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Nutrition-related reports by Tufts-NEMC EPC

Effects of Omega-3 Fatty Acids on
- Cardiovascular Disease
- Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease
- Arrhythmogenic Mechanisms in Animal and Isolated Organ/Cell Culture Studies

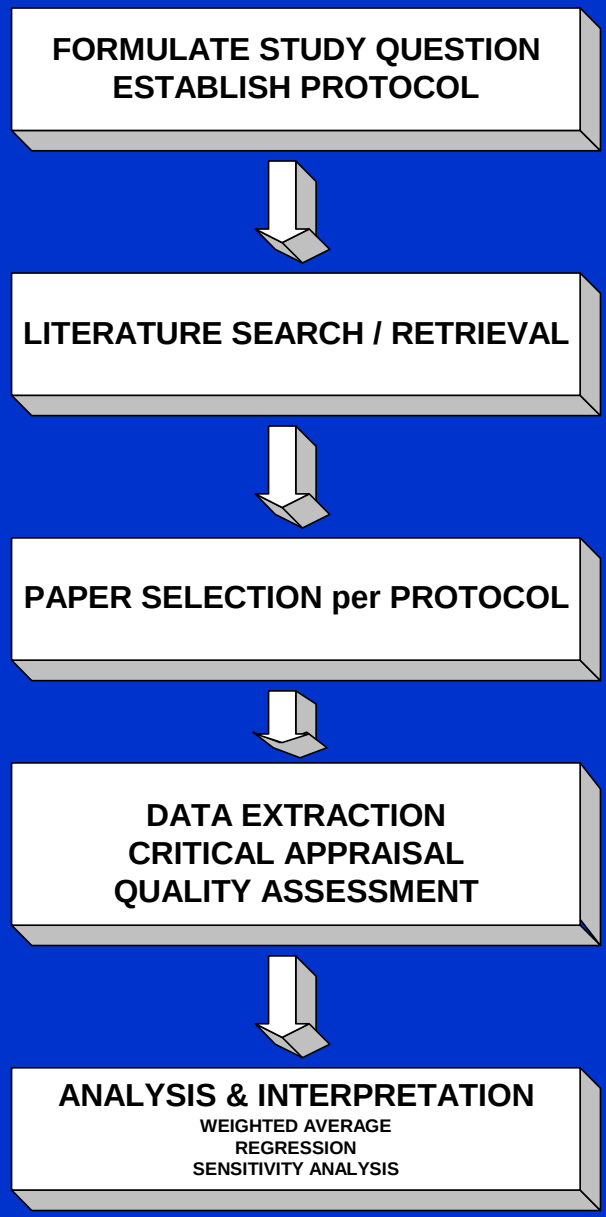
Effects of Omega-3 Fatty Acids on Organ Transplantation

Effects of Soy Products on Health Outcomes

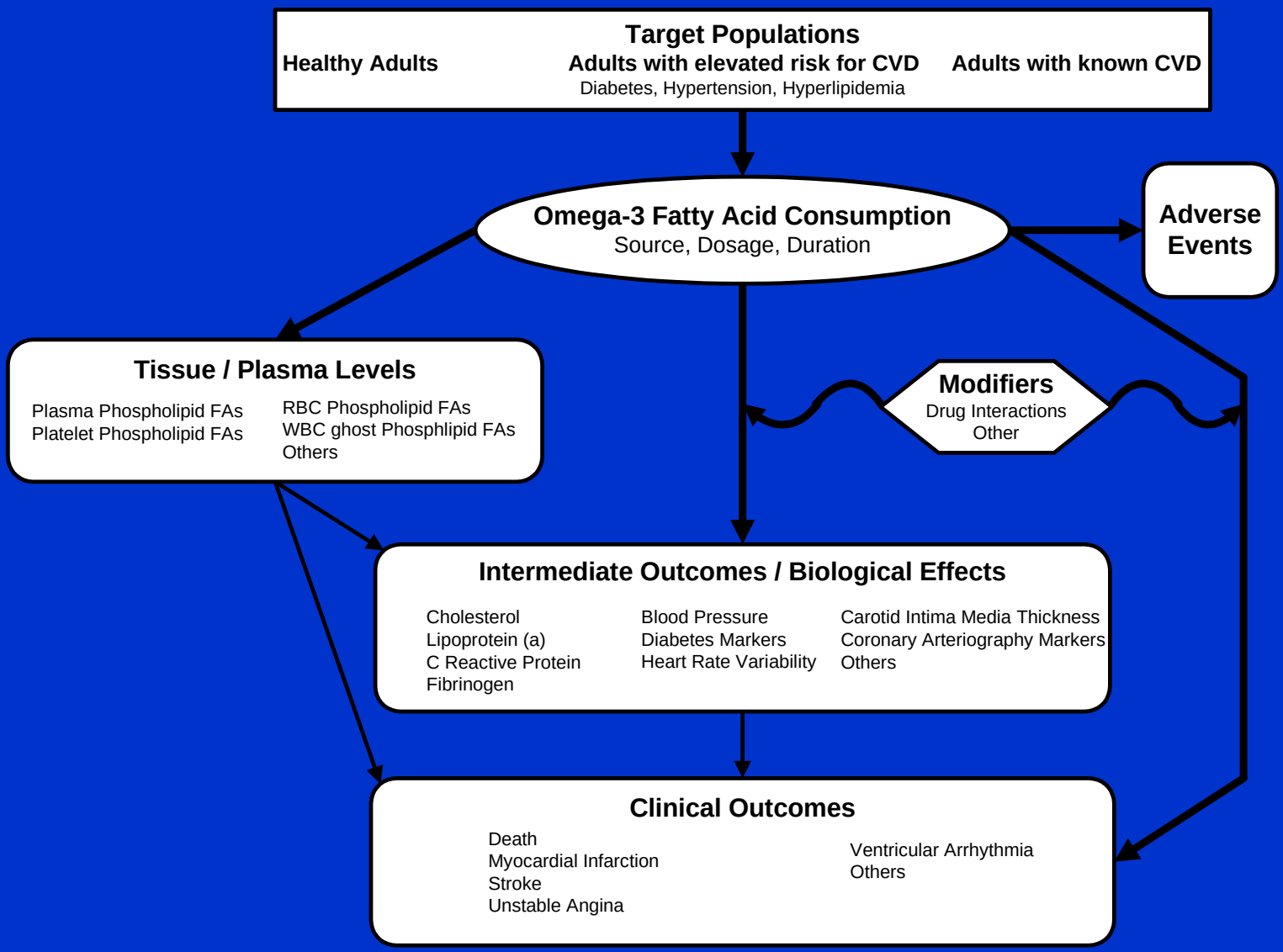
Effects of Chromium Supplementation on CVD and Glucose Metabolism

Effects of Berries and B vitamins on Age-related Neurodegeneration

Steps to Perform a Systematic Review



Analytic Framework



Evidence Report Process

- Form Technical Expert Panel
- Refine and clarify key questions
- Perform literature search
- Screen abstracts for potentially relevant articles
- Retrieve full articles
- Review articles according to criteria
- Extract data from articles that meet inclusion criteria
- Grade studies (methodological quality, applicability)
- Create evidence / summary tables / summary matrices
- Additional analyses as appropriate
- Draft report
- Send out for peer review and revise report

Methods
(Omega-3 and Human CVD)

- Literature search strategy
  - Multiple databases searched
  - Other data sources
- Eligibility criteria
  - English, Human studies
  - Quantified omega-3 (any source) and CVD
- Score study quality and applicability
  - 3 point scales
- Summarize results

Literature Search Results
(Omega-3 and Human CVD)

- Abstracts screened 7,464
- Papers retrieved & screened 807
- Articles included
  - Events 39
    - primary prevention 28
    - secondary prevention 12
  - Risk factors/Markers 123

Reporting of Evidence

- Evidence tables
  - Summarize all relevant study data
- Summary tables
  - Design, Population, Intervention/Control, Outcomes, Effect Size, Quality, Applicability
- Narratives
- Meta-analysis

Defining Criteria

- **P**opulation
- **I**ntervention
- **C**omparator
- **O**utcome
- **S**tudy Design

Counsell C. Ann Intern Med. 127(5):380-7. 1997

- **P**opulation
  - Reporting of confounders
  - Handling and reporting of withdrawals
  - Primary v Secondary prevention
- **I**ntervention
- **C**omparator
- **O**utcome
- **S**tudy Design

Outcomes	# RCTs Analyzed	# RCTs that Evaluated			
		Sub-populations	Other Covariates*	Dose / Source	Exposure Duration
Lipids	25	0	4	8	6
Fibrinogen	24	0	5	9	0
Coronary Arteriography	12	0	8	0	N/A

* Sex, Age, BMI, Baseline level, Alcohol, Drug use, Blood pressure, Wine consumption, Dietary fat

Dietary interventions may be more highly confounded by factors such as background diet, weight, exercise, etc. than drug trials.

Best reports and most rigorous trials were of Coronary Arteriography

CVD Events: No. of Studies

EPA/DHA / Fish

		RCT	Prospective Cohort	Case-Control
1º Prevention	Supplement		1	
	Diet		20	4
2º Prevention	Supplement	5		
	Diet	2	1	

However, health claims tend to be made for primary prevention

- **P**opulation
- **I**ntervention
  - Heterogeneity of interventions
  - Heterogeneity of components
  - Heterogeneity of doses
  - Inadequate description
  - Diet v Supplement
  - Artificial nature of interventions
  - Consumed v “Prescribed”
- **C**omparator
- **O**utcome
- **S**tudy Design

Soy supplements or soy-protein food products used in the experimental arm of the studies

Outcome Categories	Isoflavones Alone	Soy Protein with Isoflavones	Soy Protein without Isoflavones	Unclear Amount of Soy Protein and/or Isoflavones	Total # of Studies*
Cardiovascular	Total: 23 Advanced Care Products (1) Bonette (Novomed, Helsinki) (2) Eugenbio (1) Genistein, Lab Plant (2) NovaSoy (ADM) (3) Novogen (1) PhytoLife (1) Protoveg (2) Soya hypocotyl Iso (Fuji Oil Co) (2) Soycreme (1) Total Life Co (1) No brand name tablet (6)	Total: 60 Abacor (2) Abalon (Nutri Pharma, Oslo) (1) Altima HP-20 (Protein Technologies International) (2) Calcimel (1) Eden (1) FXP HO 159 (1) ISP powder (not specific) (19) Proderma (ALPRO, Belgium) (2) Solae – powder (2) Supro – powder (12) Supro – liquid/beverage (6) Supro – tablet/capsule (1) Soymilk (8) Tofuline (1) Unilever Best Foods, Brazil (1)	Total: 7 Essential Nutrition (1) Protein Technologies International (6)	Total: 4 ADM (1) ISP powder (not specific) (2) Scan Diet Shakes (1)	94

Isoflavones alone
Soy protein w/isoflavones
Soy protein w/o isoflavones
Tofu
Textured soy protein
Soy milk
Soy flour
Other soy products
Soy as major component of diet
Soy as dietary supplement
Casein
Animal protein
Vegetable protein
Placebo
No control

Inadequate descriptions

- Isolated soy protein (Supro 610), 25 g (baked into muffins) No isoflavone content
- Abalon (containing soy protein and a high-fixed level of isoflavones and soy cotyledon fibers), 50 g ISP, total isoflavones >165 mg
- Soy protein isolates, 20% energy intake, 2.39 mg isoflavone/g protein. No data on Kcal or amount of protein consumed.
- Fish score: 1=never eating fish, 4=once/week, 6=daily+

?Applicability to real world

- Fish oil 6 g or more per day
- Fish powder 20 tablets/day
- 1 tin (135 g) mackerel vs meat paste/day
- ISP liquid diet x 4.5 weeks
- Soy milk 1 L/day
- Metabolic lab diets

Consumed v “Prescribed”

In addition to adherence issue in drug trials:

- Variation in intake amount
  - By protocol
    - Men 71 g and Women 55 g soy protein per day
    - Generally well-defined
  - Subject-determined
    - Often not reported
    - Fish: Per week Offered 5 x Ate 3.8 x
      3 x 2.3 x
      2 x 1.5 x
      1 x 0.9 x

- **P**opulation
- **I**ntervention
- **C**omparator
  - Blinding
    - Fish oil +- peppermint
  - Equivalence
    - Soy milk: 17.5 g fat/day; Cow milk: 0 g fat/day
- **O**utcome
- **S**tudy Design

- **P**opulation
- **I**ntervention
- **C**omparator
- **O**utcome (similar to Drug trial reporting)
  - Clinical v Intermediate
    - Relatively few trials for clinical outcomes
    - Omega-3 CVD: 13 clinical v >200 intermediate
    - Soy CVD: 0 clinical
  - Reporting of secondary outcomes
    - “no significant differences were seen for…”
  - Adverse events rarely reported
  - Incomplete reporting of baseline and follow-up values
- **S**tudy Design

- **P**opulation
- **I**ntervention
- **C**omparator
- **O**utcome
- **S**tudy Design
  - RCT v Cross-over
  - Blinding, Randomization, Power, Statistical analysis
  - Intention to treat
  - Control for confounders
  - Incomplete reporting of statistical analyses
  - Net change v Comparison of final values

Net Change v Comparison of Final Values

- Rx study standard:
  - $(\text{Final} - \text{Base})_{\text{Drug}} - (\text{Final} - \text{Base})_{\text{Placebo}}$
  - Outcome = change in level
    - eg, 25% reduction in LDL
- Nutrition-related studies (~1/2)
  - $\text{Final}_{\text{Intervention}} - \text{Final}_{\text{Control}}$
  - Outcome = Final value
    - eg, LDL 15 mg/dL lower on intervention than control
  - Baseline data often missing (esp. in cross-over)

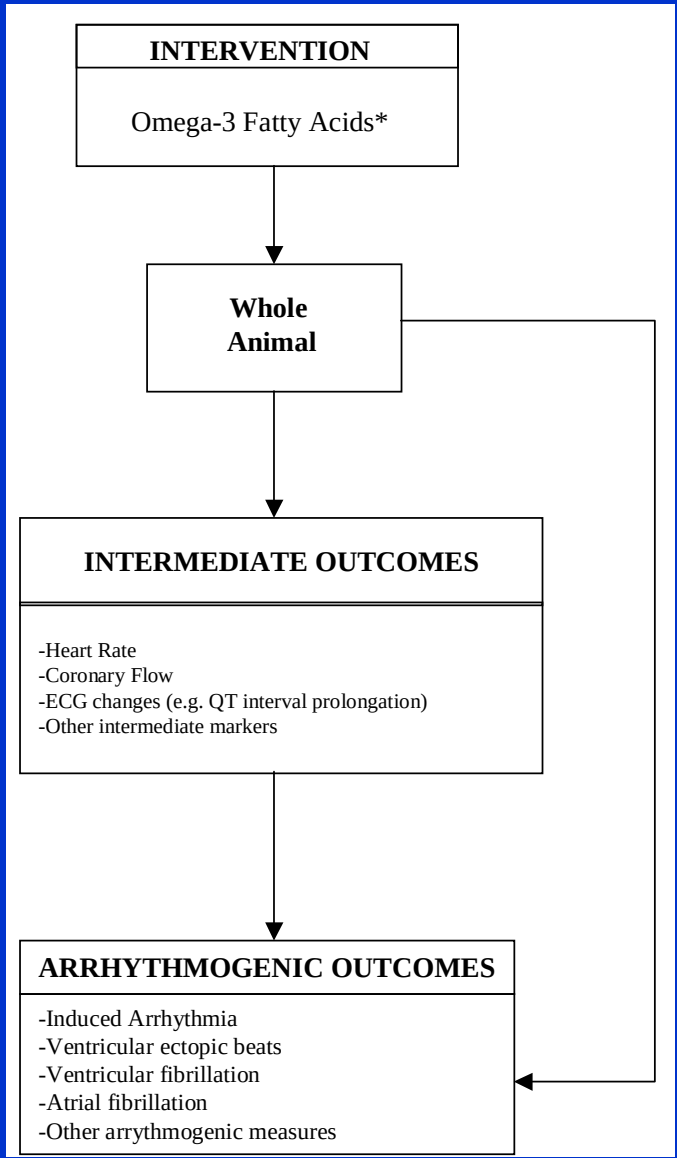
Animal / In vitro Studies

- What is the evidence from whole animal studies that omega-3 fatty acids affect arrhythmogenic outcomes (and intermediate outcomes)?
- What is the evidence from cell culture and tissue studies that omega-3 fatty acids directly affect cell organelles such as cardiac ion channels, pumps, or exchange mechanisms involved in electrogenesis?

Literature Search Results
(Animal/In Vitro Omega-3)

- Abstracts screened 1807
- Papers retrieved & screened 274
- Articles included
  - Whole animal 26
  - Whole-animal isolated organs and cells 21
  - Isolated organs and cell cultures 39

Analytic Framework



Animal / In vitro Studies

- Integration of in vitro and animal models into analytic framework for human health
  - Frequently difficult to determine how model used relates to human disease
  - May be a fault of reviewers for not sufficiently understanding the research
  - Many (?most) basic science studies are not written for the non-specialist
  - Reference to Analytic Framework may be helpful

- Investigator blinding and subject randomization
  - Basic standards of human studies are lacking in basic science studies
  - Unclear what is the effect of lack of blinding/random
- Intervention mode (fed, infused)
  - Adds to heterogeneity of studies
  - Studies rarely discuss how intervention mode may affect results
- Reporting of animals, conditions, and diets
  - Generally very minimal beyond strain and age
  - Animal source, sex, body weight, housing condition (stress factors), diet, season
  - All items that can confound analysis

- Heterogeneity
  - Rat 60
  - Dog 10
  - Guinea pig 4
  - Mouse 4
  - Monkey 3
  - Rabbit 3
  - Pig 2
  - Ferret 1
  - Cat 1
    - ➢ Lab methodology over time and between labs
- Narrow range of sources of studies
  - 70% of omega-3 studies from 1 lab
  - ~80% of berry studies from 1 lab

- Publication bias
  - All animal and in vitro studies for omega-3 fatty acids, berries & B vitamins (to date) reported positive effects
  - Null or negative effects reported only in conjunction with positive effects
  - “Primary outcome” almost always positive
- Statistical v Biological (Clinical) effect
  - Little discussion regarding whether the statistically significant findings are biologically meaningful
- Research needed on how to evaluate quality