A Non-Systematic Review of n-3 Systematic Reviews

David M. Klurfeld
USDA Agricultural Research Service
Beltsville, MD
Disclaimer

- The views presented here are those of the speaker and do not necessarily reflect official positions of the USDA or the Agricultural Research Service.

- Of course, these views should be held by any correct thinking person.
Randomized Controlled Double Blind Studies

Cohort Studies

Case Control Studies

Case Series

Case Reports

Ideas, Editorials, Opinions

Animal research

In vitro ('test tube') research

Systematic Reviews and Meta-analyses
Systematic Reviews

- **Positives**
  - Increases power
  - Theoretically, includes “all” evidence
    - >12,300 in Medline
    - Adding ~300/month
  - Help identify research gaps

- **Negatives**
  - Variable study quality
    - D Moher et al, PLoS Medicine, 2007
  - Not the final word
    - Half-life ~6 years
  - Better for assessing therapeutic interventions than epidemiological associations?
Systematic Reviews
Summary of n-3 Systematic Reviews

- MEDLINE
  - Systematic review & omega-3 = 1,938 hits
  - “Systematic review” & “omega-3” = 43 hits
  - “Systematic review” & “fish oil” = 18 hits
- 11 under AHRQ auspices
  - 10 also published in journals
- 12 from Cochrane Collaboration
  - One published elsewhere
- 15 from other sources
- 38 unique systematic reviews (1999-3/2008)
n-3 and Cardiovascular

- CVD risk factors
  - Total Cholesterol, Triglycerides, VLDL-C, Blood Pressure, LDL elevated
  - Triglycerides
    - Decrease of ~30%
    - Overall study methodology was weak
  - “Optimal quantity & type of n-3 fatty acid, ratio of n-6:n-3, and duration of treatment remain undefined.”
- Intermittent claudication (6 studies, 4 wk-2 y)
- Coronary restenosis, intimal-media thickness
n-3 and Cardiovascular

- CVD prevention in general population (23 studies)
- CVD treatment in CVD population (12 studies)
  - CVD Mortality
  - Sudden cardiac death
  - Stroke?
- Arrhythmogenic effects in patients with implantable defibrillators
- Arrhythmogenic mechanisms in animals/organs/cell culture studies (60 studies)
n-3 and Cancer

- Tumor incidence (19 studies)
- Cancer treatment (19 studies)
- Tumor behavior in animal/cell cultures studies
  - Too heterogenous, low quality
- Cancer cachexia
  - Increased weight & appetite, improved QOL, decreased post-surgical morbidity
n-3 and Intestine

- Maintenance of remission of ulcerative colitis
- Maintenance of remission of Crohn’s disease
  - Enteric coated n-3 may be effective
n-3 and Mental Health

- Dementia
- Depression
- Bipolar disorder
- Schizophrenia
- Cognitive function in aging, dementia and neurological disease
n-3 and Immunity

- Asthma
- Organ transplantation (31 studies)
  - 23 kidney, 6 heart, 1 liver, 1 bone marrow
- Systemic lupus erythematosus
n-3 and Eye Health

- Age-related macular degeneration
- Retinitis pigmentosa
n-3 and Child & Maternal Health

- Infant development
- Visual acuity in full-term infants
  - DHA improves function at 2 months, possibly at 4 months
- Visual acuity in healthy preterm infants
  - DHA improves function at 2 & 4 months
n-3 and Other Conditions

- Cystic fibrosis
- Type 2 diabetes
- Renal disease
- Osteoporosis
- All-cause mortality
Types of n-3 evaluated

- Alpha-linolenic acid – inconclusive or no effect for all endpoints assessed whether from foods or supplements

- EPA/DHA/fish oil/fish consumption – most often considered equivalent in reviews
  - Little difference in effect except that supplements are less effective in low-risk populations consuming fish regularly

- DHA/AA – infant formula supplementation

- No one has addressed n-6:n-3 ratio
Whither Systematic Reviews?
American Dietetic Association Evidence Analysis Library

- www.adaevidencelibrary.com
- Open to ADA members/subscribers
- 13 questions on n-3/EPA/DHA/fish oil
- Two 4 oz servings of fish/wk and plant based foods providing 1.5g alpha-linolenic acid
- If an individual does not eat these foods, 1g EPA/DHA may be recommended for secondary prevention
- Fair evidence – benefits exceed the harms
American Dietetic Association Evidence Analysis Library

716 questions evaluated

- Grades

- Grade I
- Grade II
- Grade III
- Grade IV
- Grade V

I – Good/Strong
II – Fair
III – Limited/weak
IV – Expert opinion only
V – Grade not assignable

37.29
16.81
13.28
29.24
3.39
FDA Use of Evidence-Based Reviews

- Draft Guidance
- Specify and measure substance of the claim
- Specify and measure the disease or health-related condition
- Intervention studies
  - Most reliable
  - Generalization from select populations to the general population may not be valid
FDA Use of Evidence-Based Reviews

- Observational studies
- Research synthesis studies
- Animal and *in vitro* studies – background info
- Consider surrogate endpoints of disease risk
  - LDL- or total cholesterol, blood pressure
  - Bone mineral density
  - Blood sugar, insulin resistance
  - Adenomatous polyps
Systematic Reviews in the Dietary Guidelines for Americans

- 2000 – Information Quality Act
  - Interpreted as requiring evidence-based review or similar approach
- 2005 DGA – “evidence-based light”
  - Considered design, quality, etc.
  - DGAC report recommended 2 servings fish/wk (8 oz) high in EPA/DHA
  - DGAC recommended 1.1-1.6 g/d of ALA
  - Reduce risk of sudden death and CHD death
  - DGA do not include specific n-3 recommendation
Systematic Reviews in the Dietary Guidelines for Americans

- 2010 DGA – nutrition evidence library will be established for DGAC
  - Call for abstractors was in Federal Register
  - Will use ADA Evidence Library
Limitations of Systematic Reviews for the Field of Nutrition

- **Drugs/Devices**
  - Intended for few
  - Sick patients
  - Treated vs untreated
  - Sharply defined primary outcome
  - Large effect
  - Response usually monotonic

- **Nutrients**
  - Intended for all
  - Healthy individuals
  - Prevention is typical
  - High vs low intake
  - Multiple systems impaired
  - Effect small in a single system but large aggregate effect and public health impact
  - Threshold effect
Limitations of Systematic Reviews for the Field of Nutrition

- Few RCT’s except for supplements
- Confounding in observational studies
- Studies tend to be of lower quality
Hill’s Viewpoints on Passing from Association to Causation

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

Correlation ≠ Proof

Positive proof of global warming.