Exclusive Webinar Presentation

Evidence-Based Nutrition: The Problem of Proof

Thursday, December 1, from 2-3 PM EST

Presented by Jeffrey B. Blumberg, PhD, FASN, FACN
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Affiliations: Dr. Blumberg is a Professor in the Friedman School of Nutrition Science and Policy and also serves as a Senior Scientist in the Antioxidants Research Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University.

Disclosures: He serves on the scientific advisory boards of AdvoCare, Cranberry Institute/Cranberry Marketing Committee, Herbalife, Pfizer Consumer Healthcare, Pharmavite, Quaker Oats and SmartyPants.
Knowing is not enough; we must apply. Willing is not enough; we must do.

- Johann Wolfgang von Goethe (1749-1832)
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
Hierarchy of Evidence-Based Nutrition

- RCT
- Observational Studies
- Animal Models
- In Vitro Studies
- Expert Opinion
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.


We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials.

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.
Revised Hierarchy of Evidence-based Nutrition

- Meta-analysis
- Systematic Reviews
- Randomized Controlled Trials
- Cohort Studies
- Case Control Studies
- Case Series/Case Reports
- Background Information/Expert Opinion
- Animal Research/Laboratory Studies
RCTs for Drugs vs. Nutrients: Control Group

- **Drugs**: drug-free state (placebo)
- **Nutrients**: “high” intake contrasted with “low” intake
RCTs for Drugs vs. Nutrients: Control Group

• **Drugs:** drug-free state (placebo)

• **Nutrients:** “high” intake contrasted with “low” intake

  Induce nutrient insufficiency or deficiency → **UNETHICAL!**
Vitamin D Insufficiency During Pregnancy

Impaired Language Development

Prospective cohort, Australia
n=743 mother-child pairs

Lower Muscle Strength

Prospective cohort, UK
n=678 mother-child pairs

Maternal 25(OH)-vitamin D concentration during pregnancy

- Quartile 1
- Quartile 2
- Quartile 3
- Quartile 4

Proportion (%) of offspring with language impairment

β=0.10, p=0.013

Harvey et al. J Clin Endocrinol Metab 2014

Randomized controlled trials of Vitamin D supplementation are required to verify these observational data that suggest that an adequate maternal vitamin D status during pregnancy is necessary for optimal language development in offspring.

- Whitehouse et al. *Pediatrics* 2012

Formal testing of this hypothesis in an interventional setting should be undertaken before the development of any clinical recommendations.

- Harvey et al. *J Clin Endocrinol Metab* 2014
Impact of Vitamin D Insufficiency During Pregnancy Requires RCTs

Randomized controlled trials of Vitamin D supplementation are required to verify these observational data that suggest that an adequate maternal vitamin D status during pregnancy is necessary for optimal language development in offspring.

- Whitehouse et al. *Pediatrics* 2012

Formal testing of this hypothesis in an interventional setting should be undertaken before the development of any clinical recommendations.

- Harvey et al. *J Clin Endocrinol Metab* 2014

UNFEASIBLE!
Healthy Aging as Outcome Criteria

**SU.VI.MAX 2**

**RCT**
- n, 3996
- age, $65.3 \pm 4.5\; y$
- intervention, 8 y
- F/U, 15 y

**SUPPLEMENT**
- Vitamin C, 120 mg
- Vitamin E, 30 mg
- β-carotene, 6 mg
- Selenium 100 μg
- Zinc, 20 mg

---

### Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
<th>Corresponding Rowe and Kahn Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good physical functioning</td>
<td>SPPB $\geq 11$ of 12</td>
<td>Maintenance of high physical and cognitive function</td>
</tr>
<tr>
<td>Good cognitive functioning</td>
<td>MMSE $\geq 27$, RI-48 $\geq 19$ of 48, and DK-TMT $\geq 5.5$</td>
<td>Maintenance of high physical and cognitive function</td>
</tr>
<tr>
<td>No limitations in IADL</td>
<td>$&lt; 1$ limitation</td>
<td>Avoiding disease and disability</td>
</tr>
<tr>
<td>No depressive symptoms</td>
<td>CES-D $&lt; 16$ of 60</td>
<td></td>
</tr>
<tr>
<td>No health-related limitations in social life</td>
<td>SF-36 responses: 1–2 for item 6 and 3–5 for item 10</td>
<td>Sustained engagement in social and productive activities</td>
</tr>
<tr>
<td>Good overall self-perceived health</td>
<td>SF-36 responses: 1–3 for item 1</td>
<td></td>
</tr>
<tr>
<td>No function-limiting pain</td>
<td>SF-36 responses: 1–3 for item 7 and 1–2 for item 8</td>
<td>Avoiding disease and disability</td>
</tr>
<tr>
<td>No incident major chronic disease</td>
<td>No incident diabetes, cancer, or cardiovascular disease during follow-up</td>
<td>Avoiding disease and disability</td>
</tr>
</tbody>
</table>

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Antioxidant Supplementation as a Predictor of Healthy Aging

<table>
<thead>
<tr>
<th>Stratification Variable</th>
<th>Total n</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>3996</td>
<td>1.07</td>
<td>0.99-1.16</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2027</td>
<td>1.16</td>
<td>1.04-1.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Women</td>
<td>1939</td>
<td>0.98</td>
<td>0.86-1.11</td>
<td></td>
</tr>
<tr>
<td>Vitamin C status, &lt;42 μmol/L</td>
<td>727</td>
<td>1.28</td>
<td>1.06-1.56</td>
<td>0.06</td>
</tr>
<tr>
<td>Zinc status, &lt;11.9 μmol/L</td>
<td>953</td>
<td>1.26</td>
<td>1.06-1.49</td>
<td>0.05</td>
</tr>
<tr>
<td>F&amp;V (&lt;400 g/d)</td>
<td>1757</td>
<td>1.17</td>
<td>1.02-1.32</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Is It Unethical or Infeasible to Restrict Intake of Foods Rich in Non-essential Bioactives?

United States

China

Mexico
Study Design for Acute Bioactive Intervention

1. Anthocyanin free diet
2. Low (poly)phenol diet
3. Fasting
4. Intervention day
5. Vascular function
6. Blood collection
7. Urine collection

Timeline:
- 1 week
- -72 h
- -12 h
- 0
- 1
- 2
- 4
- 6
- 8
- 24 h
RCTs for Drugs vs. Nutrients: Effect Scope

- **Drugs**: principally target a single system
- **Nutrients**: usually pan-systemic
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
Modulation of:

- Signal transduction pathways
- Transcription factors
- DNA acylation/methylation
- Mitochondrial function
- Autophagy
- Plasma membrane proteins/phospholipids
Polyphenols

Antioxidant related actions

ROS-removing level

ROS-scavenging (electron/hydrogen transfer)
Induction of ROS-removing enzymes (e.g., SOD, catalase, Gpx)
Induction of endogenous antioxidant-synthesizing enzymes (e.g., glutathione synthase)

ROS-formation level

Metal chelation (iron and copper)
Inhibition or repression of ROS-forming enzymes (e.g., XO, NOX, LOX, MAO, iNOS)

Cardiovascular level
(anti-inflammatory, anti-platelet aggregation, antiatherogenic*, lipid profile-normalizing, vasodilating*)

Chemo-preventive level
(antimutagenic*, antiproliferative, proapoptotic, antiangiogenic)

Gastrointestinal level
(interfering metal absorption and carbohydrate & lipid digestion/absorption)

Immunological level
(immunomodulatory, antiallergic)

Other levels
(antimicrobial, antiviral, estrogenic, neurosedating)
Cocoa Increases Flow-Mediated Dilation, Plasma Nitroso Species, and Total Flavanols

RCT XO:  
- n, 10 men
- age, 25-32 y
- dose, 917 vs 37 mg cocoa flavanols
Cocoa flavanols help maintain endothelium-dependent vasodilation, which contributes to normal blood flow. In order to obtain the claimed effect, **200 mg of cocoa flavanols should be consumed daily**. This amount could be provided by **2.5 g of high-flavanol cocoa powder** or **10 g of high-flavanol dark chocolate**, both of which can be consumed in the context of a balanced diet. The target population is the general population.
RCTs for Drugs vs. Nutrients: Effect Size

- **Drugs**: usually large and targeted

- **Nutrients**: usually modest but aggregated effect across multiple systems over time
RCTs for Drugs vs. Nutrients: Effect Size

- **Drugs**: usually large and targeted

- **Nutrients**: usually modest but aggregated effect across multiple systems over time

*For example:*

Negative Ca balance of 30 mg/d  
→ 10% loss of BMD/yr  
→ osteoporosis in 30 yr
Green Tea Flavanols Lower Systolic Blood Pressure

Onakpoya et al. *Nutr Metabol Cardiovasc Dis* 2014

- RCTs, 20
- n, 1536
Black Tea Lowers Blood Pressure and Wave Reflections after a Fat Load Challenge

Grassi et al. *Nutrients* 2015

**RCT XO**
- *n*, 19 HT
- F/U, 8 d
- dose, 158 mg flavonoids
Chronic Black Tea Intake Reduces Blood Pressure

RCT
- n, 95
- age, 35-79 y
- dose, 3 cups/d

RCTs for Drugs vs. Nutrients: Follow-up for Disease Endpoint

- **Drugs**: short-term to show efficacy (<12 mo)
- **Nutrients**: long-term (years)
### Effect of Multivitamins on Cardiovascular Disease

**Women’s Health Study**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
<th>( P_{interaction} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>0.91</td>
<td>0.82-1.02</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.98</td>
<td>0.74-1.06</td>
<td>NS</td>
</tr>
<tr>
<td>Total stroke</td>
<td>0.91</td>
<td>0.78-1.06</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.85</td>
<td>0.71-1.01</td>
<td>NS</td>
</tr>
<tr>
<td>CVD death</td>
<td>0.91</td>
<td>0.71-1.16</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Prospective cohort**
- \( n, 37,193 \)
- age, \( \geq 45 \) y
- F/U, 16.2 y

### Effect of Multivitamins on Cardiovascular Disease

**Women’s Health Study**

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<tr>
<th>Event</th>
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<tr>
<td>CVD death</td>
<td>0.91</td>
<td>0.71-1.16</td>
<td>NS</td>
</tr>
<tr>
<td>CVD $\geq 70$ y</td>
<td>0.72</td>
<td>0.48-1.08</td>
<td>0.04</td>
</tr>
<tr>
<td>CVD $&lt;3$ serv F&amp;V/d</td>
<td>0.77</td>
<td>0.55-1.09</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Prospective cohort
- $n$, 37,193
- age, $\geq 45$ y
- F/U, 16.2 y
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>CVD</th>
<th>RR</th>
<th>F/U, y</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>PC</td>
<td>21,132</td>
<td>MI</td>
<td>0.73</td>
<td>10.2</td>
<td>Rautiainen et al. AJCN 2010</td>
</tr>
<tr>
<td>CC</td>
<td>928</td>
<td>MI</td>
<td>0.66</td>
<td>--</td>
<td>Holmquist et al. J Nutr 2003</td>
</tr>
<tr>
<td>PC</td>
<td>80,082</td>
<td>CHD</td>
<td>0.76</td>
<td>14</td>
<td>Rimm et al. JAMA 1998</td>
</tr>
<tr>
<td>PC</td>
<td>381,553</td>
<td>IHD</td>
<td>0.82</td>
<td>7.0</td>
<td>Watkins et al. Am J Epi 2000</td>
</tr>
<tr>
<td>PC</td>
<td>381,553</td>
<td>Stroke</td>
<td>0.81</td>
<td>7.0</td>
<td>Watkins et al. Am J Epi 2000</td>
</tr>
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</table>

PC, prospective cohort study
CC, case control study
# Effect of Multivitamins on Cardiovascular Disease in Men

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<tr>
<th>Study</th>
<th>N</th>
<th>CVD</th>
<th>RR</th>
<th>F/U, y</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>CC</td>
<td>2053</td>
<td>MI</td>
<td>0.79</td>
<td>--</td>
<td>Holmquist et al. J Nutr 2003</td>
</tr>
<tr>
<td>RCT</td>
<td>14,641</td>
<td>MI death</td>
<td>0.61</td>
<td>13.3</td>
<td>Sesso et al. JAMA 2012</td>
</tr>
<tr>
<td>PC</td>
<td>714,527</td>
<td>IHD</td>
<td>0.80</td>
<td>7.0</td>
<td>Watkins et al. Am J Epi 2000</td>
</tr>
<tr>
<td>Cohort (M&amp;F)</td>
<td>77,719</td>
<td>CVD death</td>
<td>0.84</td>
<td>10.0</td>
<td>Pocobelli et al. Am J Epi 2009</td>
</tr>
</tbody>
</table>
Multivitamins Do Not Reduce the Risk of Cardiovascular Disease in Men: *Physicians’ Health Study II*

**MAJOR CVD EVENTS**
- Multivitamin
- Placebo

**MYOCARDIAL INFARCTION**
- Placebo
- Multivitamin

MI Death: 0.61 (0.58-0.99), *P* < 0.05

**RCT**
- n, 14,641
- age, ≥50 y
- F/U, 13.3 y

Sesso et al. *JAMA* 2012
Multivitamins Do Reduce the Risk of Cardiovascular Disease in Men: *Physicians’ Health Study I*

<table>
<thead>
<tr>
<th>Duration of Multivitamin Use</th>
<th>No use</th>
<th>&lt;10 y</th>
<th>10 – 20 y</th>
<th>≥20 y</th>
<th>(P_{\text{trend}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1293</td>
<td>211</td>
<td>67</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.94</td>
<td>0.91</td>
<td>0.56</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>(0.81 - 1.09)</td>
<td>(0.71 - 1.17)</td>
<td>(0.35 - 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac revascularization:  
HR: 0.86 (0.76 - 0.98)  

Prospective cohort  
• n, 18,530  
• age, \(\geq 40\) y
Multivitamins Reduce the Risk of Total Cancer

*Physicians’ Health Study II*

**TOTAL CANCER**
HR = 0.92 (0.86-0.99) P = 0.04

**COLORECTAL CANCER**
HR = 0.89 (0.80-1.17) P = 0.39

**RCT**
- n, 14,641
- age, ≥50 y
- F/U, 13.3 y

Gaziano et al. *JAMA* 2012
Is It Too Soon to Tell Men That Vitamins Prevent Cancer?

The PHS II study was a well-done, large-scale, blinded, randomized clinical trial with objective verification of cancer outcomes.

...the biological plausibility of the study hypothesis – that a multivitamin would be protective in a well-nourished population – is limited. This matters, because the chance that the study finding of a protective effect is true is intrinsically related (by Bayes theorem) to the plausibility of the hypothesis.
...before drawing a definitive conclusion from this study that daily multivitamins reduce the risk of cancer in men, physicians and other readers must be convinced that the observed treatment effect is real and thus is likely to be reproduced in future experience, rather than a random event that is unlikely to recur.
Is It Too Soon to Tell Men That Vitamins Prevent Cancer?

The marginal statistical significance and perplexing and somewhat counterintuitive nature of the study findings make drawing any firm conclusion premature.

Thus, it may be inappropriate to recommend that men take multivitamins to prevent cancer.
RCTs for Drugs vs. Nutrients:
Dose-Response Characteristics

- **Drugs**: usually monotonic

- **Nutrients**: usually exhibit a threshold and are often under homeostatic control
Nutrient Thresholds for Health

Response

Vitamin E Intake
Vitamin E Thresholds for Health

- Alzheimer’s disease
- Retinal function
- Vascular function
- Hemolysis
- Neurological abnormalities

Response vs. Vitamin E Intake
Implications of Nutrient Threshold Dose-Response Characteristics
**USPSTF Recommendation Statement**

...current is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men.

Vitamin D & Calcium Supplementation Do Prevent Hip Fractures in Women: Women’s Health Initiative

- 2000 mg calcium + 400 IU vitamin D₃ or placebo
- 56% of the cohort took calcium + vitamin D before the trial
- Daily calcium intake during the RCT was 1135 mg/d in the placebo group and 2000 mg/d in the supplement group

Prentice et al. Osteoporos Intl 2013
Vitamin D & Calcium Supplementation Do Prevent Hip Fractures in Women: *Women’s Health Initiative*

- 2000 mg calcium + 400 IU vitamin D₃ or placebo
- 56% of the cohort took calcium + vitamin D before the trial
- Daily calcium intake during the RCT was 1135 mg/d in the placebo group and 2000 mg/d in the supplement group
- Among the women not taking calcium or vitamin D supplements at baseline, HR = 0.62 (95% CI: 0.38-1.00)

Prentice et al. *Osteoporos Intl* 2013
Multivitamin Slows Progression to Age-Related Macular Degeneration: *Age-Related Eye Disease Study* Research Group.

**RCT**
- n, 4,575
- age, 55-80 y
- F/U, 7 y

**Diagrams**
- Probability of Advanced AMD
- Probability of Visual Acuity Loss

**Formulation**
- Vitamin C, 500 mg
- Vitamin E, 400 IU
- β-Carotene, 15 mg
- Zinc, 80 mg
- Copper, 2 mg
Lutein + Zexanthin in AREDS Formulation Reduces Risk of AMD Progression: AREDS II

Participants assigned to the control group were given the AREDS supplement, thus there is no true placebo group.

RCT
• n, 4,203
• age, 50-85 y
• F/U, 4.7

Chew et al. JAMA 2013
Predicted Plasma Lutein/Zeaxanthin Score Associated with Reduced Risk of Advanced AMD: Nurses’ Health Study – Health Professionals F/U

Prospective cohorts
• n, 102,046
• age, 64 y
• F/U, 26 y

Wu et al. JAMA Ophthalmol 2015
RCTs for Drugs vs. Nutrients: Cohort Selection

- **Drugs**: sick or high risk for disease
- **Nutrients**: healthy or with moderate risk factors
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
  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 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 IU qod**

**Vitamin C, 500 mg/d**

RCT

- **n**, 14,641
- **age**, ≥50 y
- **F/U**, 10 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
### Percent of Subjects Receiving Drugs in the Vitamin E Group

<table>
<thead>
<tr>
<th>Drugs</th>
<th>HOPE</th>
<th>HOPE 2</th>
</tr>
</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>
</tr>
</tbody>
</table>
RCTs of Nutrients in Secondary Prevention

Percent of Subjects Receiving Drugs in the Vitamin E Group

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Lonn et al. JAMA 2005

**UNETHICAL!**

Withdraw medication/polypharmacy regimens

- RCT, 26
- PC, 2

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamins for the prevention of cardiovascular disease or cancer.
The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamins for the prevention of cardiovascular disease or cancer.

Our analysis has some limitations... This is a review of trials, a study design used primarily to evaluate drug therapy. The design might not be ideally suited to evaluating nutrients.
The message is simple: Most supplements do not prevent chronic disease or death, their use is not justified, and they should be avoided.

Antioxidants, folic acid, and B vitamins are harmful or ineffective for chronic disease prevention, and further large prevention trials are no longer justified.
The case is closed – supplementing the diet of well-nourished adults with (most) mineral or vitamin supplements has no clear benefit and might even be harmful. These vitamins should not be used for chronic disease prevention. Enough is enough.
For drugs to treat disease:
• Balance of efficacy and toxicity in pharmacotherapy
• Comparative effectiveness with other drugs
• High cost

For nutrients to prevent disease:
• Broad margin between efficacy and harm
• Substitution for essential nutrients not possible
• Overlapping action of dietary bioactive components
• Low cost
Certainty vs. Confidence

Level of confidence in a decision to act:

- High benefit : risk ratio
- Important consequences of Type II error
- Low deployment cost
- Low opportunity cost
- Multiplicity of lines of evidence
- Availability of ancillary measures
Standards of Proof Remain Unchanged But Can Act for Nutrition with Less Certainty

- Requiring RCT-level evidence when this design is ill-suited or not available impedes the application of nutrition research to public health issues.

- To fail to act due to absence of conclusive RCTs jeopardizes the potential for achieving benefits with little risk and low cost.

- Nutrient-related decisions should be made at a level of certainty somewhat less than required for drugs.
Conclusions

• To act in the absence of ultimate certainty requires a broad consideration of all research approaches along with revised estimates of the necessary certainty level and confidence needed to act in support of public health.

• In assessing the balance between the potential harm of making or not making a recommendation, appropriate educational strategies will be necessary to convey varying levels of the strength of evidence.
Le mieux est l'ennemi du bien
The perfect is the enemy of the good

- Voltaire (François-Marie Arouet) 1694-1778
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