

10-Year Coronary Incidence Per 10,000 Men

(Keys 1980)

Incidence

3000

$$y=77+78x$$

$$r=0.73$$

2000

1000

0

0

5

10

15

20

25

% Diet Calories from Saturated Fat

east Finland

west Finland

Zutphen

Rome railroad

Belgrade

Zrenjanin

Velika Krsna

Slavonia

Crevalcore

Montegiorgio

Corfu

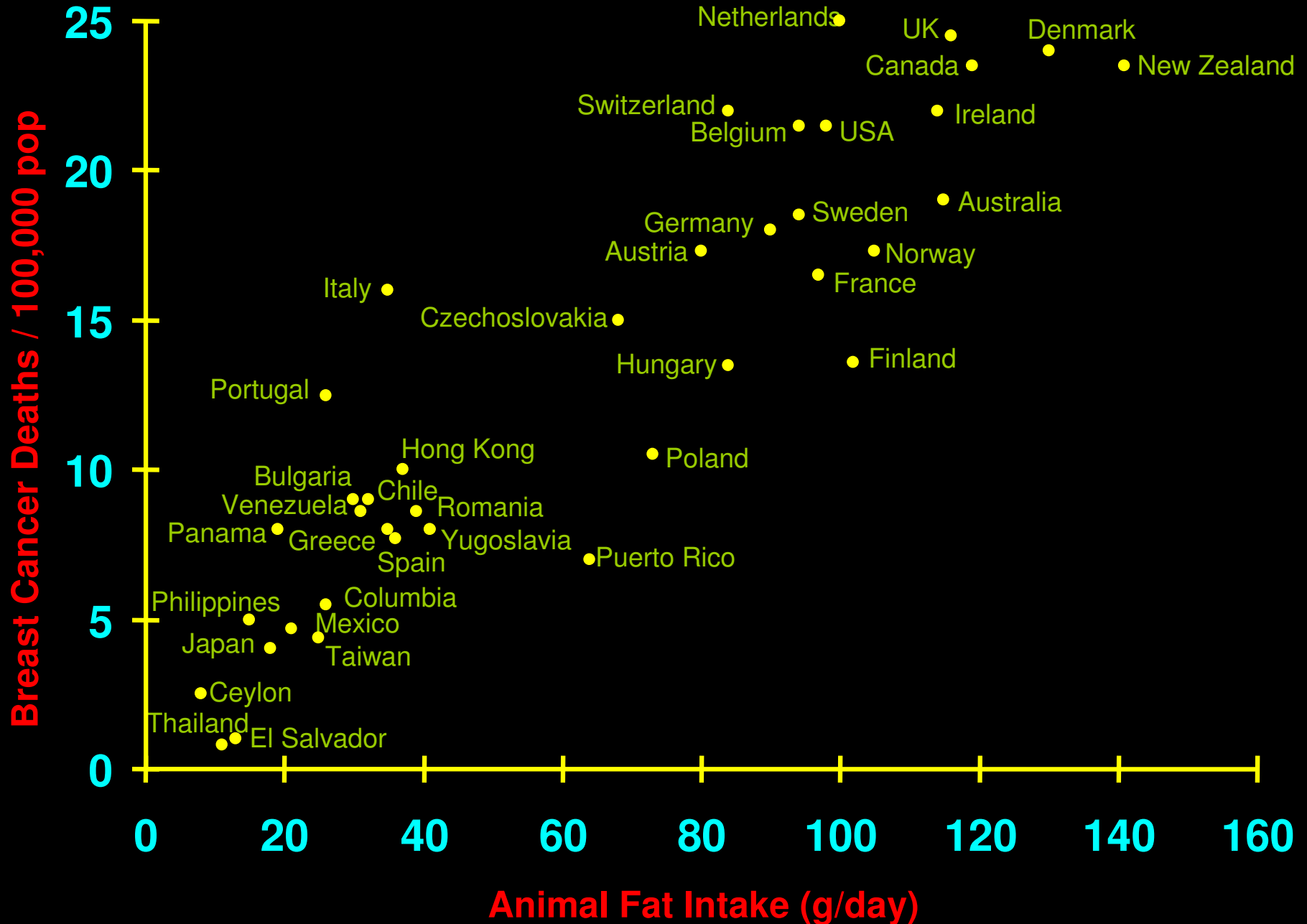
Crete

Dalmatia

Ushibuka

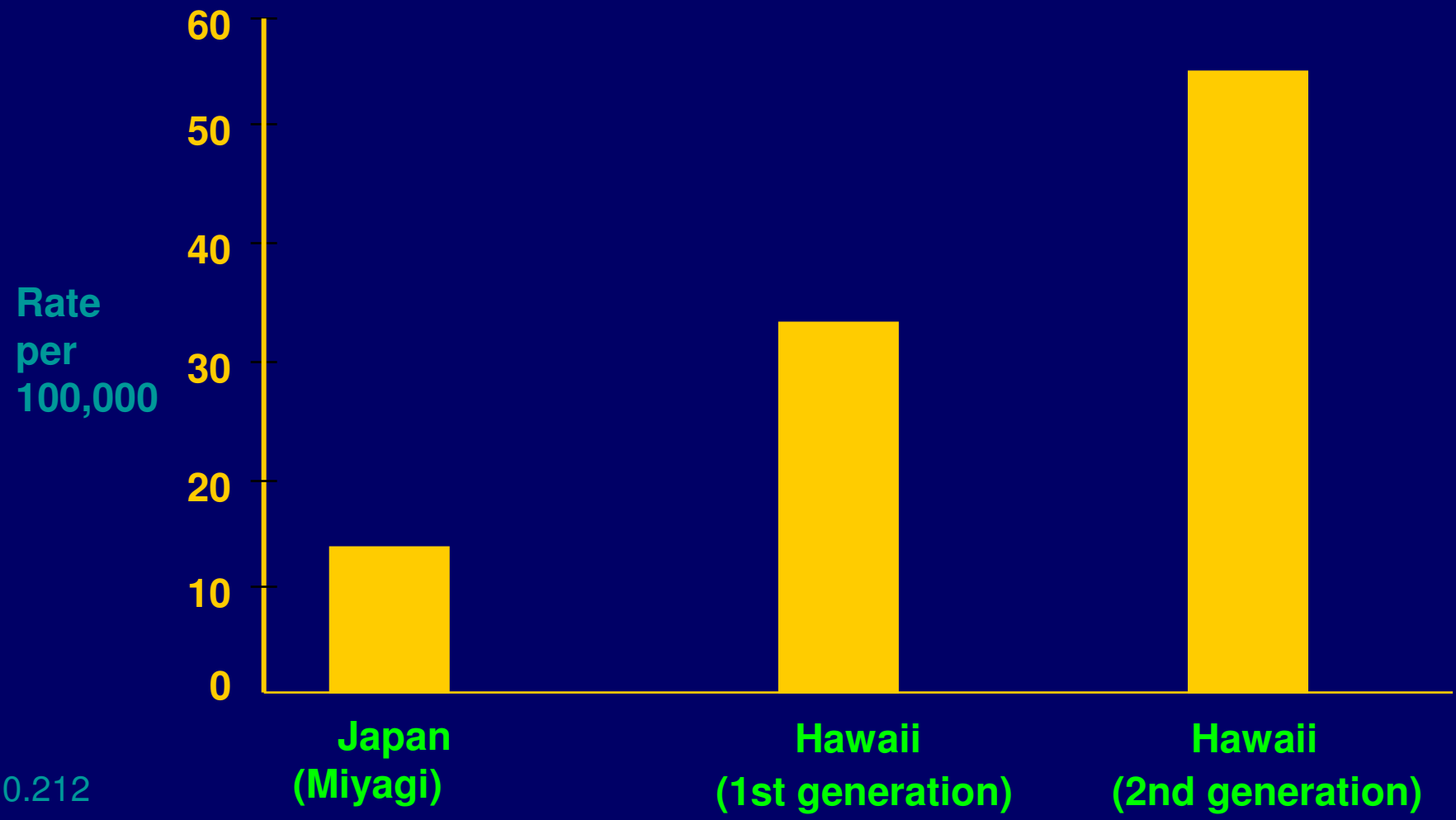
Tanushimaru

Animal Fat and Breast Cancer Mortality



Breast Cancer incidence in Japanese women in Hawaii and Japan, 1968–1977

(Kolonel et al)



Desired: Studies of individuals for better control of confounding

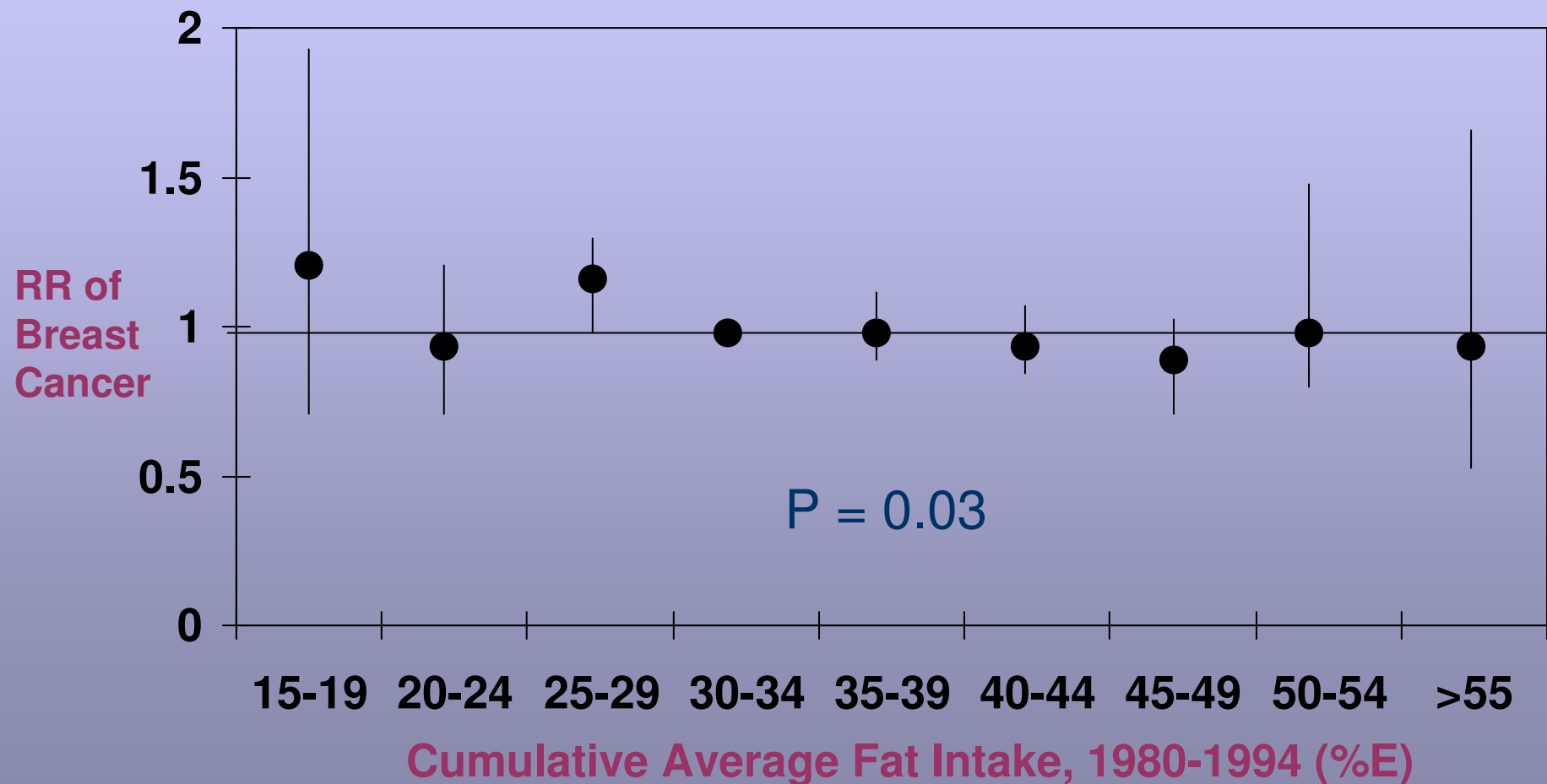
Needed:

1. Between-person variation in diet
2. Reasonably valid diet assessments

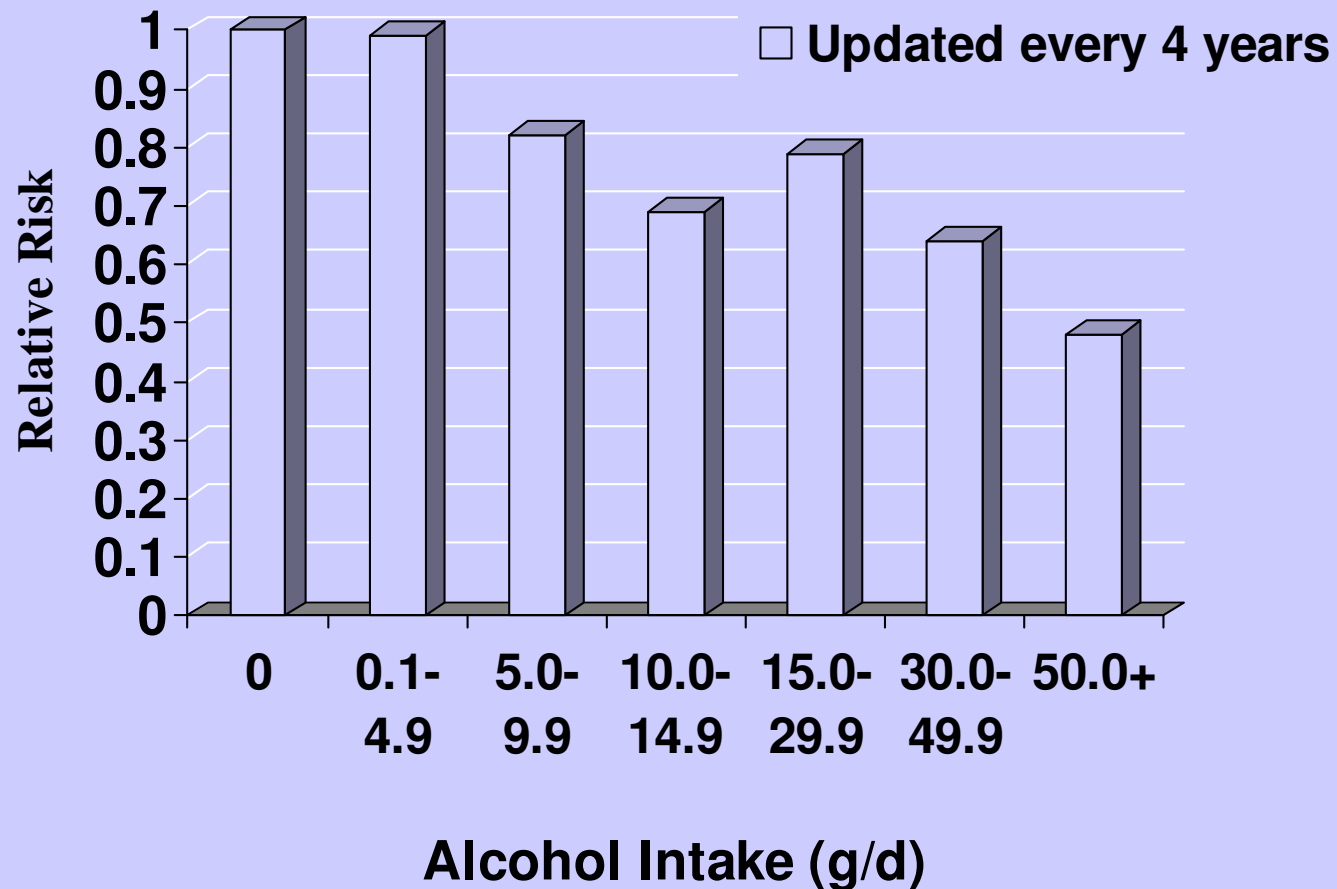
Assertion: Diet varies more between populations than within populations

This may have been true for fat intake at one time (range among countries was about 10-40% of energy) but is less so now.

Fat Intake and Breast Cancer Risk in NHS I

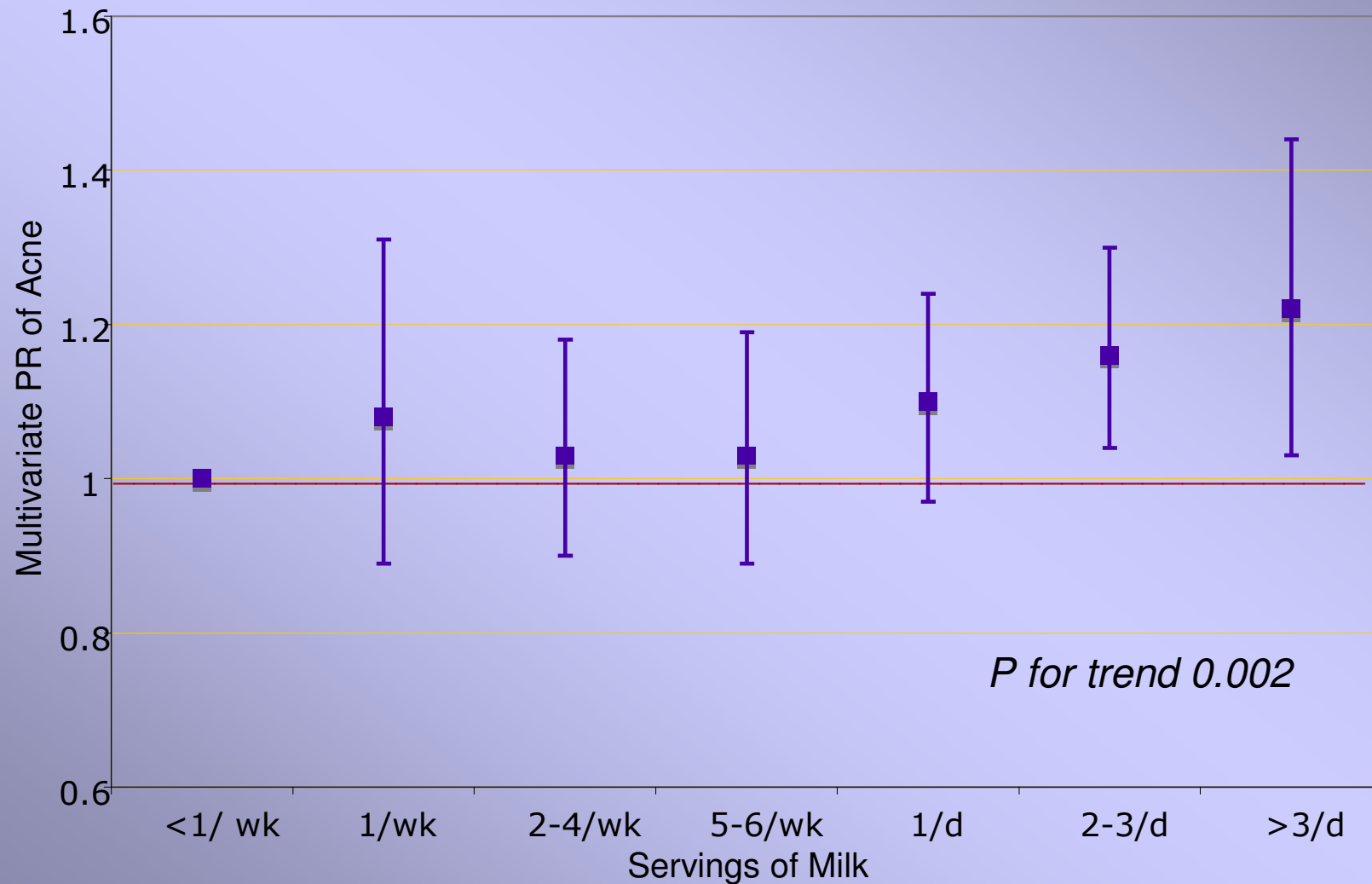


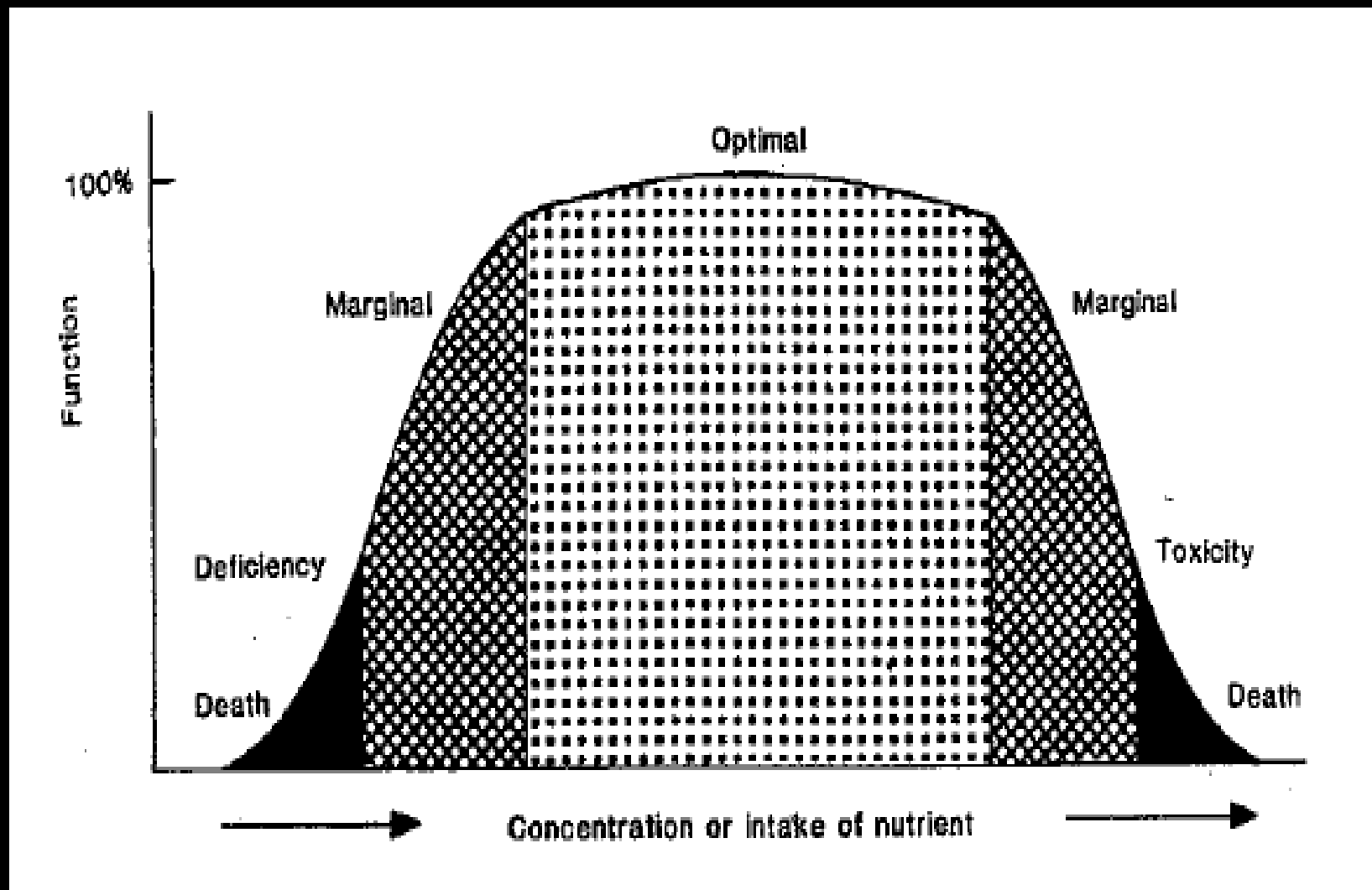
Alcohol Consumption and Risk of Myocardial Infarction



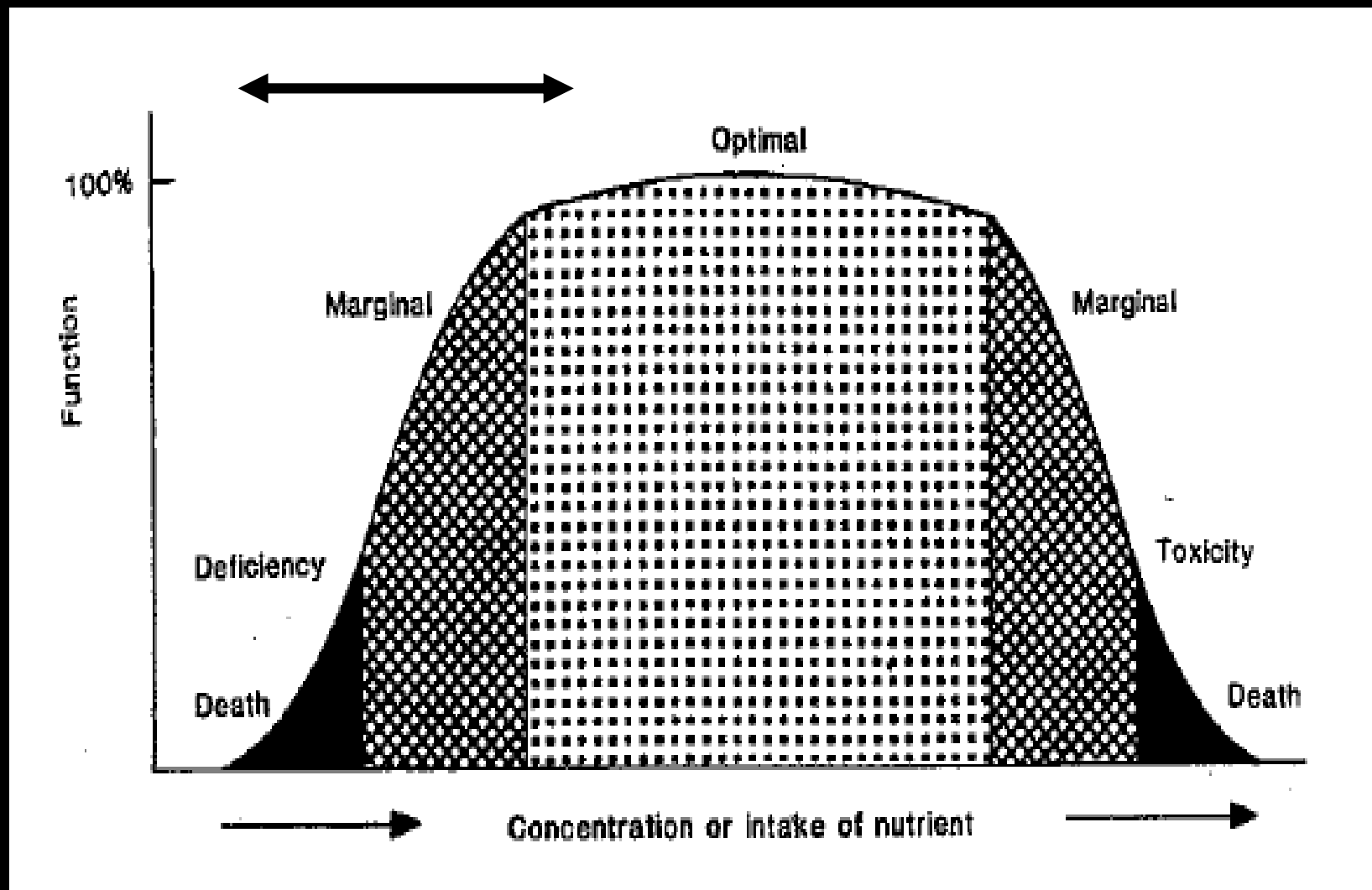
Milk Consumed During High School and Acne

(Adebamowo et al 2005)

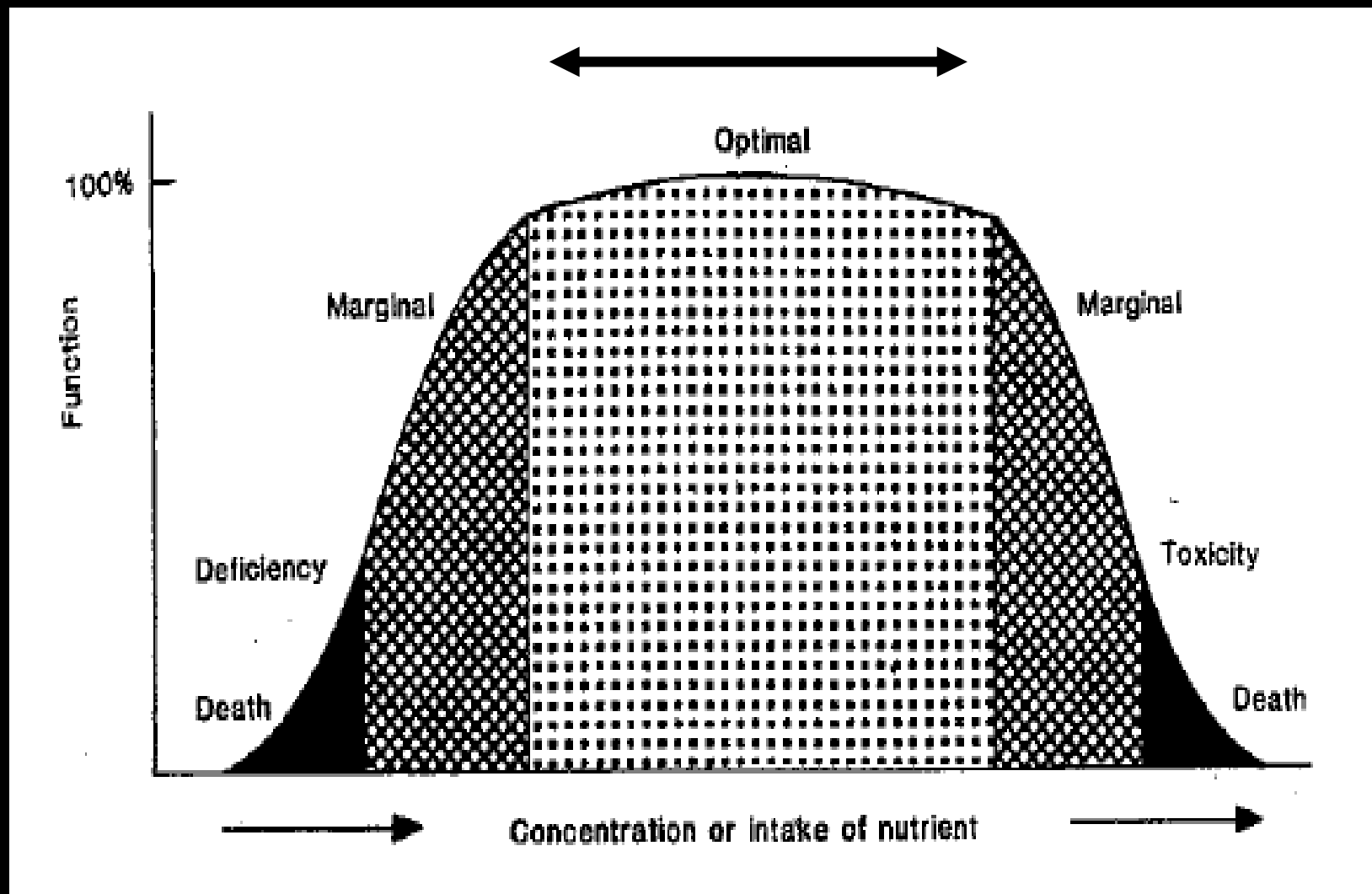




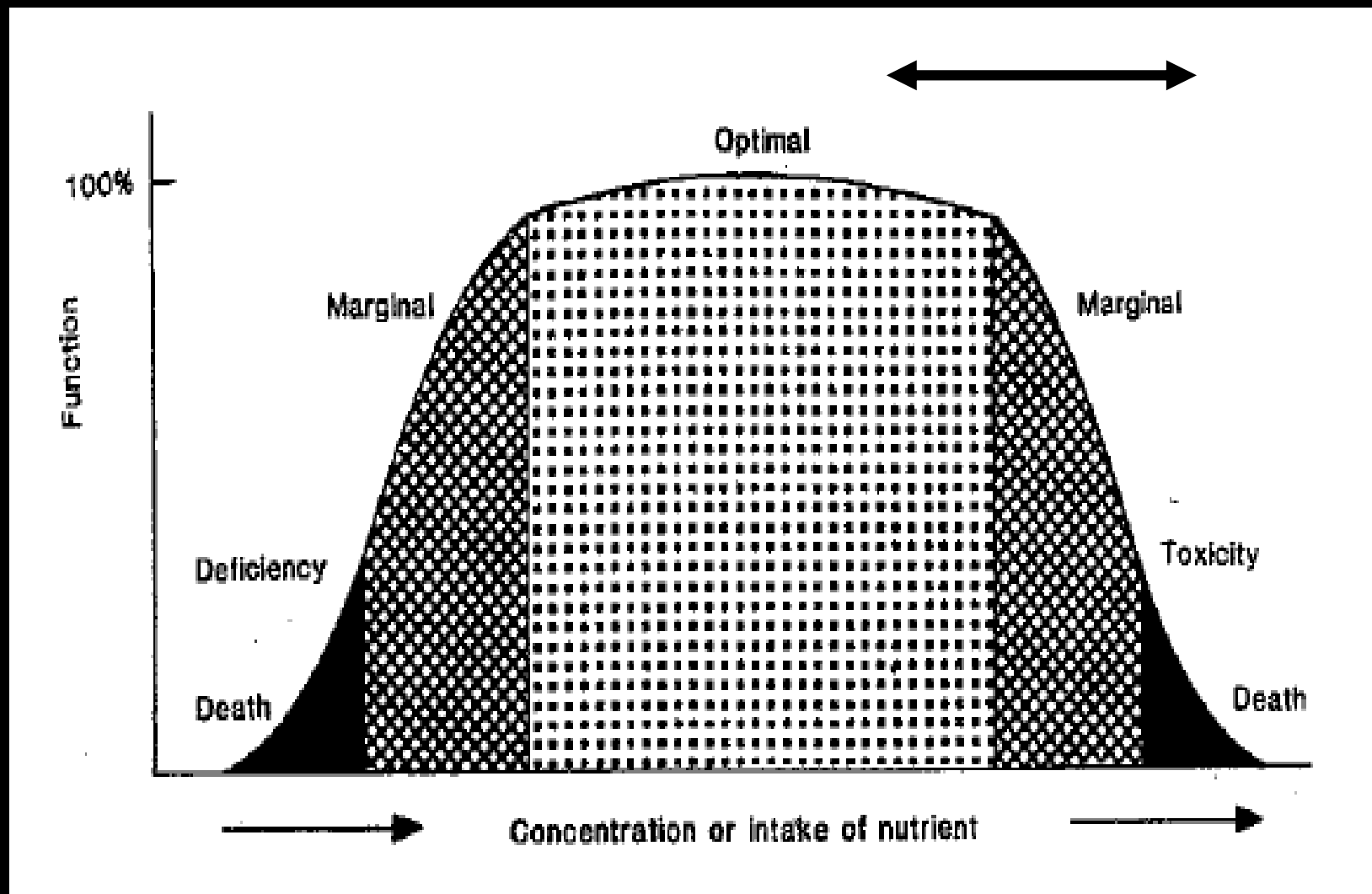
(Mertz 1981)



(Mertz 1981)



(Mertz 1981)



(Mertz 1981)

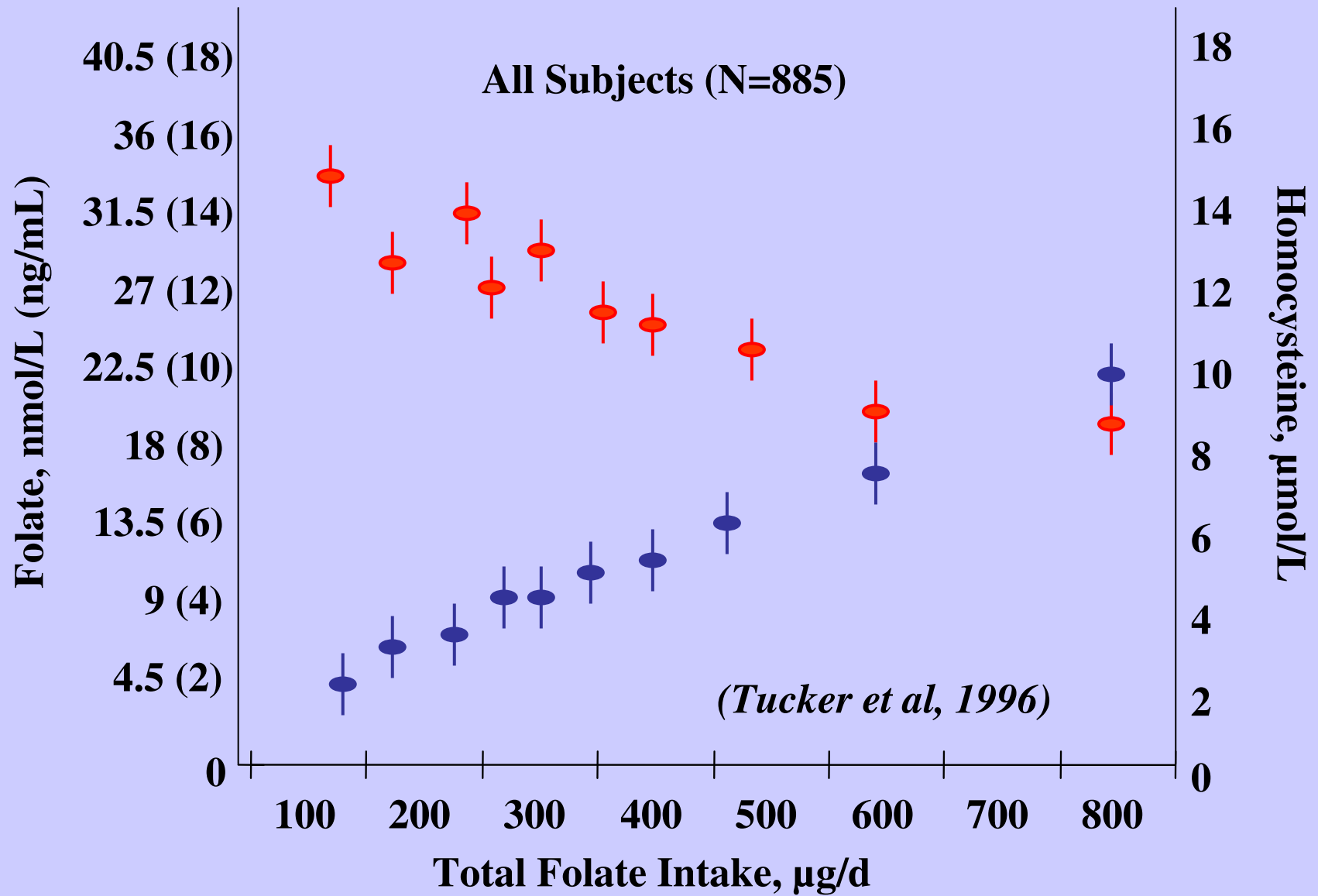
Ratio of within- to between-person variation in nutrients—men (*Beaton 1979*)

Nutrient	Ratio, crude	Ratio, nutrient density
Energy	0.9	---
Fat	1.1	3.8
PUFA	2.7	4.0
Cholesterol	2.8	15.7

For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.

DAIRY FOODS	AVERAGE USE LAST YEAR									1 2 P
	Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day	
Skim or low fat milk (8 oz. glass)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Whole milk (8 oz. glass)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cream, e.g. coffee, whipped (Tbs)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Sour cream (Tbs)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Non-dairy coffee whitener (tsp.)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Sherbet or ice milk (1/2 cup)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ice cream (1/2 cup)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Yogurt (1 cup)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cottage or ricotta cheese (1/2 cup)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cream cheese (1 oz.)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other cheese, e.g. American, cheddar, etc., plain or as part of a dish (1 slice or 1 oz. serving)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Margarine (pat), added to food or bread; exclude use in cooking	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Butter (pat), added to food or bread; exclude use in cooking	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

● Plasma Homocysteine ● Plasma Folate



Pearson correlation coefficients (deattenuated) for macronutrient intakes assessed by FFQs and the and the average of 1980 and 1986 diet records in the Nurses' Health Study

	<i>1986 FFQ vs average diet records</i>
Total fat	0.62 (0.81)
Saturated fat	0.64 (0.90)
Cholesterol	0.58 (0.78)
Protein	0.50 (0.61)
Carbohydrates	0.69 (0.79)
Mean	0.61 (0.78)

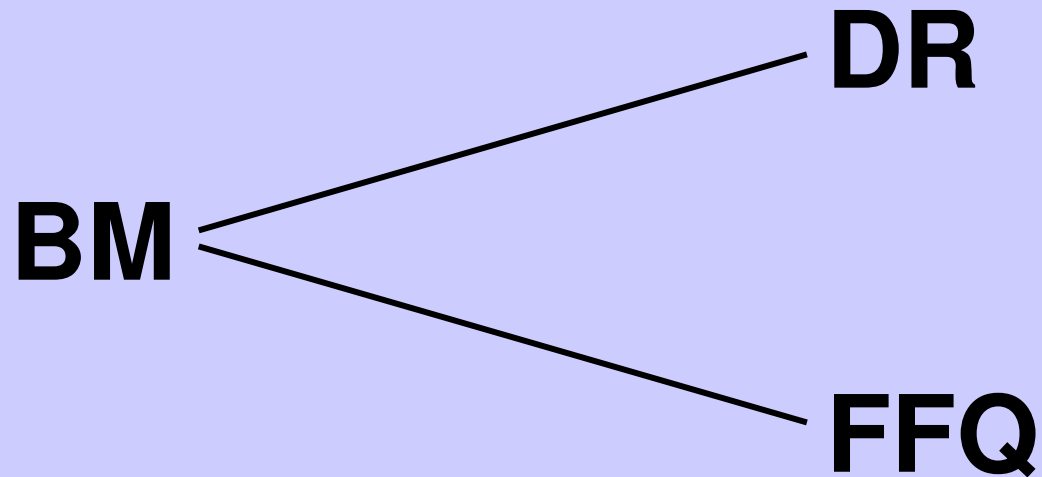
OPEN Study using DLW and urinary nitrogen as biomarkers

(Kipnis et al. Am J Epidemiol 2003; 58:14-21)

Assertions:

- Validity of FFQs has been seriously over-estimated by comparison with 24-hour recalls on diet records due to correlated errors
- Use of FFQs in nutritional epidemiology must be re-evaluated

Correlated Errors



$$E_{DR} = DR - BM$$

$$E_{FFQ} = FFQ - BM$$

***Random Error in Biomarker Creates
Appearance of Correlated Error:***

$$e_{DR} = DR - (DLW + e)$$

$$e_{FFQ} = FFQ - (DLW + e)$$

Reproducibility Correlations for Biomarkers

<i>Nutrient</i>	<i>USDA (1 year)</i>		<i>WHI (6 months)</i>
	<i>M</i>	<i>F</i>	
Energy (DLW)	0.73	0.19	0.72
Protein (UN)	0.77	0.69	0.46
Protein/energy	0.69	0.44	---

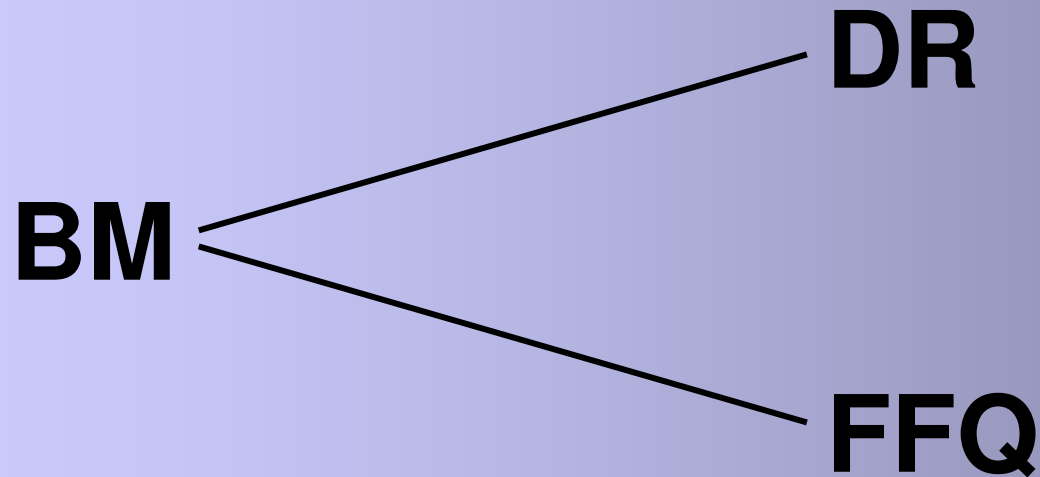
Pearson correlation coefficients (deattenuated) for fat intakes assessed by FFQs & the average intakes by 1980 & 1986 diet records

	1980 FFQ vs average diet records	1984 FFQ vs average diet records	1980, 1984, 1986 FFQ vs average diet records
Total fat	0.44 (0.57)	0.47 (0.61)	0.64 (0.83)
Saturated fat	0.50 (0.70)	0.49 (0.68)	0.68 (0.95)

Can Dietary Assessment Be Improved Further?

- Is there a role for 24-hour recall?
Diet records? A combination of methods?
- Can web-based data collection be used effectively?
- **Note:** Studies of relative validity can be useful, but appropriate temporal relationships are important.

Correlated Errors



$$E_{DR} = DR - BM$$

$$E_{FFQ} = FFQ - BM$$

Limitations of Biomarkers

- Levels often not proportional to intake or linear
- Substantial variability (error)
- Often not specific (e.g. vitamin C)
- Usually confounded by other aspects of diet
- Often susceptible to reverse causation
- Repeated measures usually costly
- Do not provide data on foods or dietary patterns
- Not useful for remote intake
- Feasible biomarkers often don't exist

Acrylamide Hemoglobin Adducts as a Biomarker (Wilson K, et al.)

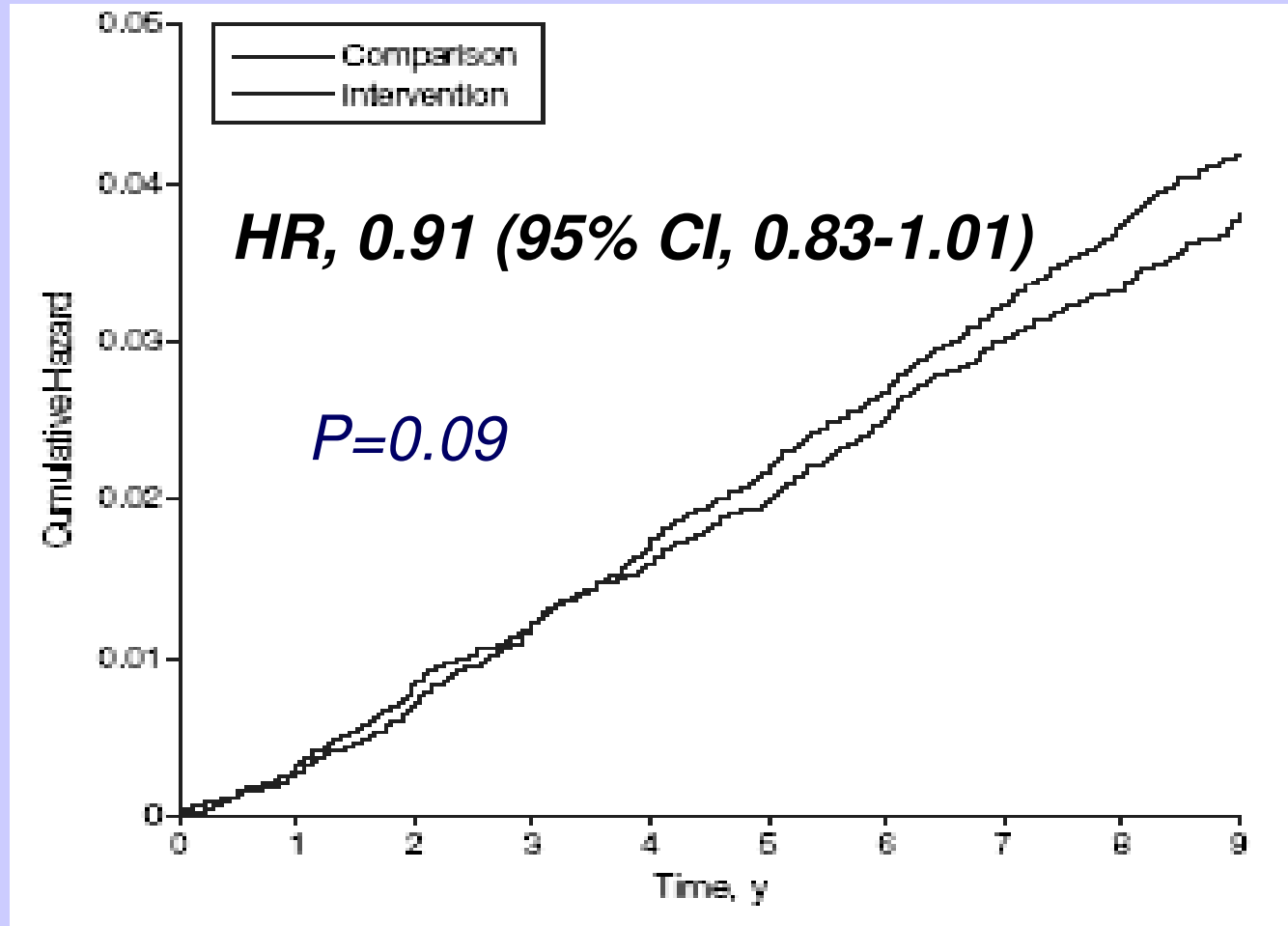
Correlation with calculated intake, adjusted for within-person variation in biomarker = 0.34 (CI: 0.23 – 0.45)

Correlation for reproducibility of biomarker = 0.77 in blood samples collected 1 to 3 years apart

Remaining Challenges

- Correlated dietary factors (specificity)
- Usual challenges of determining causality (e.g. confounding)
- Long latency and complex temporal relationships
- Non-linear dose-response relationships

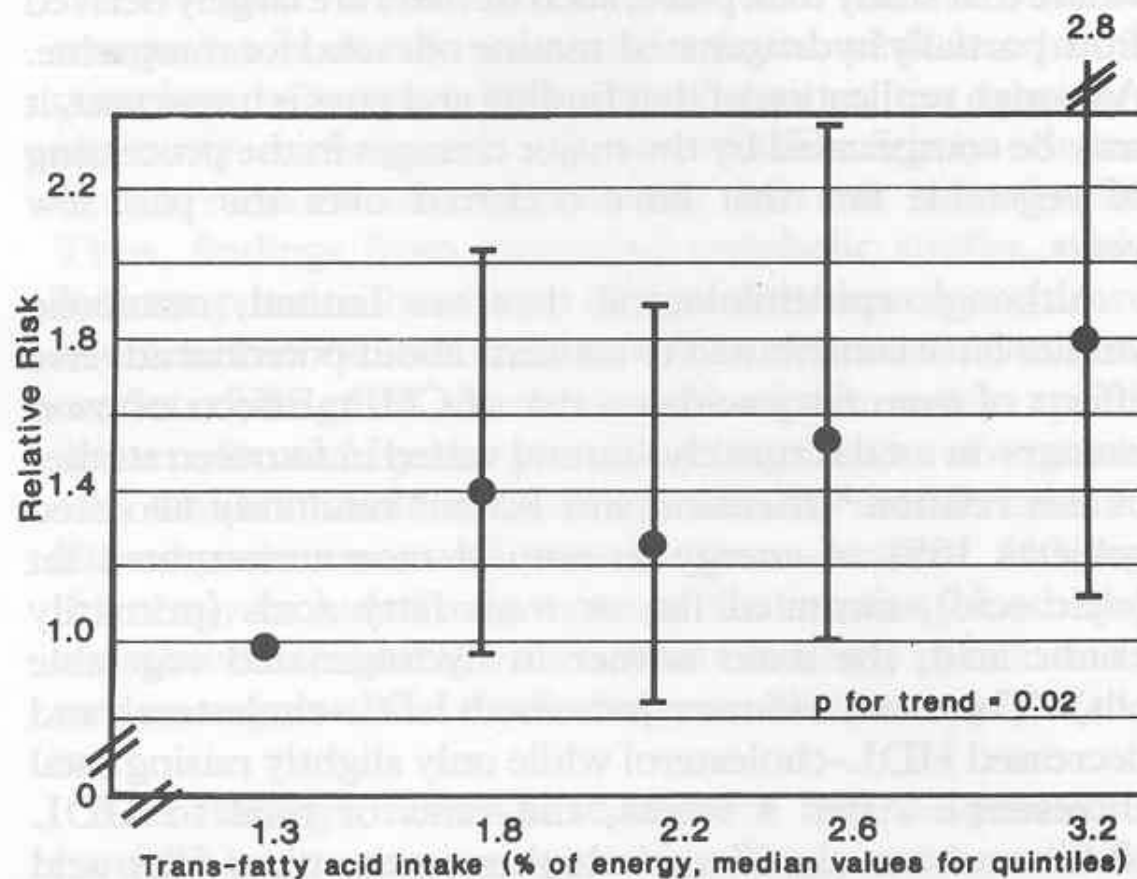
Breast Cancer Incidence in WHI



(Prentice et al. 2006)

Change in Dietary Fat, HDL, Triglycerides in the WHI
(Prentice 2006; Howard 2006)

Fat Intake (%E)	Baseline	Year 6
Control	38.8%	38.1%
Intervention	38.8%	29.8%
HDL (mg/dl)		Year 3
Control	56.4	56.4
Intervention	58.1	57.7
		(NS)
Triglyceride (mg/dl)		Year 3
Control	141.1	144.6
Intervention	138.6	142.3
		(NS)



Relative risk of CHD by *trans*-fatty-acid intake as percentage of total energy.

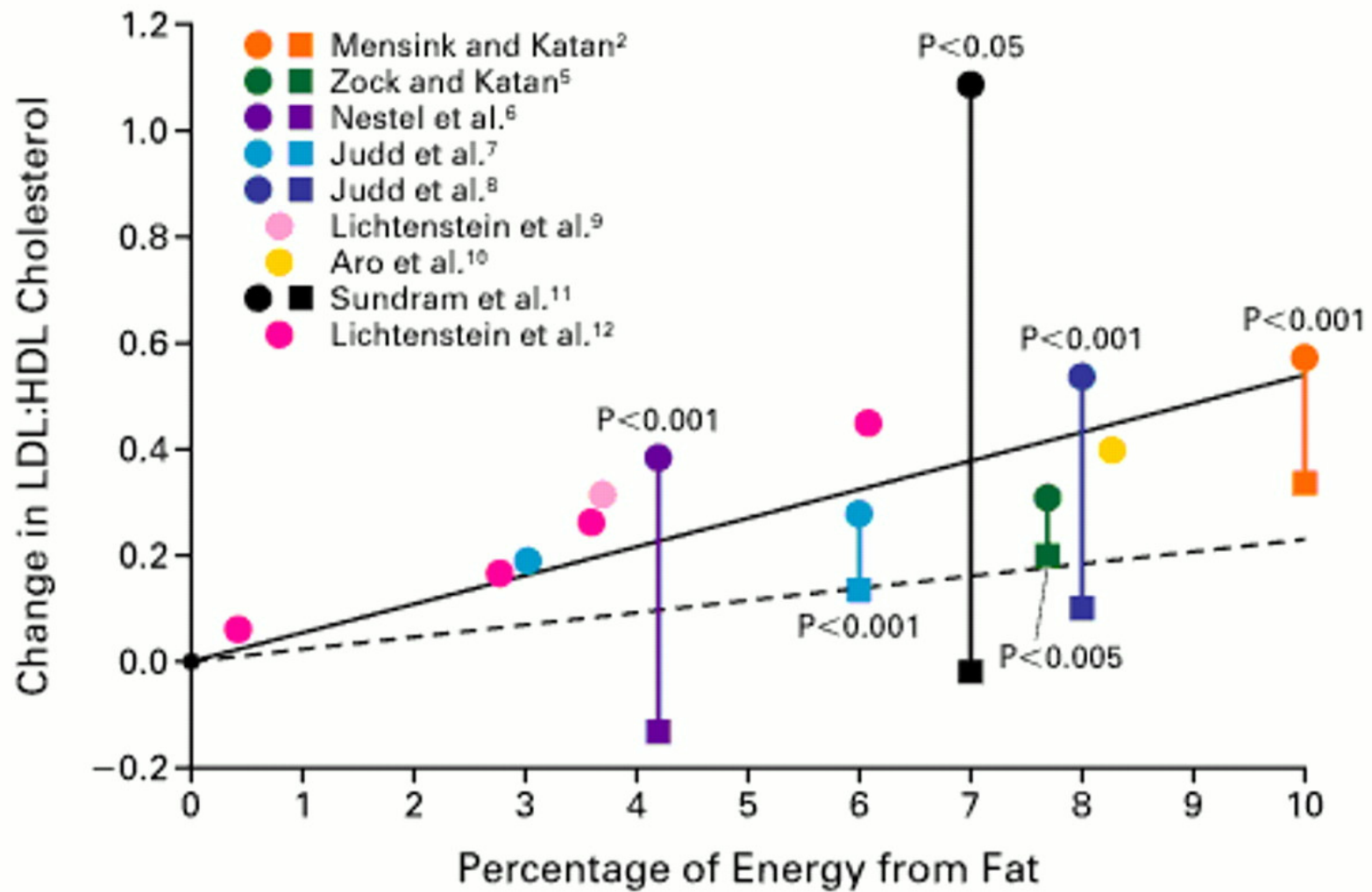
Analysis for 69 181 women who in 1980 reported no change in margarine intake in previous 10 years. Relative risks from proportional hazards model controlling for age, standard risk factors, dietary lipids, and multiple vitamin use.

Relative Risk of CHD Associated with Trans Fat Intake (for 2% of calories, or ~40 calories)

Type and Year of Study	No. of Subjects	No. of Events	Relative Risk (95% CI)
Prospective cohort studies			
Nurses' Health Study, 2005 ⁵⁵	78,778	1766	1.33
Health Professionals Follow-up Study, 2005 ⁵⁶	38,461	1702	1.26
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, 1997 ⁵³	21,930	1399	1.14
Zutphen Elderly Study, 2001 ⁵⁴	667	98	1.28
Pooled prospective studies			1.23

Pooled RR = 1.23 (1.11, 1.37)
p<0.001

(Mozaffarian et al, NEJM 2006)



(Ascherio 1999)

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Nutrition Facts

Serving Size 1 oz. (28g/About 15 chips)
Servings Per Container About 6

Amount Per Serving

Calories 150 **Calories from Fat** 90

% Daily Value*

Total Fat 10g **15%**

Saturated Fat 3g **15%**

Trans Fat 0g

Cholesterol 0mg **0%**

Sodium 200mg **8%**

Total Carbohydrate 15g **5%**

Dietary Fiber 1g **4%**

Sugars 2g

Protein 2g



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you'll understand why
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Diet Score & Risk of Heart Disease in NHS

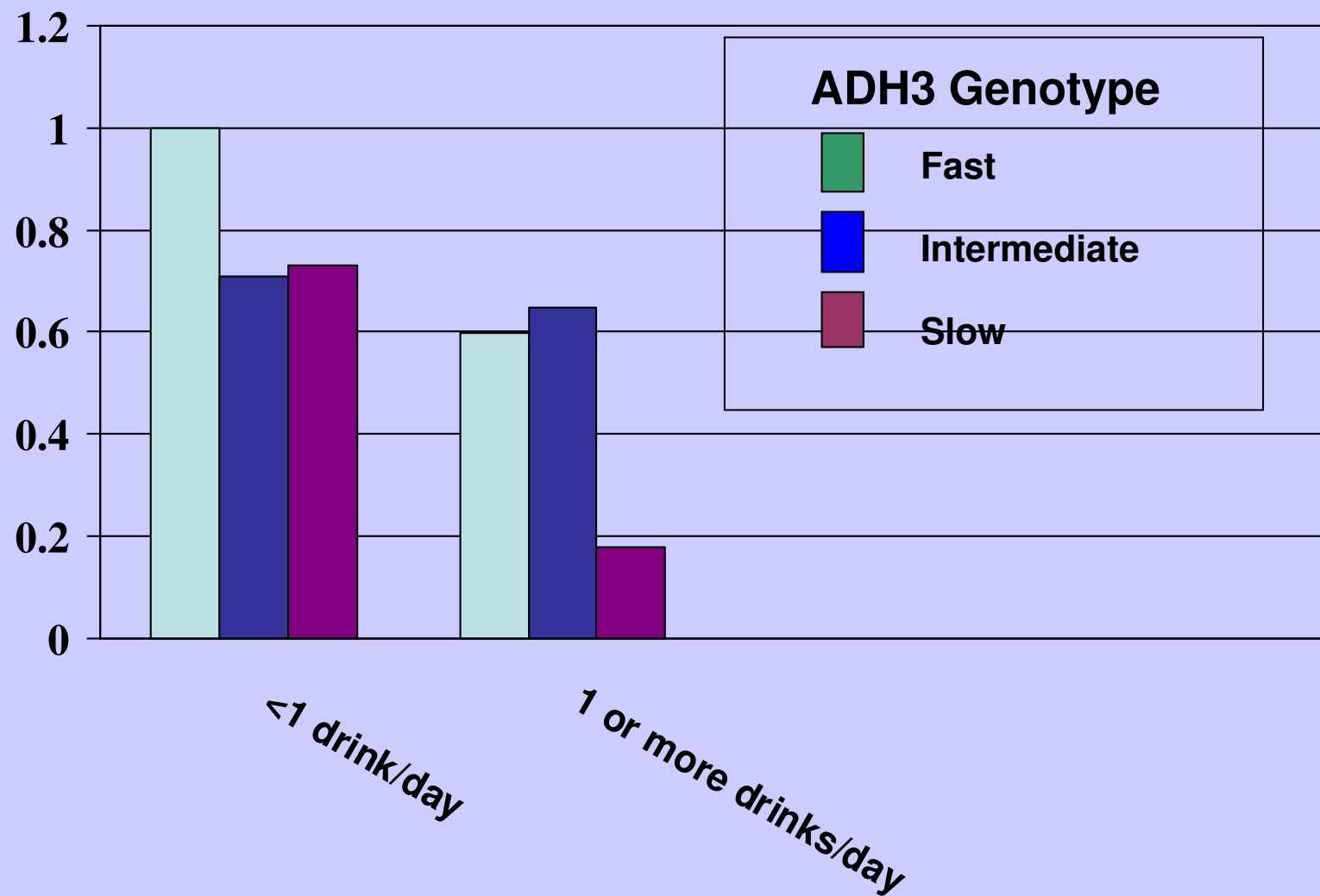


Mendelian Randomization: an alternative to randomized, controlled trials

An associations between a genetic polymorphism in a specific metabolic pathway and risk of disease implicates a substrate for, or product of, that pathway in the etiology of the disease.

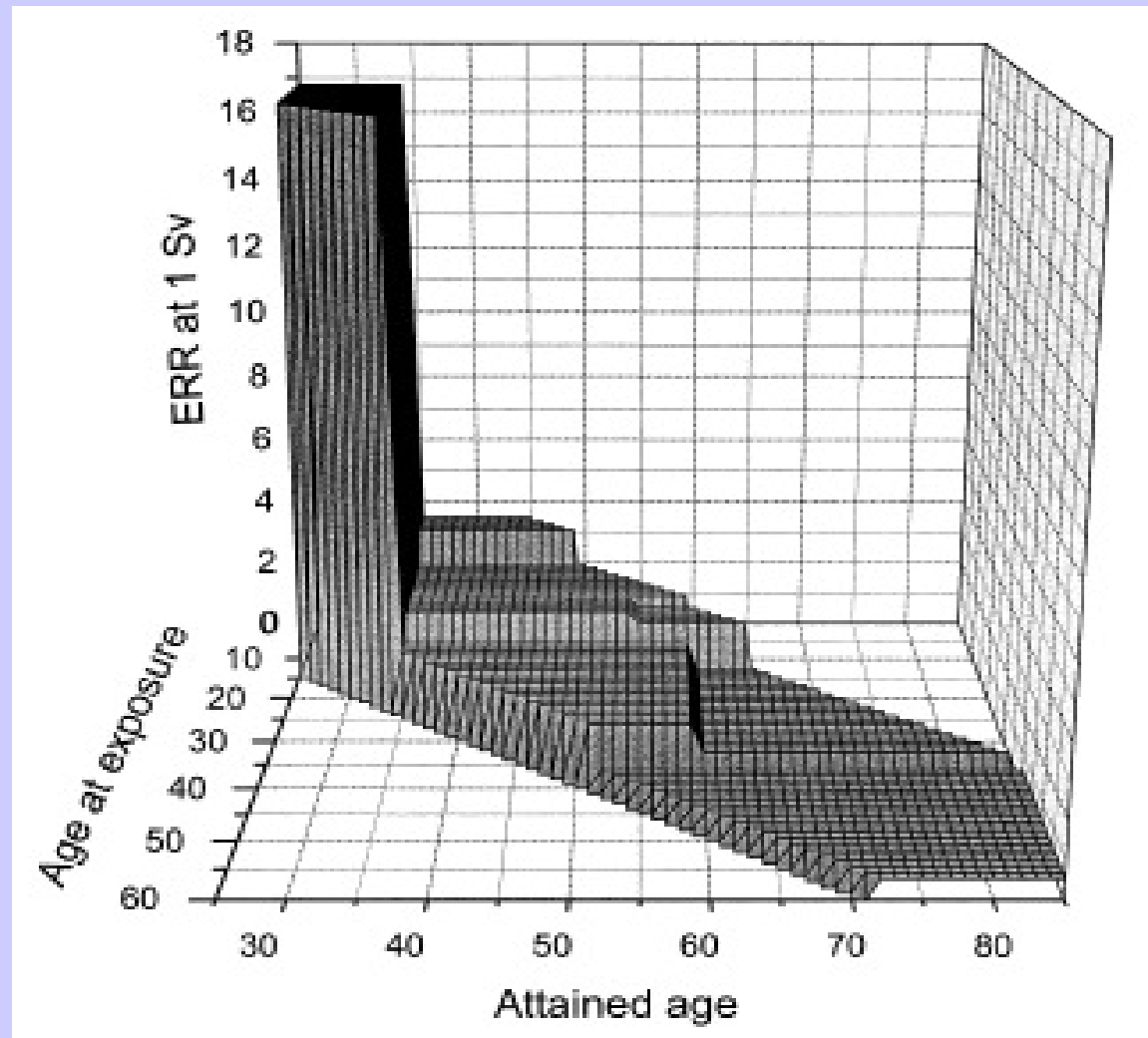
This assumes that most genetic variation (single nucleotide polymorphisms) is not correlated with, and thus not confounded by, behavioral risk factors.

Relative Risk of Myocardial Infarction



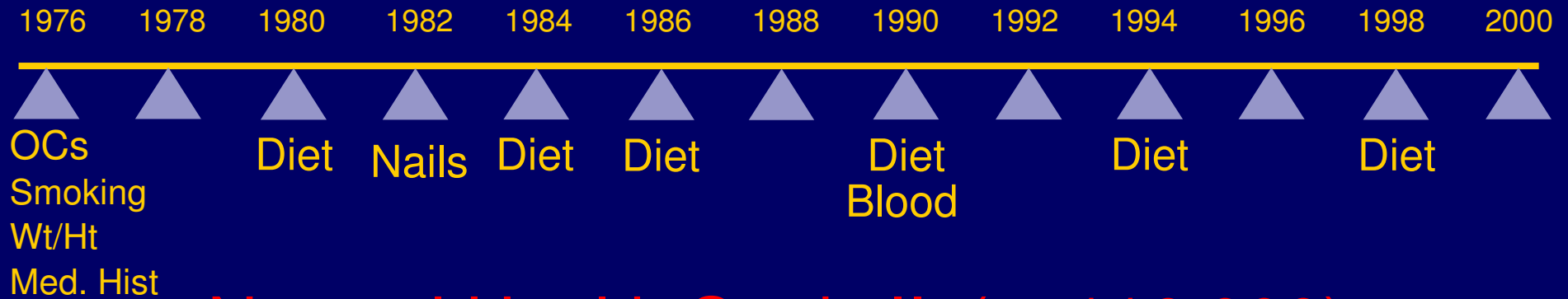
Hines et al, *NEJM* 2001

Atomic Bomb & Breast Cancer by Age at Exposure

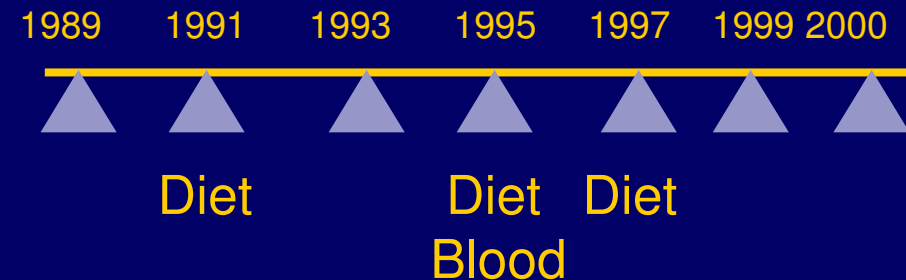


(Land et al, 2003)

Nurses' Health Study (n=121,700)



Nurses' Health Study II (n=116,000)



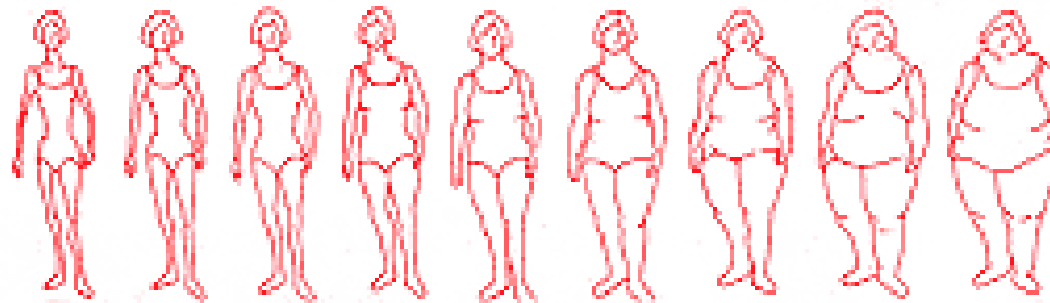
GUTS (n=15,000)



Investigators: Frank Speizer, Bernie Rosner, Meir Stampfer, Graham Colditz, David Hunter, JoAnn Manson, Sue Hankinson, Eric Rimm, Ed Giovannucci, Alberto Ascherio, Gary Curhan, Charlie Fuchs, Fran Grodstein, Michelle Holmes

Measure of Early Body Fatness

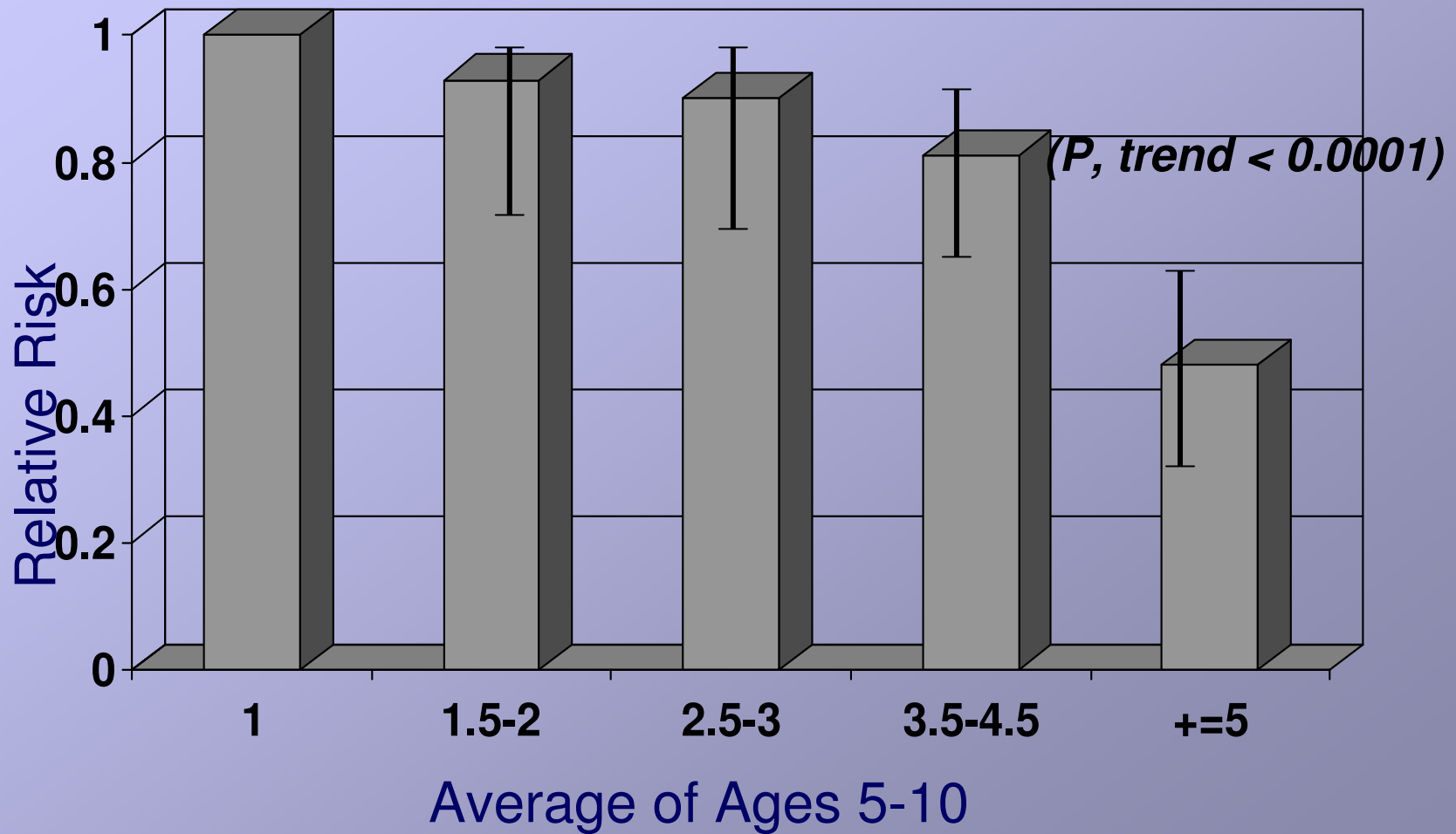
44. Which diagram best depicts your outline at each age?



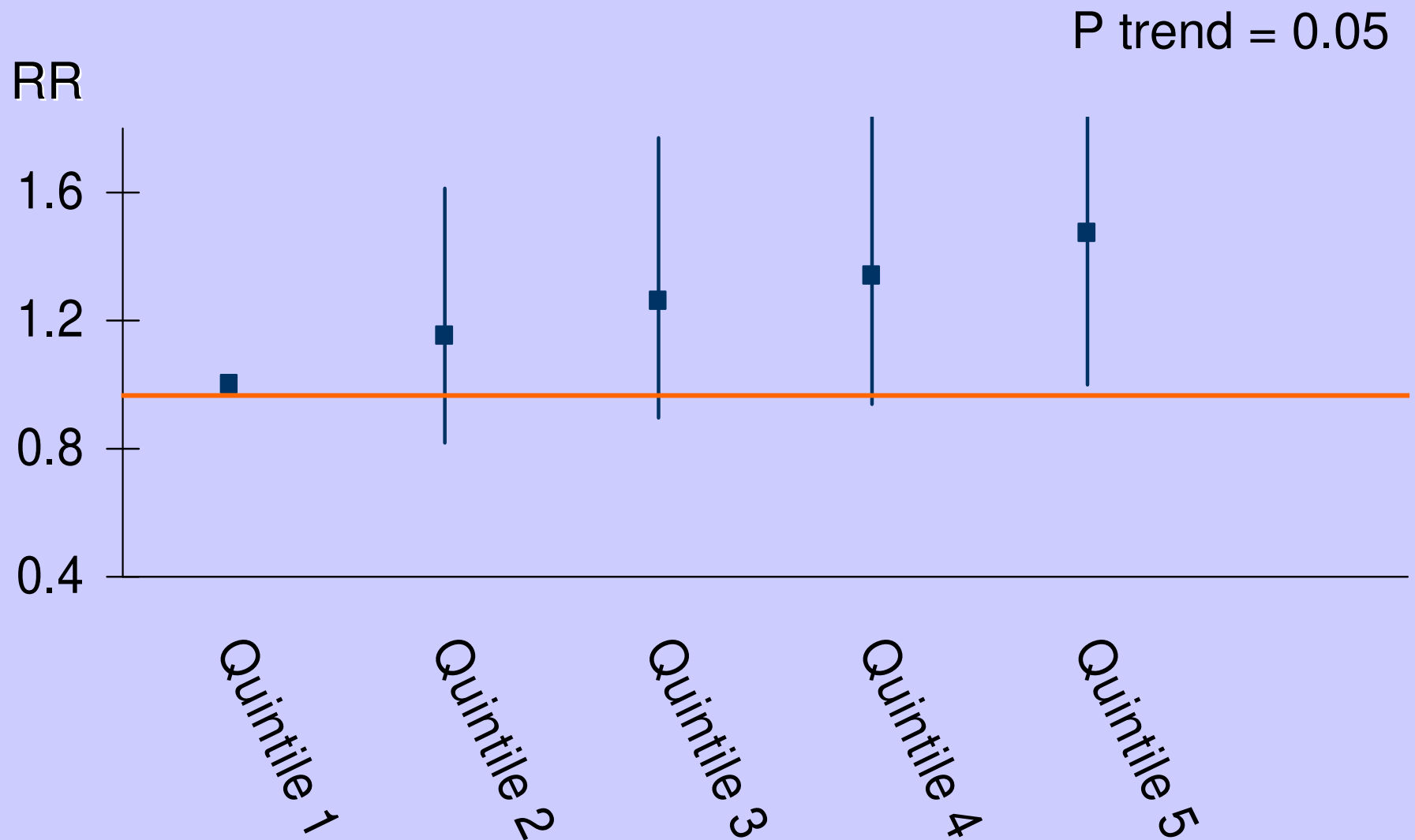
1 2 3 4 5 6 7 8 9

Currently	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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Age 10	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Age 20	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Age 30	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Age 40	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Relative Risk of Breast Cancer by Body Build at Ages 5-10 among 109,267 Women in NHSII (*Baer et al. 2004*)



Red meat intake during adolescence & risk of breast cancer



Conclusions

1. Existing dietary assessment methods can detect important diet and disease relationships.
2. Confounding will remain an important issue; using a combination of epidemiologic observations and controlled feeding studies with intermediate endpoints will often provide a strong body of evidence.
3. Long latencies complicate the study of some cancers and will require long-term studies and creative approaches.