Dietary Supplements and Health: Hype vs. Evidence

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Disclosure

I have no financial conflicts of interest related to this presentation.

I have received funding from the NIH to conduct large-scale randomized trials of vitamin D and other dietary interventions to prevent cancer and CVD. Pharmavite and Pfizer, Inc., donate study pills for our randomized trials of vitamin D and multivitamins.

Objectives

- To review the evidence that dietary supplements confer health benefits, beyond treating deficiency states.
- To describe life stages during which supplements are of benefit.
- To review high-risk subgroups that benefit from targeted supplementation.
- To discuss ways to assess quality control of commercial supplements.

Dietary Supplements: Background

- >$30 billion industry in the U.S.
- >90,000 dietary supplement products are on the market.
- 52% of U.S. adults report use of 1 or more dietary supplements.
- Vitamins and minerals are the most popular supplements (39-48% of adults).

Source: Manson JE, Bassuk SS. *JAMA*, 2018.

Vitamins/Minerals: Historical Context

In the era of nutritional deficiency diseases:

- **One nutrient → prevents or treats one disease (examples: vitamin C/scurvy, vitamin D/rickets, niacin/pellagra, thiamin/beriberi, and others).**
- **These disorders are caused by lack of the micronutrients in the diet and improve/resolve with supplementation.**
- **Vitamins and minerals came to be viewed as "miracle" cures.**

But can these principles be applied to chronic diseases of the 21st century (CVD, diabetes, cancer)?

Is more always better?

Vitamins

Fat-Soluble

Vitamin A

Vitamin D

Vitamin E

Vitamin K

Water Soluble

B vitamins
(biotin, folic acid, niacin, pantothenic acid, riboflavin, thiamin, B6, B12)

Vitamin C

Key Points

- Most randomized clinical trials of vitamin and mineral supplements have not demonstrated clear benefits for primary or secondary prevention of chronic diseases.
- Some risks have been identified with high-dose supplementation: (beta carotene, folic acid, vitamin E, or selenium).
- Supplementation is not a substitute for a healthful/balanced diet.
- Micronutrients in food are typically better absorbed by the body.
- Routine supplementation is not recommended for the general population, but a targeted approach is appropriate for certain life stages and high-risk groups.

PLACEBO Adherence and Clinical Outcomes in the Women's Health Initiative HT Trials (n=13,444)

Clinical Outcome	Adherence Category (%)	Hazard Ratio* (95% CI)
	<80	1.0 (Referent)
Clinical MI	≥80	0.69 (0.50-0.95)
Total Mortality	≥80	0.64 (0.51-0.80)
Cancer Mortality	≥80	0.60 (0.43-0.82)

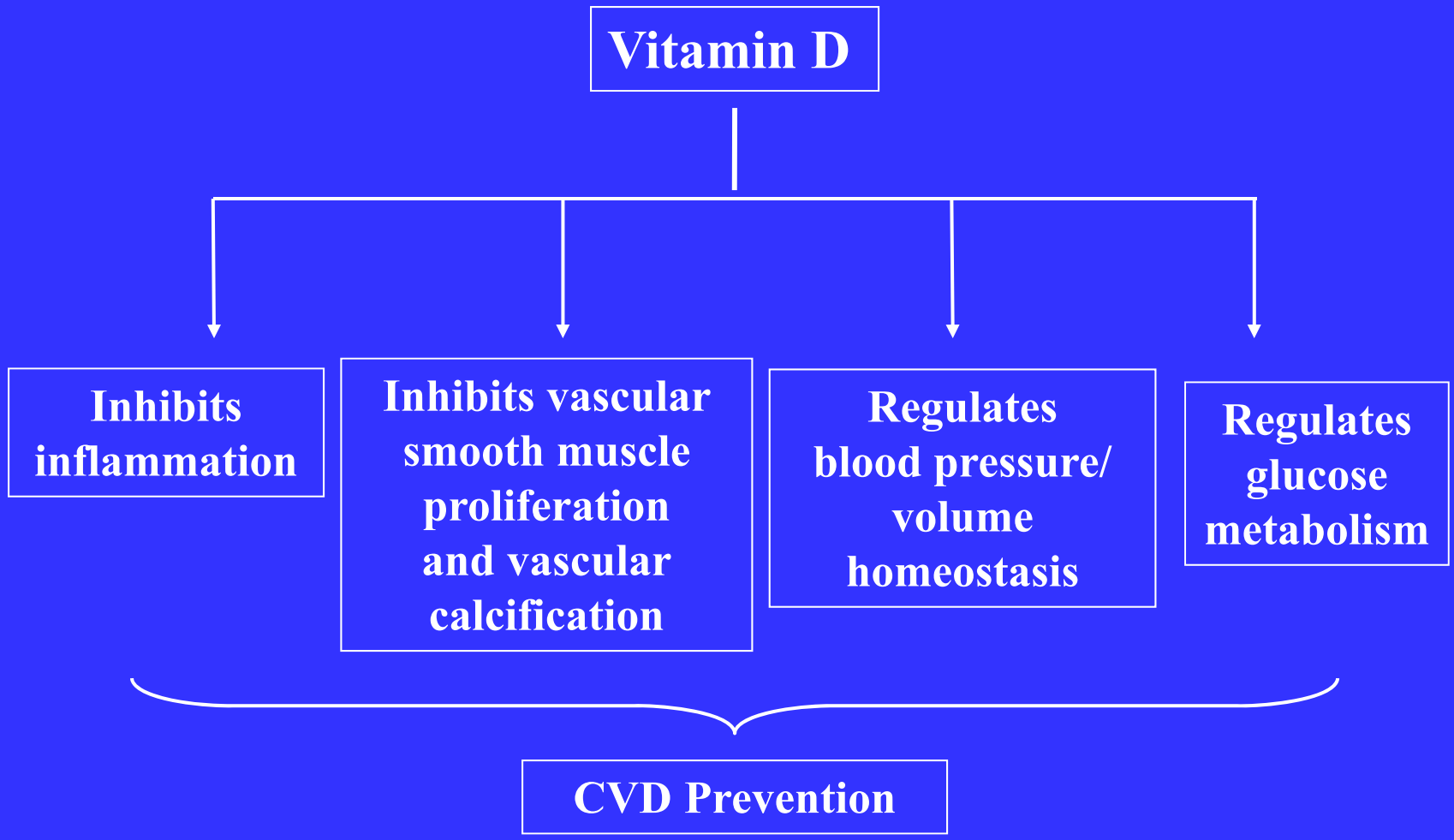
* HR adjusted for age, ethnicity, education, smoking, BMI, physical activity, multiple dietary and lifestyle factors, other medication use.

Source: Curtis, Jeffrey, et al. *Medical Care* 2011.

Hypothesized Antiatherogenic Mechanisms of Antioxidant Vitamins and Folic Acid/B Vitamins

- Antioxidant vitamins (vitamin C, E, beta carotene) inhibit the oxidation and/or uptake of LDL cholesterol. Oxidized LDL is a particularly atherogenic form of cholesterol.
- Folic acid/B_6/B_{12} impede synthesis (and reduce blood levels) of homocysteine, a risk factor for CVD.

Mechanisms by which Vitamin D May Lower CVD Risk



Adapted from: Manson JE, Bassuk SS, Lee I-M, et al. *Cont Clinical Trials* 2011.

LINXIAN, China: Nutrition Intervention Trial*
(29,584 residents aged 40-69 in rural north-central China)

Supplementation with beta carotene, vitamin E, and selenium:

Cause of Death	N	RR (95% CI)
Total mortality	2127	0.91 (0.84-0.99)
Cerebrovascular	523	0.90 (0.76-1.07)
Cancer	792	0.87 (0.75-1.00)

*5 years duration

Source: Blot WJ, et al. *JNCI* 1993.

The SU.VI.MAX Study: RCT of Antioxidant Vitamins and Minerals
(combination of vit C, vit E, ß-carotene, selenium, zinc vs placebo)

N=13,017 French Adults (7876 women, 5141 men)

	Active, N	Placebo, N	RR (95% CI)
Ischemic CVD			
Overall	134	137	0.97 (0.77-1.20)
Women	27	23	1.17 (0.67-2.05)
Men	107	114	0.82 (0.71-1.20)
Cancer			
Overall	267	295	0.90 (0.76-1.06)
Women	179	171	1.04 (0.85-1.29)
Men	88	98	0.69 (0.53-0.91)*
Total Mortality			
Overall	76	98	0.77 (0.57-1.00)
Women	36	35	1.02 (0.64-1.63)
Men	40	63	0.63 (0.42-0.93)*

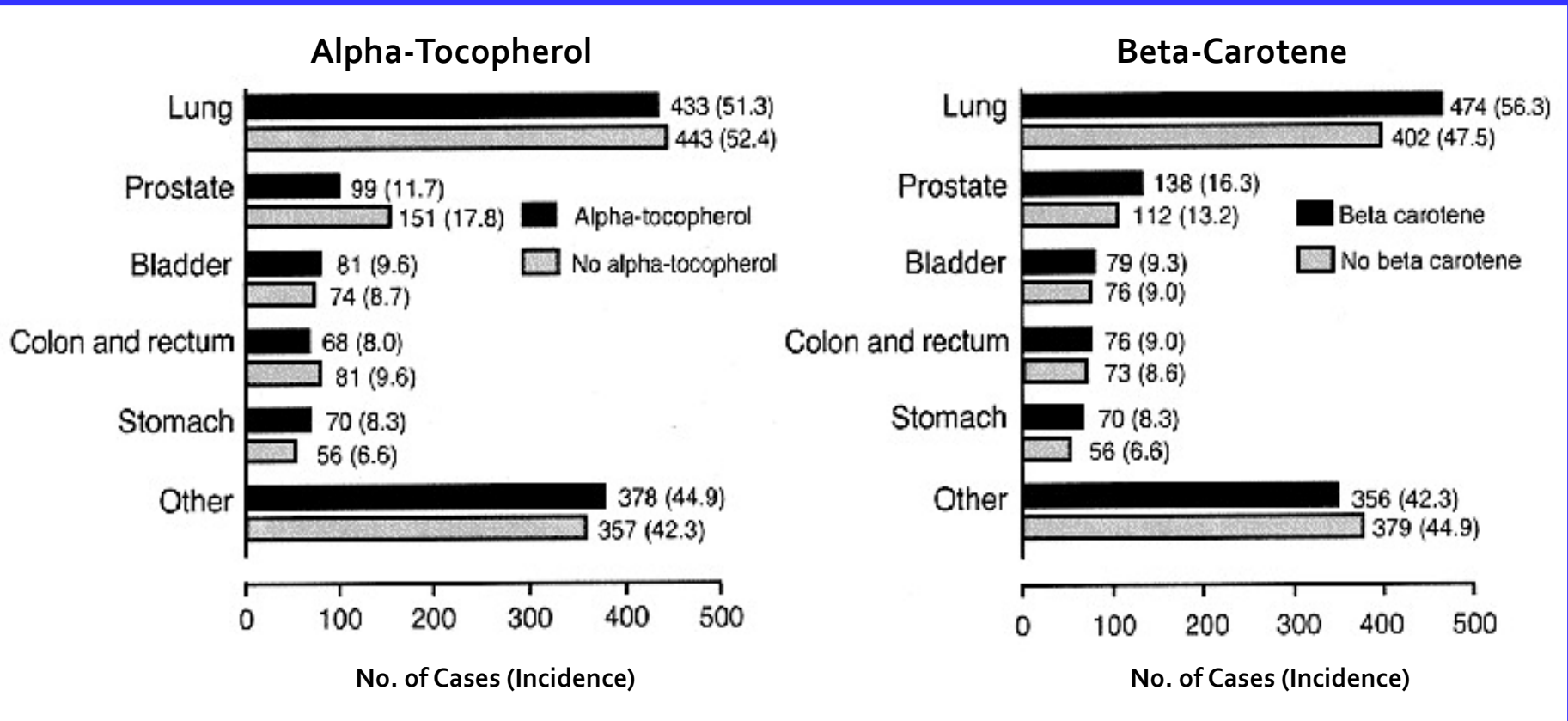
* *P* <0.05

Source: Herchberg S, et al. *Arch Intern Med* 2004.

Clinical Trials of β-Carotene

- **Carotene and Retinol Efficacy Study (CARET)**
  Potential excess risk of CVD death (RR=1.26)
- **Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)**
  No overall association with CVD
- **Physicians' Health Study (PHS)**
  No overall association with CVD
- **Women's Health Study (WHS)**
  No overall association with CVD
- **Women's Antioxidant Cardiovascular Study (WACS)**
  No overall association with CVD

Alpha-Tocopherol and Beta-Carotene Supplementation and Incidence of Cancer (per 10,000 pys): the ATBC Trial in Finnish Smokers



Source: ATBC Cancer Group. *NEJM* 1994; 330:1029.

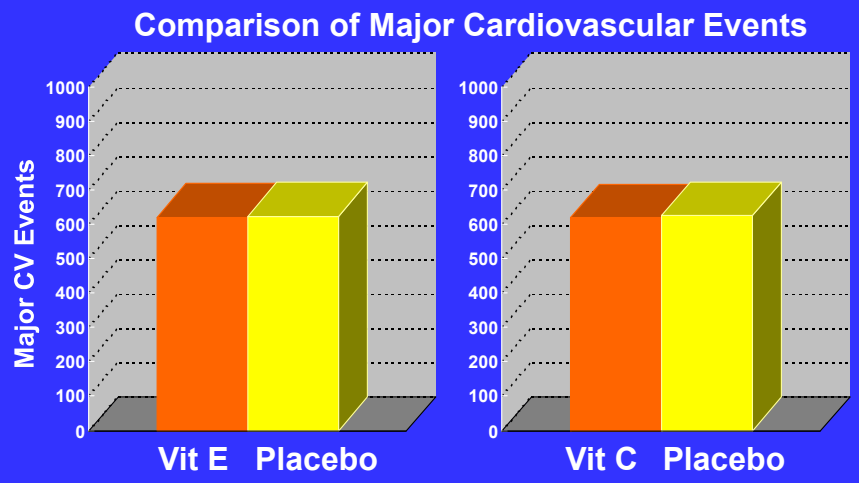
Meta-analysis of Effect Of Vitamin E on MI, Stroke, or CVD Death in High-Risk Populations

Study	Daily Dose	Duration (yr)	RR (95% CI)
ATBC	50	5.0	0.96 (0.90-1.03)
CHAOS	≥400	1.3	0.60 (0.40-0.89)
GISSI	300	3.5	0.98 (0.87-1.10)
HOPE	400	4.5	1.05 (0.95-1.16)
Total			0.97 (0.92-1.02)

Source: *N Engl J Med* 2000; 342:154-60.

Physicians' Health Study II
Randomized Trial of Vitamins E and C in CVD Prevention and Mortality in Men

Primary Endpoints: Major CV events: nonfatal MI, nonfatal stroke, fatal CVD



Results Vitamin E vs Placebo

Major CV Events:
HR (95% CI) 1.01 (0.90-1.13)

Total Mortality:
HR (95% CI) 1.07 (0.97-1.18)

Results Vitamin C vs Placebo

Major CV Events:
HR (95% CI) 0.99 (0.89-1.11)

Total Mortality:
HR (95% CI) 1.07 (0.97-1.18)

Conclusion: No compelling evidence that vitamin E or vitamin C supplements reduce the risk of CVD.

Source: Sesso H, et al. *JAMA* 2008.

SELECT Trial

Risk of Prostate Cancers with Trial Interventions

	Placebo (n=8,696)	Vitamin E (n=8,737)	Selenium (n=8,752)
Hazard Ratio (95% CI)			
as of 10/2008	1.0	1.13 (0.95-1.35)	1.05 (0.88-1.25)
as of 7/2011	1.0	1.17 (1.004-1.36)	1.09 (0.93-1.27)
Absolute Risk*	93	109	101

*Prostate cancers per 10,000 person years

Source: Klein EA, et al. *JAMA* 2011.

Meta-Analysis of Vitamin D and MI RCTs: Subgroup Analyses*

Subgroup	HR for MI (95% CI)	P-value for Interaction
Intervention		
Vitamin D alone	0.96 (0.81-1.13)	0.33
Vitamin D and calcium	1.06 (0.94-1.20)	
Vitamin D Dose Used		
≥800 IU/d	0.99 (0.85-1.15)	0.52
<800 IU/d	1.06 (0.92-1.21)	

*Results were similar for stroke and all-cause mortality.

Source: Elamin MB, et al. *JCEM* 2011; 96:1931-42.

A Randomized Trial of a Multivitamin in the Prevention of CVD in Men: The Physicians' Health Study II

HD Sesso, WC Christen, V Bubes, JP Smith,
J MacFadyen, M Schvartz, JE Manson, RJ Glynn,
JE Buring, JM Gaziano

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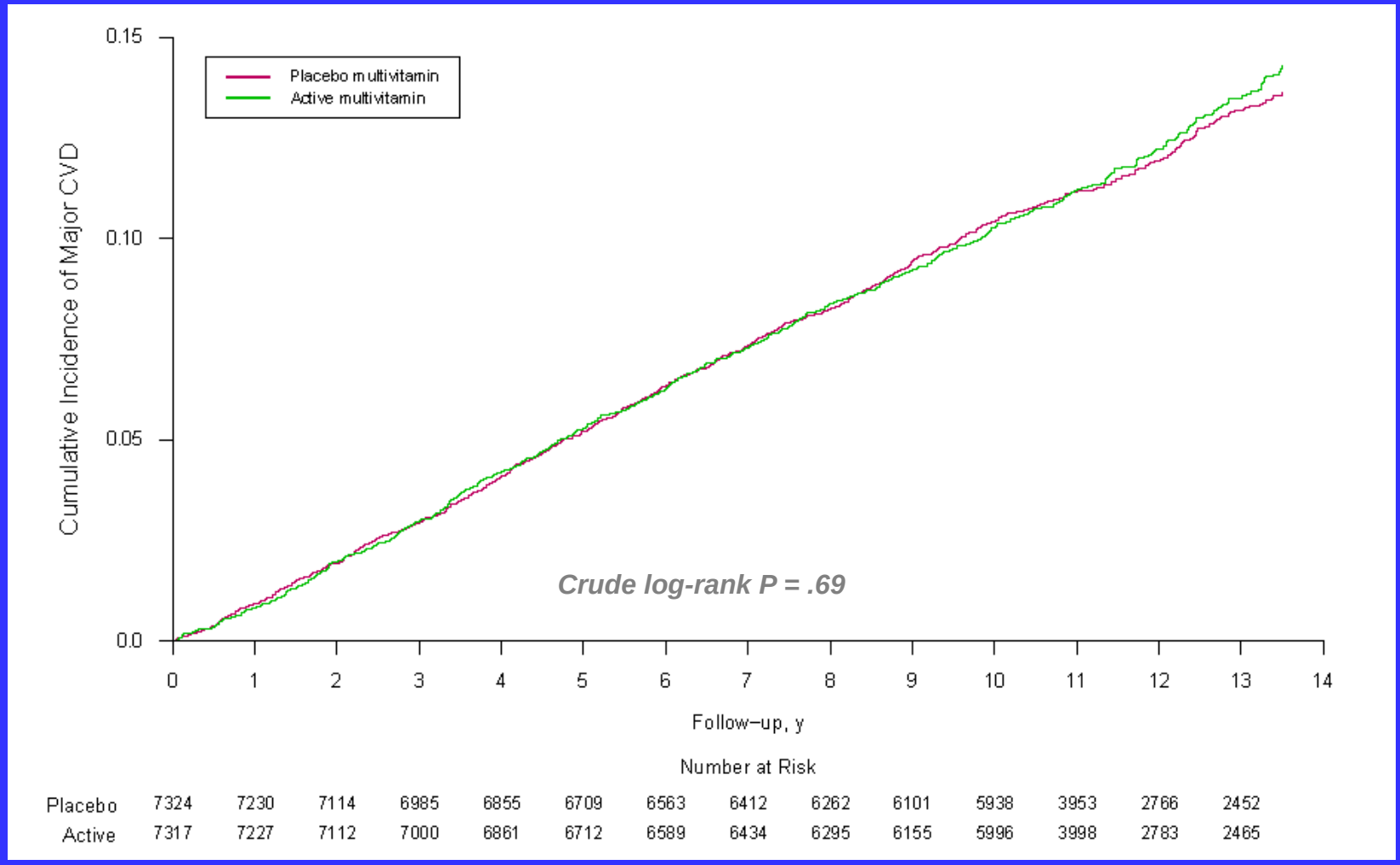
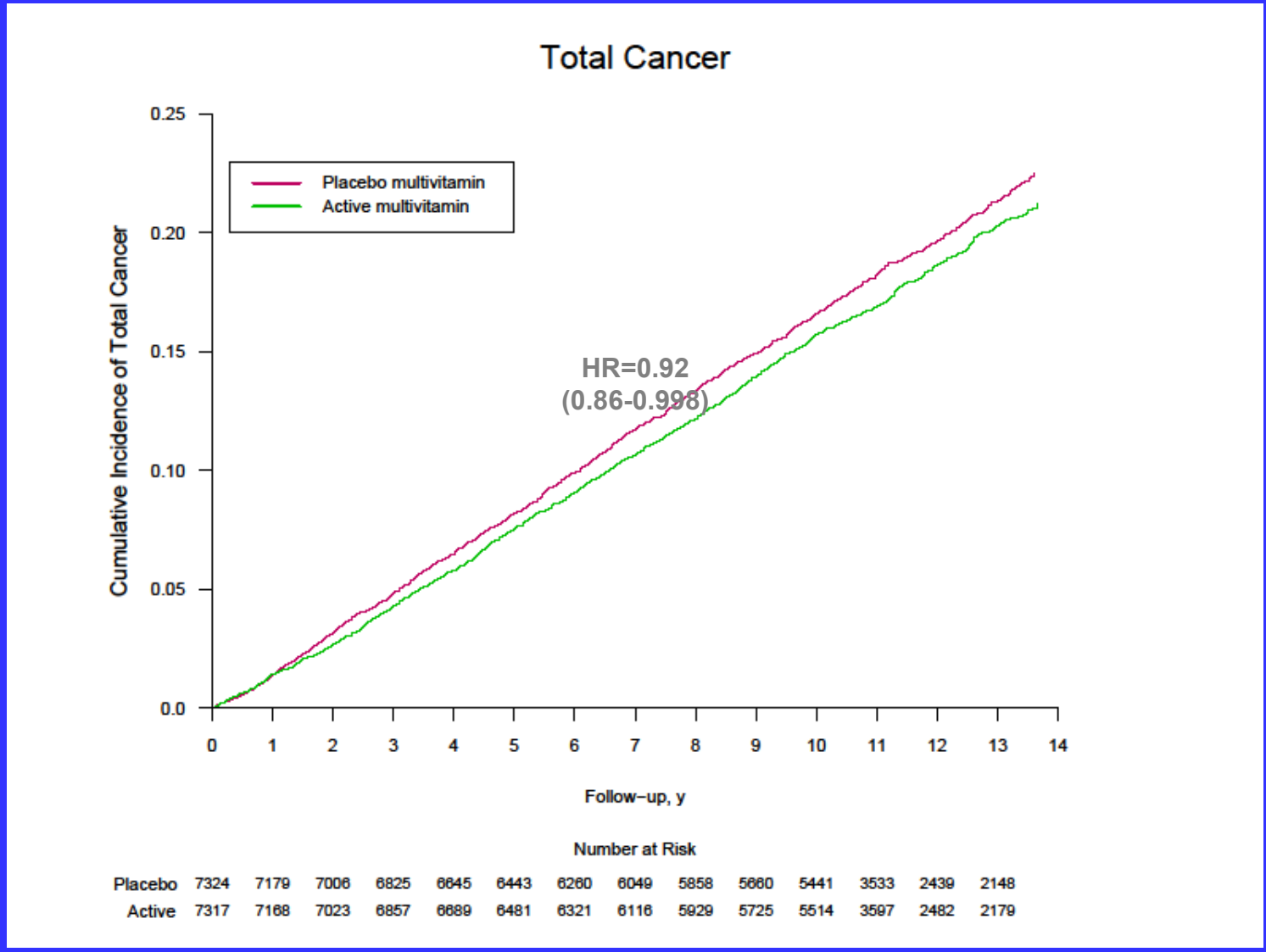
Multivitamins and Major Cardiovascular Events



Source: Sesso HD, et al. *JAMA* 2012; 308(17):1751.

Physicians' Health Study II: Multivitamins and Cancer



Source: Gaziano JM, et al. *JAMA* 2012; 308(18):1871.

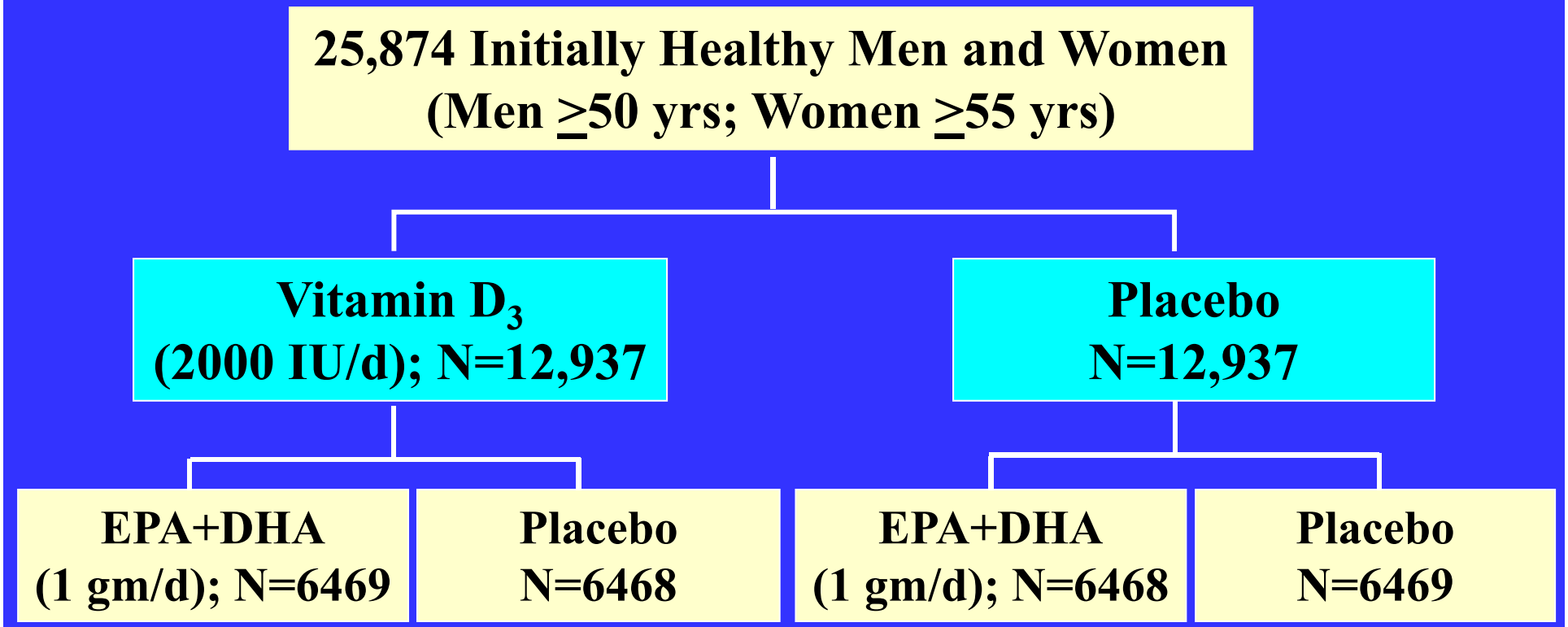
Cancer Events by Multivitamin Treatment Assignment

Outcome	Active (n = 7317)	Placebo (n = 7324)	HR (95% CI)	*P*
Total cancer	1290	1379	0.92 (0.86-0.998)	.04
Cancer mortality	403	456	0.88 (0.77-1.01)	.07
Total mortality	1345	1412	0.94 (0.88-1.02)	.13

* For men aged ≥70, HR (95% CI) for total cancer = 0.82 (0.72-0.93)
p for interaction by age = 0.06

Source: Gaziano JM, et al. *JAMA* 2012; 308(18):1871.

The *VIT*amin D and Omeg*A*-3 Tria*L* (*VITAL*): Design



Mean Treatment Period = 5.0 years
5107 African Americans
Blood collection in ~16,953, follow-up bloods in ~6000
Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)

Adapted from: Manson JE, Bassuk SS, Lee I-M, et al. *Cont Clinical Trials,* 2011.

Ancillary Studies in VITAL

- Cognitive Function
- Diabetes/Glucose Tolerance
- Hypertension
- Autoimmune Disorders
- Asthma/Respiratory Diseases
- Fractures
- DXA/Bone Microarchitecture
- Diabetic Nephropathy
- Mood Disorders/Depression
- Infections
- 2D Echocardiogram
- Macular Degeneration
- Anemia
- Atrial Fibrillation
- Mammographic Density

In-clinic visits
(in subset)

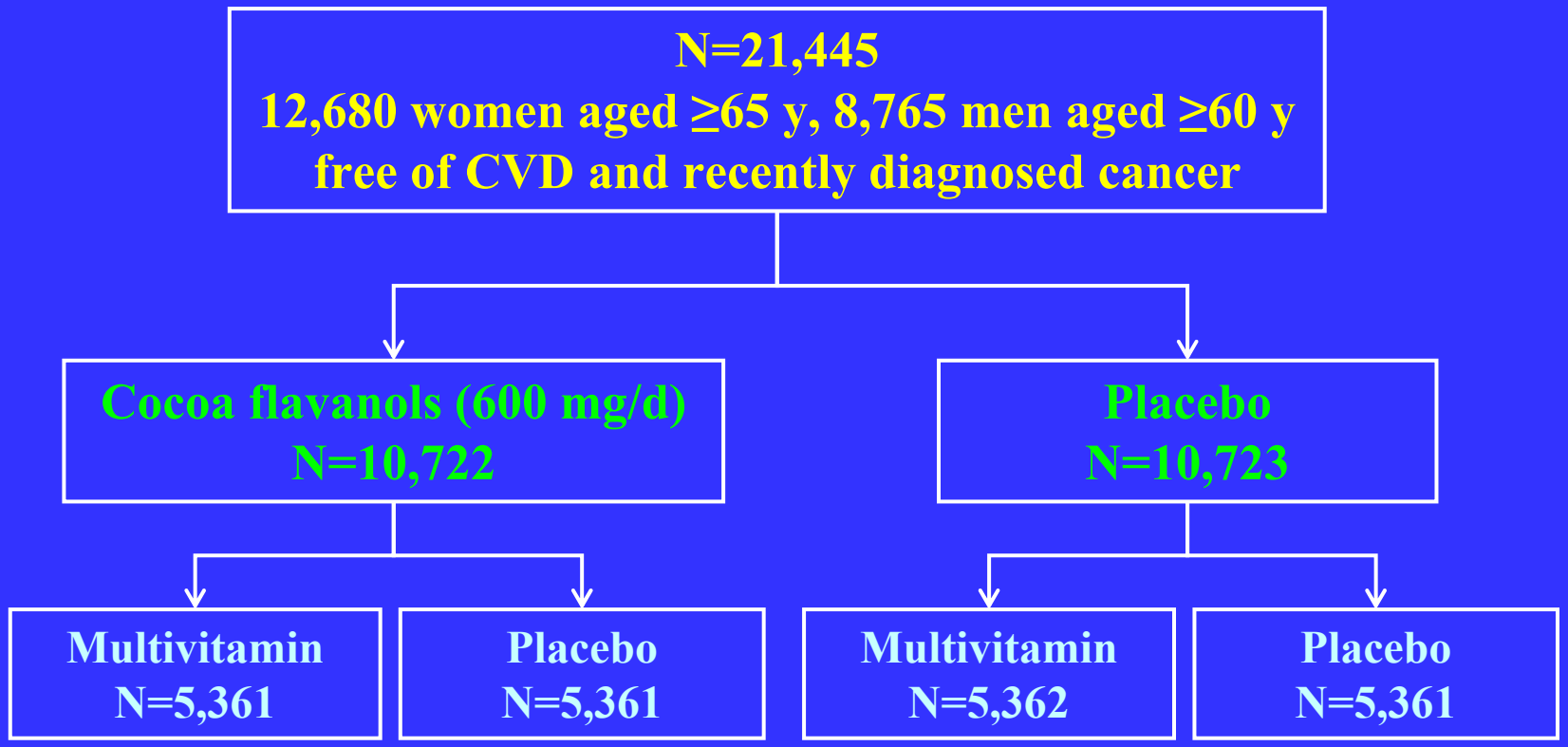
Recently funded

Telomere Biology
Heart Failure
Vitamin D Biomarkers

Pending

Vitamin D Genomics

COcoa Supplement and Multivitamin Outcomes Study (COSMOS)



Median Treatment Period = 4.0 years

Primary Outcomes: Major cardiovascular events (MI, stroke, CVD death, and coronary revascularization) and total cancer (excluding non-melanoma skin cancer)

Baseline Blood/Urine Collection: >6800 participants; follow-up samples in a subgroup

Baseline Clinic Visit: Subcohort of ~600 Boston-based participants with follow-up at 2 years

Vitamin and Mineral Supplements: General Guidance

Supplementation in a Healthy Population, by Life Stage:

- **Pregnancy:** folic acid, prenatal vitamins.
- **Infants and children:** for breastfed infants, vitamin D until weaning and iron from age 4 to 6 months.
- **Midlife and older adults:** some may benefit from supplemental vitamin B12, vitamin D, and/or calcium.

Supplementation in High Risk Subgroups

- **Medical conditions that interfere with nutrient absorption or metabolism:**
  - **Bariatric surgery: fat-soluble vitamins, B vitamins, iron, calcium, zinc, copper, multivitamins/multiminerals.**
  - **Pernicious anemia: vitamin B12 (1-2 mg/day orally or 0.1-1 mg/month intramuscularly or sublingually).**
  - **Crohn's disease, other inflammatory bowel disease, celiac disease: iron, B vitamins, vitamin D, zinc, magnesium.**

Other High Risk Subgroups

- **Osteoporosis or other bone health issues: vitamin D, calcium, magnesium.**
- **Age-related macular degeneration: specific formulation of antioxidant vitamins, zinc, and copper.**

Other Reasons for Supplementation

- **Medications (long-term use):**
  - **Proton-pump inhibitors*: vitamin B12, calcium, and magnesium.**
  - **Metformin*: vitamin B12.**
- **Restricted or suboptimal eating patterns: multivitamin/ multiminerals, vitamin B12, calcium, vitamin D, magnesium.**

Quality Control Issues

- **FDA is not authorized to review dietary supplements for safety and efficacy prior to marketing.**
- **Look at label for certification by independent testers (US Pharmacopeia, NSF International, UL, etc.) to contain the labeled dose(s) of the active ingredient(s) and not to contain microbes, heavy metals, or other toxins.**
- **Resource for information on micronutrient and other dietary supplements: website of the Office of Dietary Supplements of the NIH (www.ods.od.nih.gov).**

Interactions with Medications

- Clinicians should ask about use of micronutrient (and botanical or other dietary) supplements in counseling about potential interactions.

  Examples: supplemental vitamin K can decrease the effectiveness of warfarin, biotin (vitamin B7) can interfere with the accuracy of thyroid function, cardiac troponin, sex steroid hormone, and other lab tests, St. John's wort can speed drug breakdown.

- Ginseng, fish oil, high-dose vitamin E, others can increase bleeding risk.

- Patient-friendly interaction checkers are available free of charge online (search for "interaction checkers" on drugs.com; WebMD; or pharmacy websites).

Conclusions

- Targeted supplementation is appropriate during specific life stages and for high-risk groups.
- A daily multivitamins or individual supplements may be prudent for those with diet restrictions.
- Clinicians have an opportunity to promote appropriate use, and to curb inappropriate use, of micronutrient supplements, and these efforts are likely to improve public health.