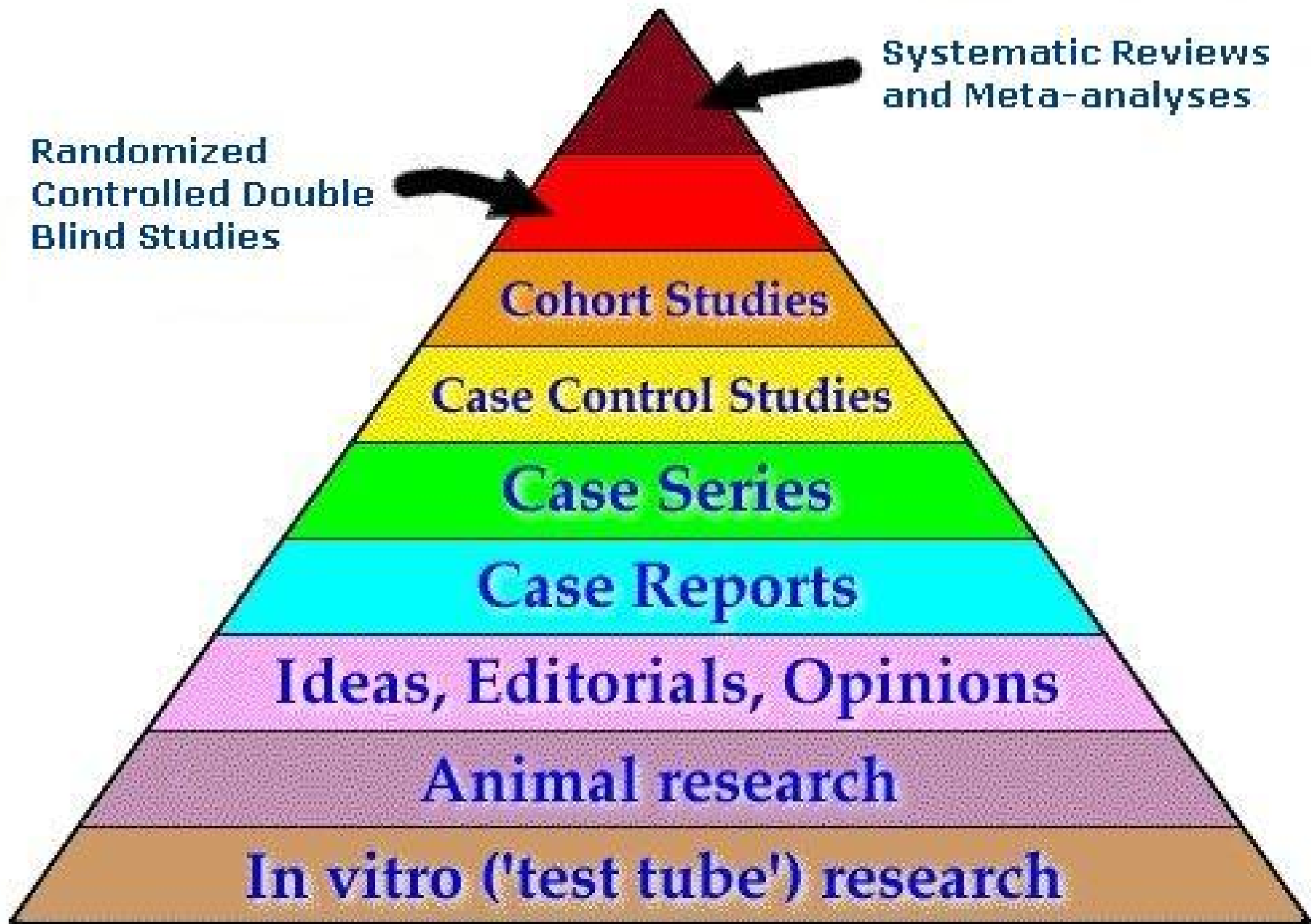

A Non-Systematic Review of n-3 Systematic Reviews

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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



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
 - KG Shojania et al, Ann Int Med, 2007
- 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

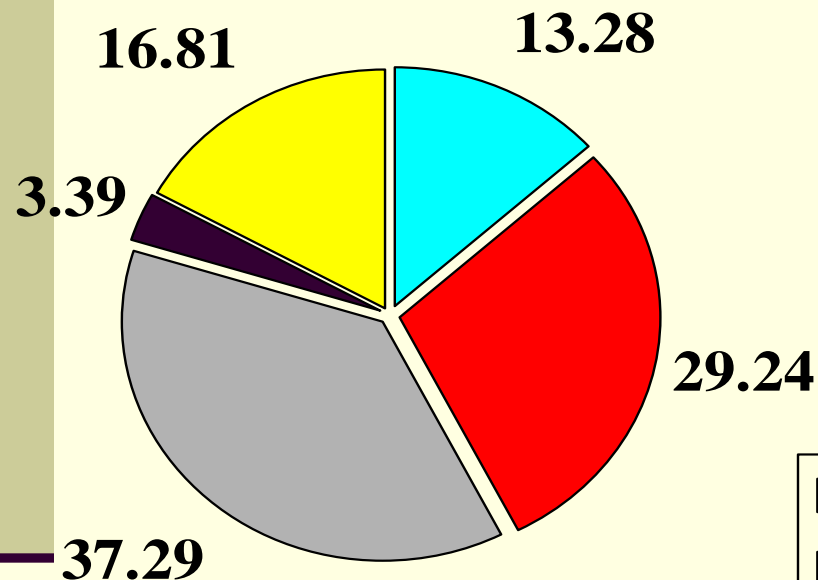
Whither Systematic Reviews?



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

FDA Use of Evidence-Based Reviews

- Draft Guidance
 - <http://www.cfsan.fda.gov/~dms/hclmgui5.html>
- 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

AB Hill, Proc Royal Soc Med 58:295 (1965)

Positive proof of global warming.



Correlation \neq Proof