Scientific Symposium
Geneva, Switzerland – 3 July 2010
CRN International
SCIENTIFIC ISSUES RELATED TO CODEX GOALS

Clinical Trials for Benefits: Evidence-Based Medicine or Nutrition?

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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. Antioxidants DRI Coverpage 2000

Contributions from Different Research Strategies

Strategy	Approaches	Features
Basic research	Cell culture	+ Precise
	Animal model	+ Lifespan
		- Extrapolation
Clinical observation	Experience with patients	+ Hypothesis generation
	Case reports/series	- Anecdotal

Contributions from Different Research Strategies

Strategy	Approaches	Features
Epidemiology	Ecologic	+ Multiple endpoints
	Analytical	+ Various nutrients
		+ Long duration
		- Inexact
		- Confounded
Intervention studies	Clinical trial	+ Exact
		- Limited doses
		- Duration
		- Expensive

Evidence-Based Medicine: Grades of Evidence Hierarchy of Research Designs for Efficacy

I. Properly randomized, controlled trial (RCT)

II.1 Well-designed controlled trial without randomization

II.2 Well-designed cohort or case-control analytic study

II.3 Multiple time series with or without intervention

III. Opinions of respected authorities; descriptive studies or case reports; reports of expert committees

US Preventive Services Task Force 1996

Evidence-Based Medicine: Acceptable Studies for Harm

- Case report
- Cohort study
- Case control study
- Expert opinion

Meta-Analysis of Five Interventions According to Research Design

Clinical Topic	Studies	N	Summary Estimate (95% CI)
Bacille Calmette-Guérin	13 RCT	359,922	0.49 (0.34-0.70)
vaccine and tuberculosis	10 CC	6,511	0.50 (0.39-0.65)
Mammography and mortality	8 RCT	429,043	0.79 (0.71-0.88)
from breast cancer	4 CC	132,456	0.61 (0.49-0.77)
Cholesterol levels and death	6RCT	36,910	1.42 (0.94-2.15)
due to trauma	14 C	9,377	1.40 (1.14-1.66)
Treatment of hypertension	14 RCT	36,894	0.58 (0.50-0.67)
and stroke	7 C	405,511	0.62 (0.60-0.65)
Treatment of hypertension	14 RCT	36,894	0.86 (0.78-0.96)
and coronary heart disease	9 C	418,343	0.77 (0.75-0.80)

RCT = Randomized controlled trial
CC = Case-control; C = Cohort

Concato et al. *N Engl J Med* 2000

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.

Concato et al. *N Engl J Med* 2000

Comparison of 136 Observational Studies and RCT

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.

Benson and Hartz. *N Engl J Med* 2000

Evidence-Based Medicine and Nutrition: RCTs as the "Gold Standard" for Drugs and Nutrients

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:

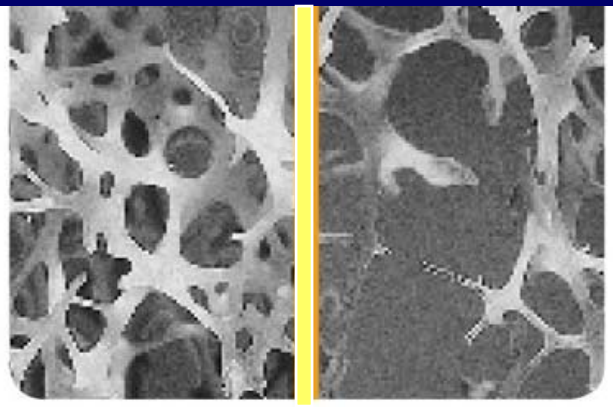
- Statins inhibit HMG-CoA reductase
- Zinc is a cofactor for >100 enzymes and plays a role in protein structure and gene expression

RCTs for Drugs vs. Nutrients: Effect Size

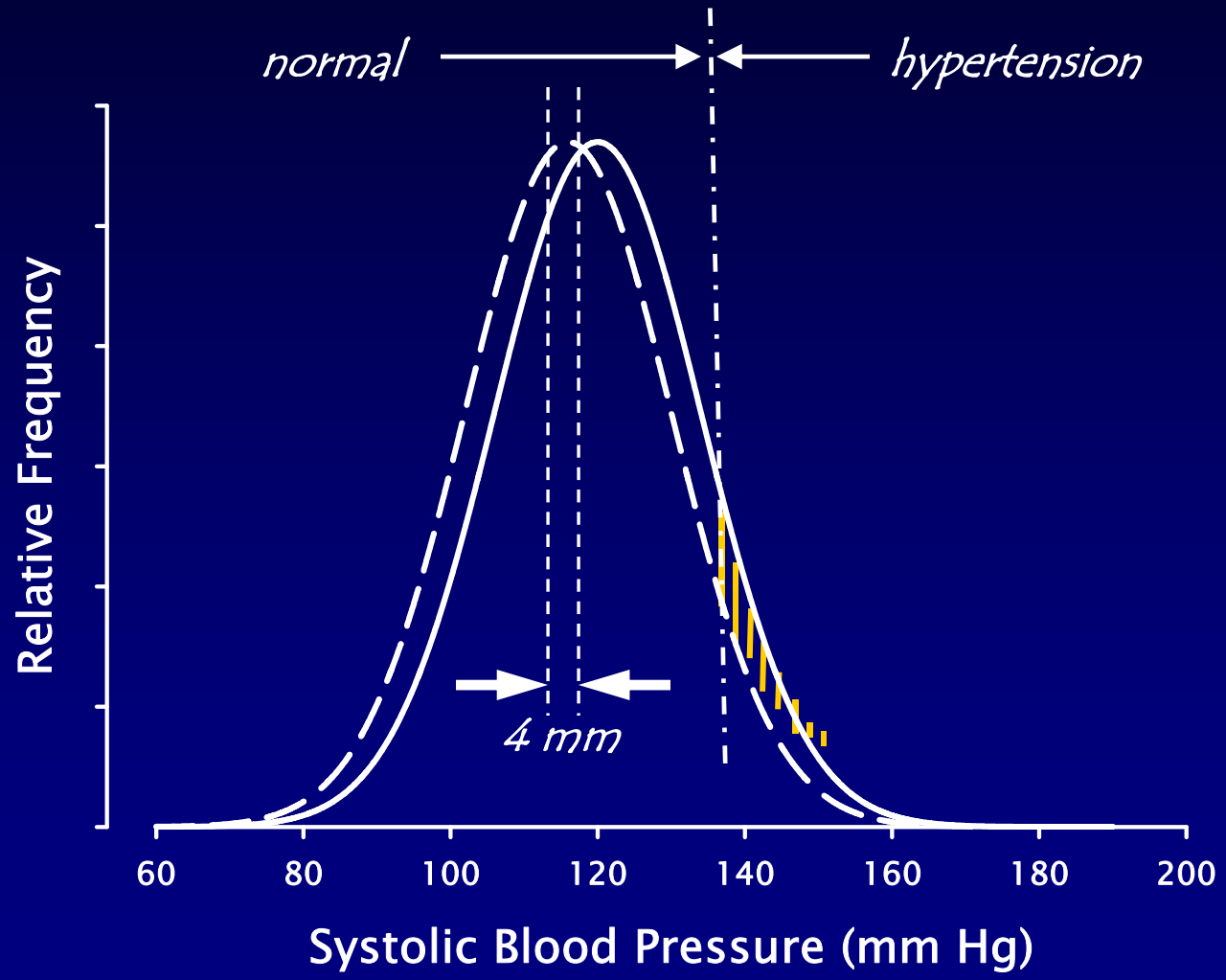
- **Drugs:** usually large and targeted
- **Nutrients:** usually modest but aggregated effect across multiple systems

For example:

Negative Ca balance of 30 mg/d
→ 10% loss of BMD/y
→ osteoporosis in 30 y

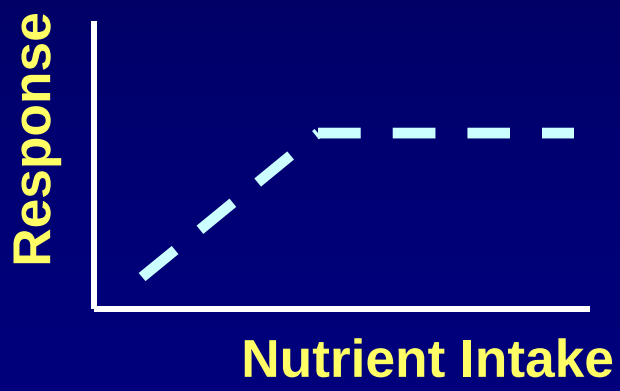


Modest Effect Size Can Affect Public Health



RCTs for Drugs vs. Nutrients: Dose-Response Characteristics

- **Drugs:** usually monotonic
- **Nutrients:** usually exhibit a threshold



RCTs for Drugs vs. Nutrients: Dose-Response Characteristics

Nutrient thresholds are different for different outcomes:

- **Vitamin D**

rickets < osteoporosis

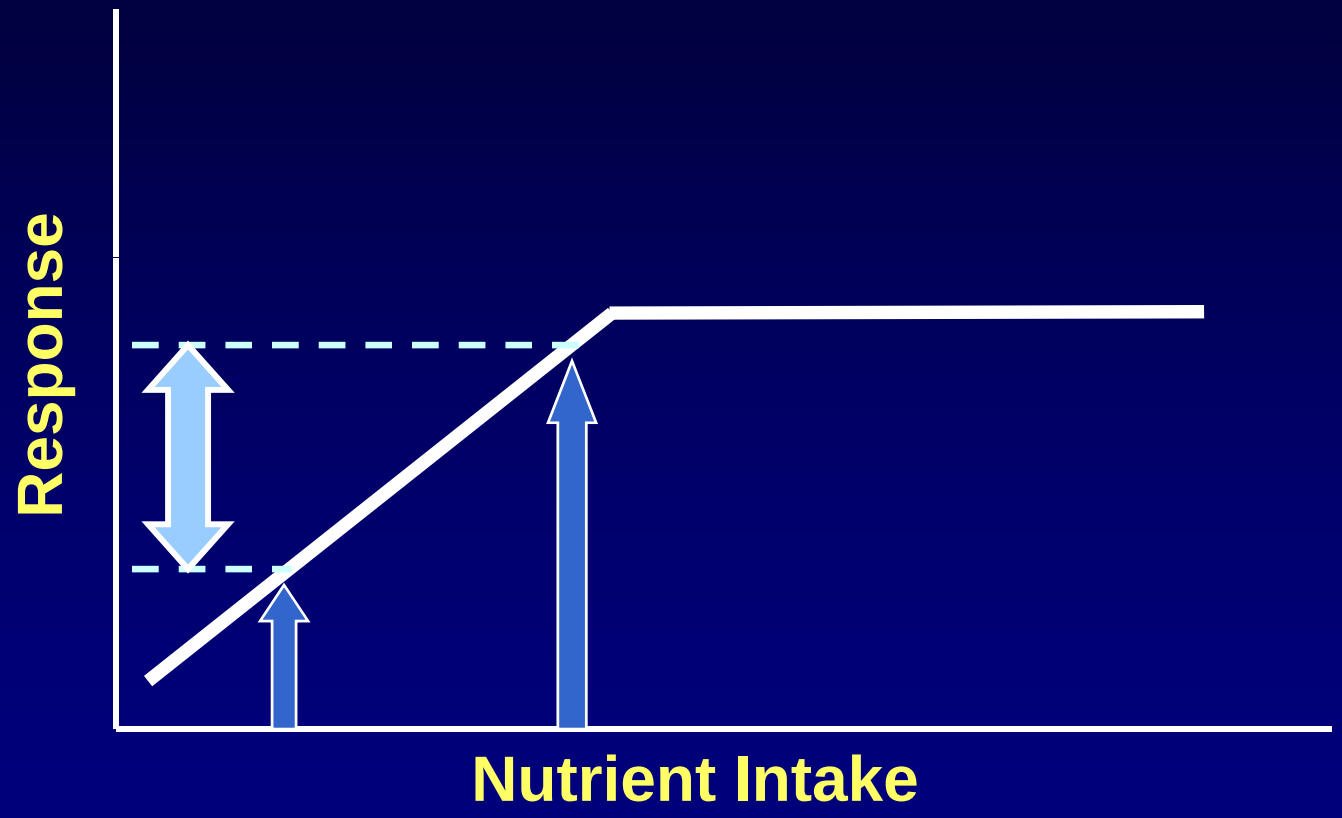
- **Vitamin E**

myopathy < immune function < venous thromboembolism

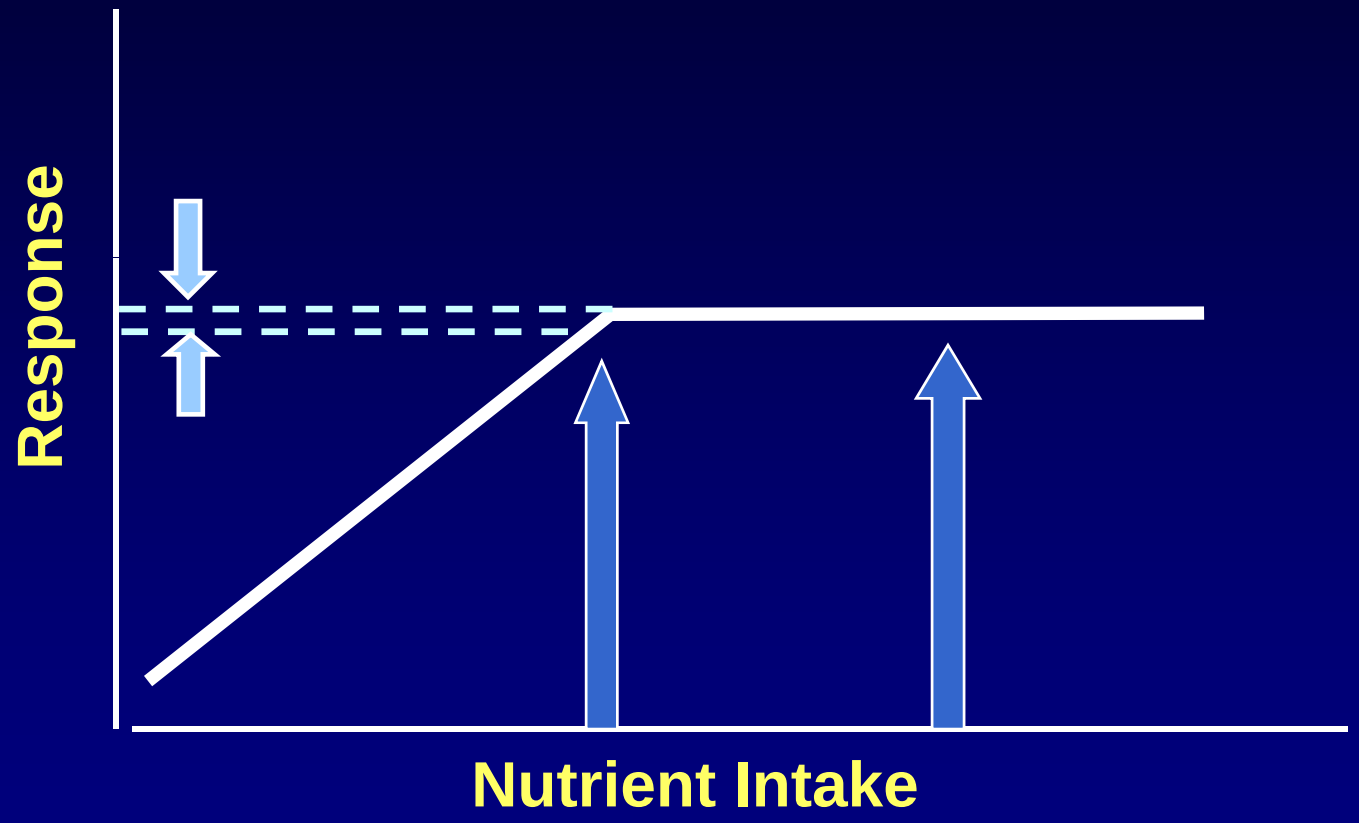
- **Folic acid**

megaloblastic anemia < neural tube birth defects

Implications of Nutrient Threshold Dose-Response Characteristics



Implications of Nutrient Threshold Dose-Response Characteristics



Implications of Nutrient Threshold Dose-Response

***Calcium for Preeclampsia Prevention*: 1135 vs. 2000 mg/d**

"Calcium did not reduce the incidence of preeclampsia"

Levine et al. *NEJM* 1997

***Women's Health Initiative*: 1154 vs. 2000 mg/d**

"Calcium did not significantly reduce hip fracture"

Jackson et al. *NEJM* 2006

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**

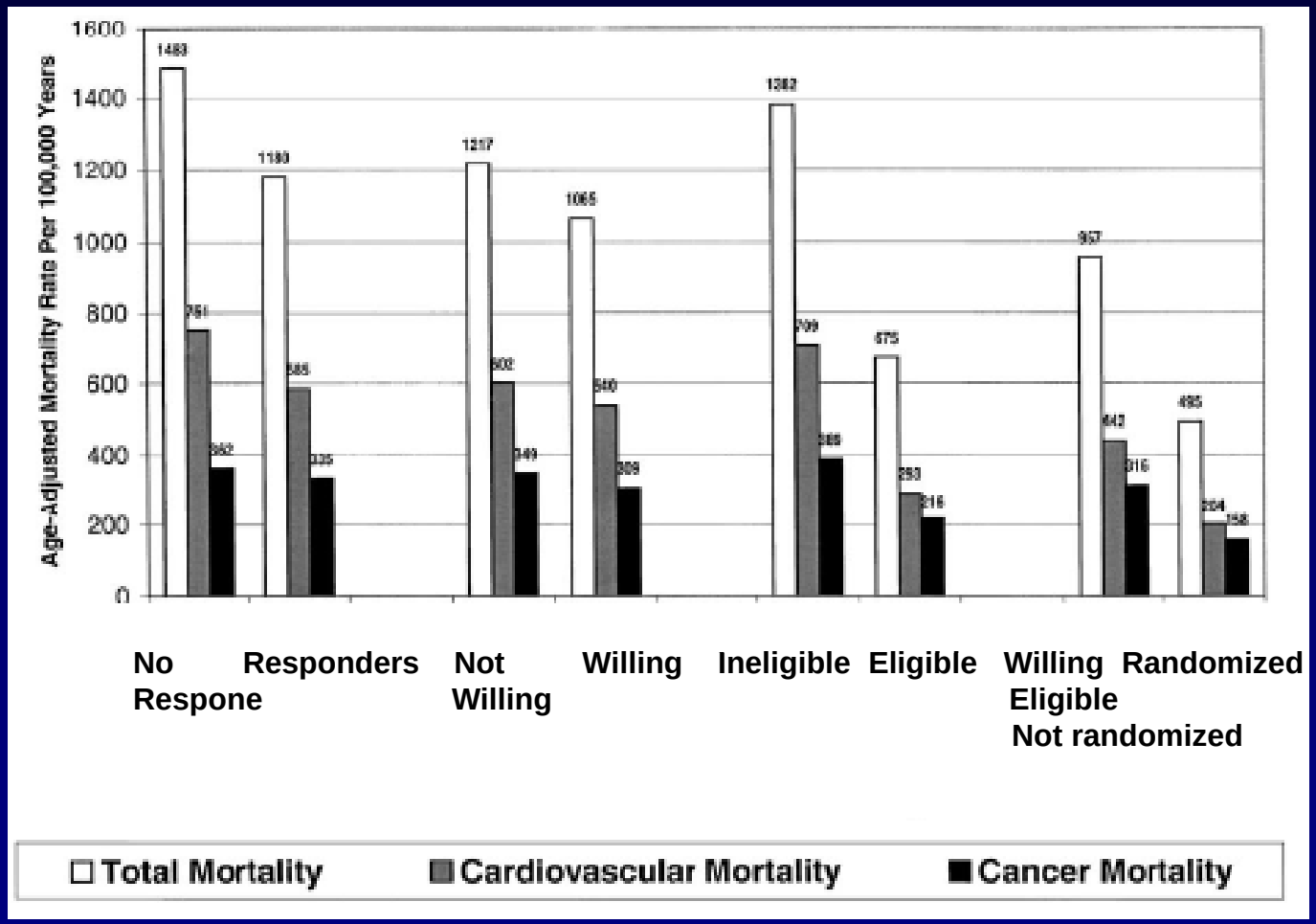
  Selection of nutrient/nutrient combinations
  Selection of form(s) and dose(s)
  Duration and follow-up periods
  Assessment of compliance

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

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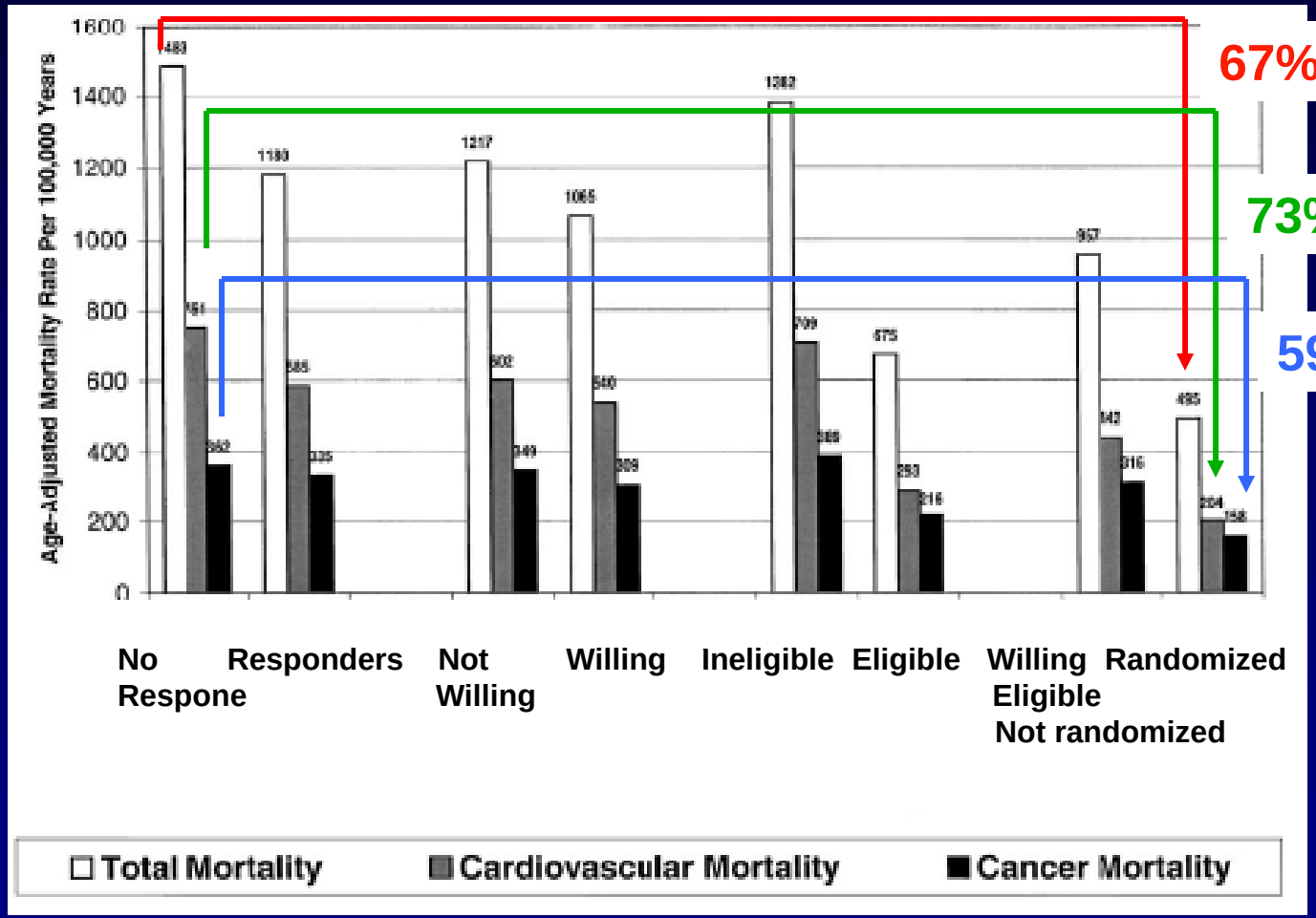
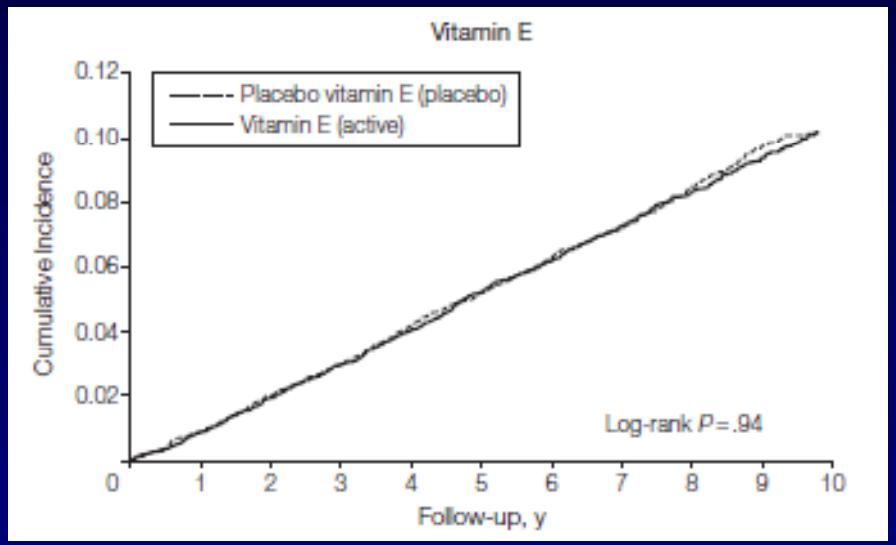


Sesso et al. *Control Clin Trials* 2002

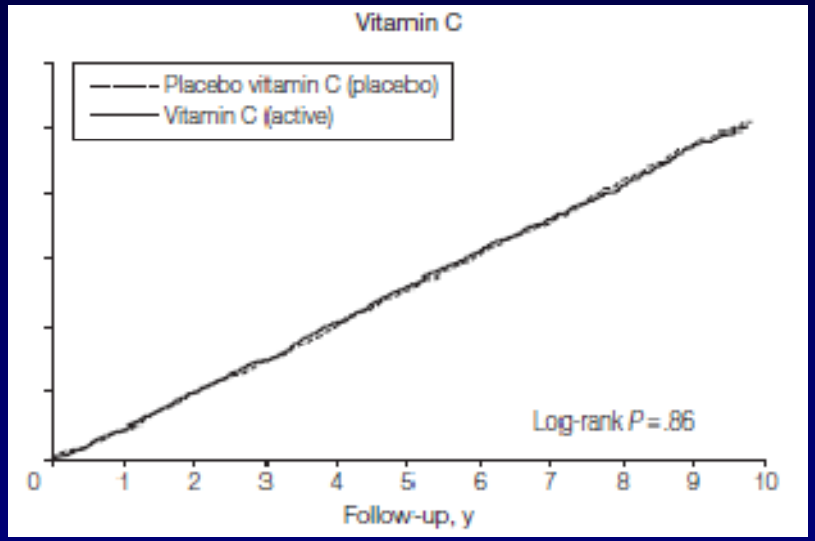
Vitamins C and E Do Not Prevent Cardiovascular Disease in Men

Physicians Health Study II

Vitamin E, 400 mg/qod



Vitamin C, 500 mg/d

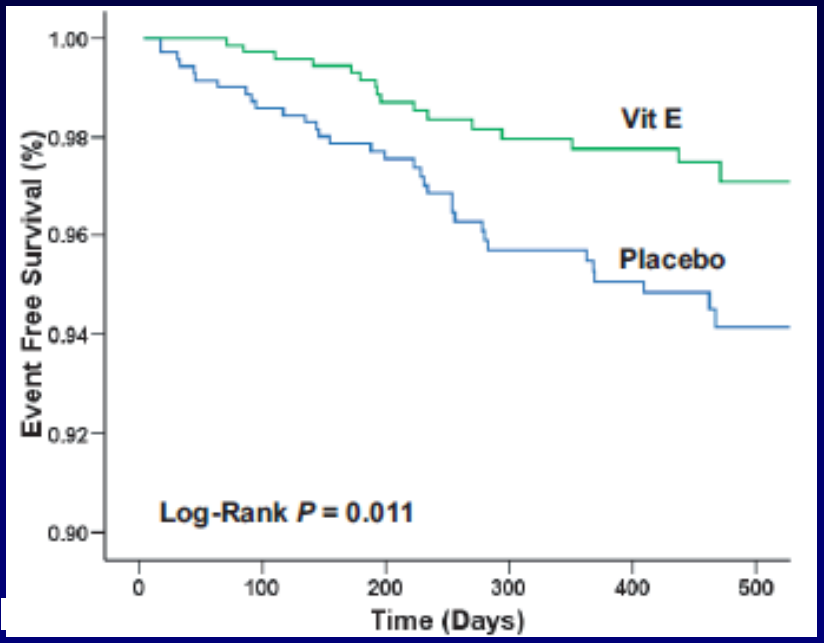


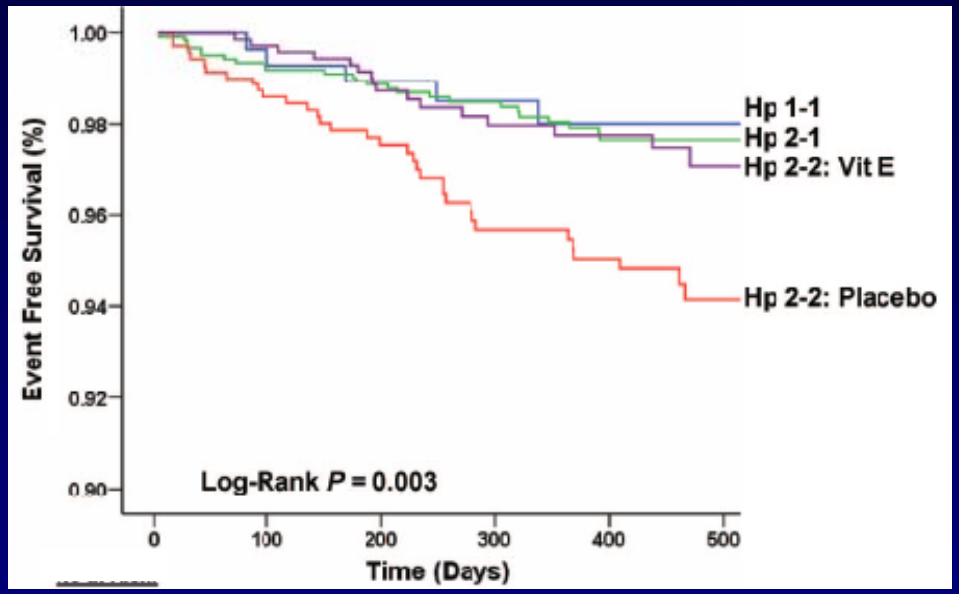
RCT
n=14,641
≥50 y

Sesso et al. *JAMA* 2008

Vitamin E Reduces Cardiovascular Events in Type 2 Diabetics with Haptoglobin 2-2 Genotype

Vitamin E, 400 IU/d





RCT, n=1434, ≥55 y
Outcome: MI, stroke, CV death

Milman et al. *Arterioscler Thromb Vasc Biol* 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

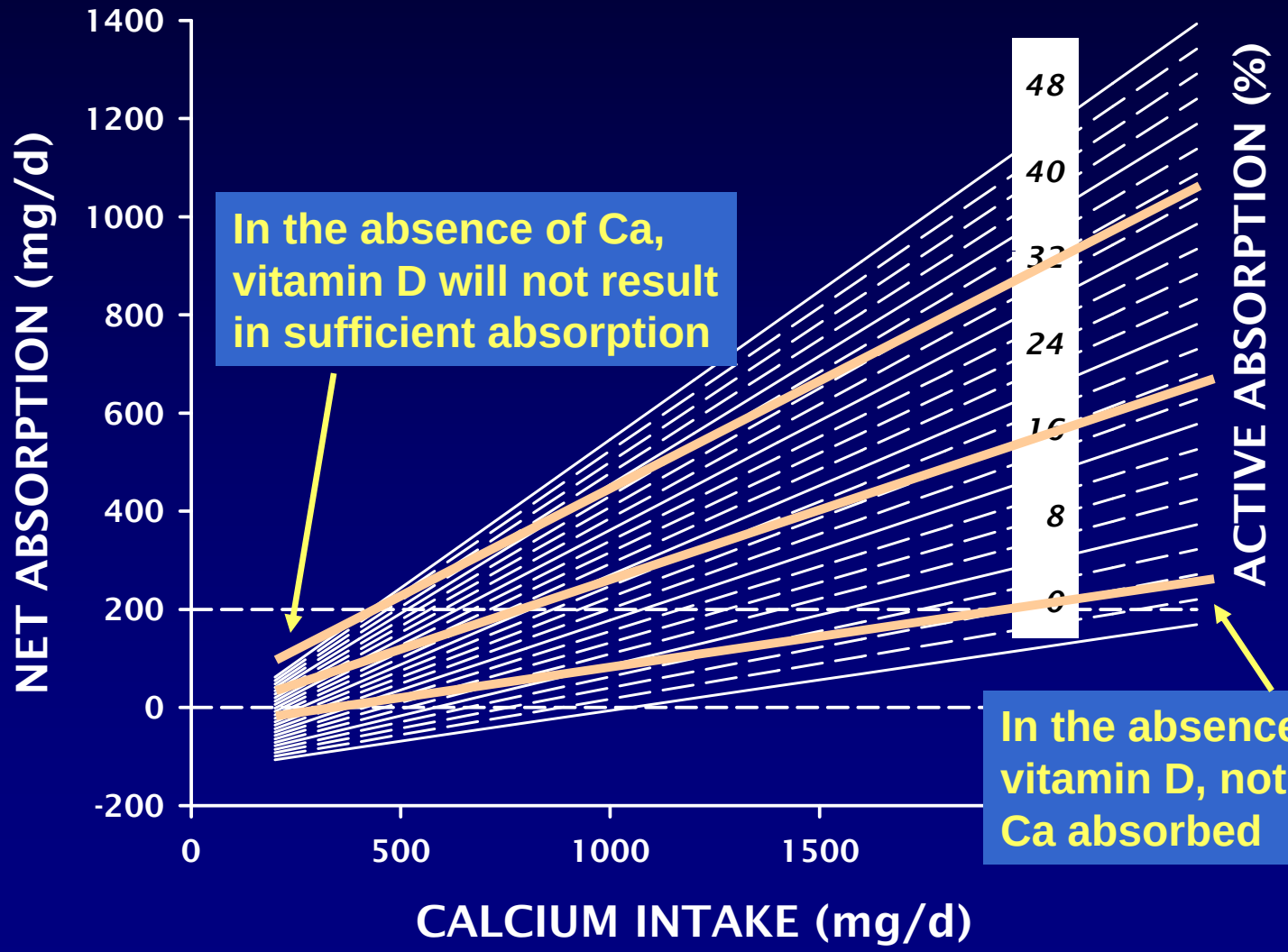
It is unethical to withdraw medications or polypharmacy regimens in RCTs of nutrients

Percent of Subjects Receiving Drugs in the Vitamin E Group

Drugs	HOPE	HOPE 2
β-Blockers	39.9	40.2
Antiplatelet agents	77.0	76.7
Lipid lowering agents	28.4	28.3
Diuretics	15.7	15.2
Calcium channel blockers	47.2	46.7

Lonn et al. *JAMA* 2005

Co-dependence of Calcium and Vitamin D for Calcium Bioavailability



Failure to Appreciate Nutrient Interactions Leads to Meta-analytic Tunnel Vision

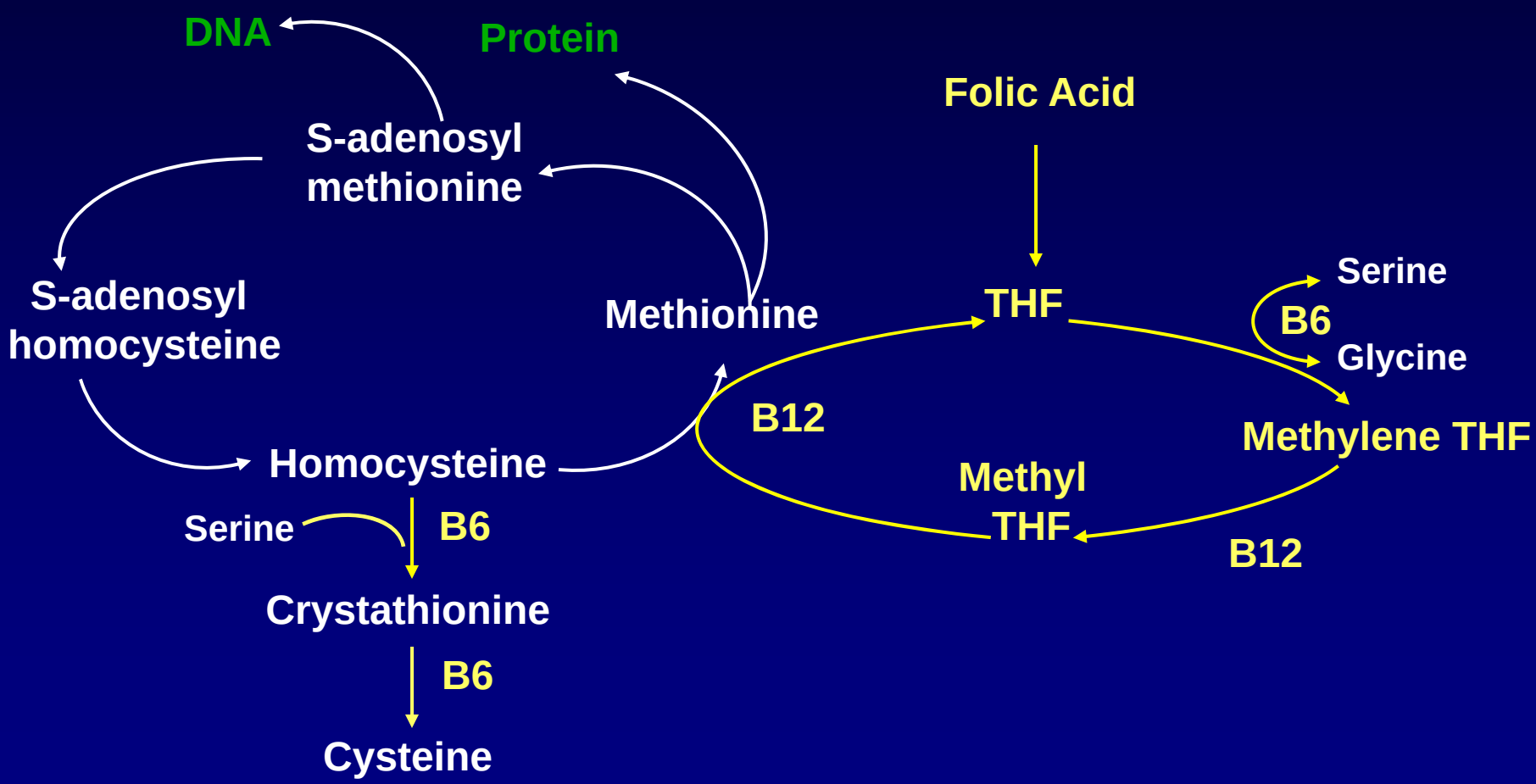
- **Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis (excluding studies using vitamin D)**

- **Meta-analysis of vitamin D supplementation for the prevention of postmenopausal osteoporosis (excluding studies using calcium)**

→ **Conclusion: Risk reduction for fractures by calcium or vitamin D are not significantly different from zero**

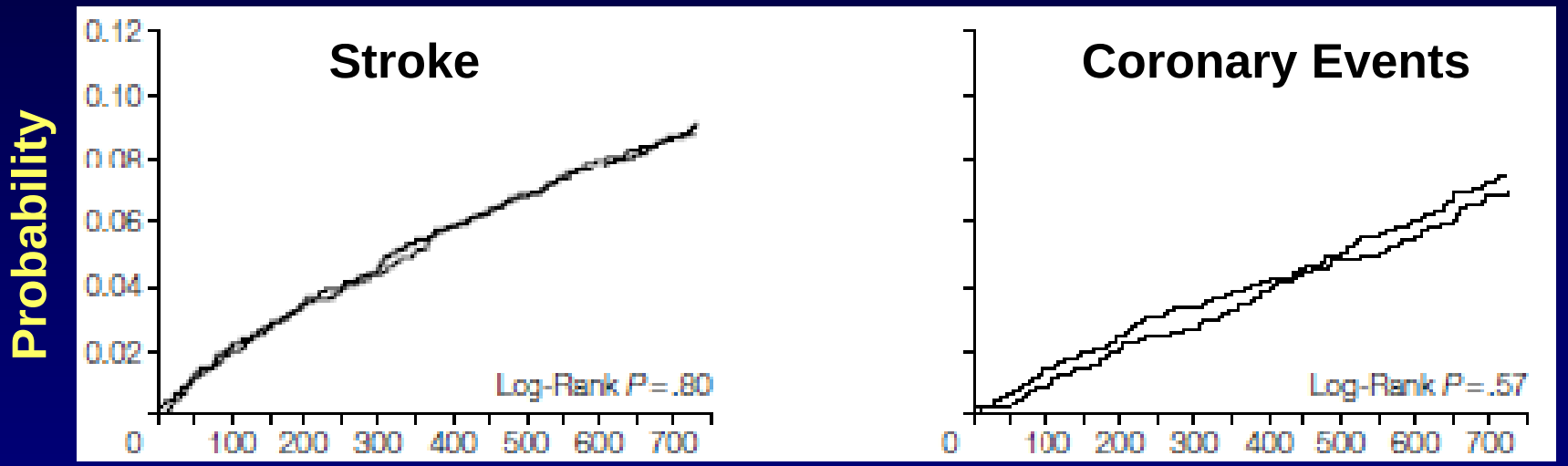
Shea et al. *Endocr Rev* 2002

Role of B Vitamins in Homocysteine Metabolism



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

Efficacy Analysis of *Vitamin Intervention for Stroke Prevention* Trial

Lack of efficacy in VISP due to:

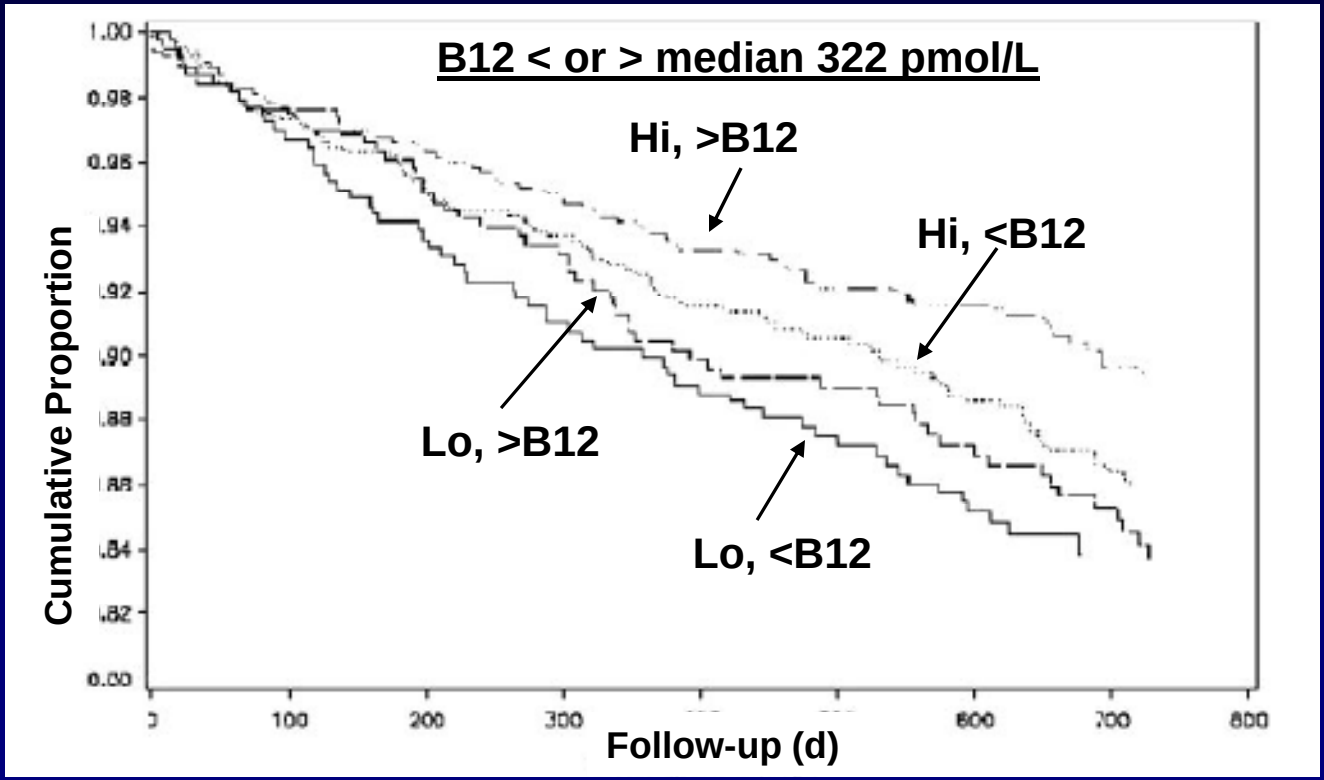
- **Folate fortification of grain products**
- **Supplementation with non-study vitamins**
- **Failure of patients with renal impairment to respond**
- **Inclusion of RDI for vitamin B12 in low-dose arm**
- **Treatment with parenteral B12 in patients with low B12**
- **Ineffective B12 dose in patients with malabsorption**

→ **So conducted an efficacy analysis limited to patients most likely to benefit from treatment**

Spence et al. *Stroke* 2005

Co-dependence of Folic Acid and Vitamin B12 for Reduction of Stroke and Coronary Events

Vitamin Intervention for Stroke Prevention



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

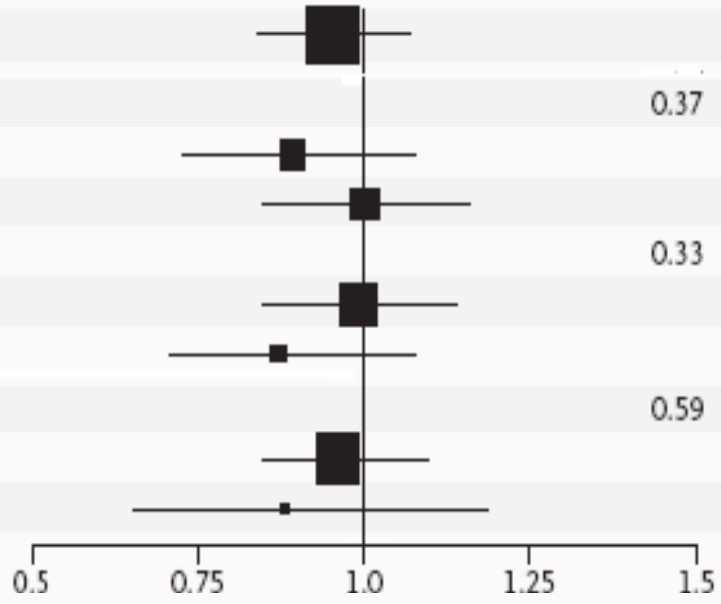
Spence et al. Stroke 2005

Effect of B Vitamins on Cardiovascular Death, MI or Stroke

Heart Outcomes Prevention Evaluation 2

Effect of Treatment in Subgroups

Group	No. of Patients	Incidence of Primary Outcome in Placebo Group %	P Value for Interaction
Overall	5522	19.8	
Age			0.37
<69 yr	2664	16.2	
≥69 yr	2858	23.1	
Regions with folate fortification			0.33
Yes	3982	18.0	
No	1540	24.5	
History of coronary artery disease			0.59
Yes	4600	19.9	
No	922	19.4	



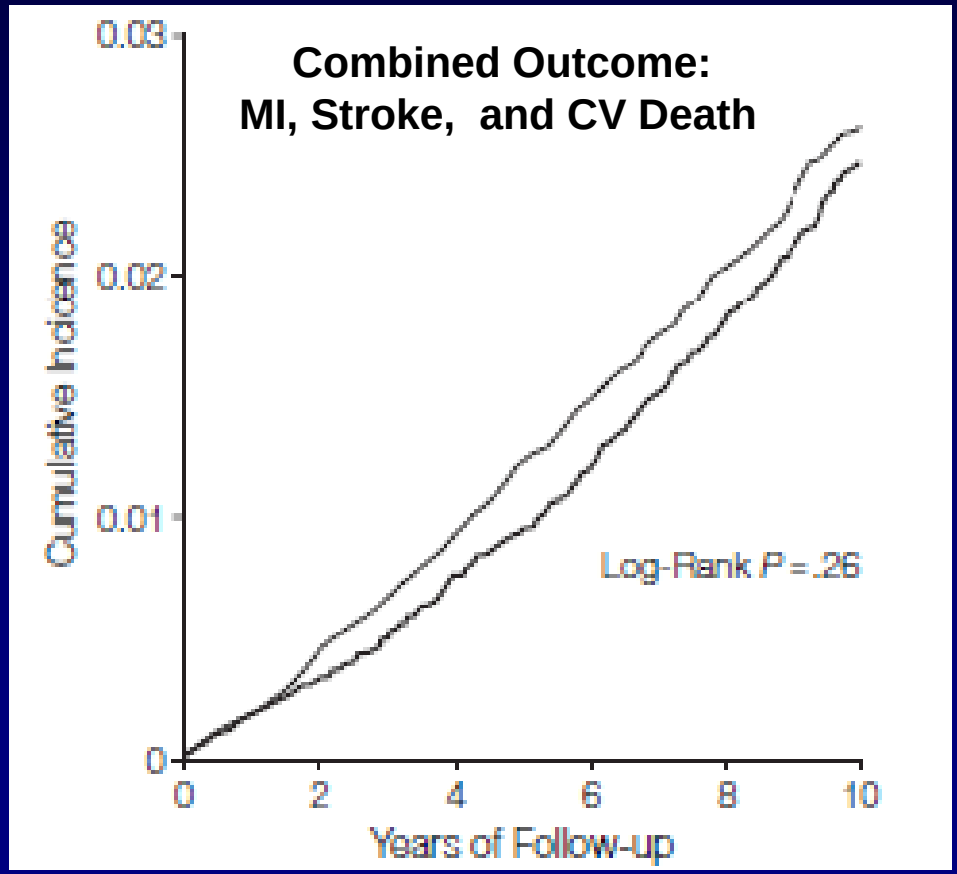
Lonn et al. *N Engl J Med* 2006

Vitamin E Supplements Do Not Reduce Risk of Cardiovascular Events in Women

Women's Health Study

Vitamin E, 600 IU qod for 10 y

RCT
n=39,876
≥45 y



Lee et al. *JAMA* 2005

Vitamin E Supplements Do Reduce Risk of Cardiovascular Disease and Stroke in Women in Subgroup Analyses

Vitamin E, 600 IU qod for 10 y

Women's Health Study **(n=39,876; ≥45 y)**

- **24% ↓ cardiovascular disease deaths**
- **26% ↓ major cardiovascular events in ≥65 y**

  Lee et al. *JAMA* 2005
- **21% ↓ venous thromboembolism**

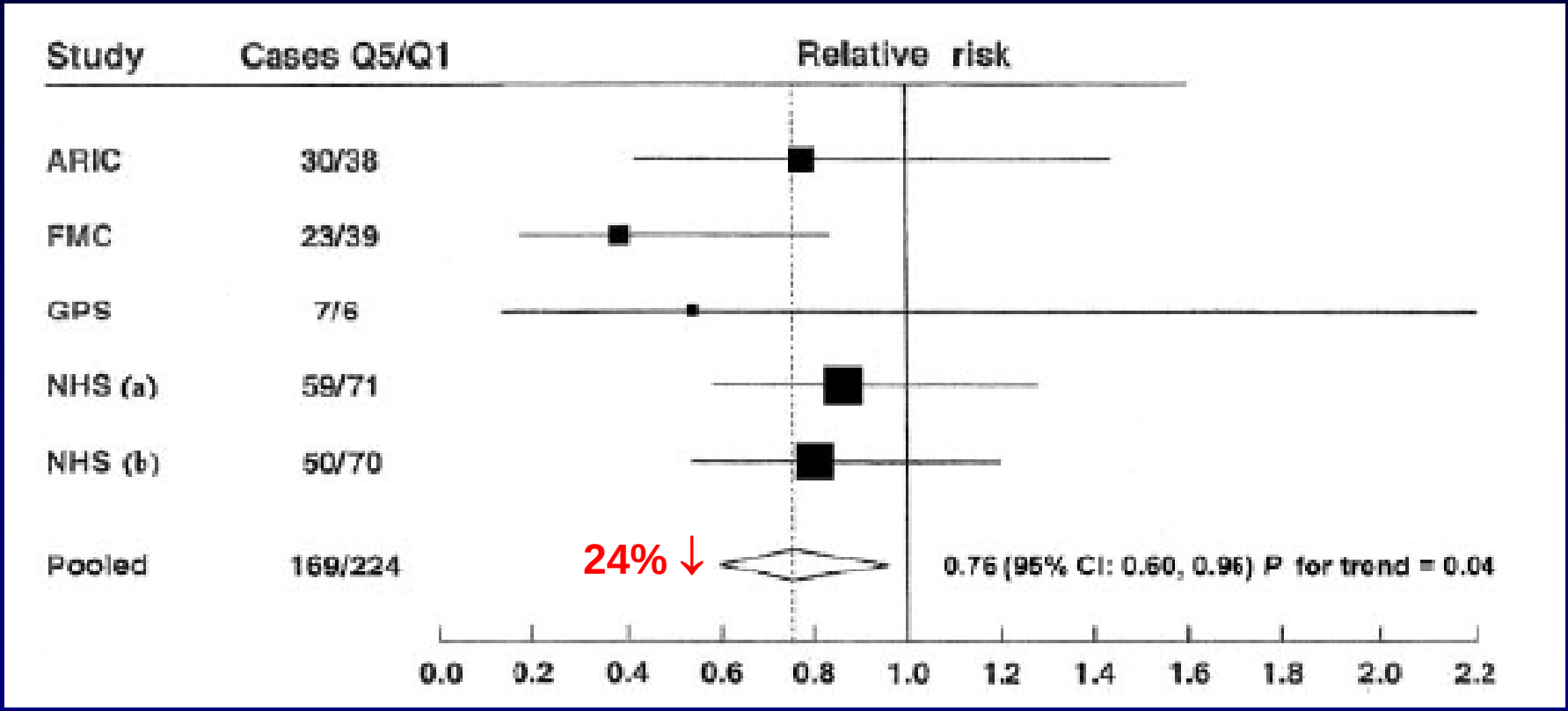
  Glynn et al. *Circulation* 2007

Women's Antioxidant Cardiovascular Study **(n=8171; ≥40 y)**

- **23% ↓ heart attack, stroke, cardiovascular deaths**

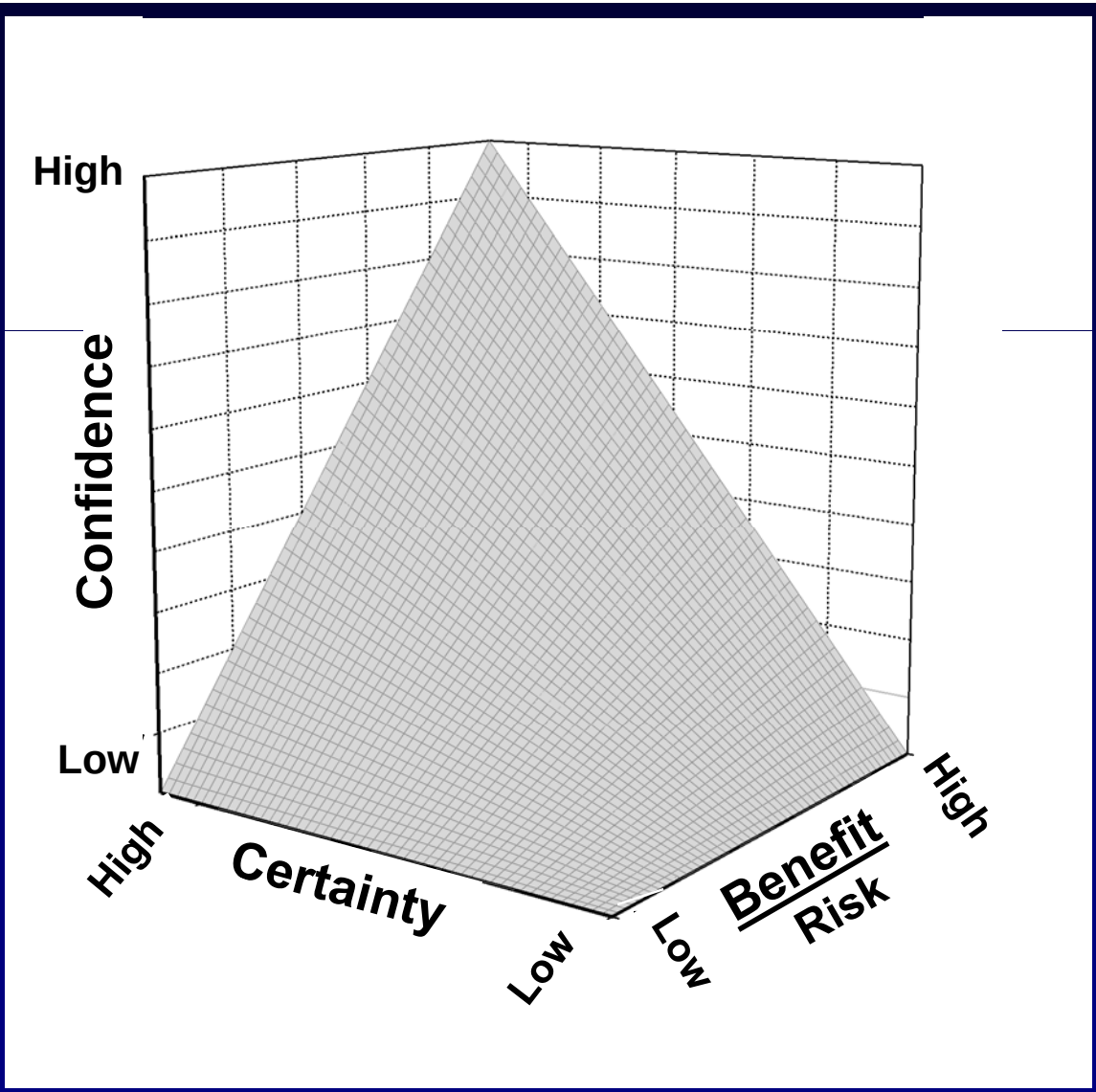
  Cook et al. *Arch Intern* Med 2007

Vitamin E Reduces the Risk of Coronary Heart Disease in Women: Pooled Cohort Analysis



Knekt et al. *Am J Clin Nutr* 2004

Relationship Between Certainty of Evidence, Benefit:Risk, and Confidence to Act



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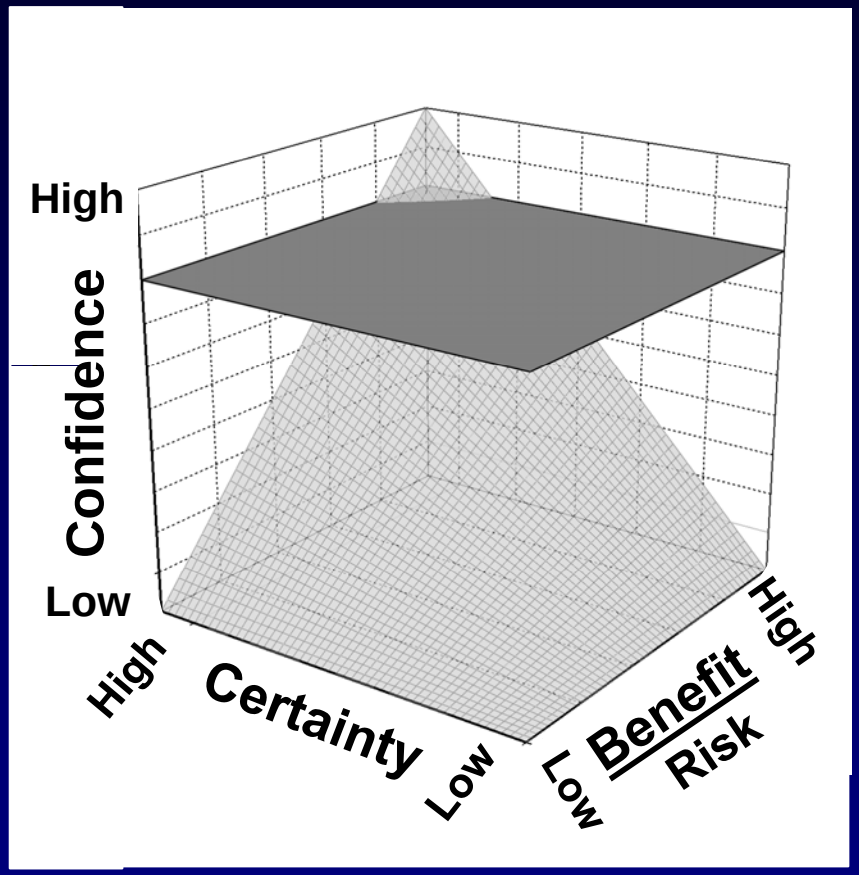
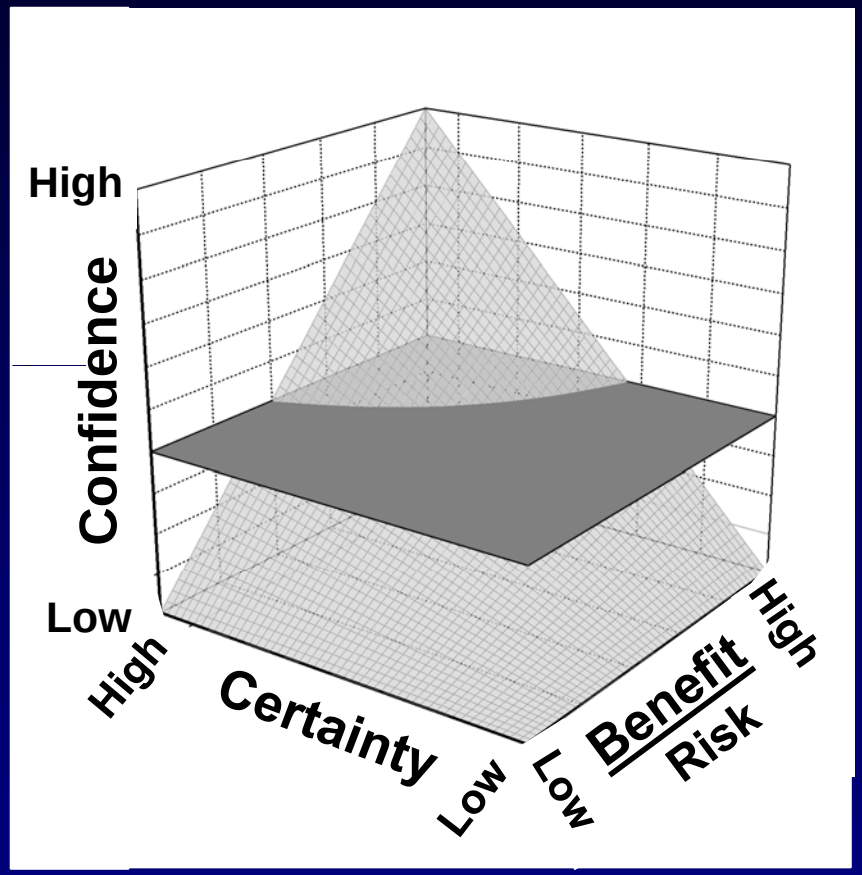




Dietary Reference Intakes are Based on Scientific Judgment

The scientific data used to develop DRIs have come from observational and experimental studies… After careful review and analysis of the evidence, including examination of the extent of congruence of findings, scientific judgment was used to determine the basis for establishing the values.

Food and Nutrition Board, IOM 2000

Evidence Base for DHHS/USDA Dietary Guidelines for Americans 2005

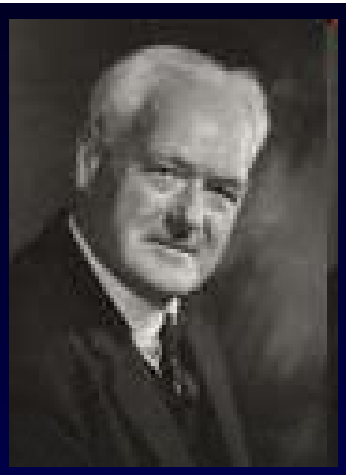
The primary types of studies used were observational studies and clinical trials. Specific types of observational studies were cross-sectional studies, case-control studies, and cohort studies.

Major sources of evidence were the *Dietary Reference Intake* reports prepared by expert committees convened by the Institute of Medicine.

www.health.gov/dietaryguidelines/dga2005

Strengths of Observational Studies

- More likely to include broad representation of the population at risk
- Closer relationship to “real world” use of foods and supplements
- When the relative risk is large in size (RR <0.70)
- When the required duration of exposure is long
- Sometimes only feasible or ethical approach



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