Nutrition and Problems of Proof

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Knowing is not enough; we must apply
Willing is not enough; we must do.

- Johann Wolfgang von Goethe
(1749-1832)

IOM FNB. DRI Coverpage 2000
Hierarchy of Evidence-Based Nutrition

- RCT
- Observational studies
- Animal models
- In vitro studies
- Expert opinion
RCT, Observational Studies and the Hierarchy of Research Designs

The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and education of health care professionals.

Evidence-Based Nutrition: RCTs as the “Gold Standard”

RCTs are given the greatest weight for evidence because they are the experimental design which best permits strong causal inference.

However, RCTs as implemented have limited generalizability and impose constraints ill-suited to testing of nutrients.
RCTs for Drugs vs. Nutrients: Control Group

- **Drugs:** drug-free state (placebo)
- **Nutrients:** “high” intake contrasted with “low” intake (creating a nutrient-free state is unethical)
RCTs for Drugs vs. Nutrients:
Effect Scope

- **Drugs:** principally target a single system

- **Nutrients:** usually pan-systemic

*For example:*

- Statins inhibit HMG-CoA reductase

- Zinc is a cofactor for >100 enzymes and plays a role in protein structure and gene expression
RCTs for Drugs vs. Nutrients: Effect Size

- **Drugs:** usually large and targeted
- **Nutrients:** usually modest but aggregated effect across multiple systems

For example:

Negative Ca balance of 30 mg/d
→ 10% loss of BMD/y
→ osteoporosis in 30 y
RCTs for Drugs vs. Nutrients: Dose-Response Characteristics

- **Drugs:** usually monotonic
- **Nutrients:** usually exhibit a threshold
  often under homeostatic control
RCTs for Drugs vs. Nutrients: Dose-Response Characteristics

Nutrients have multiple sites of action so it is possible to have abnormal function in one parameter, while other parameters requiring the same nutrient appear within normal ranges.

Yates Food Nutr Bull 2007
Implications of Nutrient Threshold Dose-Response Characteristics
Implications of Nutrient Threshold
Dose-Response Characteristics

Response

Nutrient Intake
RCTs of Nutrients in Primary Prevention

- Cohort Considerations
  - Health status
  - Baseline nutrient intake and status
  - Susceptibility to outcome
  - Synergies with non-intervention nutrients

- Intervention Considerations
  - Selection of nutrient/nutrient combinations
  - Selection of form(s) and dose(s)
  - Duration and follow-up periods
  - Assessment of compliance
RCTs of Nutrients in Primary Prevention

*Physicians Health Study II*

Baseline Questionnaires
n=261,248

Respondents
n=112,160

Sesso et al. *Control Clin Trials* 2002
RCTs of Nutrients in Primary Prevention

Physicians Health Study II

Baseline Questionnaires
n=261,248

Respondents
n=112,160

Sesso et al. Control Clin Trials 2002
Vitamins C and E Do Not Prevent Cardiovascular Disease in Men

Physicians Health Study II

Vitamin E, 400 mg/qod

Vitamin C, 500 mg/d

RCT, n=14,641, ≥50 y

Sesso et al. JAMA 2008
RCTs for Drugs vs. Nutrients: Adjuvants and Interactions

- **Drugs**: balance, complement, eliminate or exclude other drugs
- **Nutrients**: additive, antagonistic, synergistic interactions and drug-nutrient interactions are discounted
RCTs of Nutrients in Secondary Prevention

It is unethical to withdraw medications or polypharmacy regimens in RCTs of nutrients

Percent of Subjects Receiving Drugs in the Vitamin E Group

<table>
<thead>
<tr>
<th>Drugs</th>
<th>HOPE</th>
<th>HOPE 2</th>
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</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>39.9</td>
<td>40.2</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>77.0</td>
<td>76.7</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td>28.4</td>
<td>28.3</td>
</tr>
<tr>
<td>Diuretics</td>
<td>15.7</td>
<td>15.2</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>47.2</td>
<td>46.7</td>
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</tbody>
</table>

Lonn et al. *JAMA* 2005
Co-dependence of Calcium and Vitamin D for Calcium Bioavailability

In the absence of Ca, vitamin D will not result in sufficient absorption.

In the absence of vitamin D, not enough Ca absorbed.
Role of B Vitamins in Homocysteine Metabolism

- S-adenosyl homocysteine
- Homocysteine
- Serine
- Crystathionine
- Cysteine
- Methionine
- THF
- Methylene THF
- B12
- Folic Acid
- DNA
- Protein

- Serine
- B6
- Glycine

B6

B12
B Vitamins Do Not Reduce Risk for Stroke and Coronary Events

Vitamin Intervention for Stroke Prevention

RCT, n=3680, 66 y, hx stroke

Toole et al. *JAMA* 2004
Co-dependence of Folic Acid and Vitamin B12 for Reduction of Stroke and Coronary Events

*Vitamin Intervention for Stroke Prevention*

**B12 < or > median 322 pmol/L**

- Hi, >B12
- Hi, <B12
- Lo, >B12
- Lo, <B12

**Hi v. Lo Dose**

- B12, 400 v. 6 μg
- B6, 25 v. 0.2 mg
- FA, 2.5 v. 0.02 mg

**RCT, n=2155, 66 y, hx stroke**

Spence et al. Stroke 2005
Dependence of Outcome on Study Duration
Meta-analysis of Homocysteine Lowering Therapy

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Overall</td>
<td>0.93 (0.85-1.03)</td>
<td>0.16</td>
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<tr>
<td>Duration</td>
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<tr>
<td>&lt;3 y</td>
<td>1.03 (0.84-1.27)</td>
<td>NS</td>
</tr>
<tr>
<td>≥3 y</td>
<td>0.87 (0.78-0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>Homocysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>1.02 (0.86-1.22)</td>
<td>NS</td>
</tr>
<tr>
<td>≥20%</td>
<td>0.87 (0.77-0.98)</td>
<td>0.02</td>
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<tr>
<td>Stroke prevention</td>
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<td></td>
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<tr>
<td>Secondary</td>
<td>1.11 (0.83-1.49)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-secondary</td>
<td>0.84 (0.74-0.94)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Lee et al. *Stroke* 2010
Relationship Between Certainty of Evidence, Benefit:Risk, and Confidence to Act

Blumberg et al. *Nutr Rev* 2010
Relationship Between Certainty of Evidence, Risk:Benefit, and Confidence to Act

Blumberg et al. Nutr Rev 2010
Hill’s Criteria of Causation

*The Environment and Disease: Association or Causation?*

- Consistency of association
- Specificity of association
- Strength of association
- Experimental evidence
- Plausibility
- Temporality
- Biological gradient
- Coherence
- Analogy

Hill *Proc R Soc Med* 1965