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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

1. **FORMULATE STUDY QUESTION**
   - ESTABLISH PROTOCOL

2. **LITERATURE SEARCH / RETRIEVAL**

3. **PAPER SELECTION**
   - per PROTOCOL

4. **DATA EXTRACTION**
   - CRITICAL APPRAISAL
   - QUALITY ASSESSMENT

5. **ANALYSIS & INTERPRETATION**
   - WEIGHTED AVERAGE
   - REGRESSION
   - SENSITIVITY ANALYSIS
Analytic Framework

Target Populations
- Healthy Adults
- Adults with elevated risk for CVD
  - Diabetes, Hypertension, Hyperlipidemia
- Adults with known CVD

Omega-3 Fatty Acid Consumption
Source, Dosage, Duration

Adverse Events

Modifiers
- Drug Interactions
- Other

Intermediate Outcomes / Biological Effects
- Cholesterol
- Lipoprotein (a)
- C Reactive Protein
- Fibrinogen
- Blood Pressure
- Diabetes Markers
- Heart Rate Variability
- Carotid Intima Media Thickness
- Coronary Arteriography Markers
- Others

Clinical Outcomes
- Death
- Myocardial Infarction
- Stroke
- Unstable Angina
- Ventricular Arrhythmia
- Others

Tissue / Plasma Levels
- Plasma Phospholipid FAs
- Platelet Phospholipid FAs
- RBC Phospholipid FAs
- WBC ghost Phospholipid FAs
- Others
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

- Population
- Intervention
- Comparator
- Outcome
- Study Design

• Population
  – Reporting of confounders
  – Handling and reporting of withdrawals
  – Primary v Secondary prevention

• Intervention

• Comparator

• Outcome

• Study Design
### Outcomes

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

* 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
### EPA/DHA / Fish

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Prospective Cohort</th>
<th>Case-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1º Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplement</td>
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<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>2º Prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplement</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>2</td>
<td>1</td>
<td></td>
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</tbody>
</table>

However, health claims tend to be made for primary prevention.
• Population
• Intervention
  – Heterogeneity of interventions
  – Heterogeneity of components
  – Heterogeneity of doses
  – Inadequate description
  – Diet v Supplement
  – Artificial nature of interventions
  – Consumed v “Prescribed”
• Comparator
• Outcome
• Study Design
<table>
<thead>
<tr>
<th>Outcome Categories</th>
<th>Isoflavones Alone</th>
<th>Soy Protein with Isoflavones</th>
<th>Soy Protein without Isoflavones</th>
<th>Unclear Amount of Soy Protein and/or Isoflavones</th>
<th>Total # of Studies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Total: 23</td>
<td>Total: 60</td>
<td>Total: 7</td>
<td>Total: 4</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Advanced Care</td>
<td>Abacor (2)</td>
<td>Essential Nutrition (1)</td>
<td>ADM (1)</td>
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<tr>
<td></td>
<td>Products (1)</td>
<td>Abalon (Nutri Pharma, Oslo) (1)</td>
<td>Protein Technologies International (6)</td>
<td>ISP powder (not specific) (2)</td>
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<tr>
<td></td>
<td>Bonette (Novomed, Helsinki) (2)</td>
<td>Altima HP-20 (Protein Technologies International) (2)</td>
<td>Calcimel (1)</td>
<td>Scan Diet Shakes (1)</td>
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<td>Eugenbio (1)</td>
<td>Genistein, Lab Plant (2)</td>
<td>Eden (1)</td>
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<tr>
<td></td>
<td>NovaSoy (ADM) (3)</td>
<td>NovaSoy (ADM) (3)</td>
<td>FXP HO 159 (1)</td>
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<tr>
<td></td>
<td>Novogen (1)</td>
<td>PhytoLife (1)</td>
<td>ISP powder (not specific)</td>
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<tr>
<td></td>
<td>Protoveg (2)</td>
<td>Soya hypocotyl Iso (Fuji Oil Co) (2)</td>
<td>Proderma (ALPRO, Belgium) (2)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Soycreme (1)</td>
<td>Total Life Co (1)</td>
<td>Solae – powder (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Life Co (1)</td>
<td>No brand name tablet (6)</td>
<td>Supro – powder (12)</td>
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<tr>
<td>Isoflavones alone</td>
<td>Tofu</td>
<td>Soy as major component of diet</td>
<td>Casein</td>
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<tr>
<td>Soy protein w/isoflavones</td>
<td>Textured soy protein</td>
<td>Soy as dietary supplement</td>
<td>Animal protein</td>
<td></td>
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<tr>
<td>Soy protein w/o isoflavones</td>
<td>Soy milk</td>
<td>Vegetable protein</td>
<td>Vegetable protein</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Soy flour</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other soy products</td>
<td>No control</td>
<td>No control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
• **Population**

• **Intervention**

• **Comparator**
  – Blinding
    • Fish oil +- peppermint
  – Equivalence
    • Soy milk: 17.5 g fat/day; Cow milk: 0 g fat/day

• **Outcome**

• **Study Design**
• **Population**

• **Intervention**

• **Comparator**

• **Outcome** (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

• **Study Design**
• **Population**
• **Intervention**
• **Comparator**
• **Outcome**
• **Study 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)
  – Final_{\text{Intervention}} - 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

**INTERVENTION**

Omega-3 Fatty Acids*

**Whole Animal**

**INTERMEDIATE OUTCOMES**

- Heart Rate
- Coronary Flow
- ECG changes (e.g. QT interval prolongation)
- Other intermediate markers

**ARRHYTHMOGENIC OUTCOMES**

- Induced Arrhythmia
- Ventricular ectopic beats
- Ventricular fibrillation
- Atrial fibrillation
- Other arrhythmogenic measures
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