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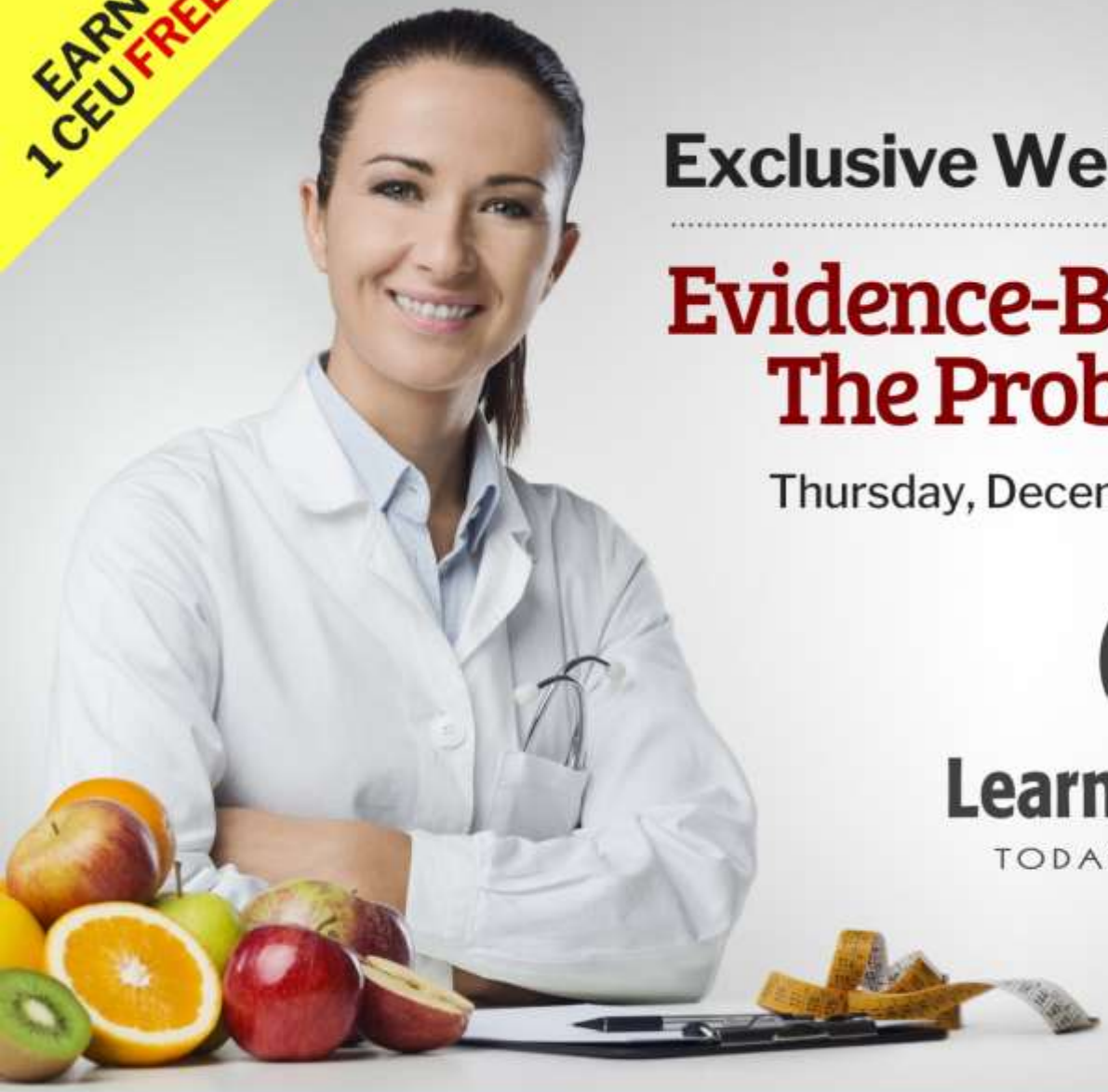


Exclusive Webinar Presentation

Evidence-Based Nutrition: The Problem of Proof

Thursday, December 1, from 2-3 PM EST

Learning Library
TODAY'S DIETITIAN

Presented by Jeffrey B. Blumberg, PhD, FASN, FACN

Jeffrey B. Blumberg, PhD, FASN, FACN

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.

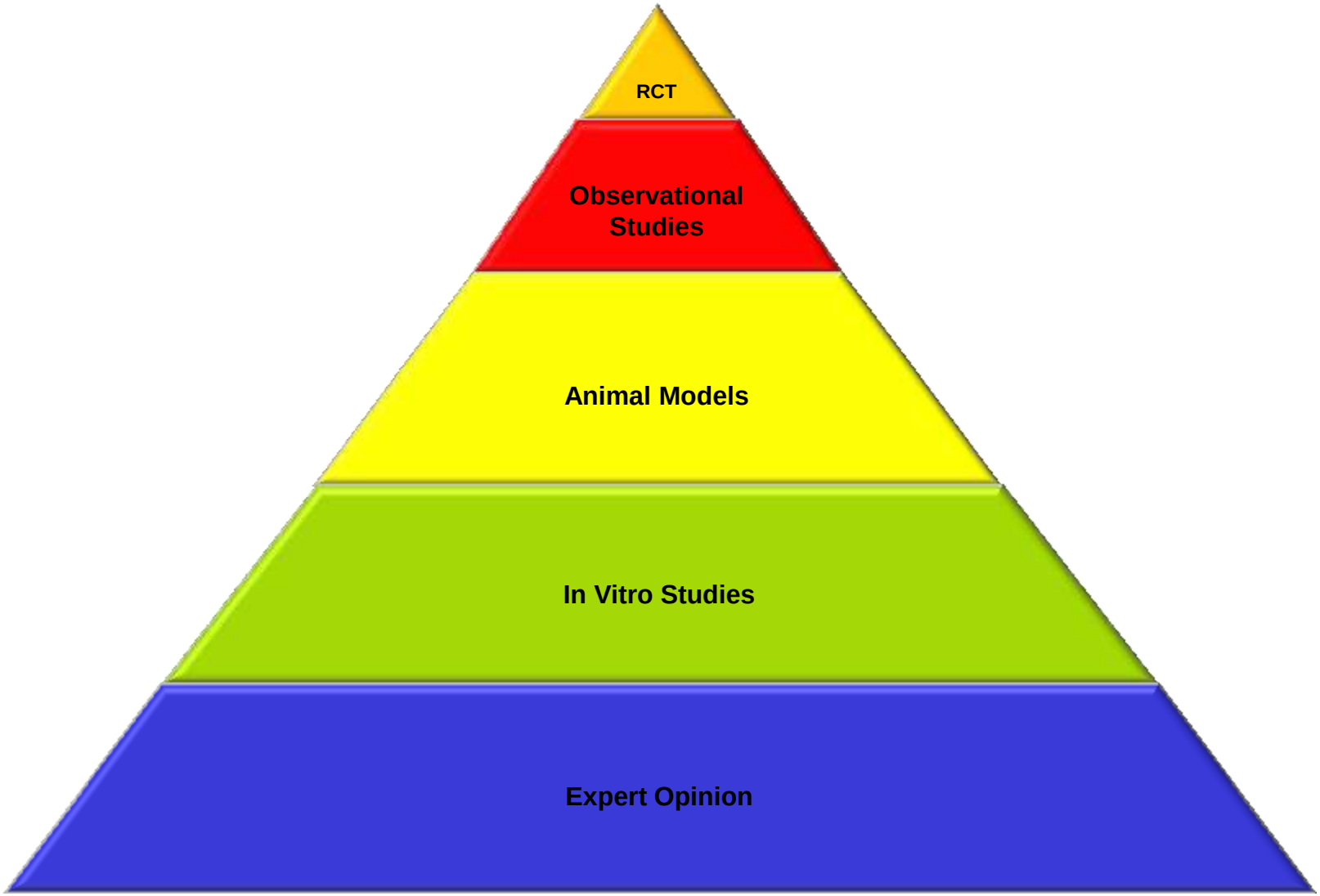
- Johann Wolfgang von Goethe
(1749-1832)

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



RCTs, 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

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 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

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

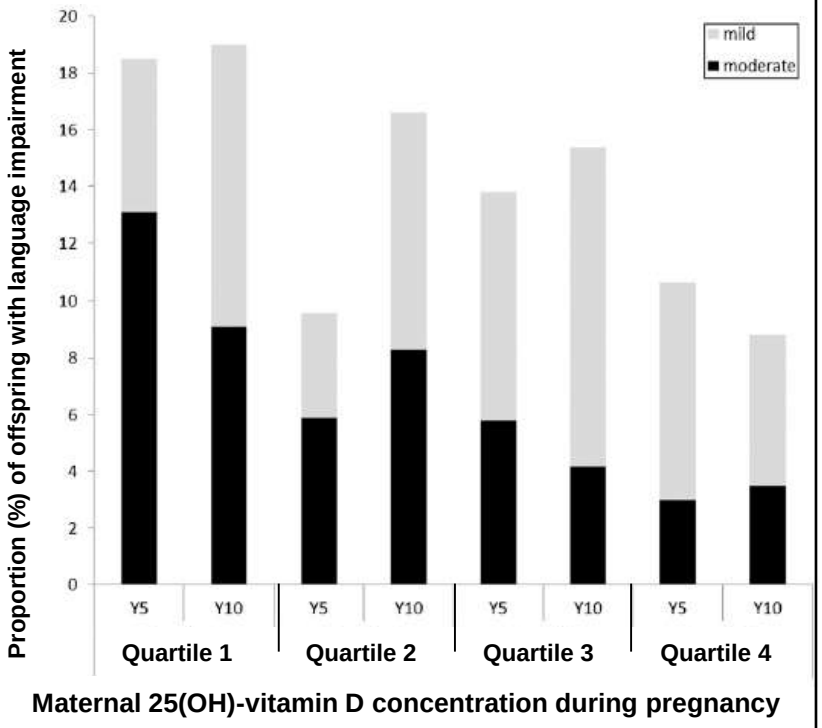
- **Drugs:** drug-free state (placebo)

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

Induce nutrient insufficiency
or deficiency ➡

Vitamin D Insufficiency During Pregnancy

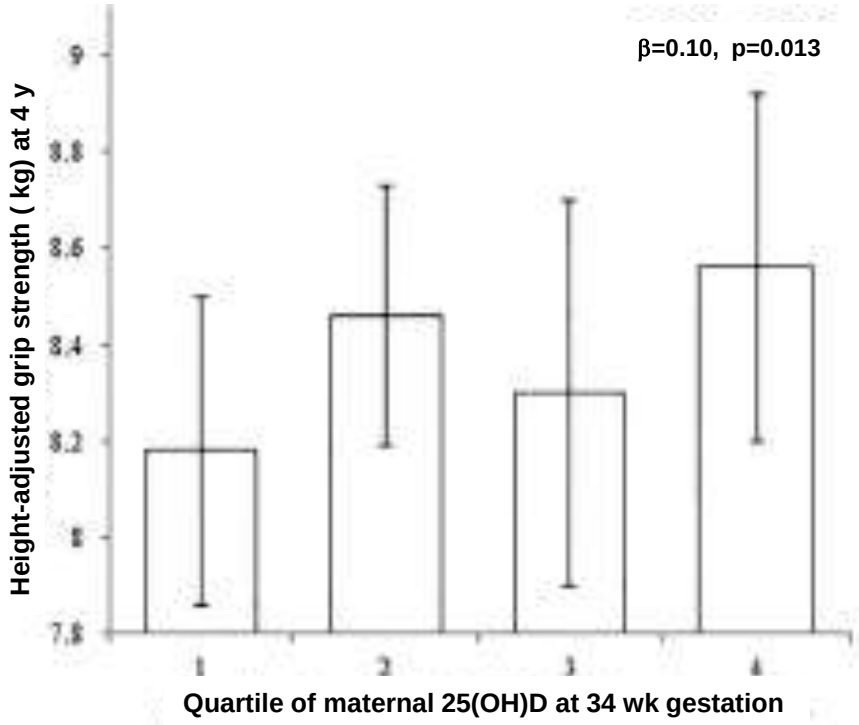
Impaired Language Development



Prospective cohort, Australia
n=743 mother-child pairs

Whitehouse et al. *Pediatrics* 2012

Lower Muscle Strength



Prospective cohort, UK
n=678 mother-child pairs

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

Impact of Vitamin D Insufficiency During Pregnancy Requires RCTs

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- W*trics* 2012

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

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

Healthy Aging as Outcome Criteria
SU.VI.MAX 2

RCT
- n, 3996
- age, 65.3 ± 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[a]	Definition	Corresponding Rowe and Kahn Criterion[b]
Good physical functioning	SPPB ≥11 of 12	Maintenance of high physical and cognitive function
Good cognitive functioning	MMSE ≥27, RI-48 ≥19 of 48, and DK-TMT ≥5.5	Maintenance of high physical and cognitive function
No limitations in IADL	<1 limitation	Avoiding disease and disability
No depressive symptoms	CES-D <16 of 60	
No health-related limitations in social life	SF-36 responses: 1–2 for item 6 and 3–5 for item 10	Sustained engagement in social and productive activities
Good overall self-perceived health	SF-36 responses: 1–3 for item 1	
No function-limiting pain	SF-36 responses: 1–3 for item 7 and 1–2 for item 8	Avoiding disease and disability
No incident major chronic disease	No incident diabetes, cancer, or cardiovascular disease during follow-up	Avoiding disease and disability

Assmann et al. *Am J Epidemiol* 2015

Antioxidant Supplementation as a Predictor of Healthy Aging

Stratification Variable	Total n	RR	95% CI	P
All participants	3996	1.07	0.99-1.16	
Men	2027	1.16	1.04-1.29	0.03
Women	1939	0.98	0.86-1.11	
Vitamin C status, <42 μmol/L	727	1.28	1.06-1.56	0.06
Zinc status, <11.9 μmol/L	953	1.26	1.06-1.49	0.05
F&V (<400 g/d)	1757	1.17	1.02-1.32	0.22

Assmann et al. *Am J Epidemiol* 2015

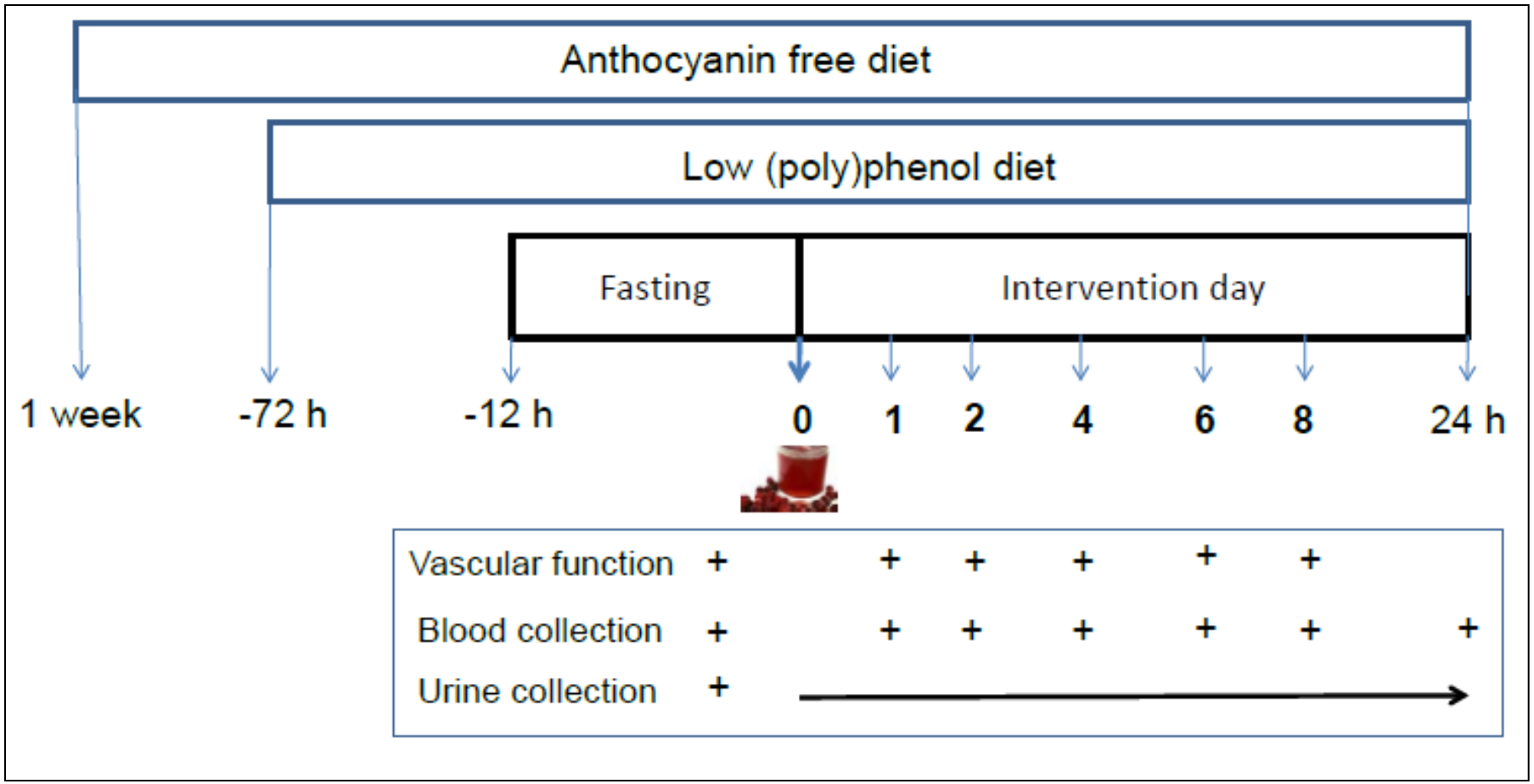
Is It Unethical or Infeasible to Restrict Intake of Foods Rich in Non-essential Bioactives?

United States

China

Mexico

Study Design for Acute Bioactive Intervention



Rodriguez-Mateos (University of Düsseldorf) 2015

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
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For example:

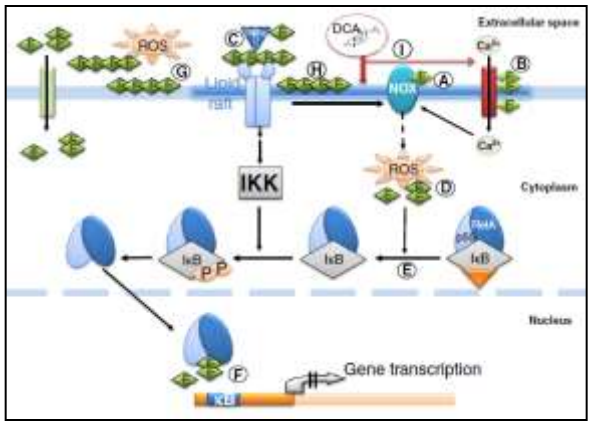
- Statins inhibit HMG-CoA reductase

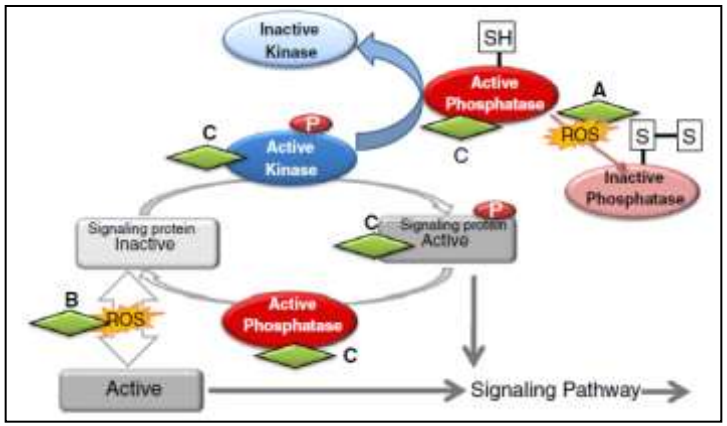
- Zinc is a cofactor for >100 enzymes and plays a role in protein structure and gene expression

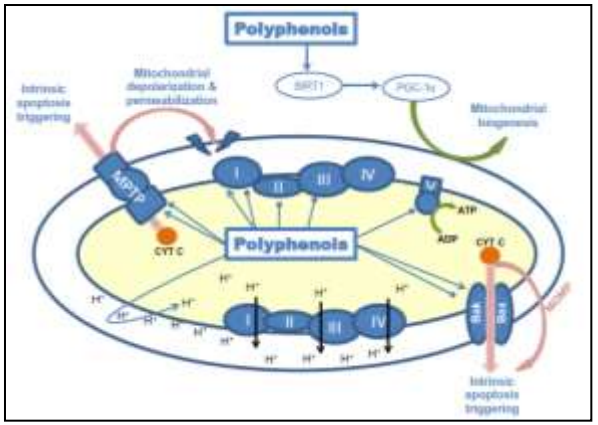
(Poly)phenol Mechanisms of Action

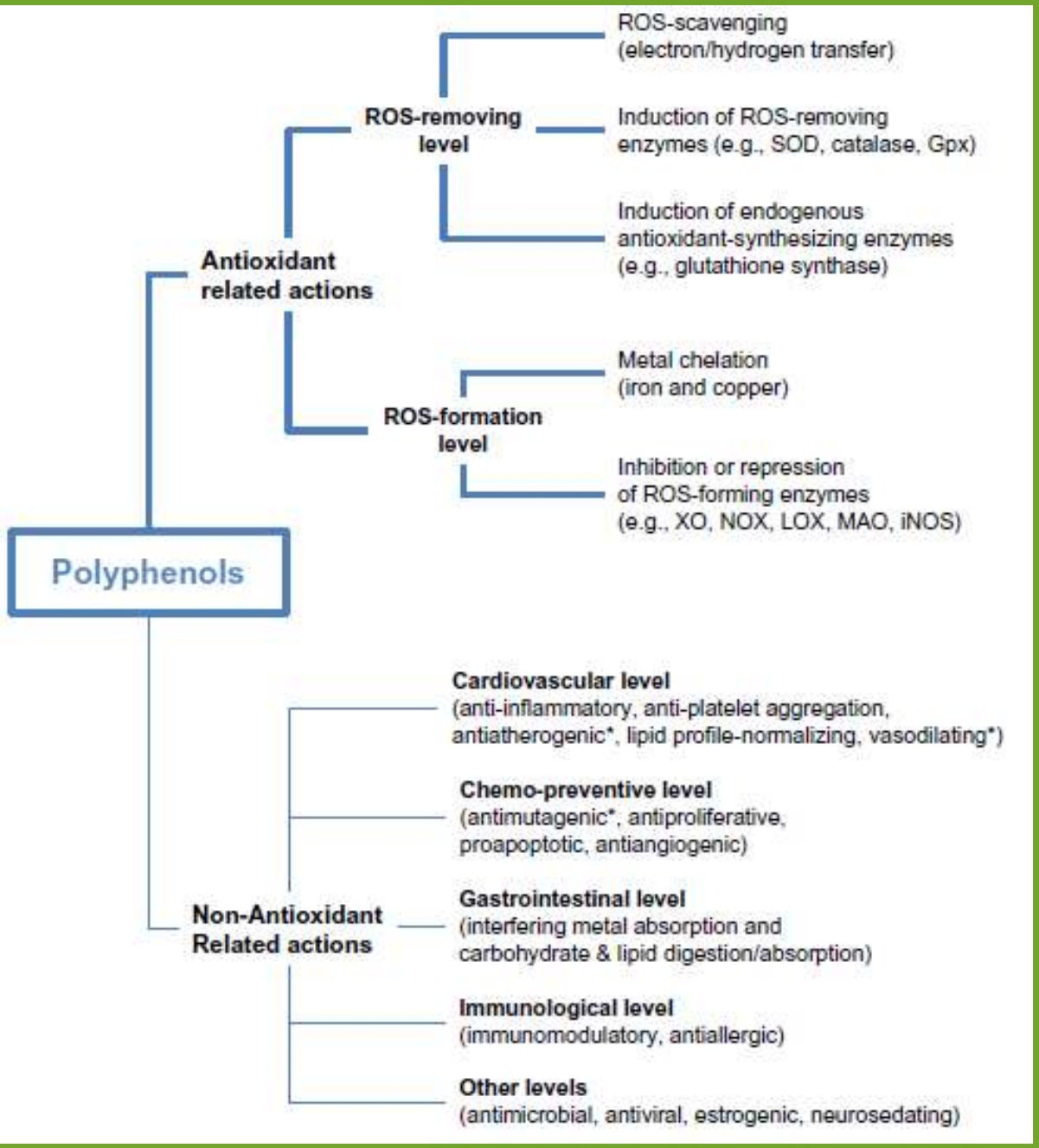
Modulation of:

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



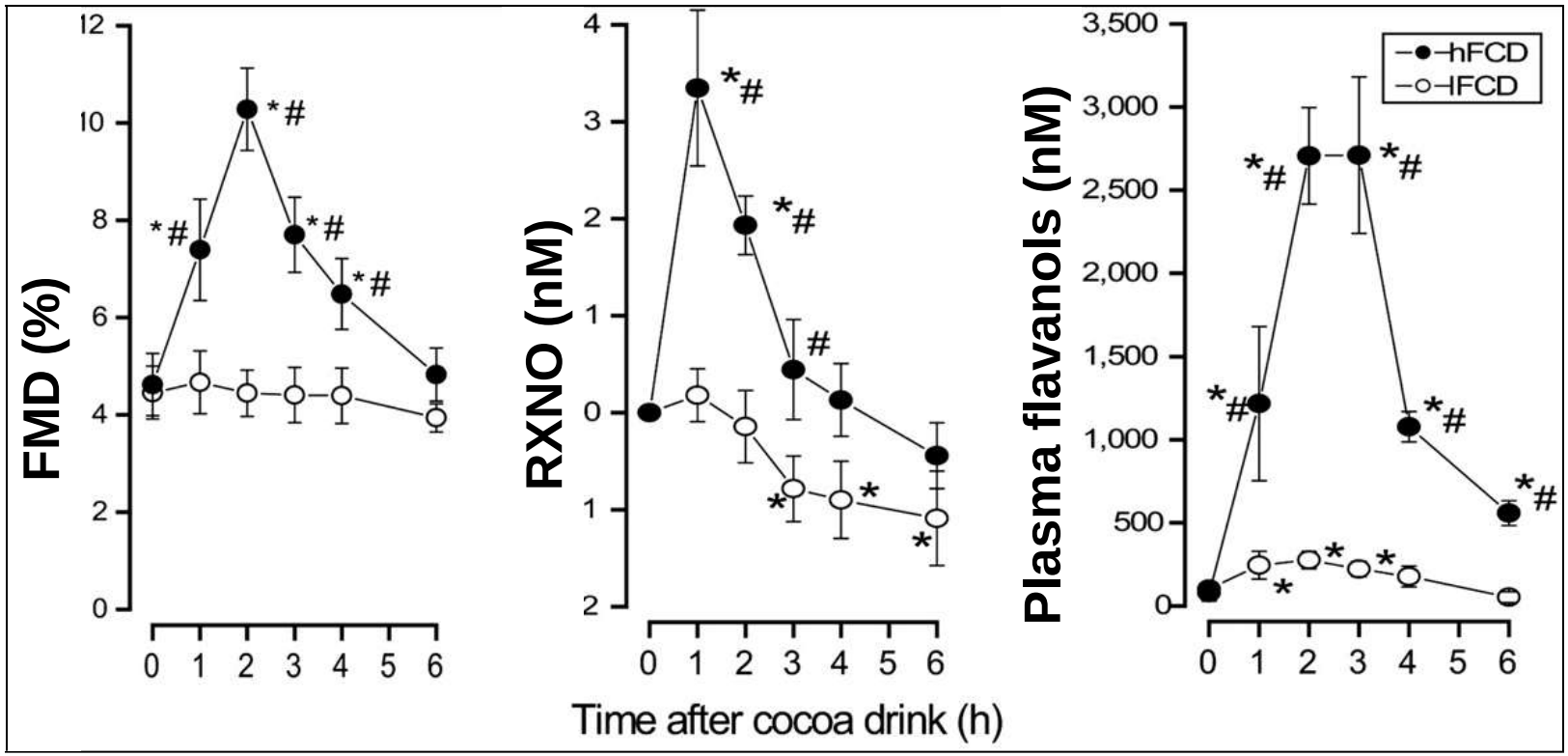






Sandoval-Acuna et al. *Arch Biochem Biophys* 2014

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

Schroeter et al. *PNAS* 2006

efsa: European Food Safety Authority

Scientific Opinion on the substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

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.

Agostoni et al. *EFSA J* 2012

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

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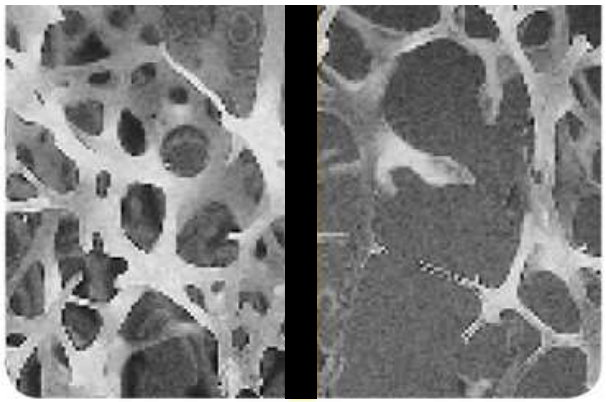
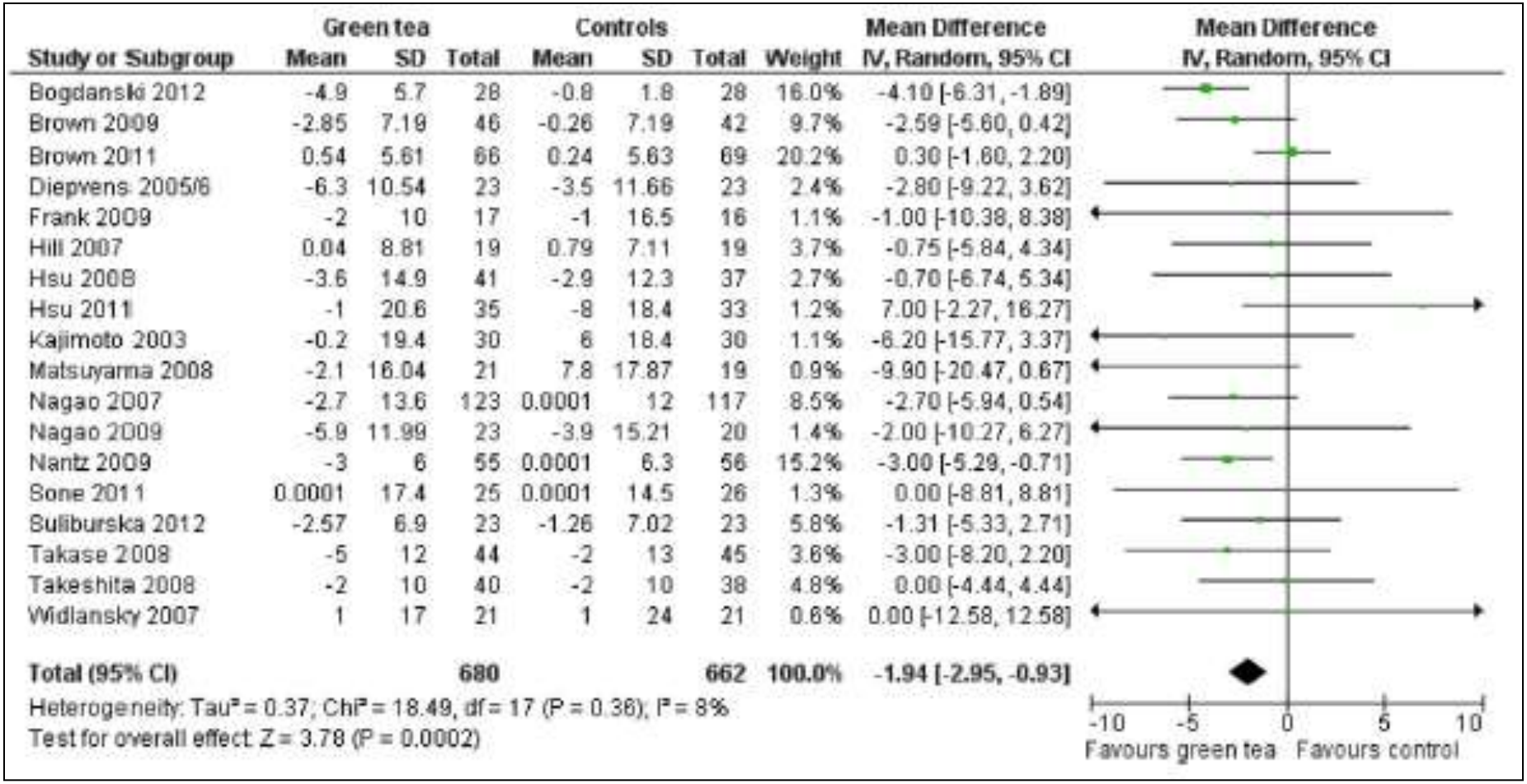
For example:

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



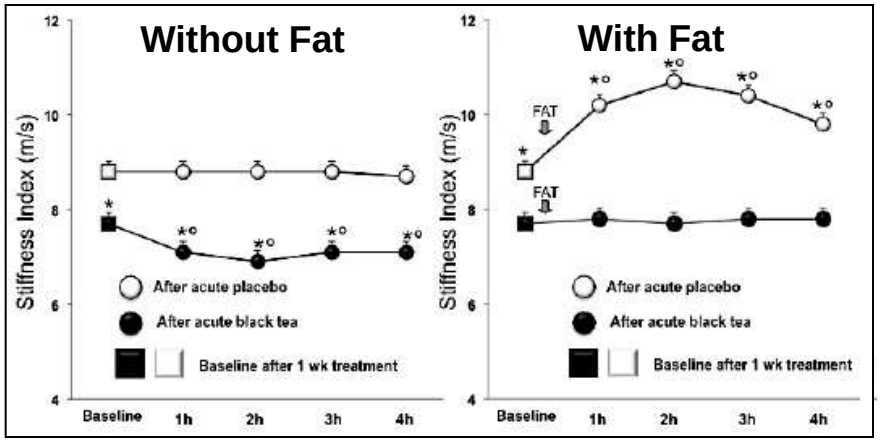
Green Tea Flavanols Lower Systolic Blood Pressure

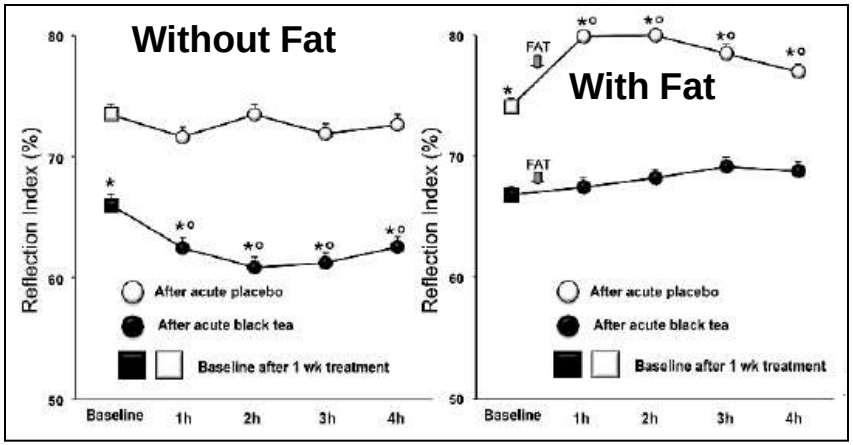


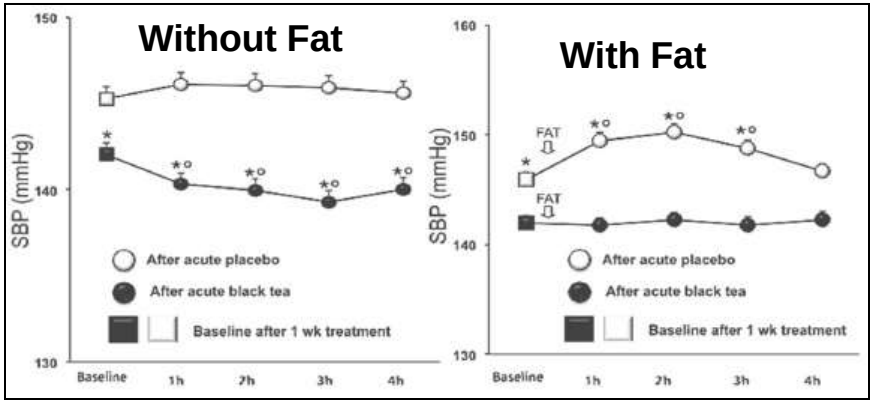
- RCTs, 20
- n, 1536

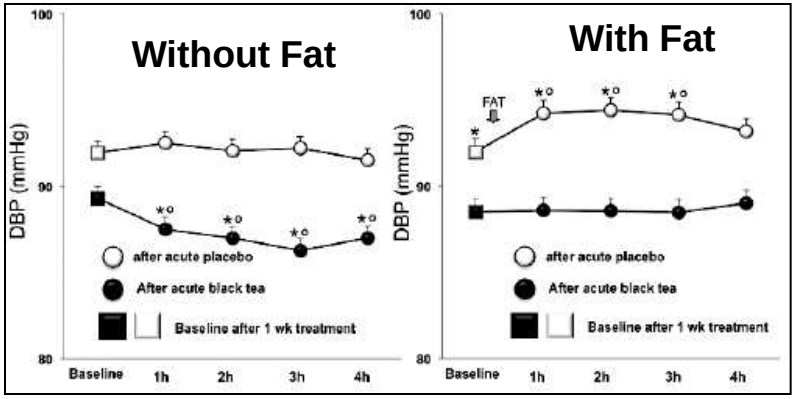
Onakpoya et al. *Nutr Metabol Cardiovasc Dis* 2014

Black Tea Lowers Blood Pressure and Wave Reflections after a Fat Load Challenge









RCT XO

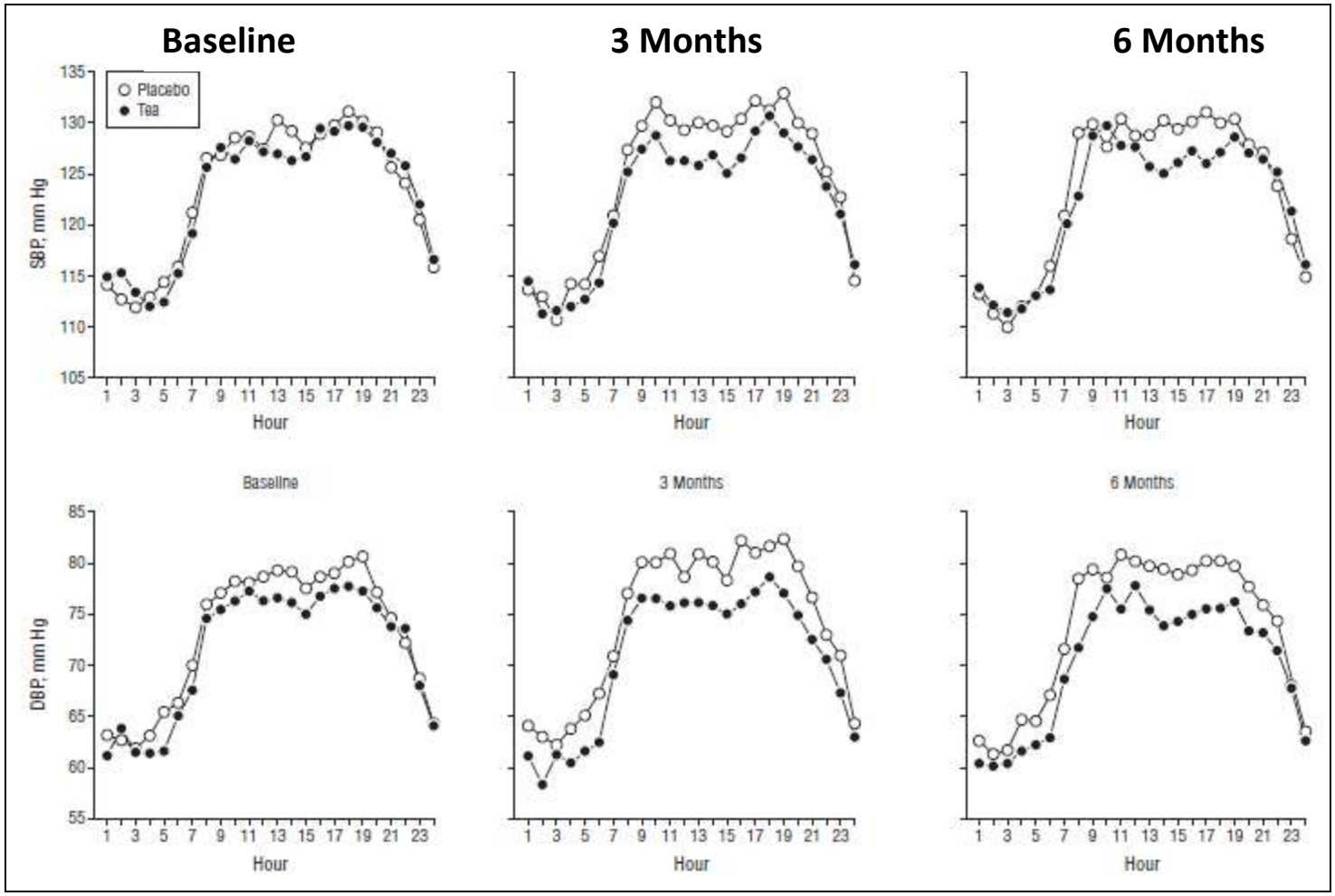
- n, 19 HT
- F/U, 8 d
- dose, 158 mg flavonoids

Grassi et al. *Nutrients* 2015

Chronic Black Tea Intake Reduces Blood Pressure

RCT

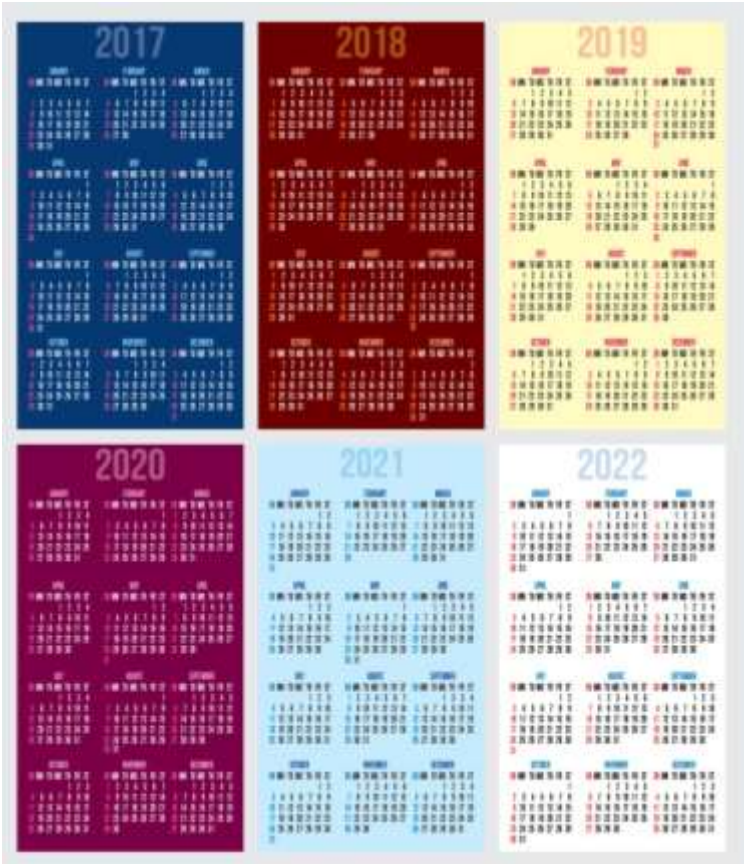
- n, 95
- age, 35-79 y
- dose,
  3 cups/d



Hodgson et al. *Arch Intern Med* 2012

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

	HR	95% CI	$P_{interaction}$
CVD	0.91	0.82-1.02	NS
Myocardial infarction	0.98	0.74-1.06	NS
Total stroke	0.91	0.78-1.06	NS
Ischemic stroke	0.85	0.71-1.01	NS
CVD death	0.91	0.71-1.16	NS

Prospective cohort

- n, 37,193
- age, ≥45 y
- F/U, 16.2 y

Rautiainen et al. *Am J Clin Nutr* 2015

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Myocardial infarction	0.98	0.74-1.06	NS
Total stroke	0.91	0.78-1.06	NS
Ischemic stroke	0.85	0.71-1.01	NS
CVD death	0.91	0.71-1.16	NS
CVD ≥70 y	**0.72**	**0.48-1.08**	**0.04**
CVD <3 serv F&V/d	**0.77**	**0.55-1.09**	**0.01**

Prospective cohort
- n, 37,193
- age, ≥45 y
- F/U, 16.2 y

Rautiainen et al. *Am J Clin Nutr* 2015

Effect of Multivitamins on Cardiovascular Disease in Women

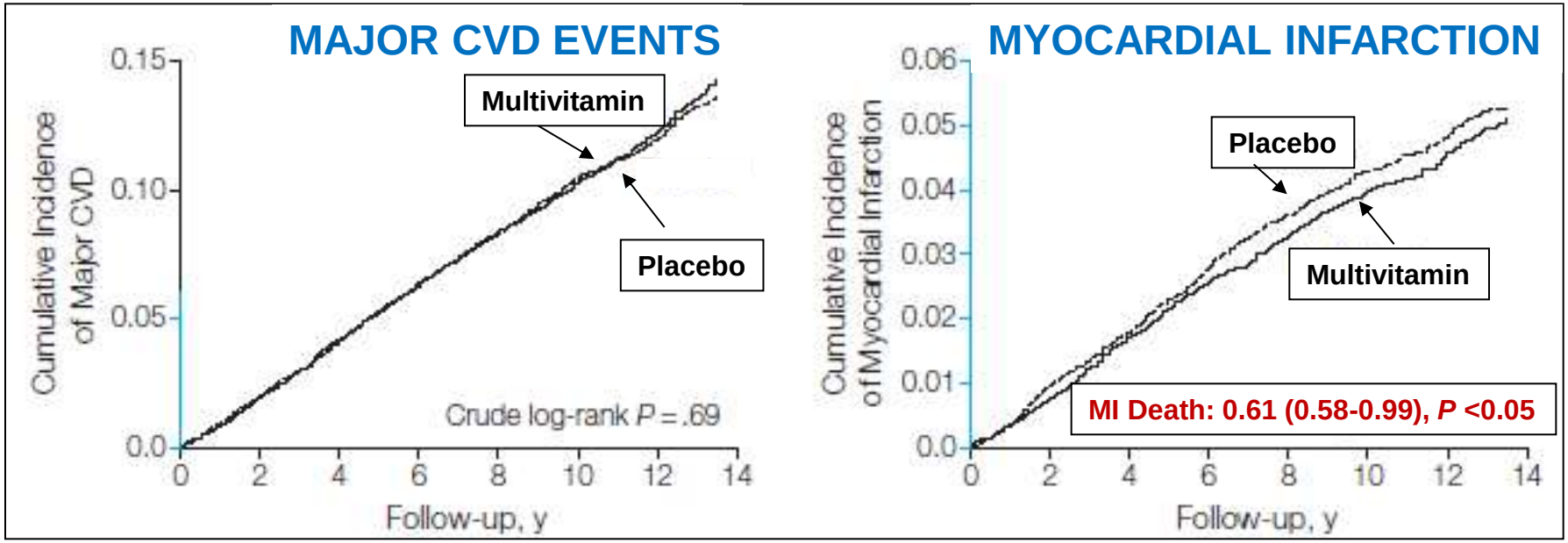
Study	N	CVD	RR	F/U, y	Reference
PC	21,132	MI	0.73	10.2	Rautiainen et al. AJCN 2010
CC	928	MI	0.66	--	Holmquist et al. J Nutr 2003
PC	80,082	CHD	0.76	14	Rimm et al. JAMA 1998
PC	381,553	IHD	0.82	7.0	Watkins et al. Am J Epi 2000
PC	381,553	Stroke	0.81	7.0	Watkins et al. Am J Epi 2000

PC, prospective cohort study
CC, case control study

Effect of Multivitamins on Cardiovascular Disease in Men

Study	N	CVD	RR	F/U, y	Ref.
CC	2053	MI	0.79	--	Holmquist et al. J Nutr 2003
RCT	14,641	MI death	0.61	13.3	Sesso et al. JAMA 2012
PC	714,527	IHD	0.80	7.0	Watkins et al. Am J Epi 2000
Cohort (M&F)	77,719	CVD death	0.84	10.0	Pocobelli et al. Am J Epi 2009

Multivitamins Do Not Reduce the Risk of Cardiovascular Disease in Men: *Physicians' Health Study II*



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*

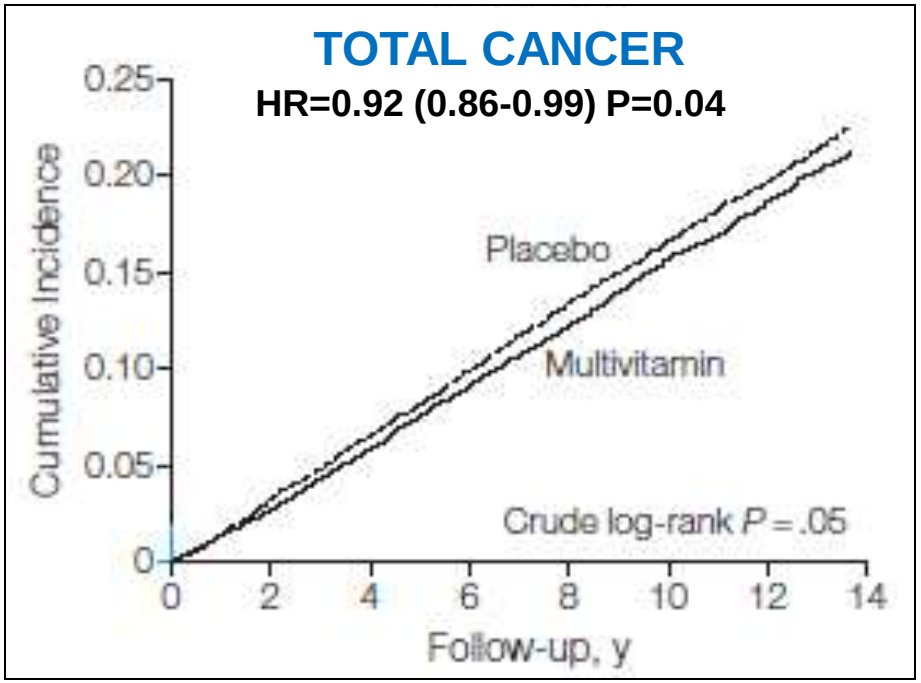
Duration of Multivitamin Use					
	No use	**<10 y**	**10 – 20 y**	**≥20 y**	**P_{trend}**
Cases	1293	211	67	18	
HR (95% CI)	1.00 --	0.94 (0.81-1.09)	0.91 (0.71-1.17)	0.56 (0.35-0.90)	0.05

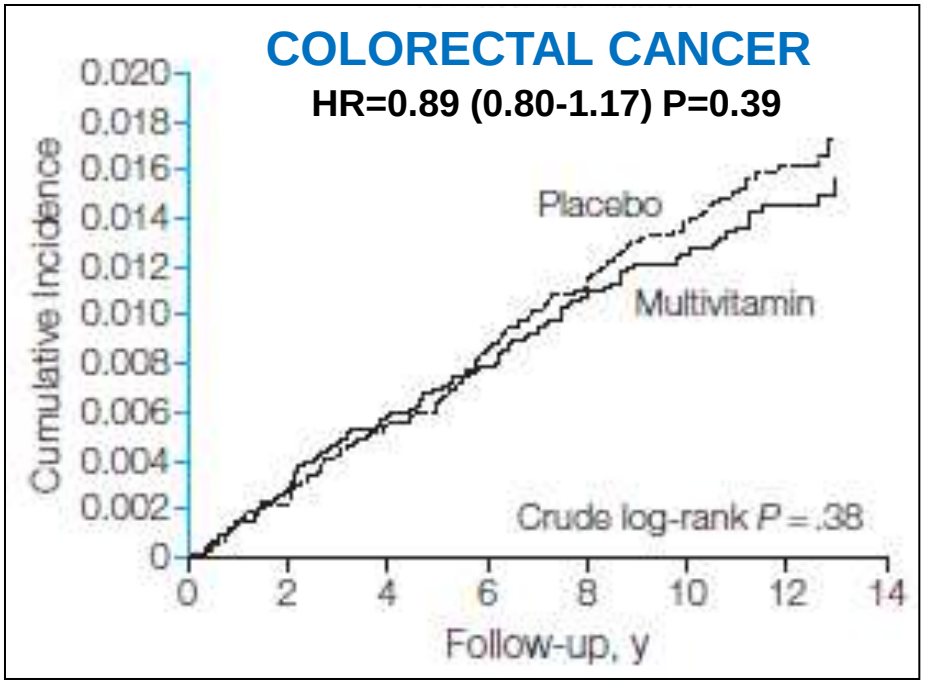
Cardiac revascularization:
HR: 0.86 (0.76-0.98)

Prospective cohort
- n, 18,530
- age, ≥40 y

Rautiainen et al. *J Nutr* 2016

Multivitamins Reduce the Risk of Total Cancer
Physicians' Health Study II





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.

Bach and Lewis. *JAMA* 2012

Is It Too Soon to Tell Men That Vitamins Prevent Cancer?

…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.

Bach and Lewis. *JAMA* 2012

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.

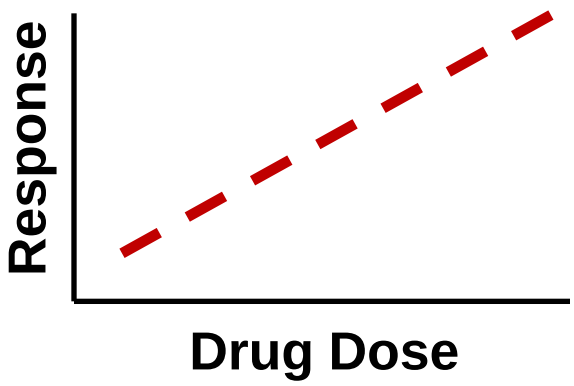
Thus, it may be inappropriate to recommend that men take multivitamins to prevent cancer.

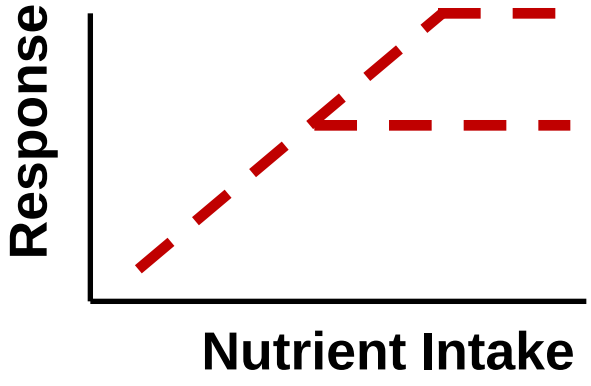
Bach and Lewis. *JAMA* 2012

RCTs for Drugs vs. Nutrients:
Dose-Response Characteristics

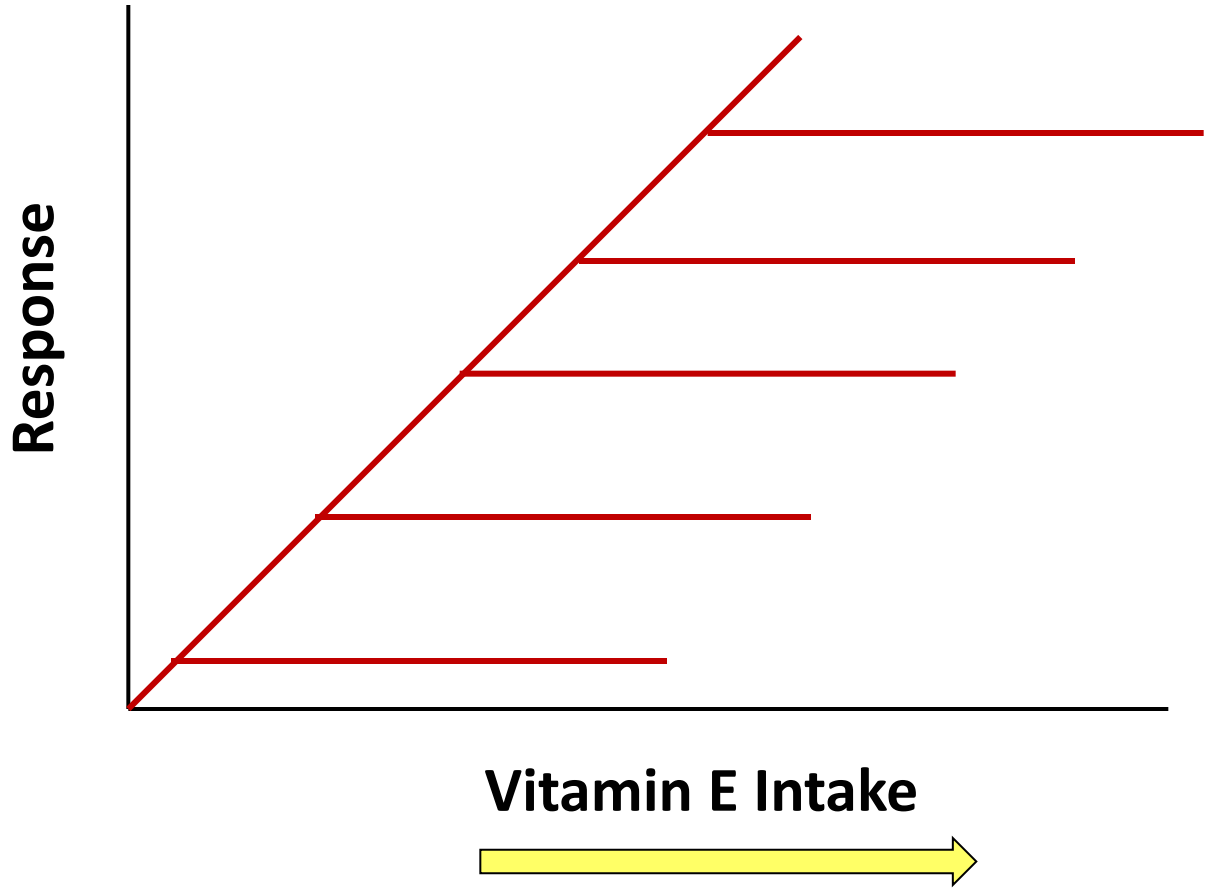
- **Drugs:** usually monotonic

- **Nutrients:** usually exhibit a threshold and are often under homeostatic control

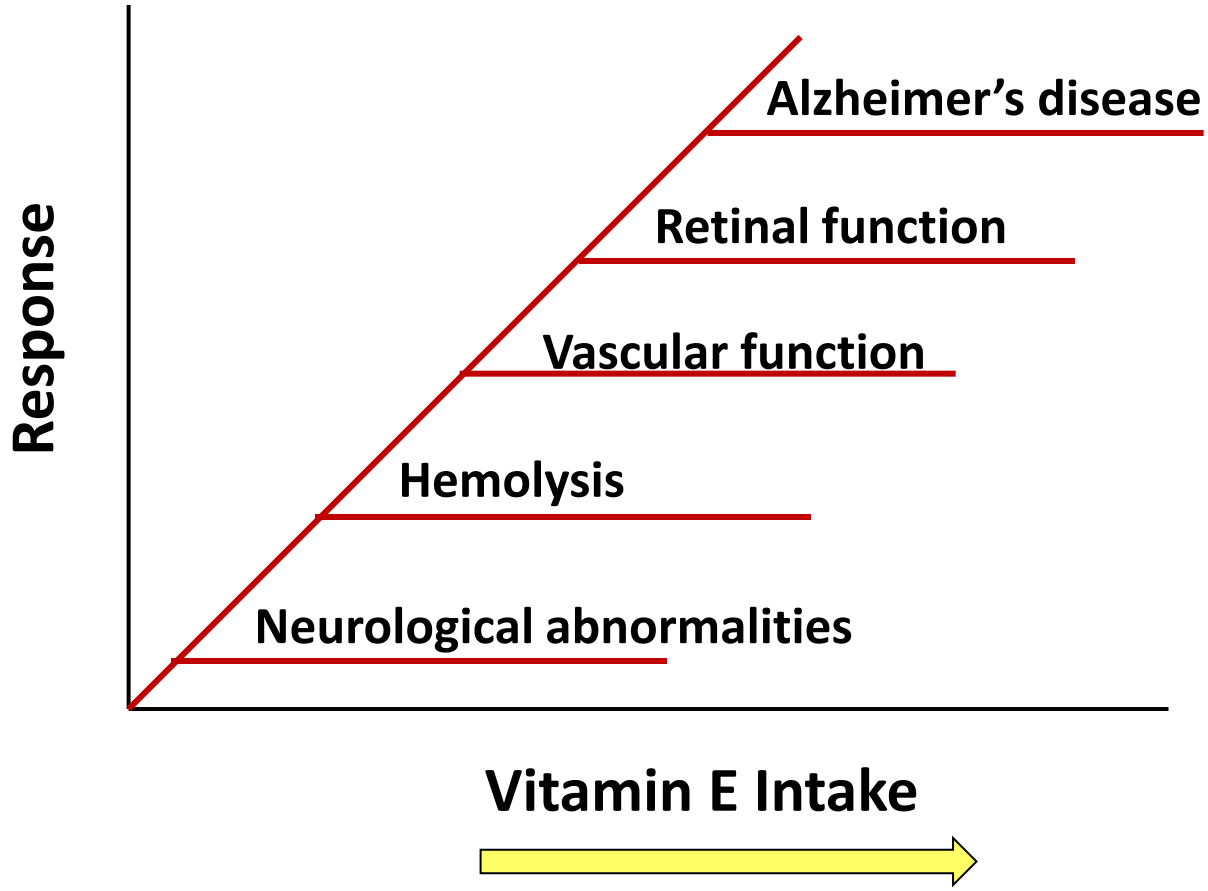




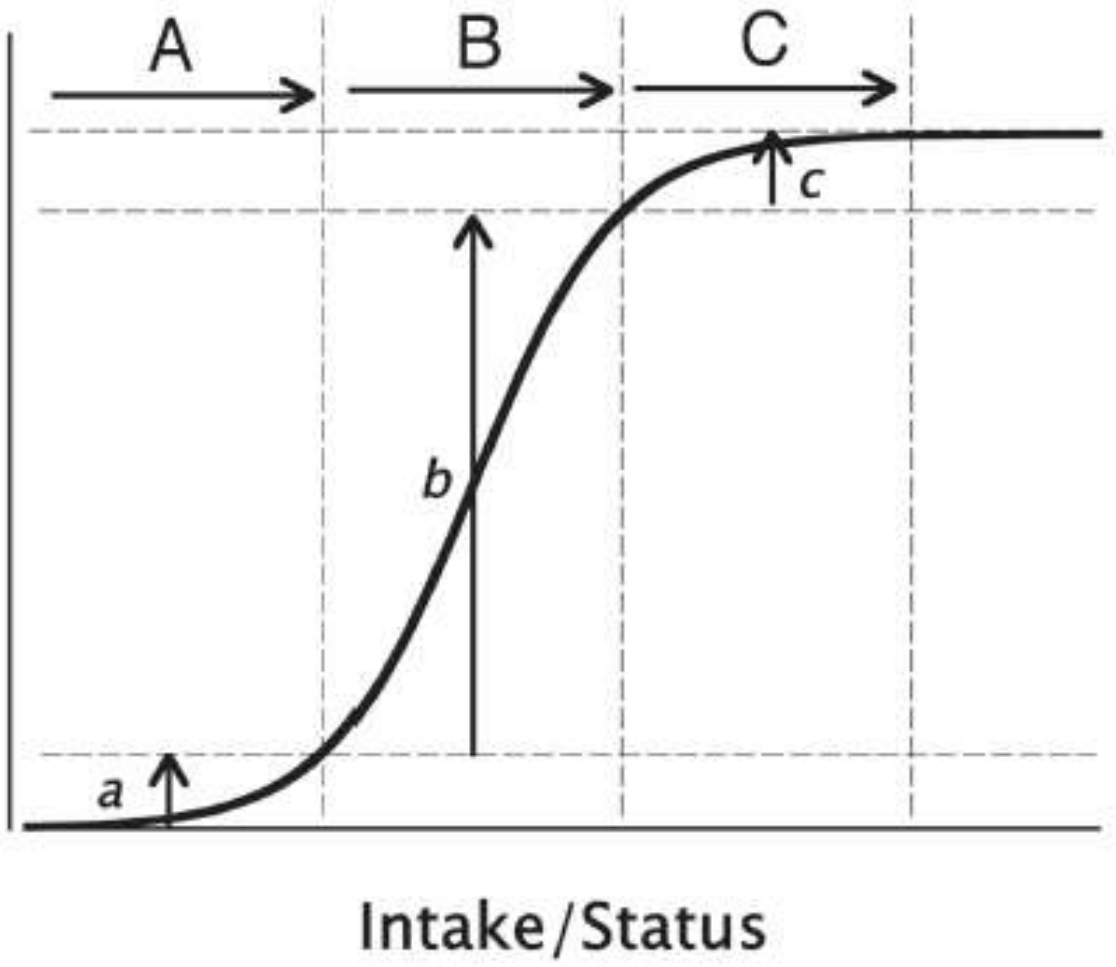
Nutrient Thresholds for Health



Vitamin E Thresholds for Health



Implications of Nutrient Threshold Dose-Response Characteristics



Vitamin D and Calcium Supplementation Do Not Prevent Fractures in Adults: Meta-analysis

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.

Moyers et al. *Ann Intern Med* 2013

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

- 2000 mg calcium + 400 IU vitamin D_3 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

RCT
- n, 36,282
- age, 50-79 y
- F/U, 7 y

Prentice et al. *Osteoporos Intl* 2013

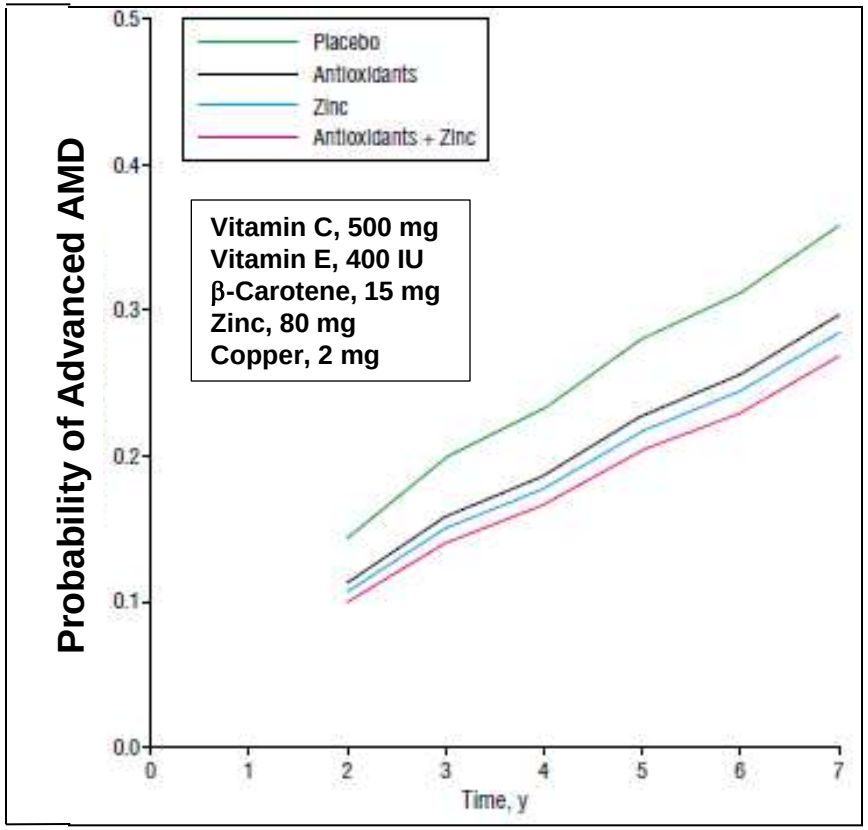
Vitamin D & Calcium Supplementation Do Prevent Hip Fractures in Women: *Women's Health Initiative*

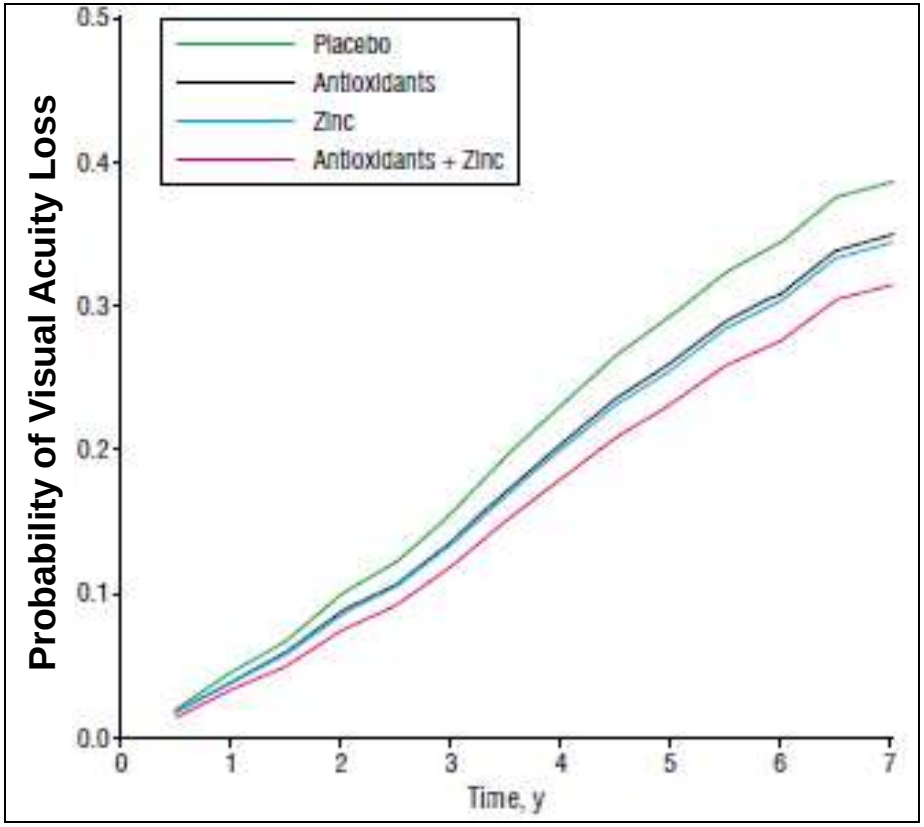
- 2000 mg calcium + 400 IU vitamin D_3 or placebo
- 56% of the cohort took calcium + vitamin D before the trial
- Daily calcium intake during the RCT was 1135 mg/d in the placebo group and 2000 mg/d in the supplement group
- Among the women not taking calcium or vitamin D supplements at baseline, HR = 0.62 (95% CI: 0.38-1.00)

RCT
- n, 36,282
- age, 50-79 y
- F/U, 7 y

Prentice et al. *Osteoporos Intl* 2013

Multivitamin Slows Progression to Age-Related Macular Degeneration: *Age-Related Eye Disease Study*



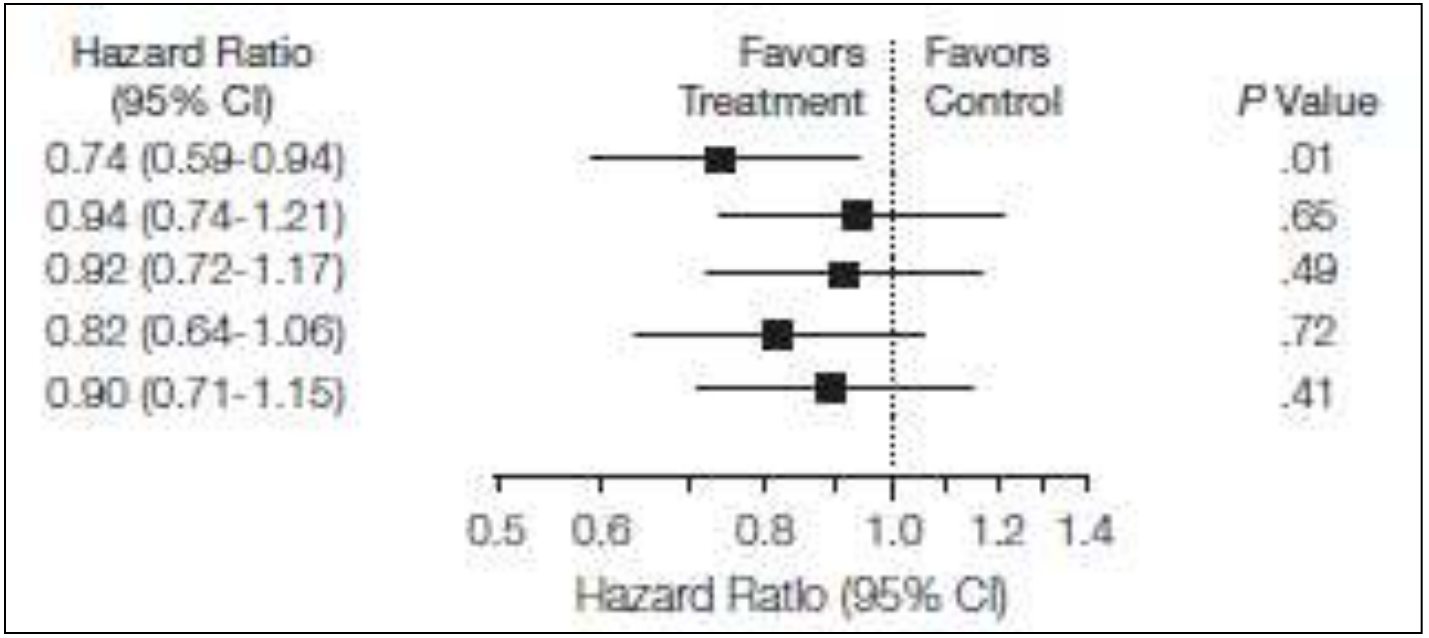


RCT

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

AREDS Research Group. *Arch Ophthalmol* 2001

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

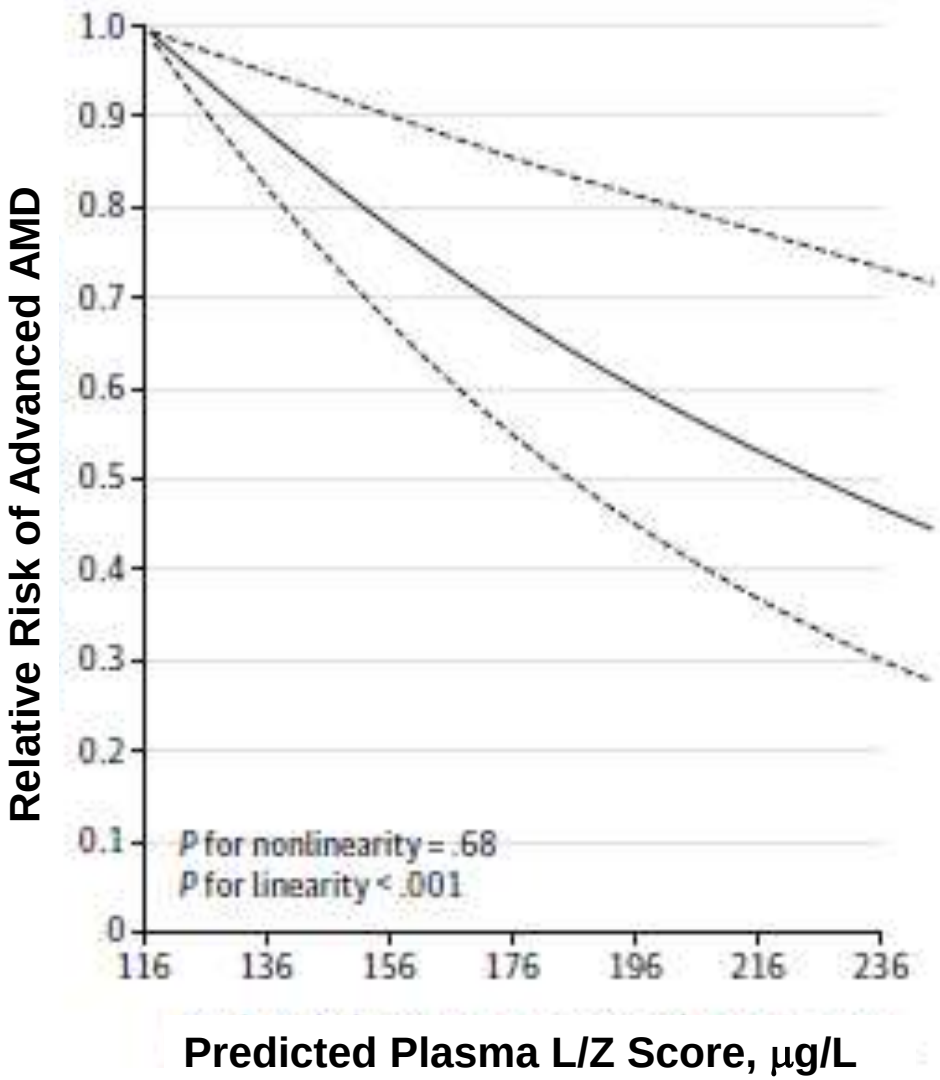
Chew et al. *JAMA* 2013

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

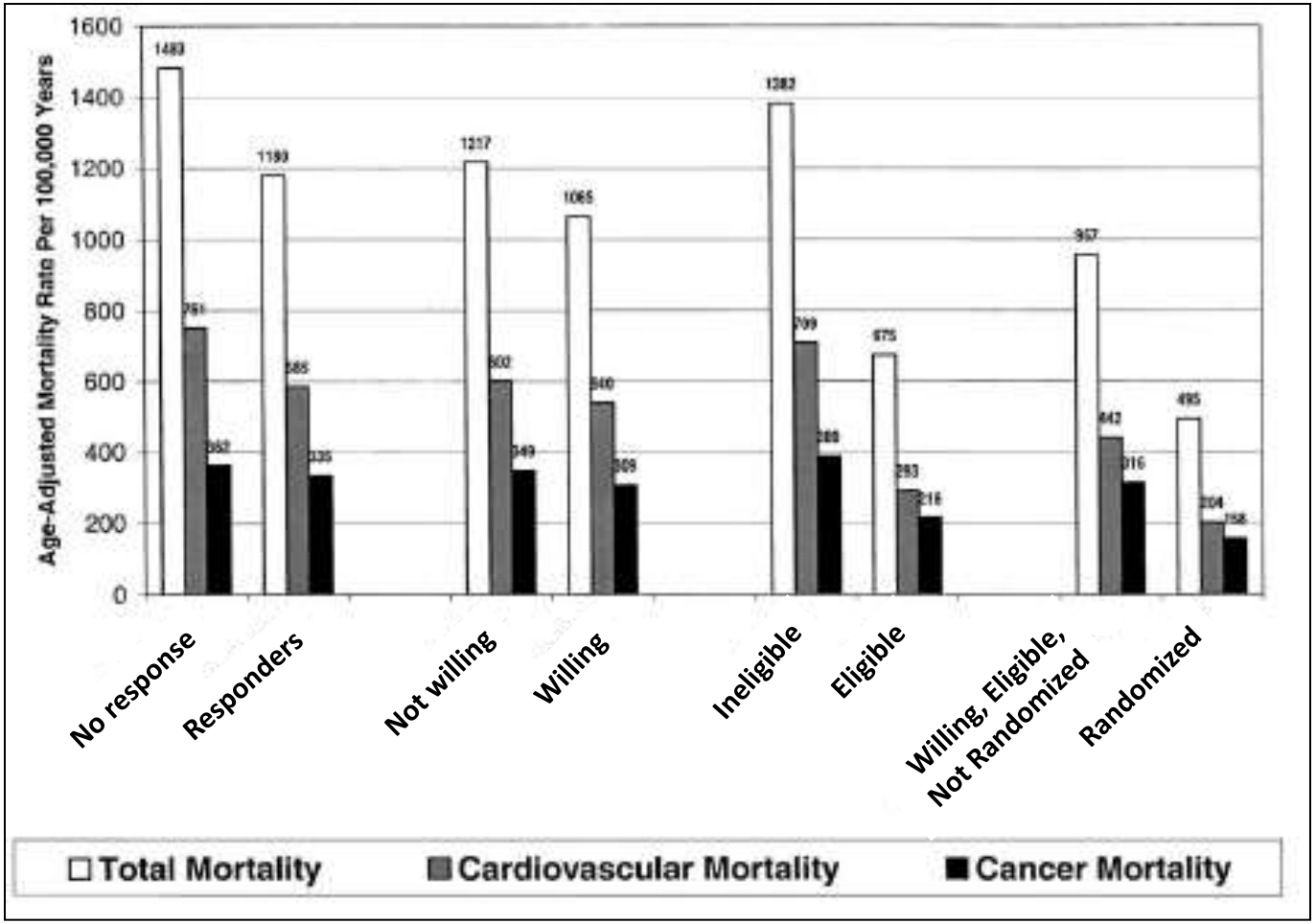
RCTs of Nutrients in Primary Prevention

- **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

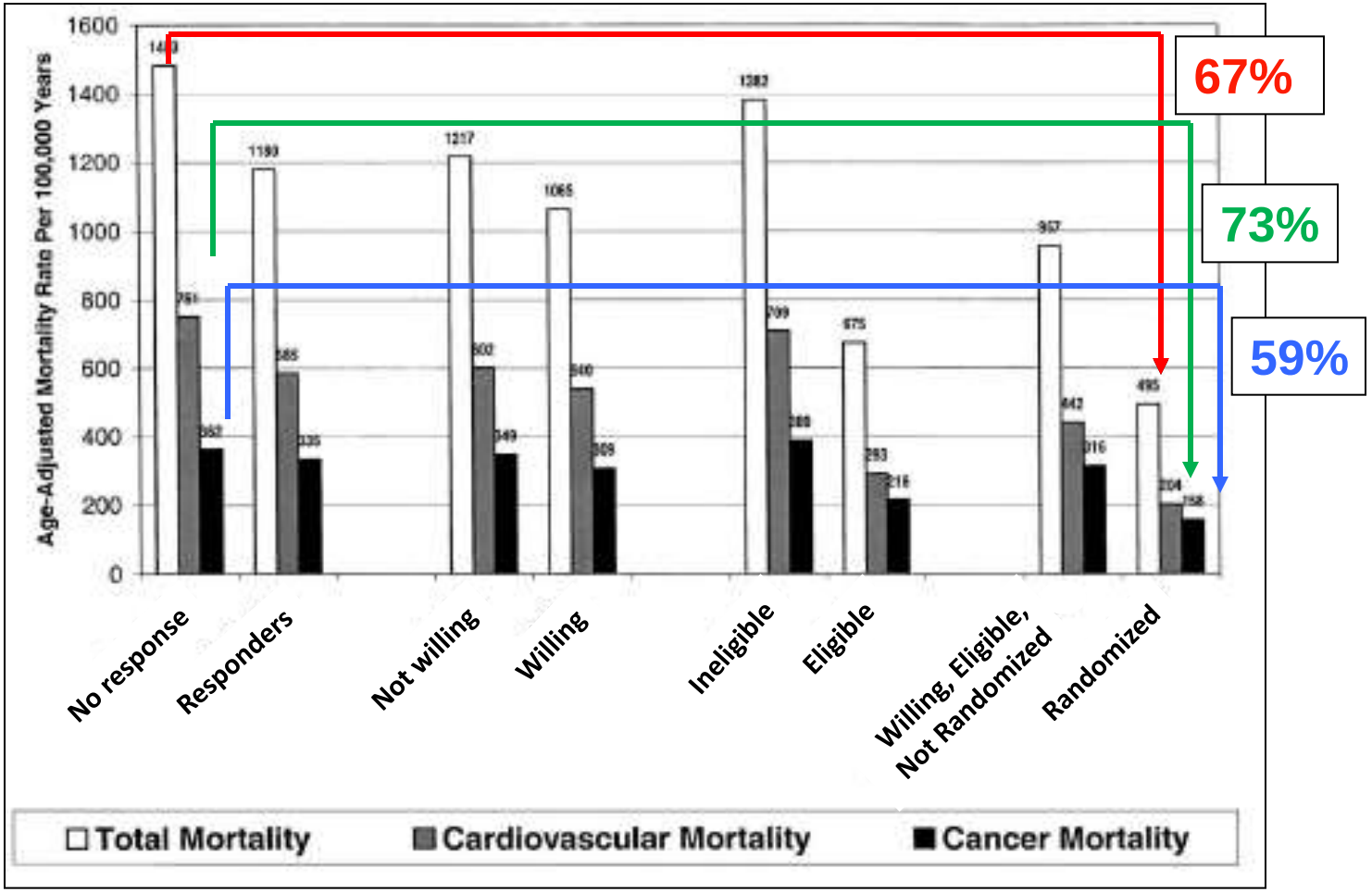
- Baseline
  n, 261,248
- Respondents
  n, 112,160



Sesso et al. *Control Clin Trials* 2002

RCTs of Nutrients in Primary Prevention
Physicians Health Study II

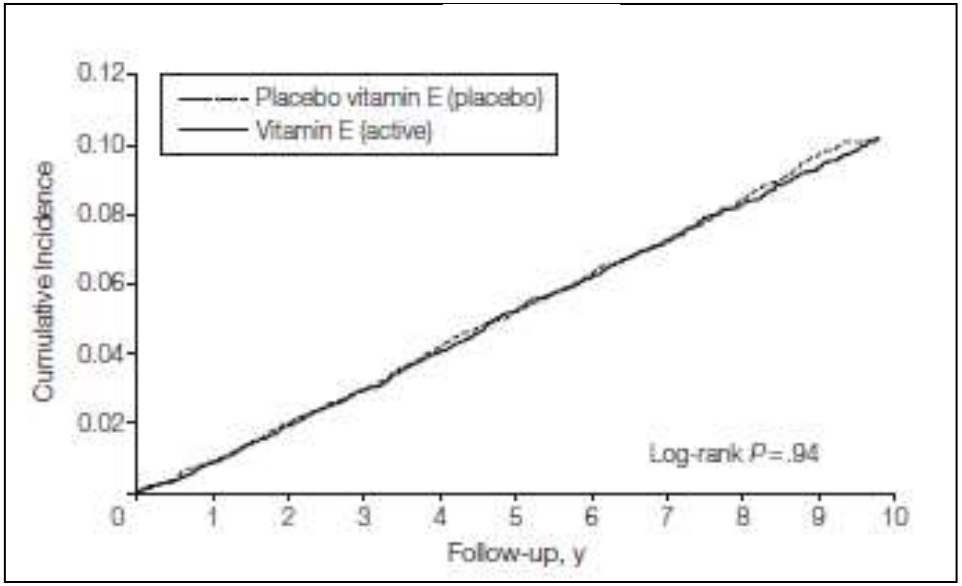
- Baseline
  n, 261,248
- Respondents
  n, 112,160



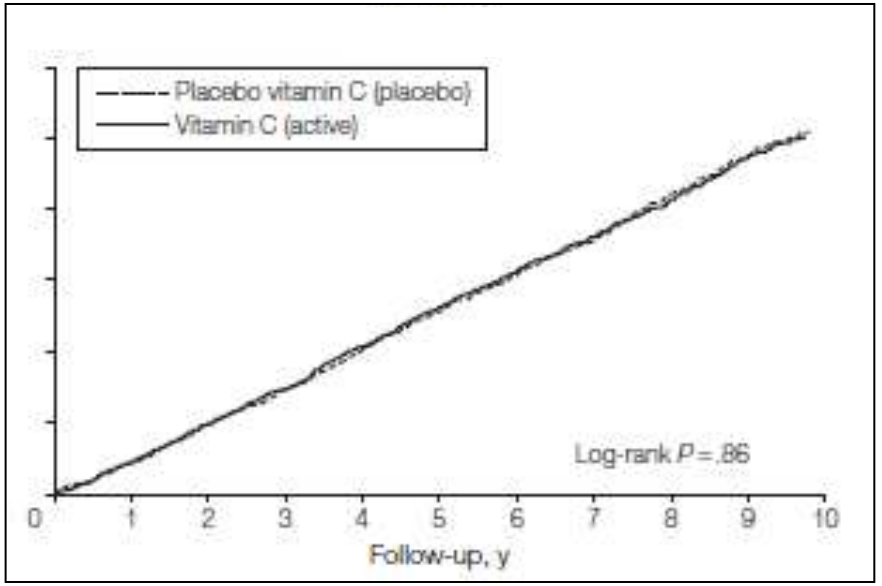
Sesso et al. *Control Clin Trials* 2002

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

RCTs of Nutrients in Secondary Prevention

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

RCTs of Nutrients in Secondary Prevention

Percent of Subjects Receiving Drugs in the Vitamin E Group

Drugs	HOPE	HOPE 2
β-Blockers		40.2
Antiplatelet agents	77.0	
Lipid lowering	28.4	
Diureti	15.7	5.2
n channel blockers	47.2	46.7

Withdraw medication/polypharmacy regimens

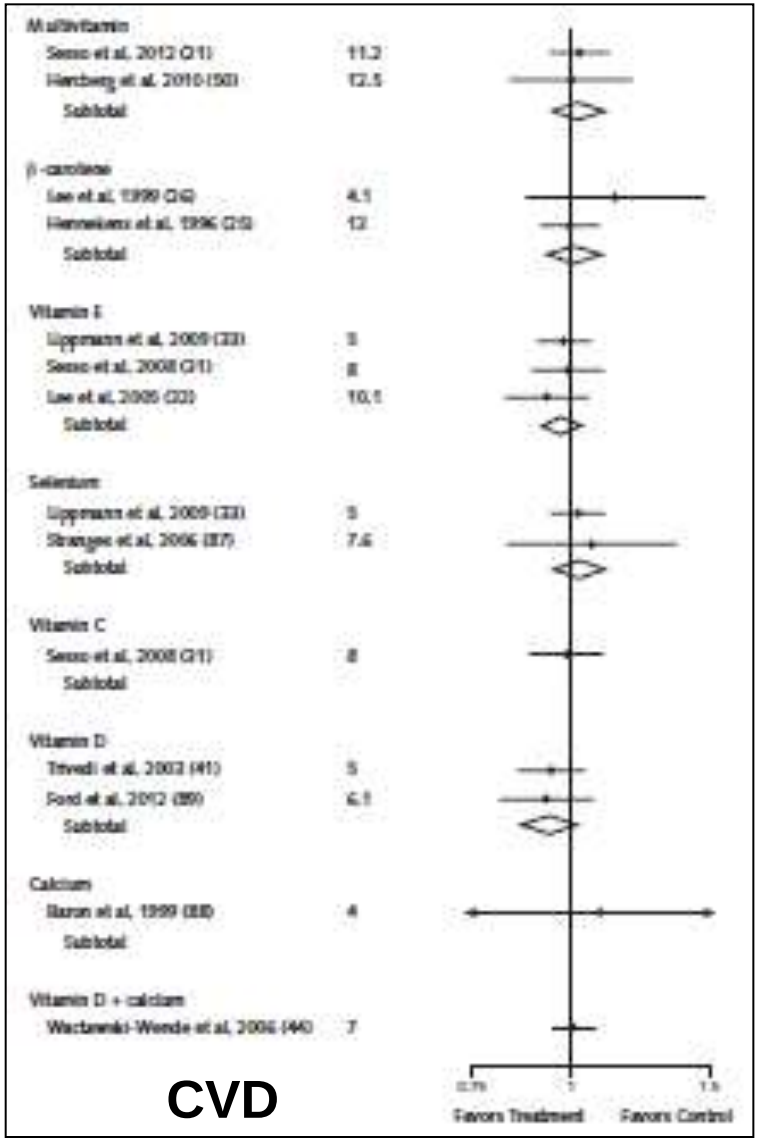
UNETHICAL!

Lonn et al. *JAMA* 2005

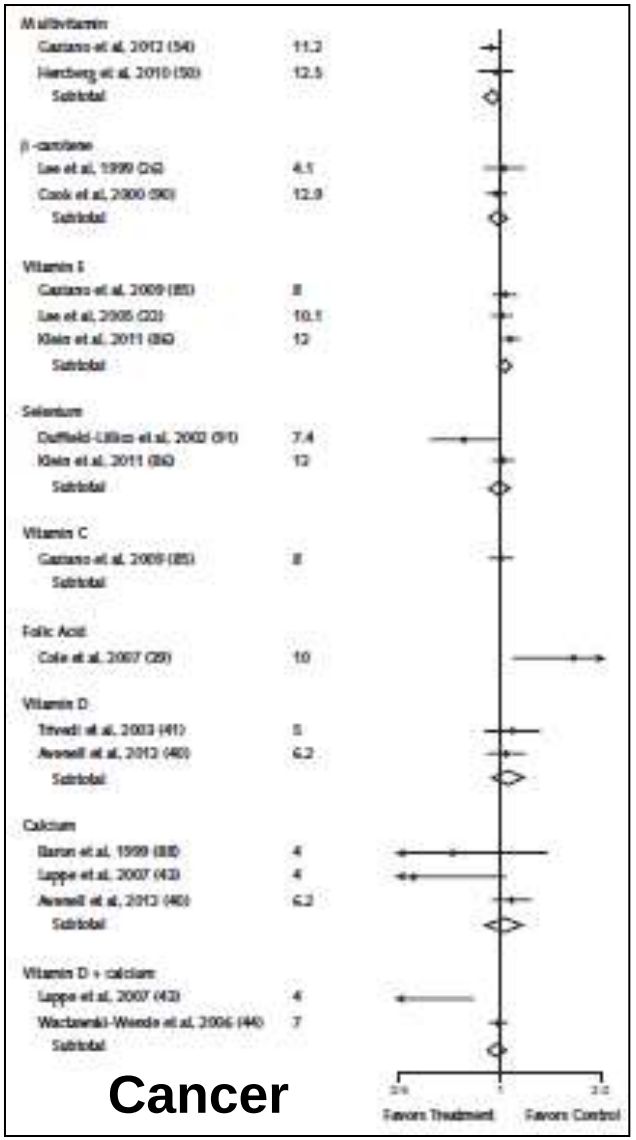
Annals of Internal Medicine: Vitamin & Mineral Supplements in the Primary Prevention of Cardiovascular Disease & Cancer: An Updated Systematic Evidence Review for the U.S. Preventative Services Task Force

- RCT, 26
- PC, 2

Fortman et al. *Ann Intern Med* 2013



CVD



Cancer

Annals of Internal Medicine: Vitamin & Mineral Supplements in the Primary Prevention of Cardiovascular Disease & Cancer: An Updated Systematic Evidence Review for the U.S. Preventative Services Task Force

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.

Fortmann et al. *Arch Intern Med* 2013
Moyer et al. *Ann Intern Med* 2014

Annals of Internal Medicine: Vitamin & Mineral Supplements in the Primary Prevention of Cardiovascular Disease & Cancer: An Updated Systematic Evidence Review for the U.S. Preventative Services Task Force

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.

Fortmann et al. *Arch Intern Med* 2013
Moyer et al. *Ann Intern Med* 2014

Annals of Internal Medicine:
Enough is Enough: Stop Wasting Money on Vitamins & Supplements

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.

Guallar et al. *Ann Intern Med* 2013

Annals of Internal Medicine:
Enough is Enough: Stop Wasting Money on Vitamins & Supplements

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.

Guallar et al. *Ann Intern Med* 2013

How Much Certainty is Necessary?

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:

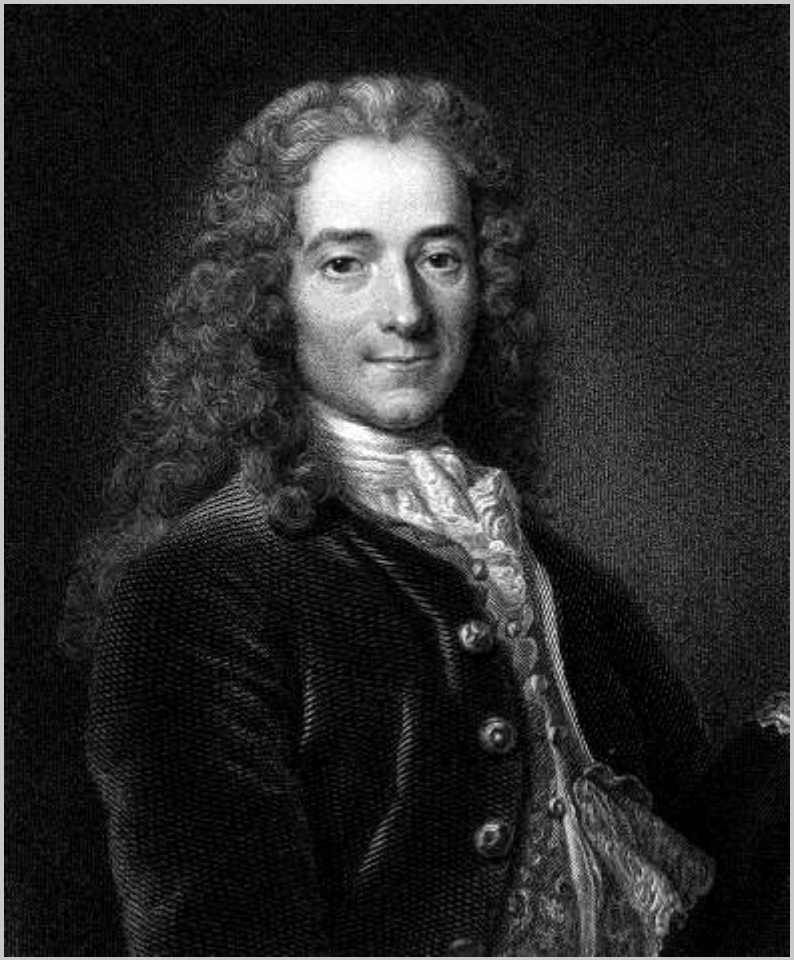
- High benefit : risk ratio
- Important consequences of Type II error
- Low deployment cost
- Low opportunity cost
- Multiplicity of lines of evidence
- Availability of ancillary measures

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

Questions?

Credit Claiming

You must complete a brief evaluation of the program in order to obtain your certificate. The evaluation will be available for 1 year; you do not have to complete it today.

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2. Click "Take Course" on the webinar description page.
3. Select "Start/Resume Course" to complete and submit the evaluation.
4. Download and print your certificate.

Please Note: If you access the Evaluation between 3-4 pm ET on 12/1, you may experience a slow connection due to a high volume of users.