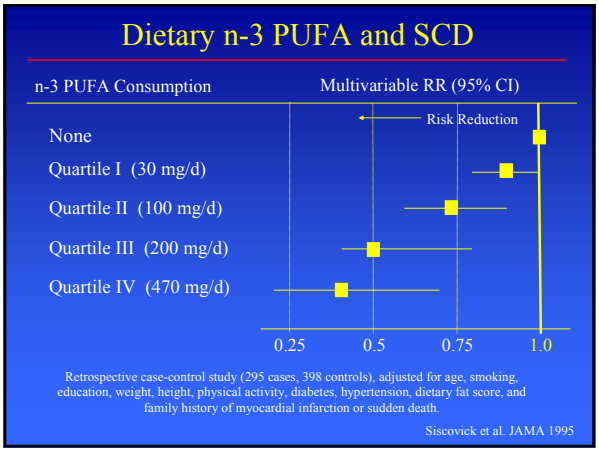
Total Fat, Saturated Fat → Serum Total and LDL Cholesterol → Coronary Heart Disease

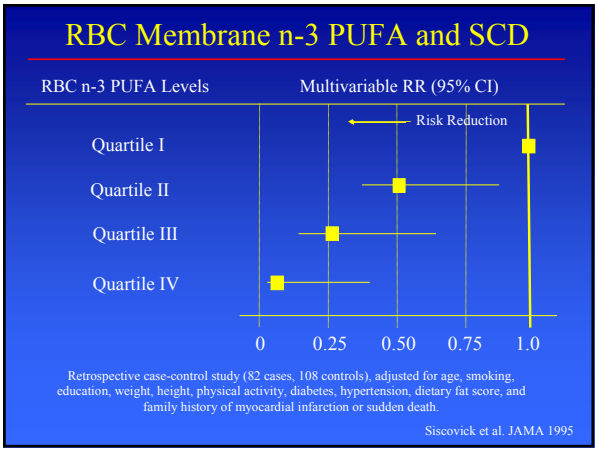
A More Complete Diet-Heart Paradigm

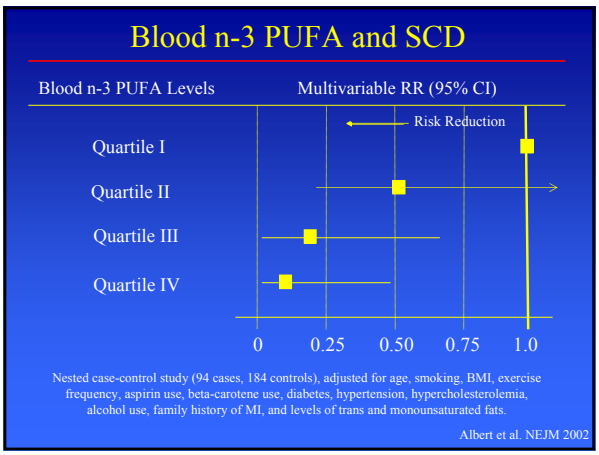


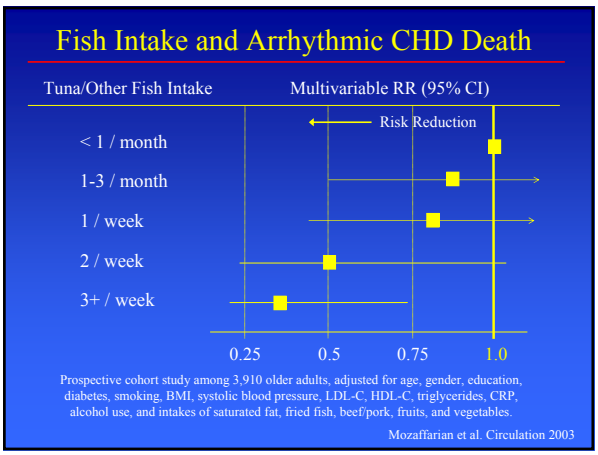
Mozaffarian D. Curr Atheroscler Rep 2005

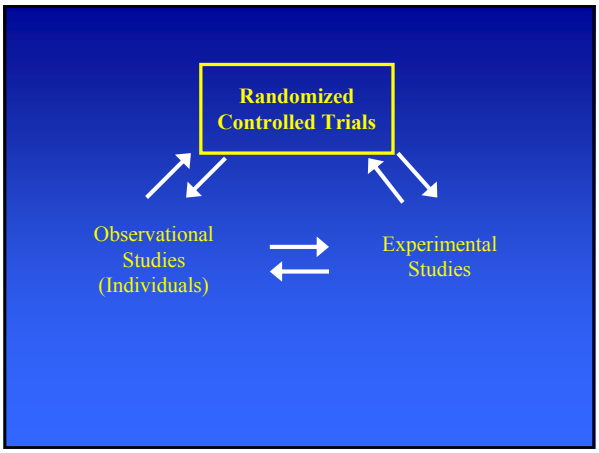

Randomized Controlled Trials
Observational Studies (Individuals)
Experimental Studies

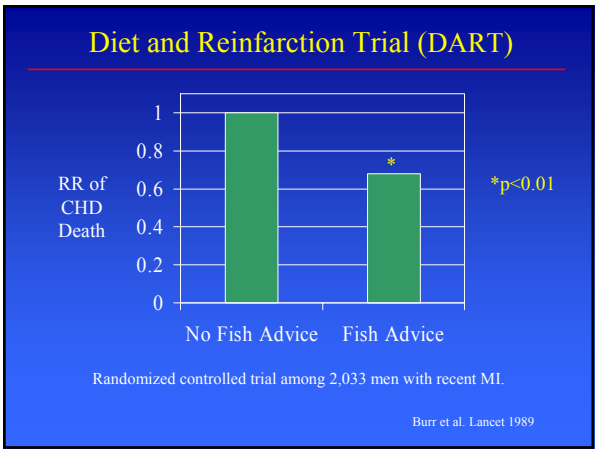

Dietary n-3 PUFA and SCD
n-3 PUFA Consumption
Multivariable RR (95% CI)
Risk Reduction
None
Quartile I (30 mg/d)
Quartile II (100 mg/d)
Quartile III (200 mg/d)
Quartile IV (470 mg/d)
0.25
0.5
0.75
1.0
Retrospective case-control study (295 cases, 398 controls), adjusted for age, smoking, education, weight, height, physical activity, diabetes, hypertension, dietary fat score, and family history of myocardial infarction or sudden death.
Siscovick et al. JAMA 1995

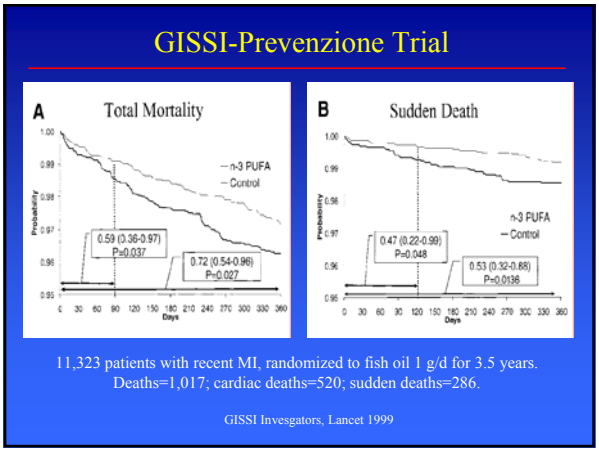

RBC Membrane n-3 PUFA and SCD
RBC n-3 PUFA Levels
Multivariable RR (95% CI)
Risk Reduction
Quartile I
Quartile II
Quartile III
Quartile IV
0
0.25
0.50
0.75
1.0
Retrospective case-control study (82 cases, 108 controls), adjusted for age, smoking, education, weight, height, physical activity, diabetes, hypertension, dietary fat score, and family history of myocardial infarction or sudden death.
Siscovick et al. JAMA 1995

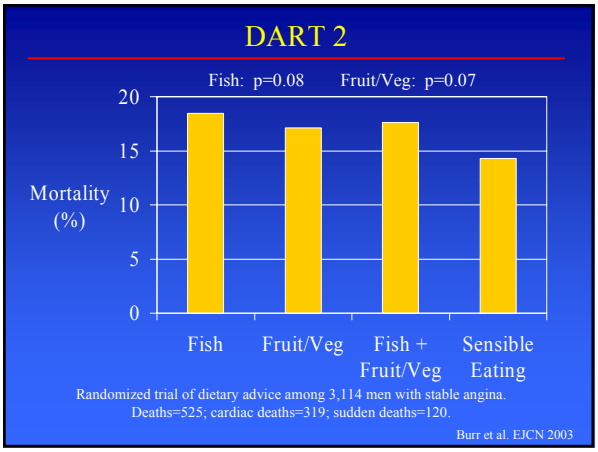

Blood n-3 PUFA and SCD
Blood n-3 PUFA Levels
Multivariable RR (95% CI)
Risk Reduction
Quartile I
Quartile II
Quartile III
Quartile IV
0
0.25
0.50
0.75
1.0
Nested case-control study (94 cases, 184 controls), adjusted for age, smoking, BMI, exercise frequency, aspirin use, beta-carotene use, diabetes, hypertension, hypercholesterolemia, alcohol use, family history of MI, and levels of trans and monounsaturated fats.
Albert et al. NEJM 2002

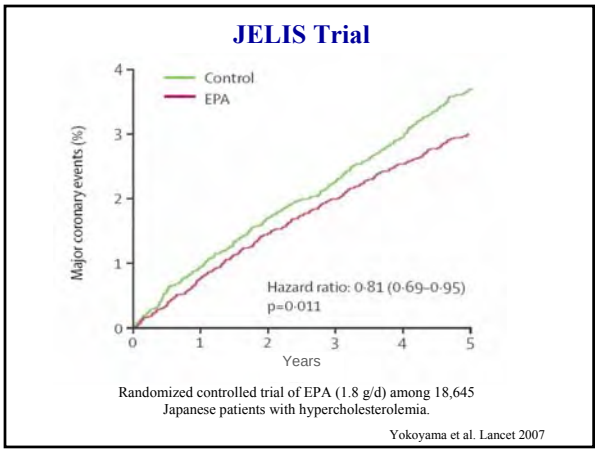

Fish Intake and Arrhythmic CHD Death
Tuna/Other Fish Intake
Multivariable RR (95% CI)
Risk Reduction
< 1 / month
1-3 / month
1 / week
2 / week
3+ / week
0.25
0.5
0.75
1.0
Prospective cohort study among 3,910 older adults, adjusted for age, gender, education, diabetes, smoking, BMI, systolic blood pressure, LDL-C, HDL-C, triglycerides, CRP, alcohol use, and intakes of saturated fat, fried fish, beef/pork, fruits, and vegetables.
Mozaffarian et al. Circulation 2003

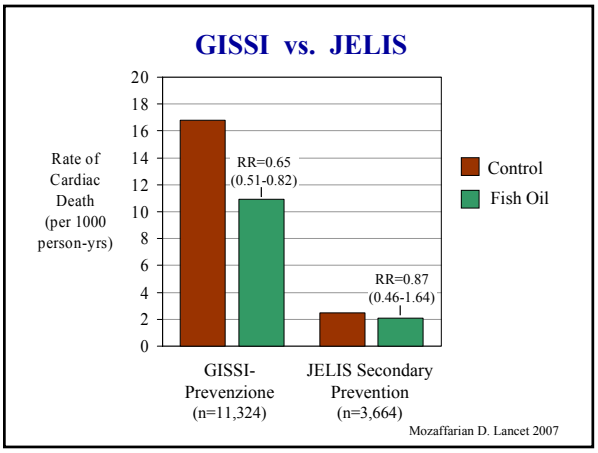

Randomized Controlled Trials
Observational Studies (Individuals)
Experimental Studies

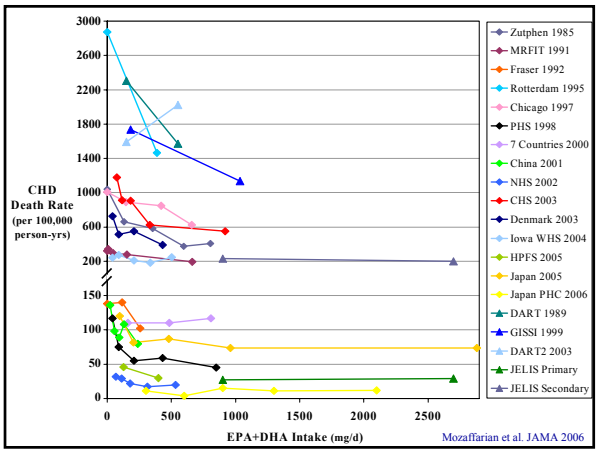

Diet and Reinfarction Trial (DART)
RR of CHD Death
1
0.8
0.6
0.4
0.2
0
*
*p<0.01
No Fish Advice
Fish Advice
Randomized controlled trial among 2,033 men with recent MI.
Burr et al. Lancet 1989

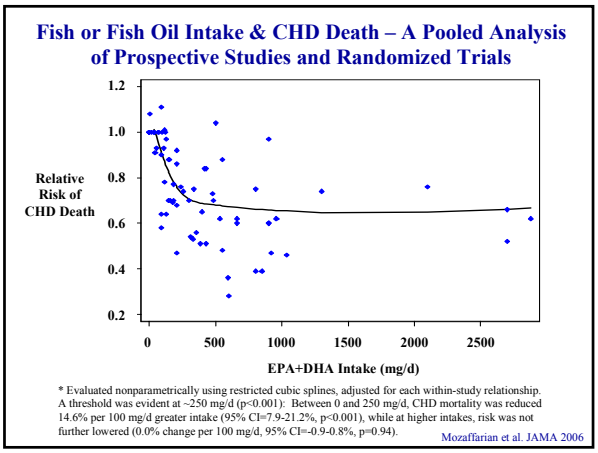

GISSI-Prevenzione Trial
A
Total Mortality
n-3 PUFA
Control
0.59 (0.36-0.97)
P=0.037
0.72 (0.54-0.96)
P=0.027
B
Sudden Death
n-3 PUFA
Control
0.47 (0.22-0.99)
P=0.048
0.53 (0.32-0.88)
P=0.0136
11,323 patients with recent MI, randomized to fish oil 1 g/d for 3.5 years.
Deaths=1,017; cardiac deaths=520; sudden deaths=286.
GISSI Invesgators, Lancet 1999

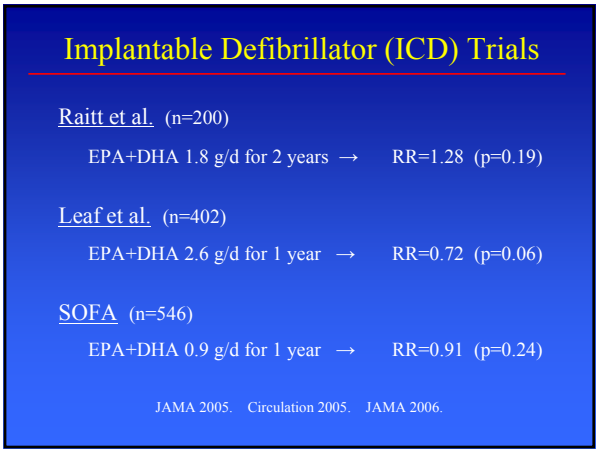

DART 2
Fish: p=0.08
Fruit/Veg: p=0.07
Mortality (%)
20
15
10
5
0
Fish
Fruit/Veg
Fish + Fruit/Veg
Sensible Eating
Randomized trial of dietary advice among 3,114 men with stable angina.
Deaths=525; cardiac deaths=319; sudden deaths=120.
Burr et al. EJCN 2003

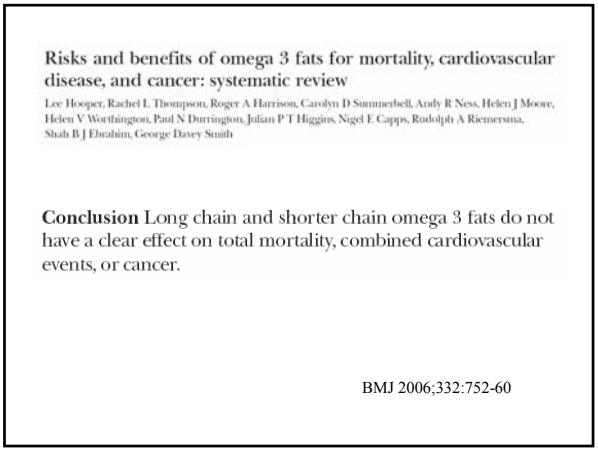

JELIS Trial
Control
EPA
Major coronary events (%)
4
3
2
1
0
Hazard ratio: 0·81 (0·69–0·95)
p=0·011
0
1
2
3
4
5
Years
Randomized controlled trial of EPA (1.8 g/d) among 18,645
Japanese patients with hypercholesterolemia.
Yokoyama et al. Lancet 2007

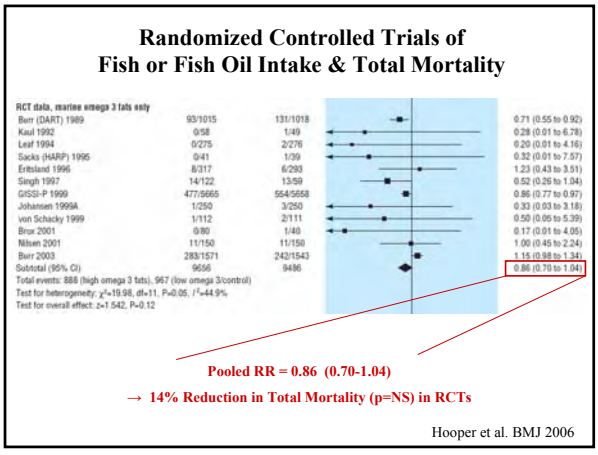

GISSI vs. JELIS
Rate of Cardiac Death (per 1000 person-yrs)
20
18
16
14
12
10
8
6
4
2
0
RR=0.65
(0.51-0.82)
RR=0.87
(0.46-1.64)
Control
Fish Oil
GISSI-Prevenzione (n=11,324)
JELIS Secondary Prevention (n=3,664)
Mozaffarian D. Lancet 2007

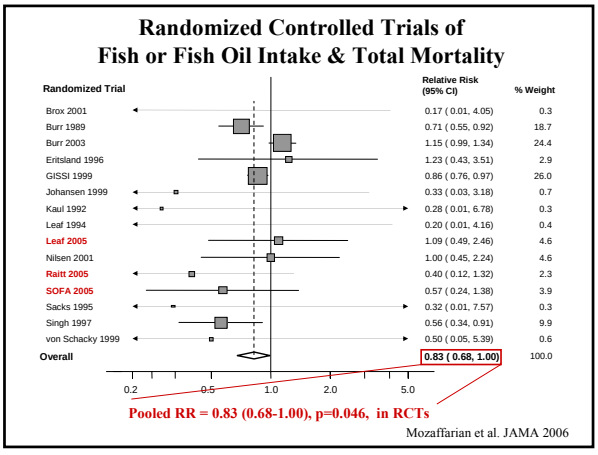

CHD Death Rate (per 100,000 person-yrs)
EPA+DHA Intake (mg/d)
Zutphen 1985
MRFIT 1991
Fraser 1992
Rotterdam 1995
Chicago 1997
PHS 1998
7 Countries 2000
China 2001
NHS 2002
CHS 2003
Denmark 2003
Iowa WHS 2004
HPFS 2005
Japan 2005
Japan PHC 2006
DART 1989
GISSI 1999
DART2 2003
JELIS Primary
JELIS Secondary
Mozaffarian et al. JAMA 2006


Fish or Fish Oil Intake & CHD Death – A Pooled Analysis of Prospective Studies and Randomized Trials
Relative Risk of CHD Death
EPA+DHA Intake (mg/d)
* Evaluated nonparametrically using restricted cubic splines, adjusted for each within-study relationship. A threshold was evident at ~250 mg/d (p<0.001): Between 0 and 250 mg/d, CHD mortality was reduced 14.6% per 100 mg/d greater intake (95% CI=7.9-21.2%, p<0.001), while at higher intakes, risk was not further lowered (0.0% change per 100 mg/d, 95% CI=-0.9-0.8%, p=0.94).
Mozaffarian et al. JAMA 2006

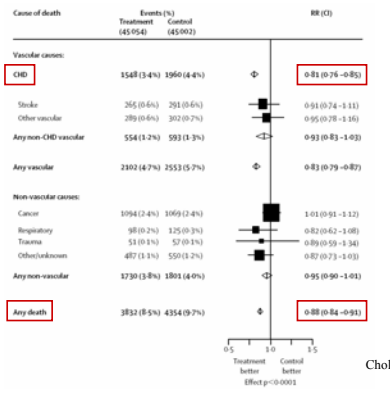

Implantable Defibrillator (ICD) Trials
Raitt et al. (n=200)
EPA+DHA 1.8 g/d for 2 years → RR=1.28 (p=0.19)
Leaf et al. (n=402)
EPA+DHA 2.6 g/d for 1 year → RR=0.72 (p=0.06)
SOFA (n=546)
EPA+DHA 0.9 g/d for 1 year → RR=0.91 (p=0.24)
JAMA 2005. Circulation 2005. JAMA 2006.


Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review
Lee Hooper, Rachel L Thompson, Roger A Harrison, Carolyn D Summerbell, Andy R Ness, Helen J Moore, Helen V Worthington, Paul N Durrington, Julian P T Higgins, Nigel E Capps, Rudolph A Riemersma, Shah B J Ebrahim, George Davey Smith
Conclusion Long chain and shorter chain omega 3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer.
BMJ 2006;332:752-60


Randomized Controlled Trials of Fish or Fish Oil Intake & Total Mortality
Pooled RR = 0.86 (0.70-1.04)
→ 14% Reduction in Total Mortality (p=NS) in RCTs
Hooper et al. BMJ 2006


Randomized Controlled Trials of Fish or Fish Oil Intake & Total Mortality
Randomized Trial
Relative Risk (95% CI)
% Weight
Brox 2001 0.17 (0.01, 4.05) 0.3
Burr 1989 0.71 (0.55, 0.92) 18.7
Burr 2003 1.15 (0.99, 1.34) 24.4
Eritsland 1996 1.23 (0.43, 3.51) 2.9
GISSI 1999 0.86 (0.76, 0.97) 26.0
Johansen 1999 0.33 (0.03, 3.18) 0.7
Kaul 1992 0.28 (0.01, 6.78) 0.3
Leaf 1994 0.20 (0.01, 4.16) 0.4
Leaf 2005 1.09 (0.49, 2.46) 4.6
Nilsen 2001 1.00 (0.45, 2.24) 4.6
Raitt 2005 0.40 (0.12, 1.32) 2.3
SOFA 2005 0.57 (0.24, 1.38) 3.9
Sacks 1995 0.32 (0.01, 7.57) 0.3
Singh 1997 0.56 (0.34, 0.91) 9.9
von Schacky 1999 0.50 (0.05, 5.39) 0.6
Overall 0.83 (0.68, 1.00) 100.0
Pooled RR = 0.83 (0.68-1.00), p=0.046, in RCTs
Mozaffarian et al. JAMA 2006

Statins & Mortality: Metaanalysis of RCTs



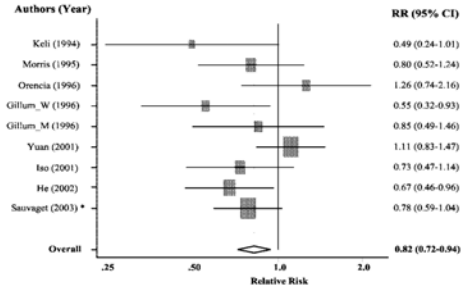
19% reduction in CHD death

12% reduction in total mortality

Cholesterol Treatment Trialists' Collaborators, Lancet 2005

Fish Intake and Stroke

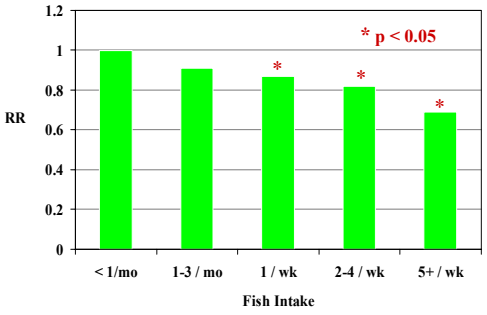
Fish Intake and Ischemic Stroke: Meta-Analysis of Prospective Studies



RR=0.82 (95% CI=0.72-0.94) for fish intake 2-4/week, compared to <1/month

He et al. Stroke 2004

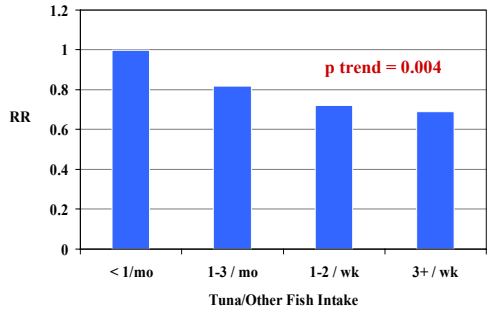
Fish Intake and Ischemic Stroke: Meta-Analysis of Prospective Studies



He et al. Stroke 2004

Fish Intake and Atrial Fibrillation

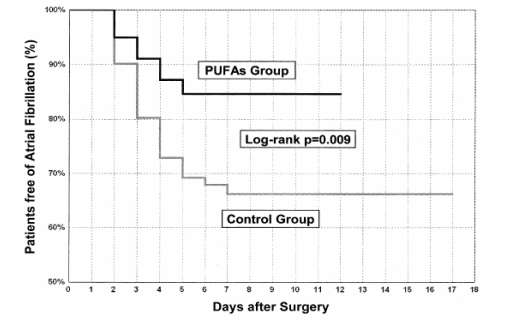
Fish Intake and Atrial Fibrillation



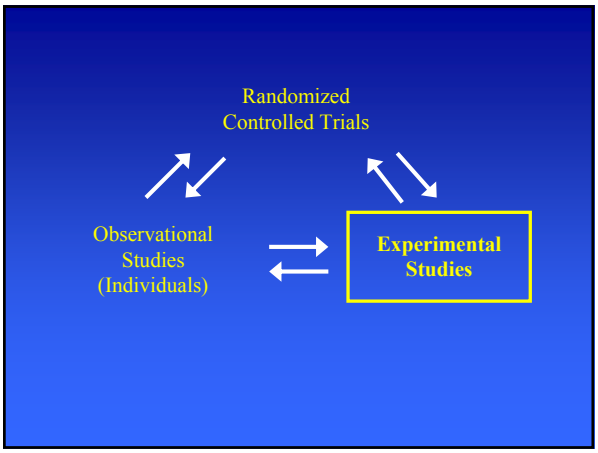
Multivariate-adjusted RR, among 3,815 older adults followed for 12 years.

Mozaffarian et al. Circulation 2004

Randomized Controlled Trial Among 160 Patients Undergoing Coronary Bypass Surgery



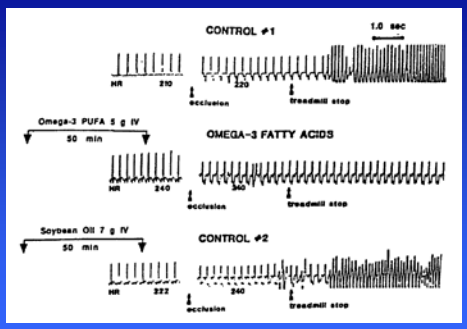
Calo et al. JACC 2005



Fish or Fish Oil Intake and CV Health – Experimental Effects

- Anti-arrhythmic
- Heart rate / autonomic tone
- Vascular resistance / BP
- LV diastolic filling
- Endothelial function
- Inflammation
- Triglycerides
- Thrombosis

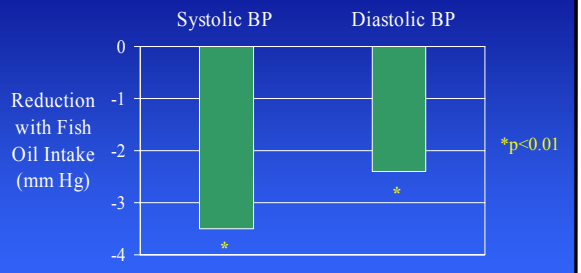
Anti-Arrhythmic Effects



Exercising dogs with prior MI and ischemia-induced VF.

Billman et al. Proc Natl Acad Sci 1994

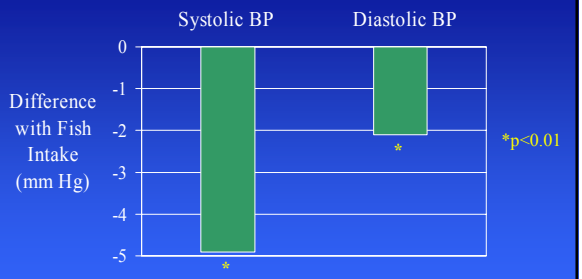
Fish Oil and BP: Meta-Analysis of RCTs



Among adults > age 45 years.

Geleijnse et al. J Hypertens 2002

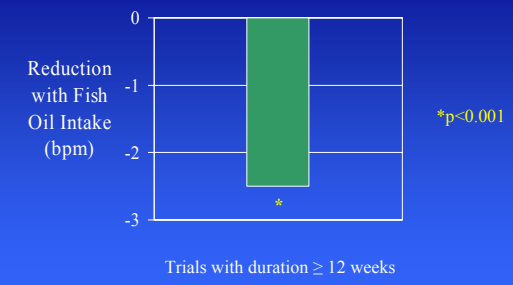
Dietary Fish Intake and BP



Comparing fish intake 3+/week to <1/month (n = 5,073)

Mozaffarian et al. Am J Cardiol 2006

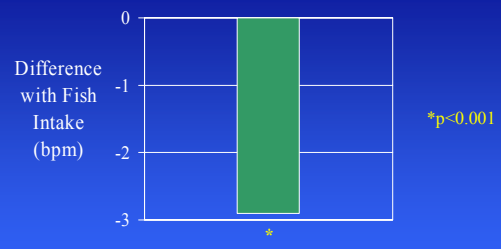
Fish Oil and Heart Rate: Meta-Analysis of RCTs



Trials with duration ≥ 12 weeks

Mozaffarian et al. Circulation 2005

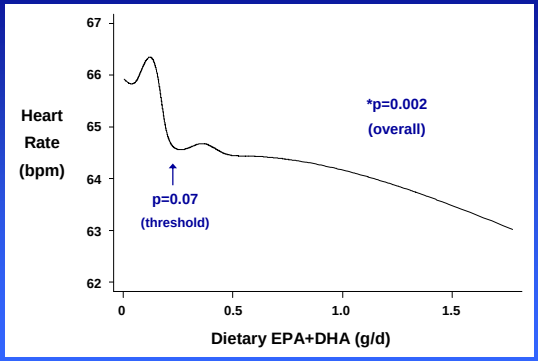
Dietary Fish Intake and Heart Rate



Comparing fish intake 3+/week to <1/month
(n = 5,073)

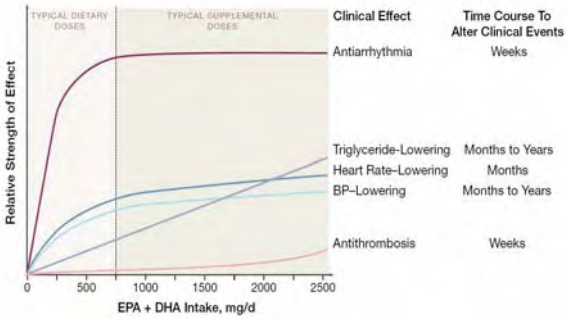
Mozaffarian et al. Am J Cardiol 2006

Dietary EPA+DHA and Heart Rate (n ~3,000)



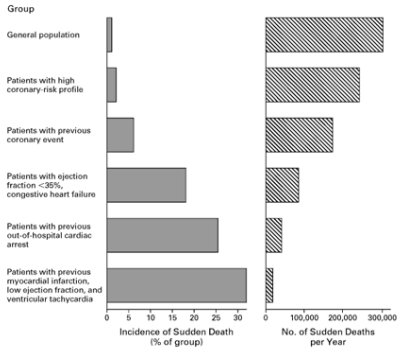
Mozaffarian et al. JACC 2006

Heterogeneity of Mechanisms – Varying Dose-Responses and Time-Responses



Mozaffarian et al. JAMA 2006

Fish and n-3 PUFA: The First Line Treatment for Primary Prevention of SCD



Essential Dietary Habits for CVD Health

1. Seafood / n-3 PUFA
2. No Trans Fat
3. Whole Grains
4. Fruits, Vegetables
5. Unsaturated Fats
6. Legumes, Nuts
7. Low Saturated Fat (men)
8. Smaller Portion Sizes
9. Rare Sweetened Drinks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– David Siscovick, U. of Washington
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Questions and Answers

Q. Have you reviewed the report on mercury suggesting that it may mute the effect of polyunsaturated fatty acids? (Gochfeld)

A. To my knowledge, there have been five studies on this subject and the results have been mixed. Overall, a conclusive effect cannot be determined, which may be due to the design of the studies. The two studies that indicate a modest harm from mercury indicated that fish with mercury had less of a benefit than fish without mercury.

Q. Some people choose fish oil in an attempt to decrease mercury consumption; however, there is a substantial part of the elderly population that is also on blood thinners. Could this cause spontaneous bleeds? (Mahaffey)

A. Fish oil from fish is the important portion of the fish for cardiovascular health. In general, thrombosis is not anticipated to occur with fish oil consumption levels below 5 grams per day.

Q. Did any studies look at the fatty acid composition? (Fitzgerald)

A. Analyses were performed using EPA only or DHA only. Overall, both fatty acids have similar effects, but individual risk factors differed.