

Observational Studies
vs.
Randomized Controlled Trials

Edward Giovannucci, MD, ScD
Harvard School of Public Health
Harvard Medical School
Boston MA 02115

- (1) The relevance of observational data as compared to clinical data for the purposes of identifying relevant endpoints and developing dose-response relationships for establishing recommended intakes for generally healthy persons
- (2) Relevant confounders for data interpretation from the perspective of major and minor confounders or even such factors as obesity and physical activity
- (3) The state of knowledge for vitamin D, as compared to other nutrients of current and past interest such as vitamin E or beta-carotene (i.e., whether the plausibility for vitamin D is stronger than for other micronutrients)

(1) The relevance of observational data as compared to clinical data for the purposes of identifying relevant endpoints and developing dose-response relationships for establishing recommended intakes for generally healthy persons

(2) Relevant confounders for data interpretation from the perspective of major and minor confounders or even such factors as obesity and physical activity

(3) The state of knowledge for vitamin D, as compared to other nutrients of current and past interest such as vitamin E or beta-carotene (i.e., whether the plausibility for vitamin D is stronger than for other micronutrients)

Randomized Trials (RCTs) vs. Observational Data

- § Dose
- § Compliance
- § Duration
- § Confounding

Randomized Trials (RCTs) vs. Observational Data

∅ Dose

∅ Compliance

∅ Duration

§ Confounding

Common assumption:

Dose-response is only addressable in RCTs.

Is this always true?

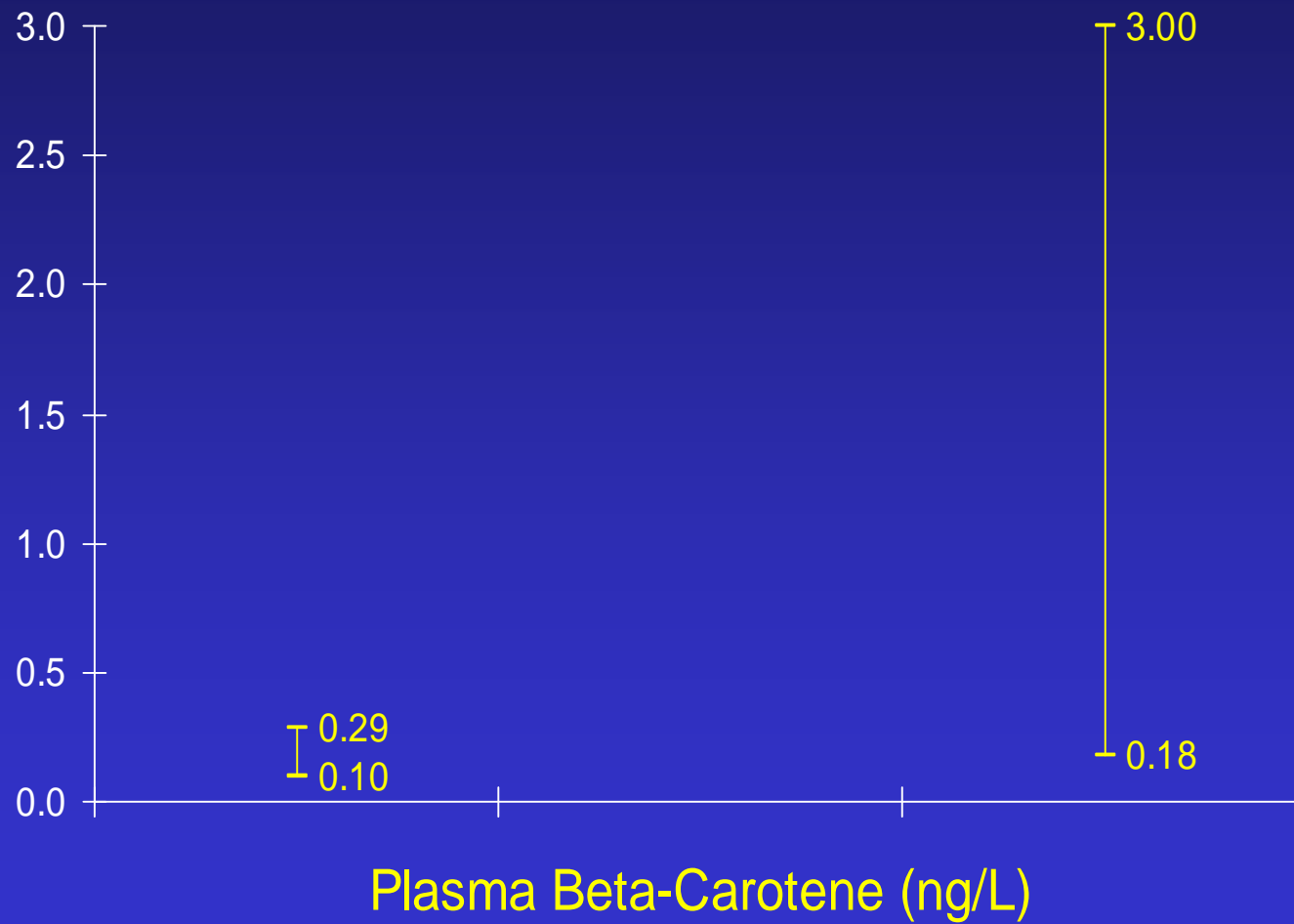
Ranges in RCTs have not always tested the dose-response relation implied in the observational data.

Examples: β -carotene

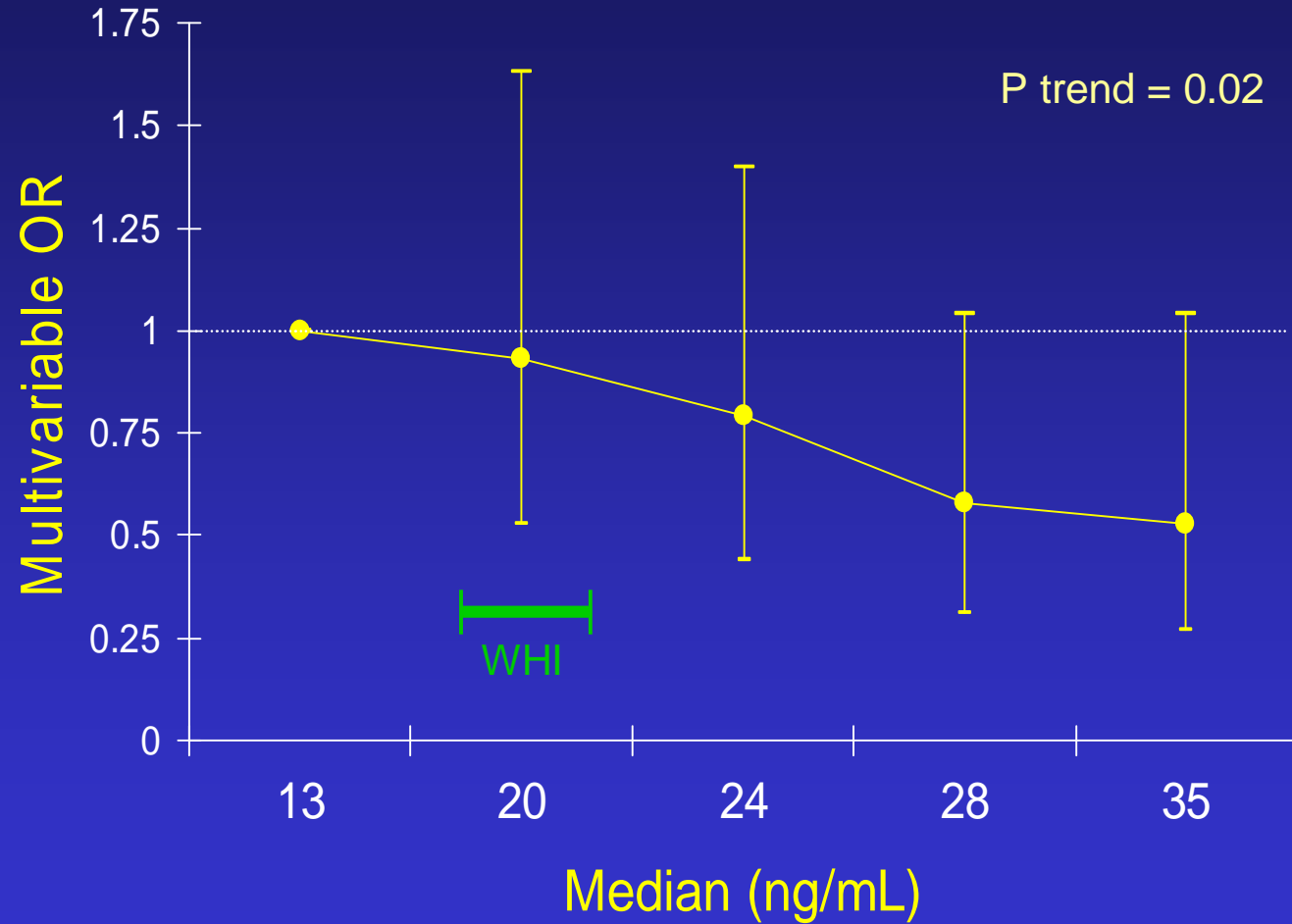
Vitamin D

Range in
Observational
Studies

Range in
RCT
(ATBC)



Plasma 25(OH) Vitamin D and Colorectal Cancer Nurses' Health Study



Compliance

e.g. dietary fat

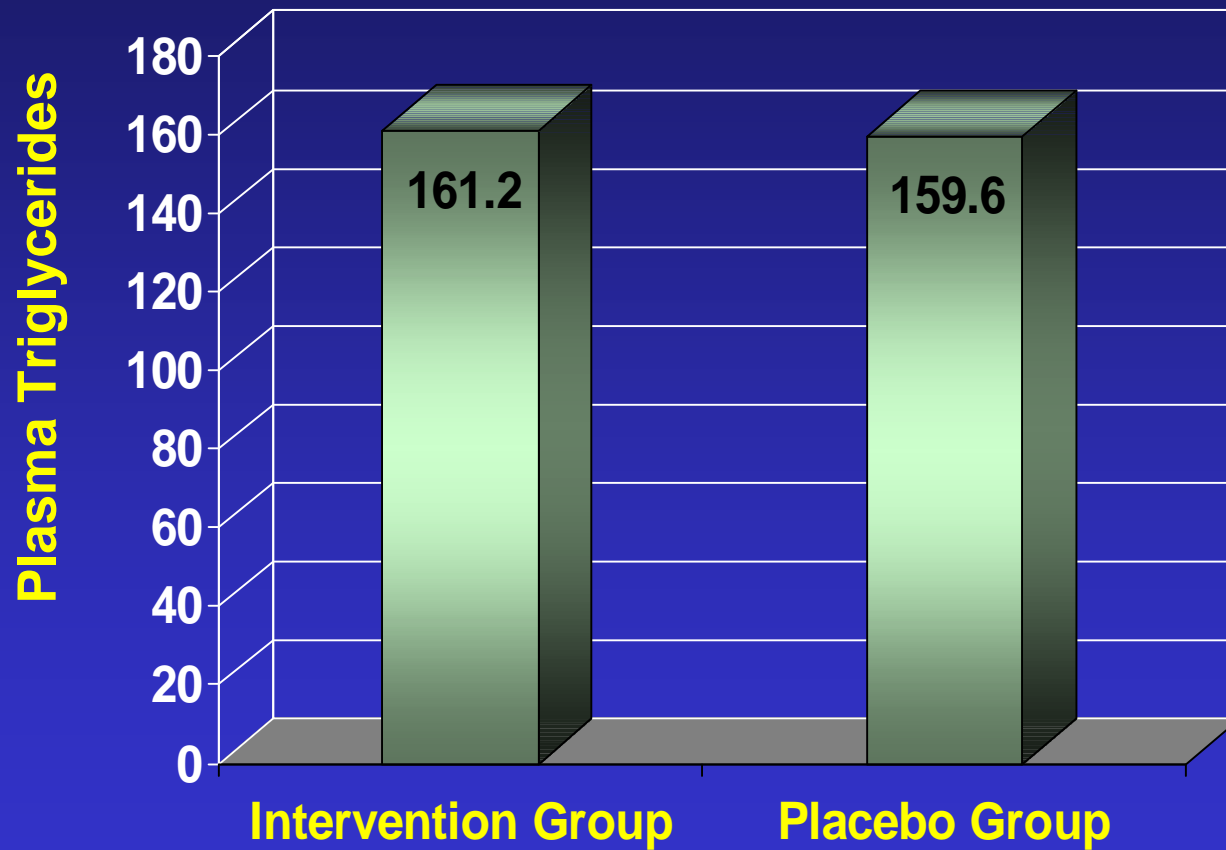
Example

Studies of dietary fat:

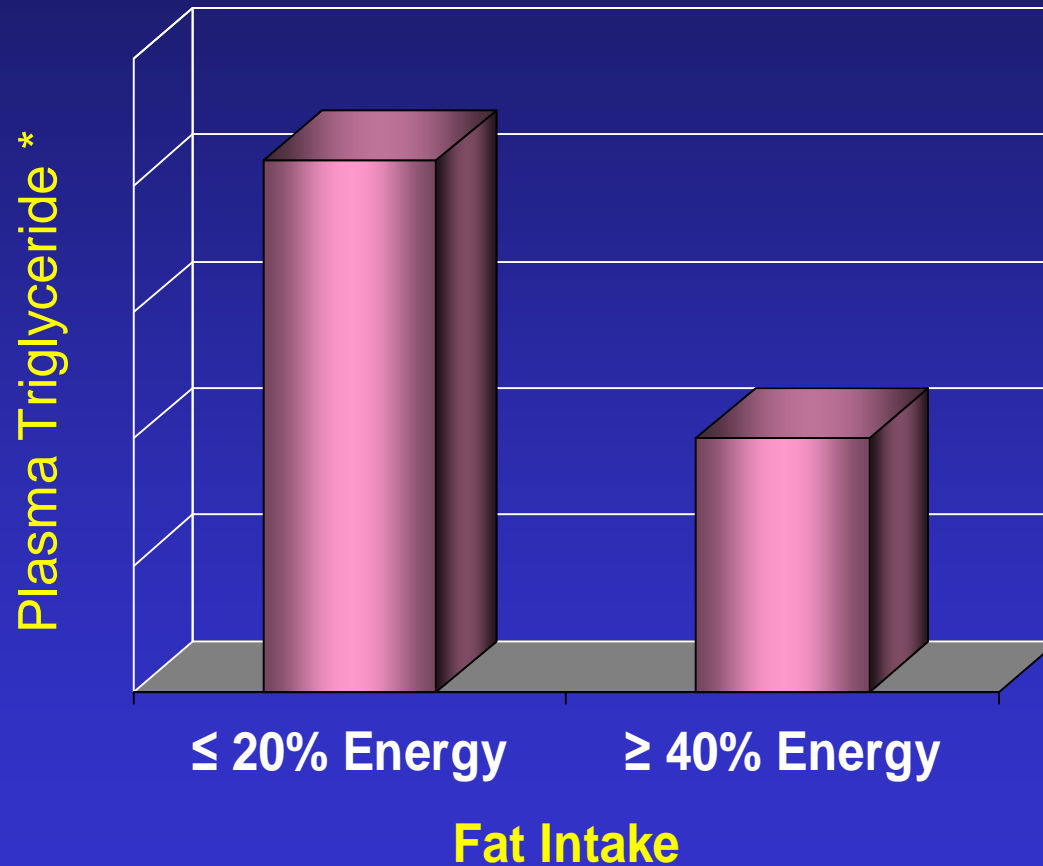
In iso-caloric studies, low dietary fat increases plasma triglycerides.

There is no good biomarker
of total fat intake, but as
% of energy from fat increases,
serum triglyceride levels go down.

Women's Health Initiative (Year 3, mean)



Nurses Health Study and Health Professionals Follow-Up Study



* Adjusted for age, BMI, physical activity

Unpublished

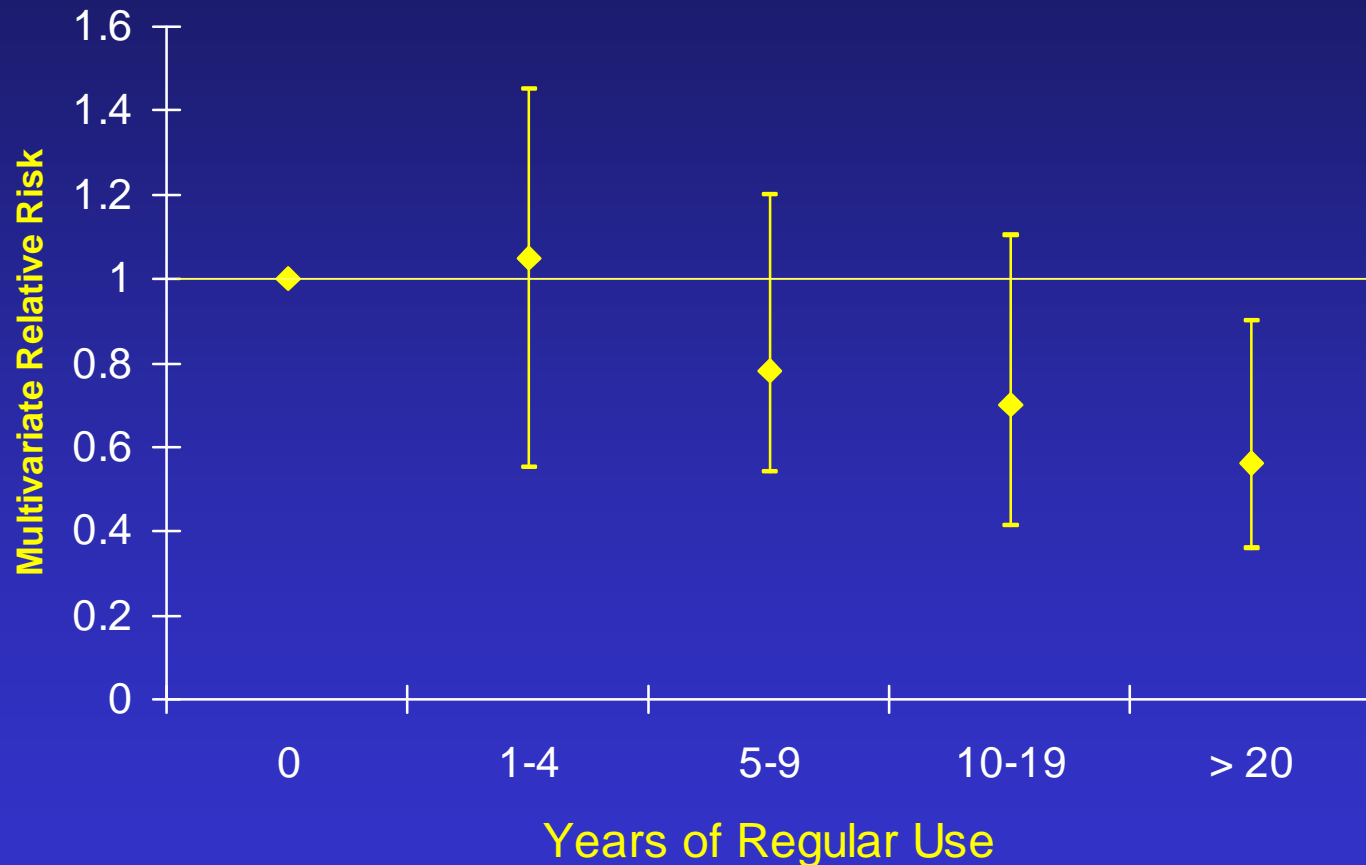
Duration

For chronic diseases, such as cancer, the relevant exposure may occur over decades or could be relevant much longer before the diagnosis.

Examples: aspirin
vitamin D

- Observational data consistently suggest that aspirin intake lowered risk of colorectal cancer, especially after 10-15 years of use
- Initial RCTs did not show an association

RR and 95% CI of Colorectal Cancer According to Years of Aspirin Use Nurses Health Study



Giovannucci et al., *NEJM* 1995

Hazards Ratio (95% CI) of Colorectal Cancer Associated with Aspirin Use

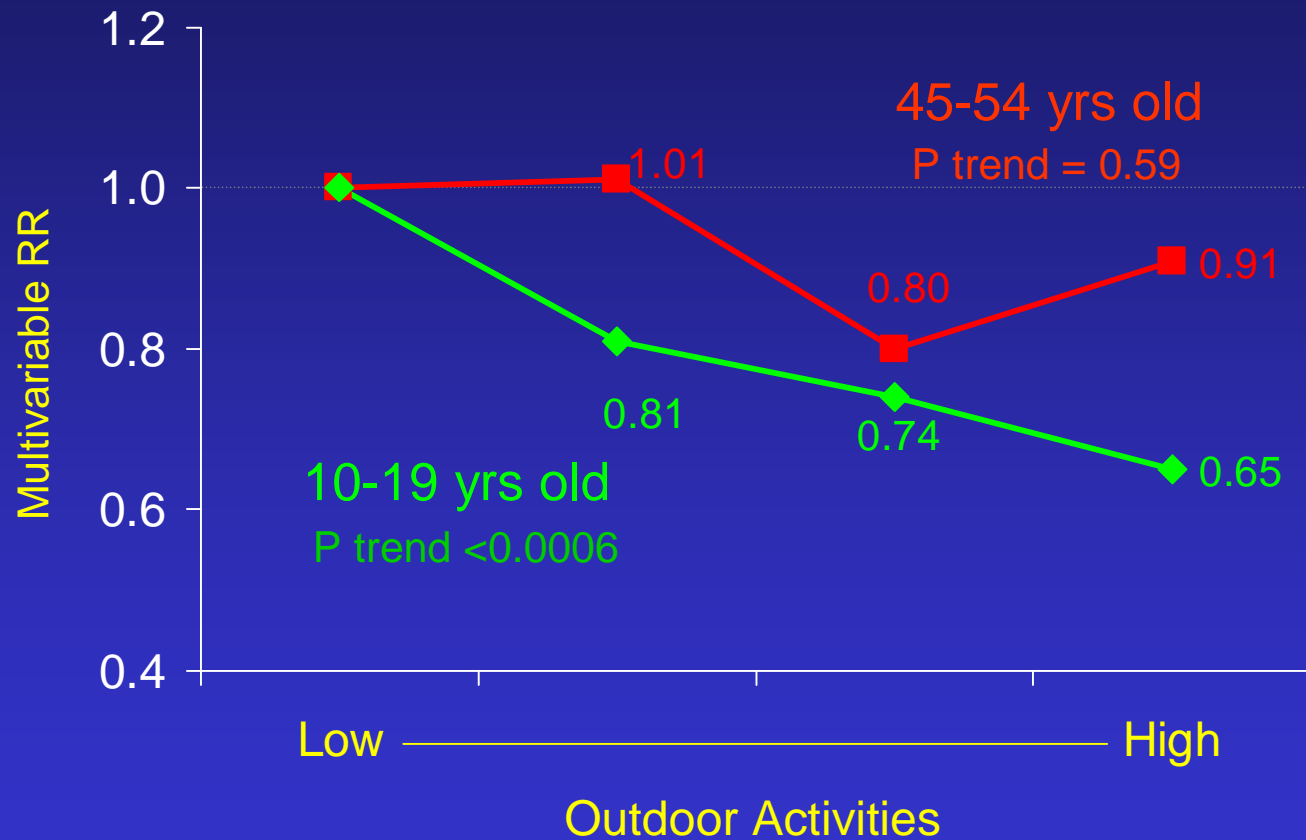
	<u>0-9 Years</u>	<u>10-19 Years</u>
UK-TIA Trial	1.14 (0.49-2.61)	0.51 (0.25-1.00)
British Doctors Aspirin Trial	0.82 (0.45-1.49)	0.64 (0.42-0.97)
Pooled	0.92 (0.56-1.49)	0.60 (0.42-0.87)

Nurses' Health Study

Colorectal Cancer

Vitamin D Intake	RR High vs. Low	P-trend
Single Assessment	0.84	0.16
~ 10 years	0.77	0.11
~ 20 years	0.33	0.003

Case-Control Study of Breast Cancer



- (1) The relevance of observational data as compared to clinical data for the purposes of identifying relevant endpoints and developing dose-response relationships for establishing recommended intakes for generally healthy persons
- (2) Relevant confounders for data interpretation from the perspective of major and minor confounders or even such factors as obesity and physical activity**
- (3) The state of knowledge for vitamin D, as compared to other nutrients of current and past interest such as vitamin E or beta-carotene (i.e., whether the plausibility for vitamin D is stronger than for other micronutrients)

Confounding

- § Key factor to consider in observational studies.
- § Attempt to control for it through multivariate analysis
- § In nutritional studies, particularly difficult to isolate a micronutrient

For example, does:

Beta-carotene = fruits and vegetables?

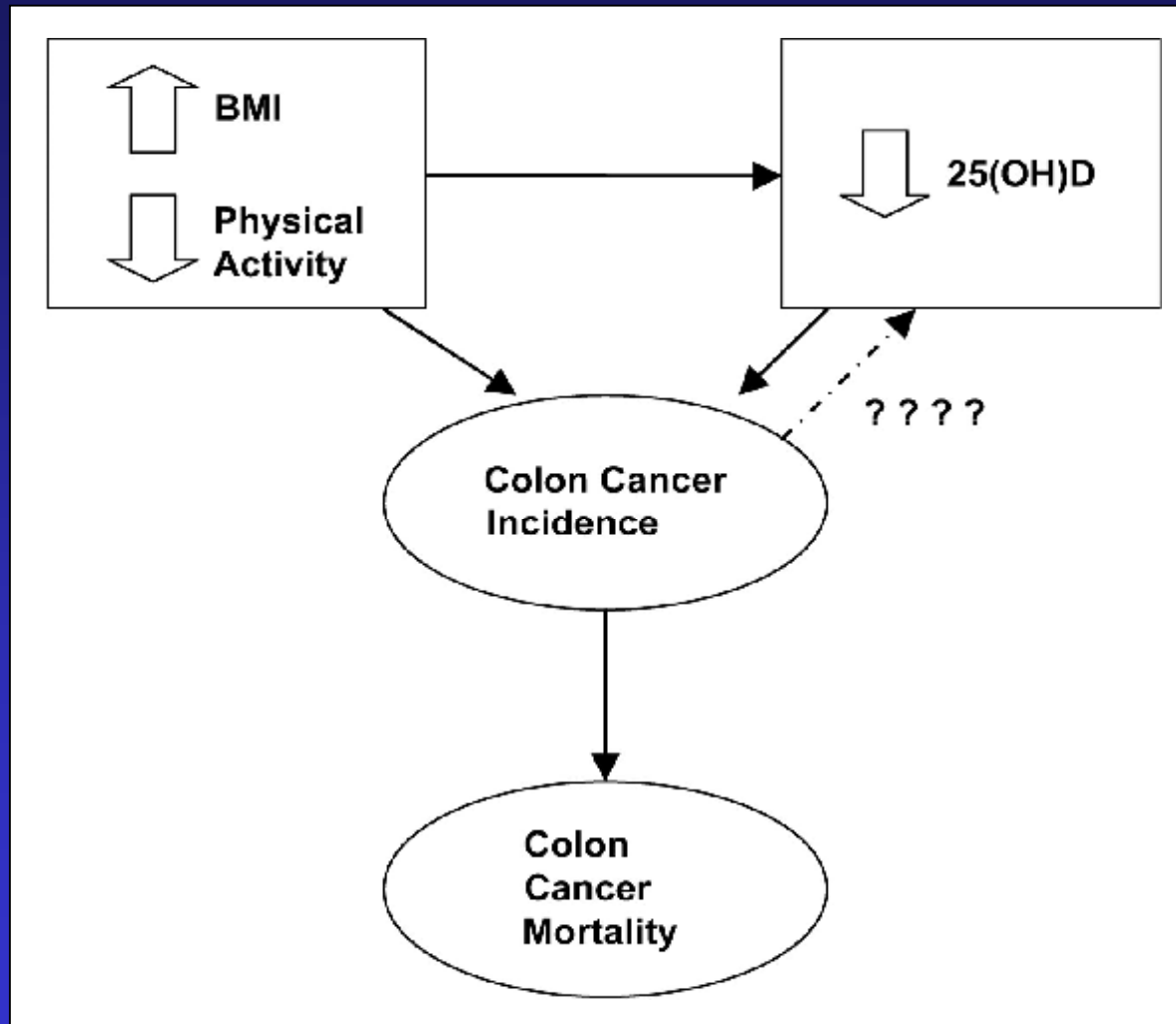
Lycopene = tomato products?

Calcium = dairy products?

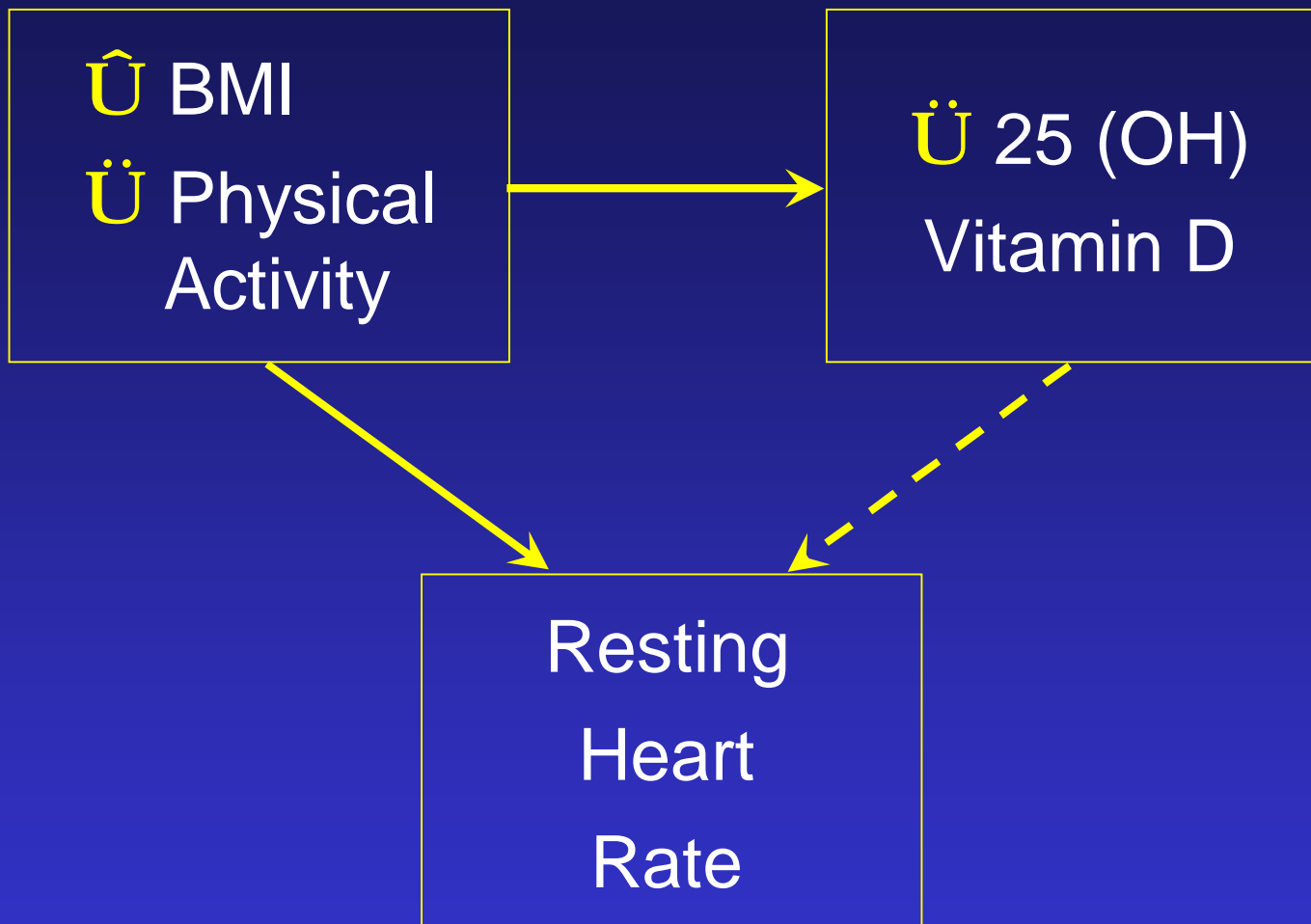
Confounding: Vitamin D

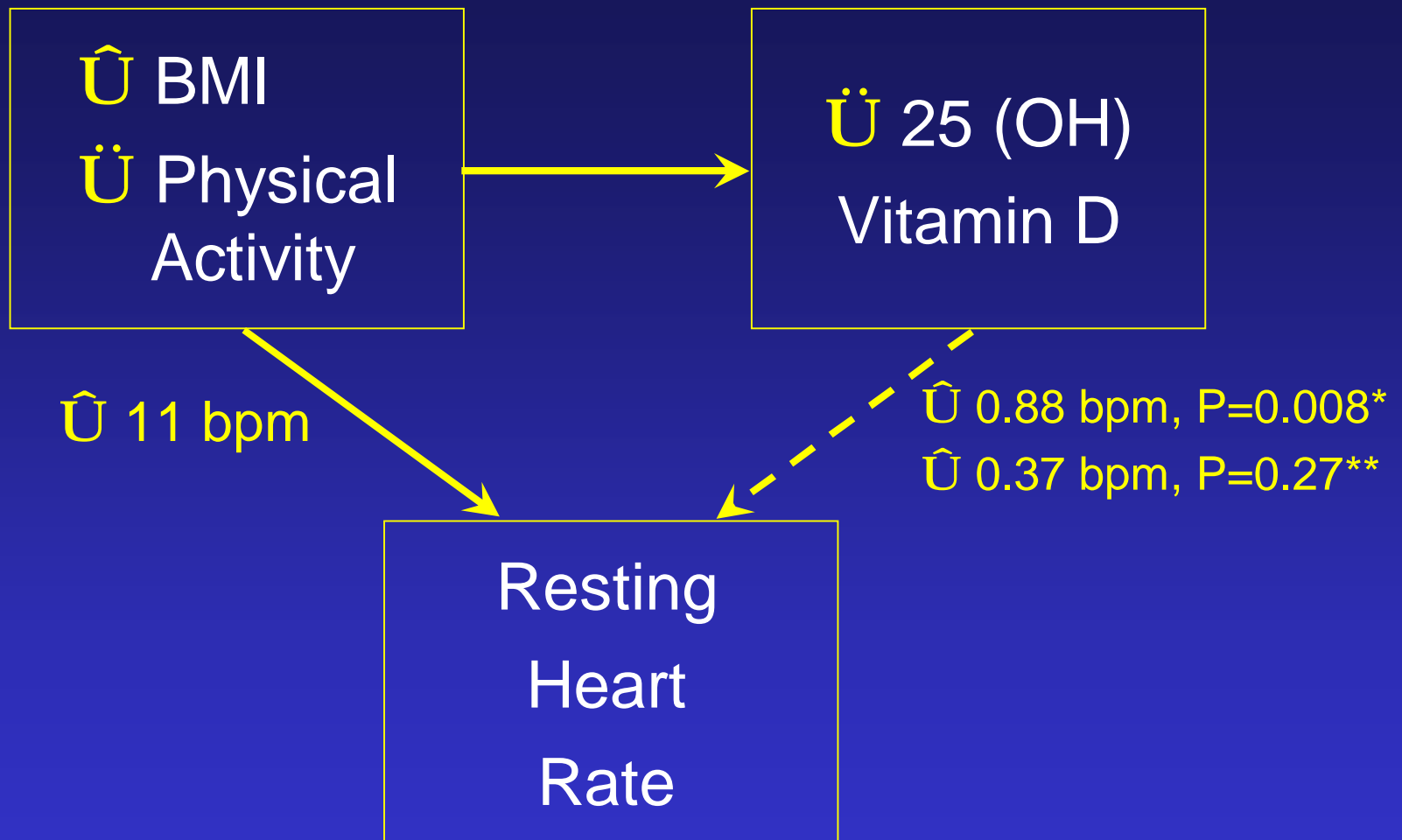
- Qualitatively different from nutritional studies
- Diet contributes about 10-15% of total vitamin D
- Correlation between vitamin D intake and 25(OH)D levels are modest and easily controllable
- Arguably, the most important potential confounders to consider are physical activity and body mass index (BMI)

Interrelationship Among Risk Factors for Colon Cancer



Empirically use an outcome clearly associated with BMI and physical activity, but not vitamin D, to address if physical activity and BMI could be controlled for in the Health Professionals Follow-Up Study





* unadjusted – per 10 ng/mL decrement in 25(OH)D

** adjusted for BMI and physical activity

Summary

- § A modest spurious association was induced between low 25 (OH) D and resting pulse due to confounding by BMI and physical activity
- § This spurious association was entirely removed when adjusted for BMI and physical activity
- § This finding suggests that BMI and physical activity can be controlled for in studies of 25(OH)D

- (1) The relevance of observational data as compared to clinical data for the purposes of identifying relevant endpoints and developing dose-response relationships for establishing recommended intakes for generally healthy persons
- (2) Relevant confounders for data interpretation from the perspective of major and minor confounders or even such factors as obesity and physical activity
- (3) The state of knowledge for vitamin D, as compared to other nutrients of current and past interest such as vitamin E or beta-carotene (i.e., whether the plausibility for vitamin D is stronger than for other micronutrients)**

Vitamin D vs. Micronutrients

- § Confounding issues entirely different
- § Vitamin D is part of a well established endocrine / paracrine / autocrine system with strong biologic effects
- § At least some of the purported benefits of vitamin D are seen in RCTs (e.g. reduction in fractures, falls, PTH levels)
- § Conceptually different, addressing “deficiency” vs. “mega-dose” supplementation

