

*“Wine is a thing marvellously suited to man, in health as in sickness, if it is administered appropriately, and in just measure in accordance with the individual constitution.” Hippocrates (460–377 BC)*

# Classification of evidence-level

<u>Publication type</u>	<u>Evidence</u>	<u>Strength</u>
Meta-analysis of RCT	Ia	A
<u>RCT = randomised, controlled trial</u>	Ib	
Controlled, non-randomised trial	IIa	B
<u>Cohort studies</u>	IIb	
Case-control studies	III	C
<u>Cross-sectional studies</u>		
Expert opinions	IV	D

*"In God we trust. All others must bring data."*

# The famous cross-sectional study in relation to wine & health published by Cochrane et al in the Lancet 1979

THE LANCET, MAY 12, 1979

## Public Health

### FACTORS ASSOCIATED WITH CARDIAC MORTALITY IN DEVELOPED COUNTRIES WITH PARTICULAR REFERENCE TO THE CONSUMPTION OF WINE

A. S. ST. LEGER

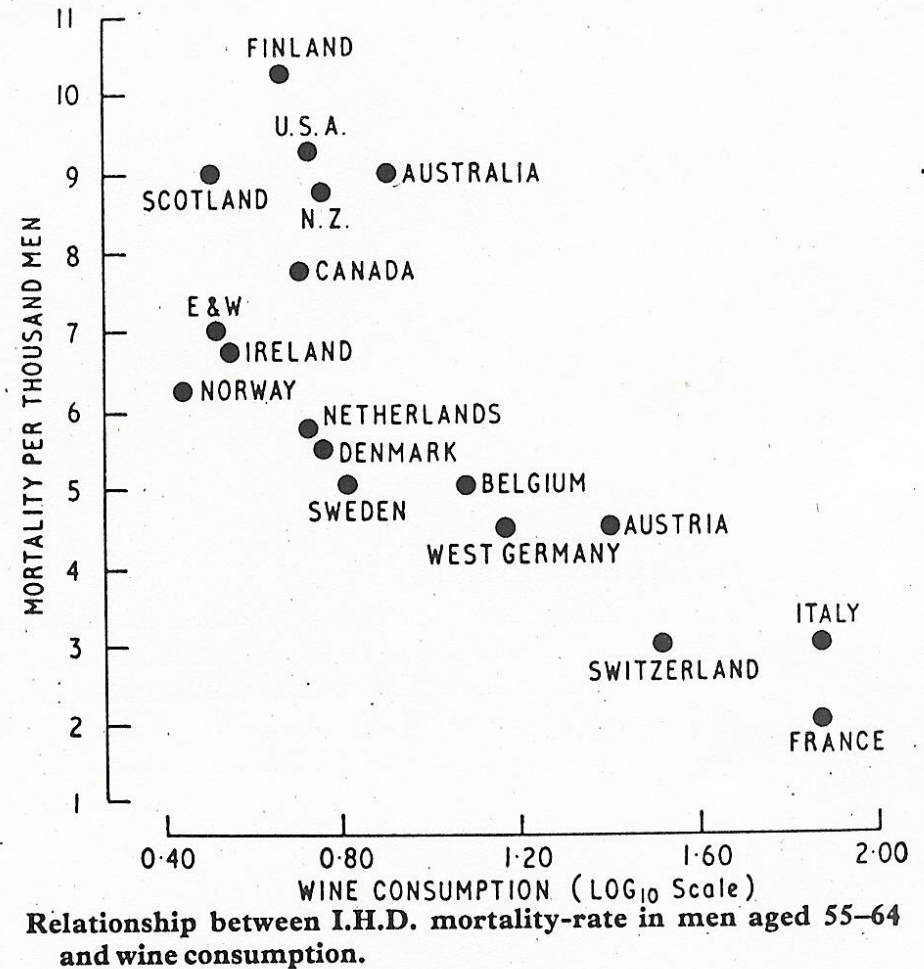
A. L. COCHRANE\*

F. MOORE

*Medical Research Council Epidemiology Unit, Cardiff CF2 3AS*

**Summary** Deaths from ischaemic heart-disease in 18 developed countries are not strongly associated with health-service factors such as doctor and nurse density. There is a negative association with gross national product per capita and a positive but inconsistent association with saturated and monounsaturated fat intake. The principal finding is a strong and specific negative association between ischaemic heart-disease deaths and alcohol consumption. This is shown to be wholly attributable to wine consumption.

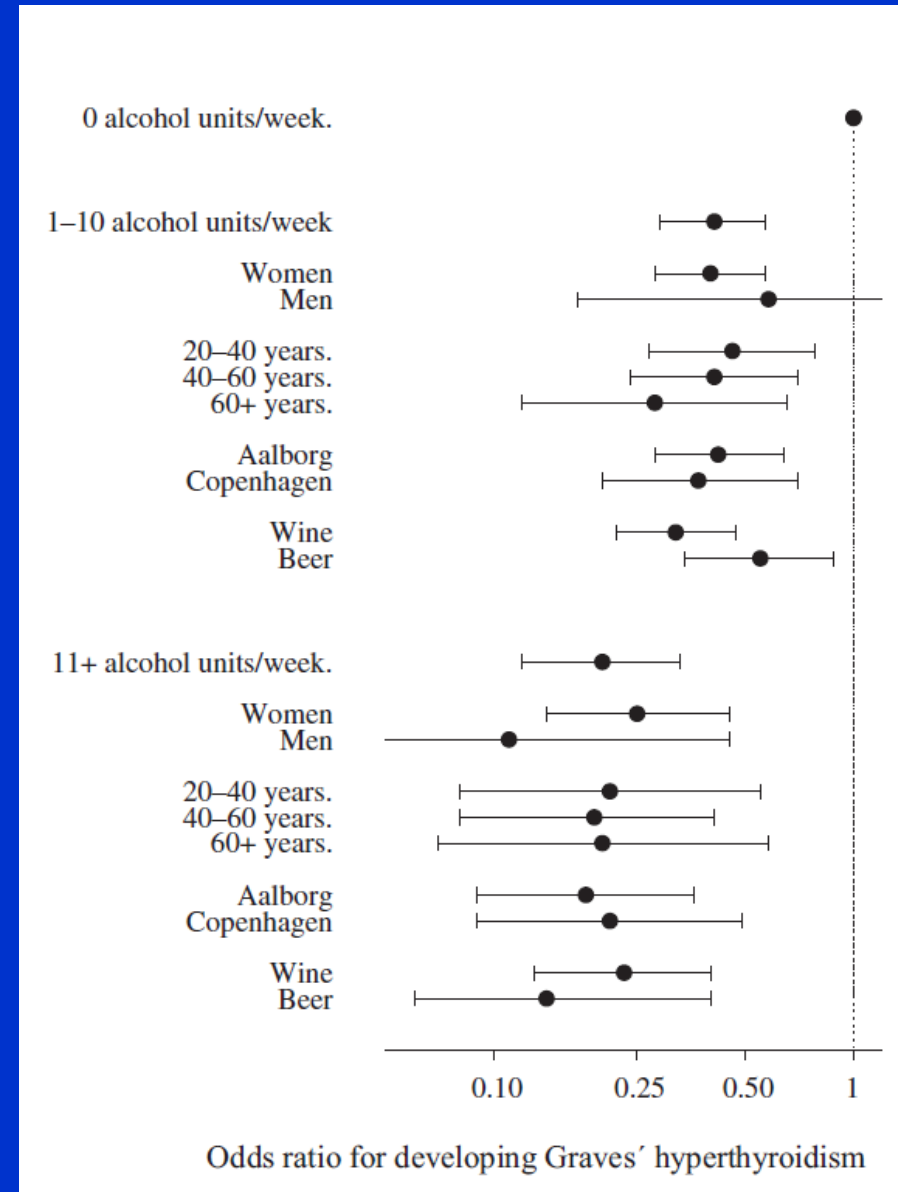
THE LANCET, MAY 12, 1979



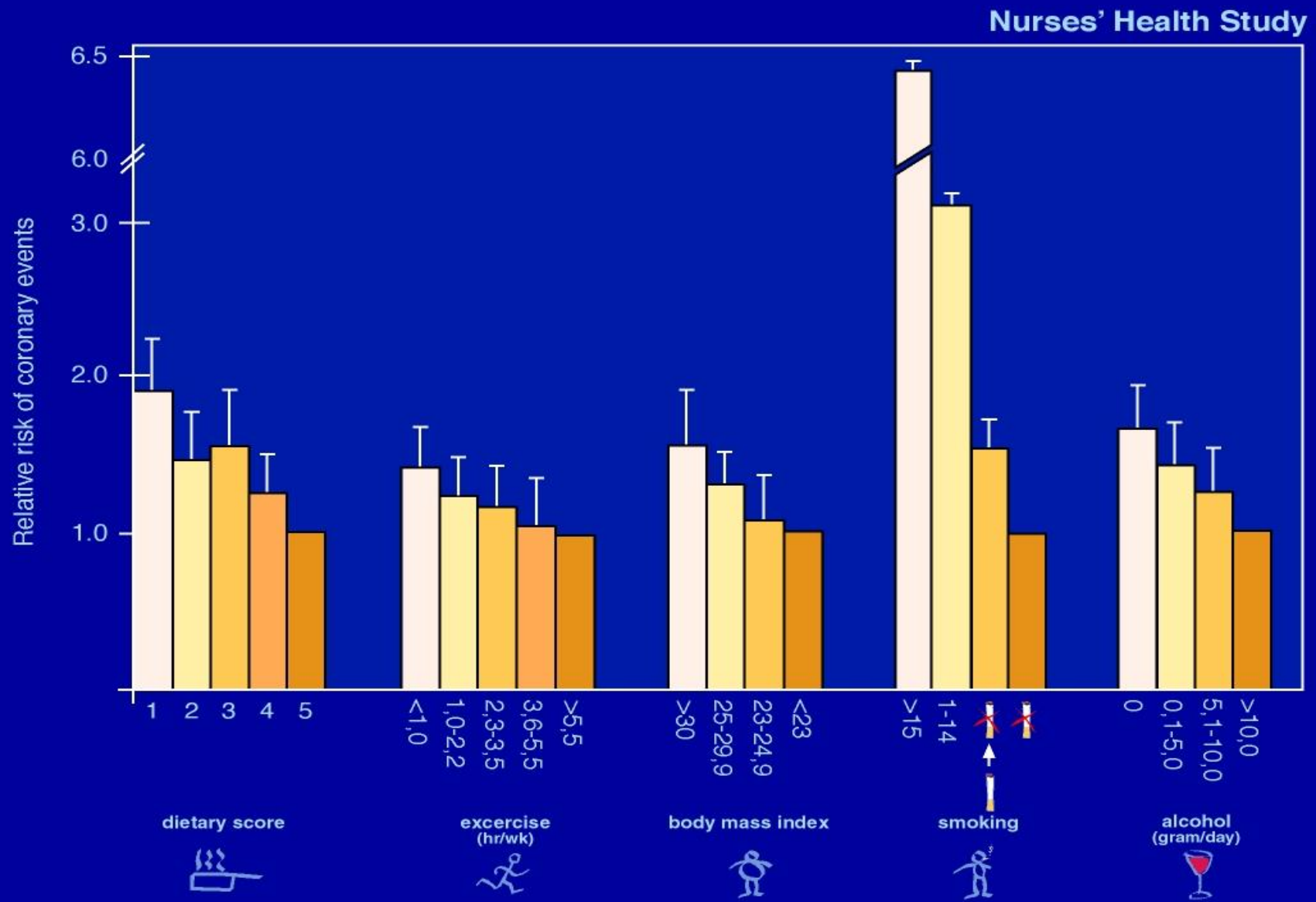
# Case-control study

*Clinical Endocrinology 2013;79:111-19*

- Inexpensive and not time-consuming study; well suited for rare diseases like e.g. autoimmune diseases:
- Moderate alcohol intake is associated with a considerable reduction in the risk of:
- Graves' disease with hyperthyroidism →
- Autoimmune hypothyroidism
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Autoimmune diabetes.



Most human wine & health evidence originates from observational cohort studies such as the large American "Nurses' Health Study"



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Case reports / Expert opinions	IV	D



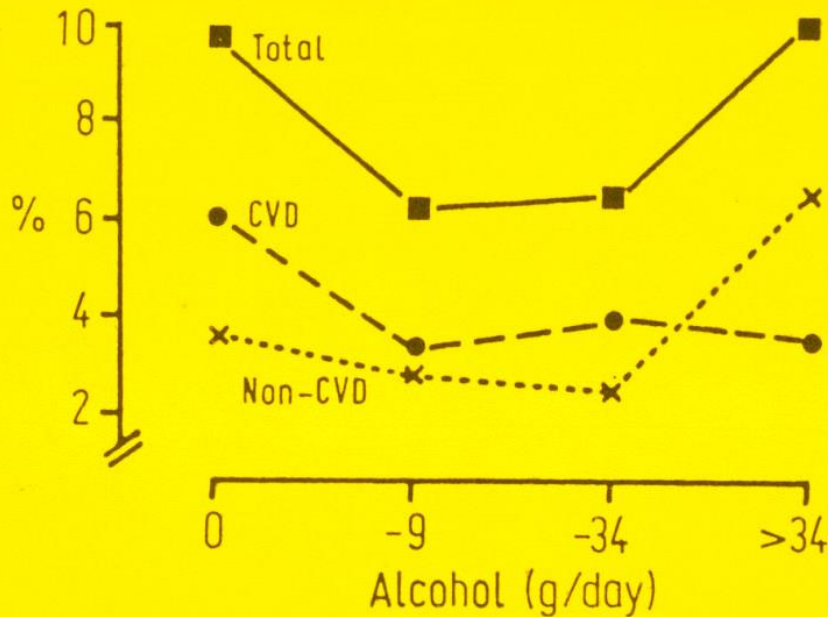
# Randomised, Controlled Trial

- Any randomized controlled study would need to be large, on the order of at least 7500 patients, and would need to be conducted over at least 4 years.
- The patient cohort must be very compliant, and clinical monitoring would need to be of the highest quality.
- Methods would be needed to ensure that the control group had not started drinking.
- However, in a prospective trial, if just one glass of wine per day could reduce mortality by the same 17 - 18% as suggested in a recent meta-analysis, these data would provide strong evidence that a glass of wine/day is a major and cost-effective therapeutic intervention.

*Circulation editorial 2007;116:1306-17*



# Alcohol and mortality: The U-shaped curve



10-year mortality (age-adjusted %) all causes, cardiovascular (CVD) and non-cardiovascular (non-CVD) causes according to daily alcohol consumption.

- Left downstroke:  
↓ cardiovascular disease
- U-curve nadir:  
1 – 3 drinks per day
- Right upstroke:  
↑ alcoholic liver disease  
↑ cancer

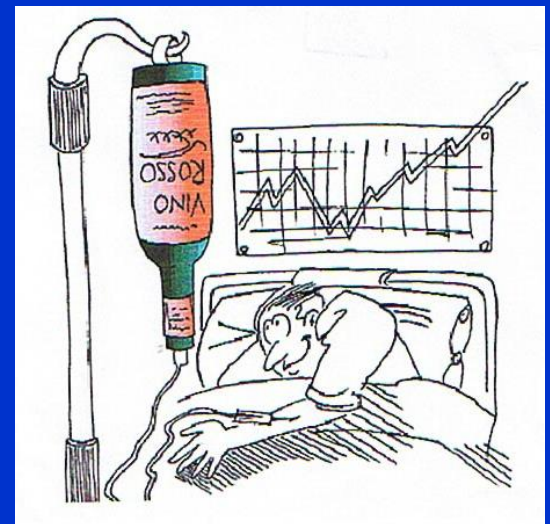
- The first U-shaped curve was found in a study of 1422 male civil servants in London (the Whitehall Study) investigating the relation between alcohol consumption and mortality over 10 years of follow-up. *Lancet 1981 Mar 14;1(8220 Pt 1):580-3*



# Alcohol and cardiovascular disease

- The association of alcohol and cardiovascular health is compatible with existing theory and knowledge of the process of atherosclerosis:
  - ↑ HDL cholesterol level
  - ↑ Endothelial cell-dependent vaso-relaxation
  - ↑ Fibrinolysis
  - ↑ Insulin sensitivity
  - ↓ Platelet aggregation
  - ↓ Coagulation factor VII & fibrinogen
  - ↓ Myocardial ischemia-reperfusion injury
- Circulation. 2010;121:1951-59*

*Sir Austin Bradford Hills*  
*Criteria of Causation*  
*outlines the minimal conditions needed to establish a causal relationship between two items.*



Binge-drinking is not recommended...





# ALCOHOLIC DRINKS, AND THE RISK OF CANCER World Cancer Research Fund Report 2007

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	Cancer site	Exposure	Cancer site
Convincing			Alcoholic drinks	Mouth, pharynx and larynx Oesophagus Colorectum (men) <sup>1</sup> Breast (pre- and postmenopause)
Probable			Alcoholic drinks	Liver <sup>2</sup> Colorectum (women) <sup>1</sup>

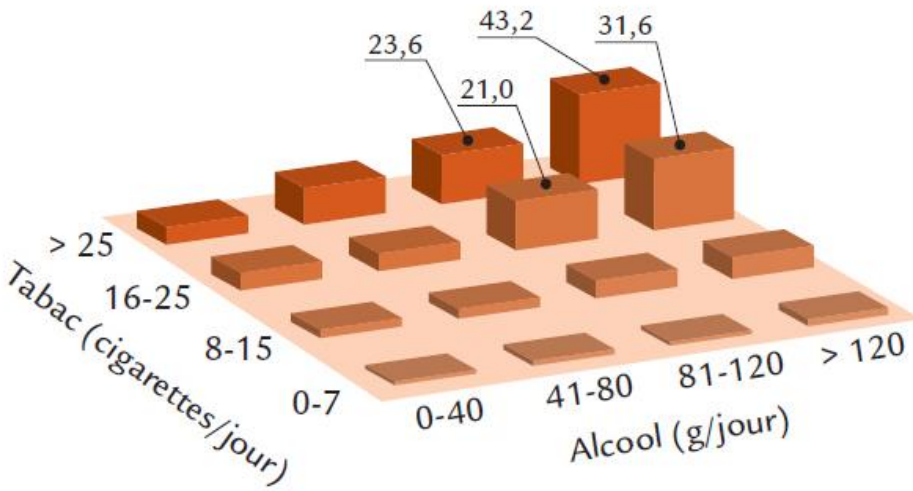
- WCRF/AICR's Expert Report, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, 2007, sets out Recommendations for Cancer Prevention based on a comprehensive review of the scientific evidence in this area.
- Colo-rectum cancer: Increased risk is only apparent above a threshold of 30 g/day of ethanol for both sexes.
- Liver cancer: Cirrhosis is an essential precursor of liver cancer caused by alcohol.

- The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx, oesophagus is convincing – especially for heavy drinking smokers.

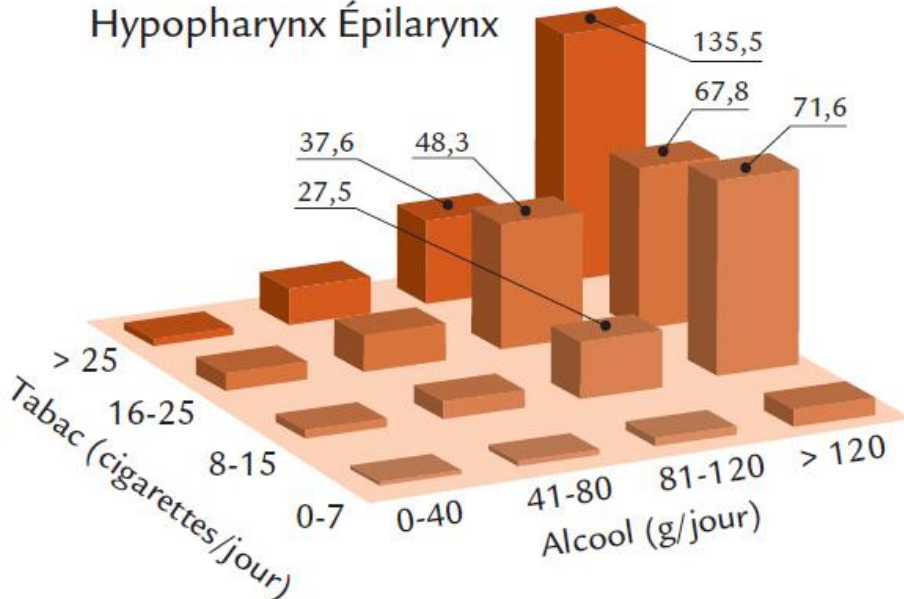
**EFFET COMBINÉ DE L'ALCOOL ET DU TABAC SUR LE RISQUE RELATIF ESTIMÉ DE CANCER DU LARYNX [TUYNIS, 1988]**

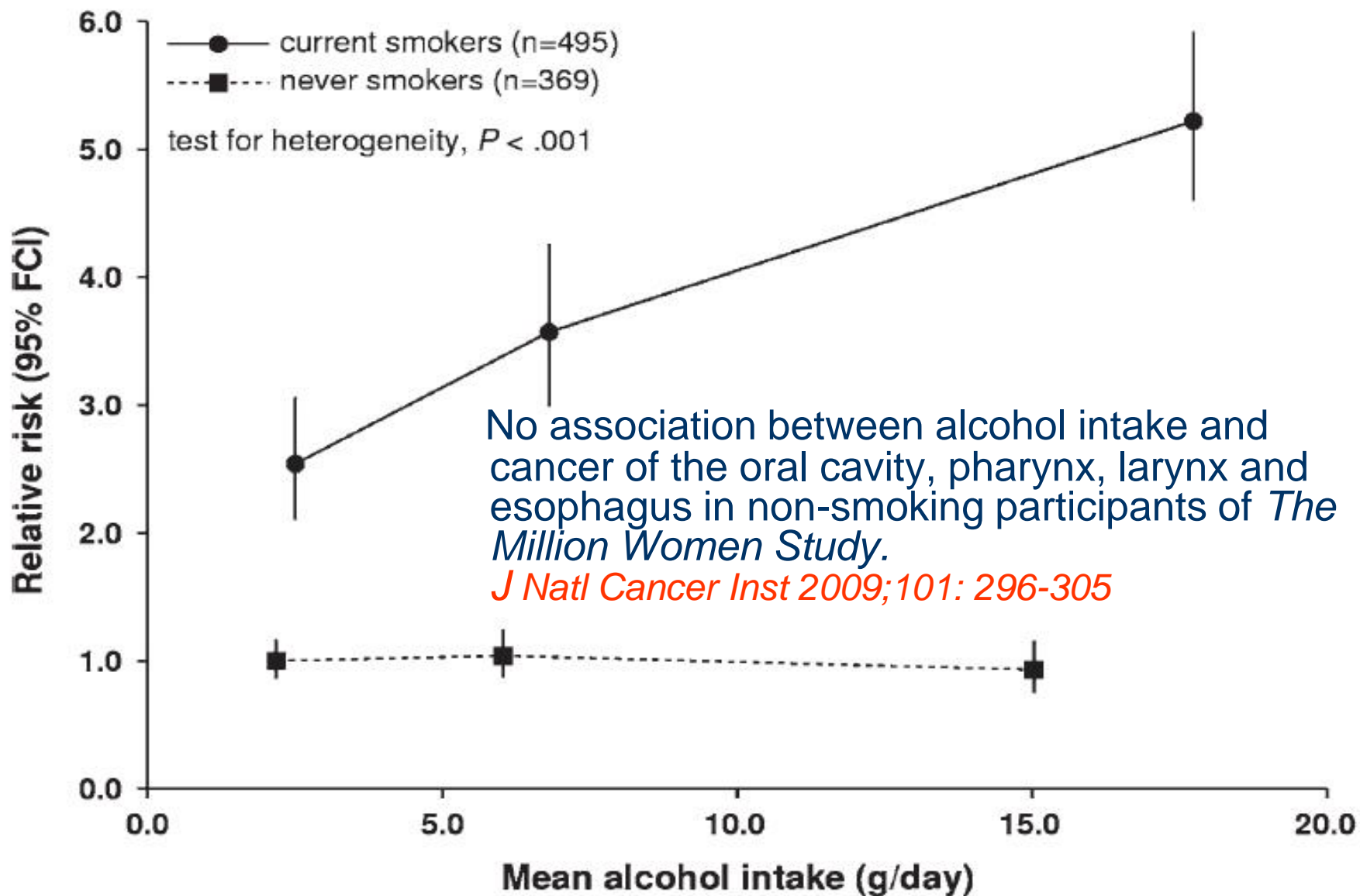
L'analyse statistique montre que l'augmentation importante du risque relatif pour la combinaison alcool-tabac suit un modèle multiplicatif et illustre la synergie entre ces deux facteurs de risque.

Endolarynx



Hypopharynx Épilarynx



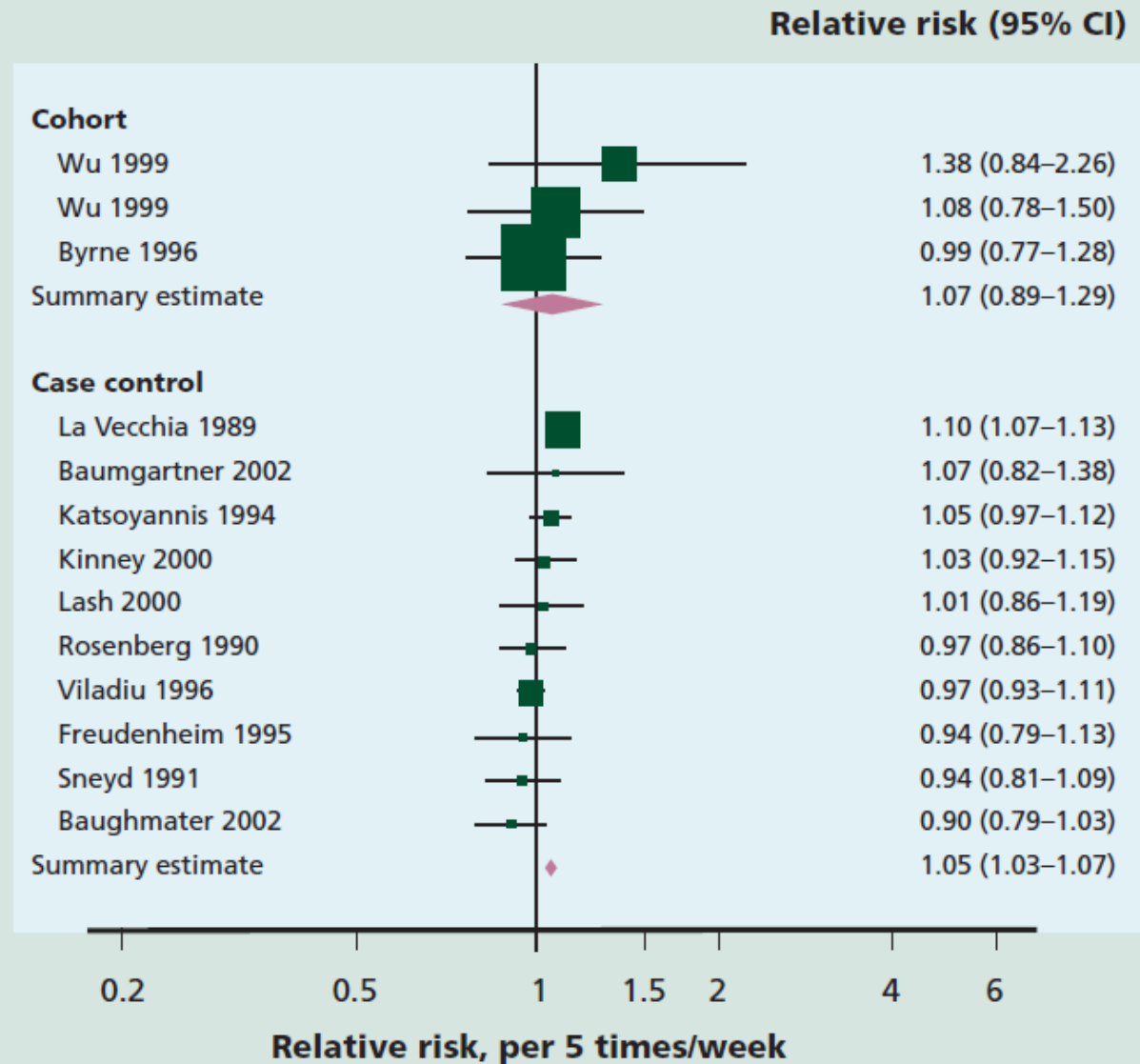


**Figure** . . Relative risk (95% floated confidence interval) of cancers of the upper aerodigestive tract (cancer of the oral cavity and pharynx, lanynx and esophagus by alcohol intake and smoking (drinkers only).

- There is consistent evidence from case-control and cohort studies.
- A dose-response relationship is apparent and no threshold was identified.
- There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status (400  $\mu\text{g}$ ) partially mitigates the risk from increased alcohol consumption.

**Figure 4.8.13**

**Alcoholic drinks and breast cancer; cohort and case-control studies**

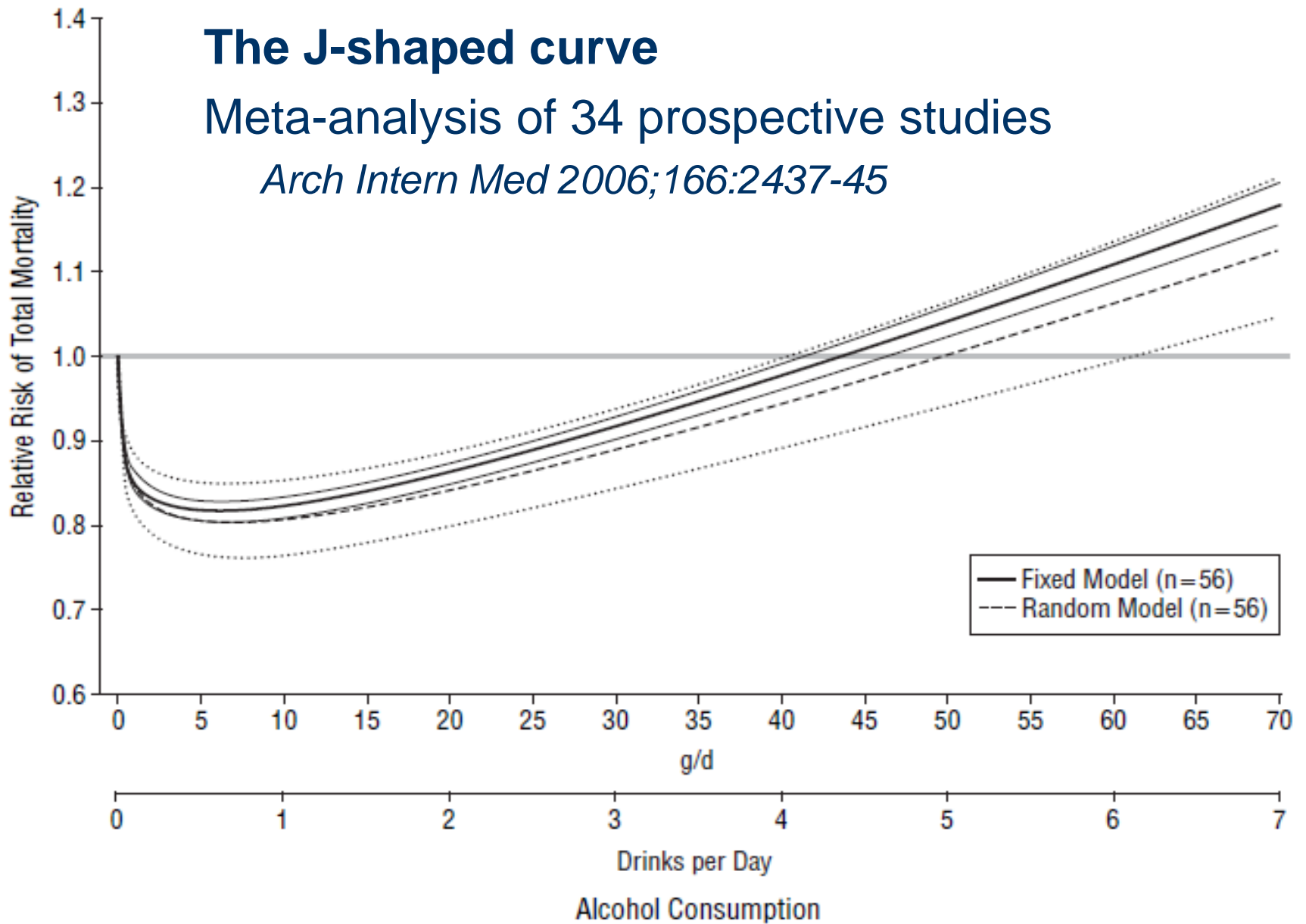




# The J-shaped curve

Meta-analysis of 34 prospective studies

*Arch Intern Med* 2006;166:2437-45

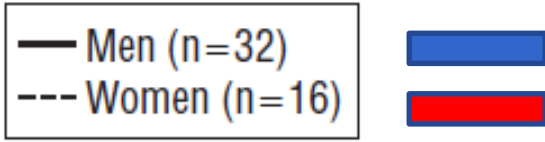


**Figure 1.** Relative risk of total mortality (95% confidence interval) and alcohol intake extracted from 56 curves using fixed- and random-effects models.

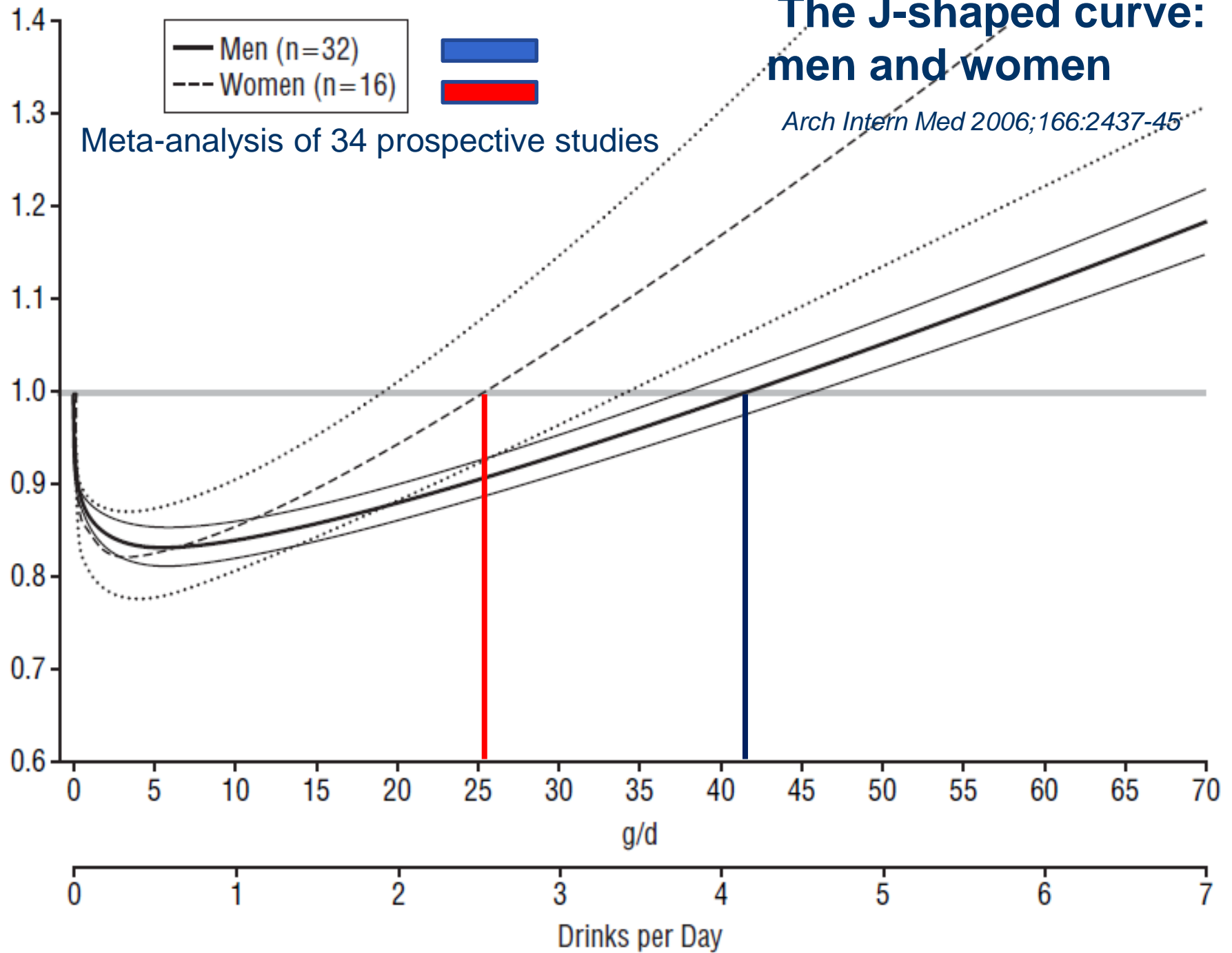
# The J-shaped curve: men and women

*Arch Intern Med 2006;166:2437-45*

Meta-analysis of 34 prospective studies



Relative Risk of Total Mortality



# Blood Alcohol Content & Body Water

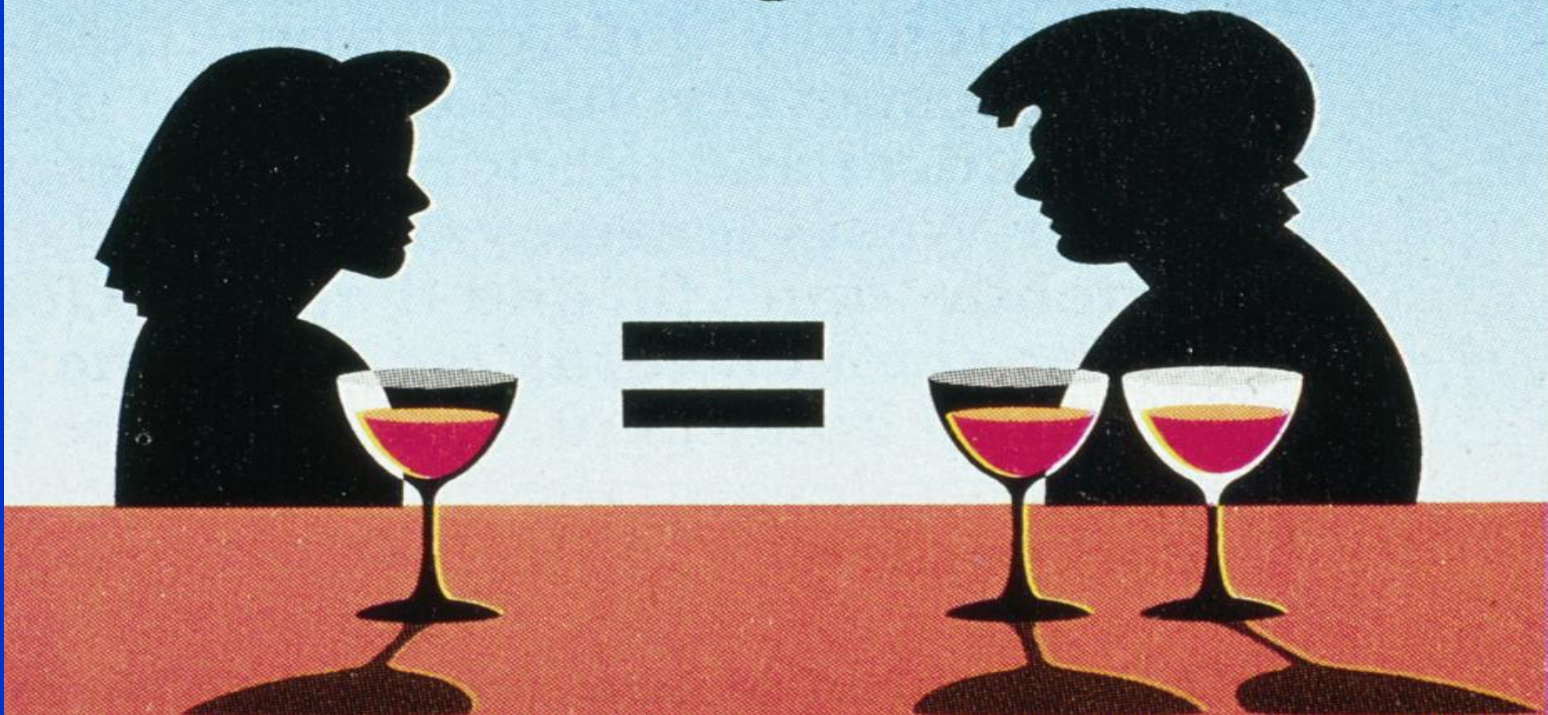
- **Blood alcohol content (BAC)** is the concentration of alcohol in blood measured as mass per volume.
- A BAC of  $0.02\% = 0.2 \text{ ‰} = 0.2$  grams of alcohol per 1000 grams of blood.
- In the UK, BAC is reported as milligrams of alcohol per 100 millilitres of blood. (a BAC of  $0.08\%$  is expressed as 80 mg per 100 ml).
- Due to low water content of fat in breasts and buttocks a man has an excess of about 10 liters of body water compared to a woman of same age and weight.

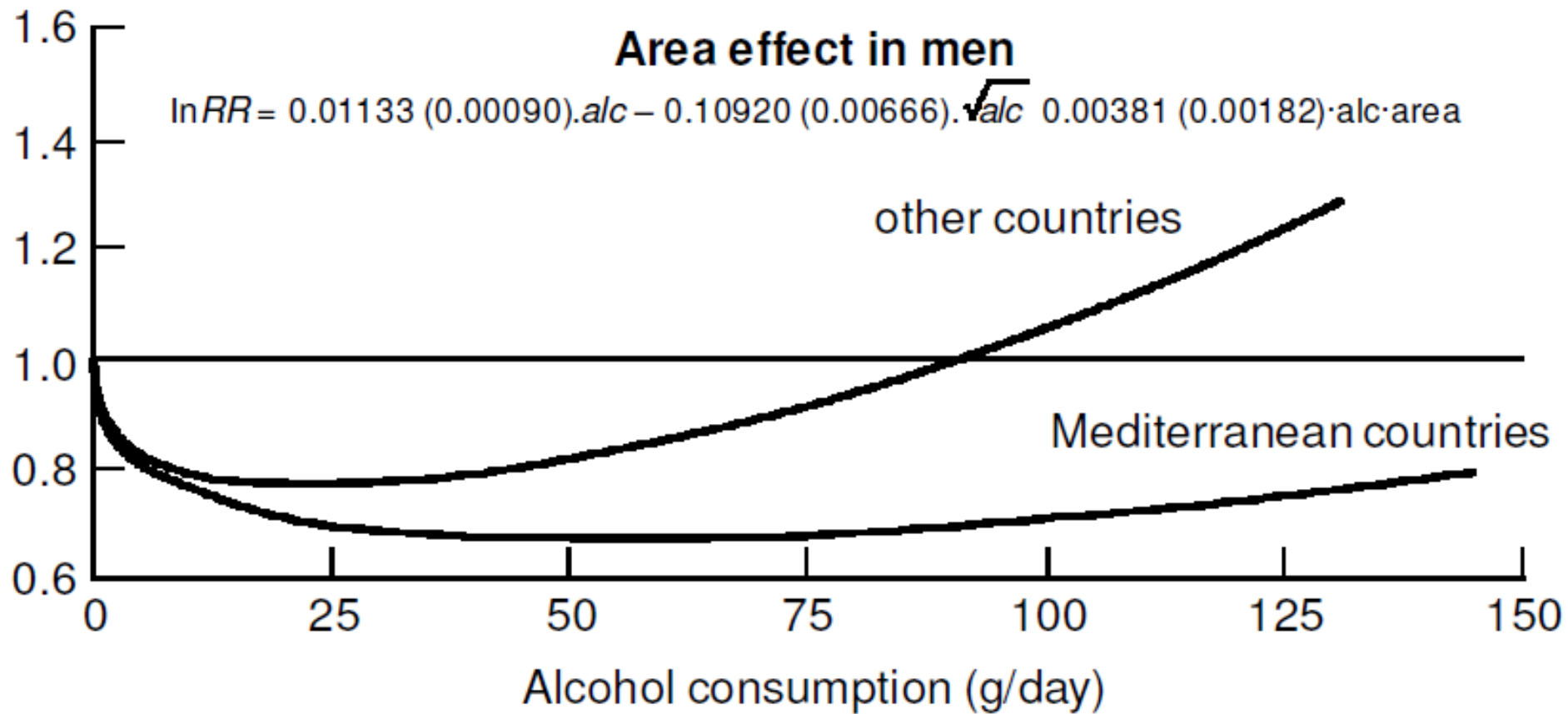




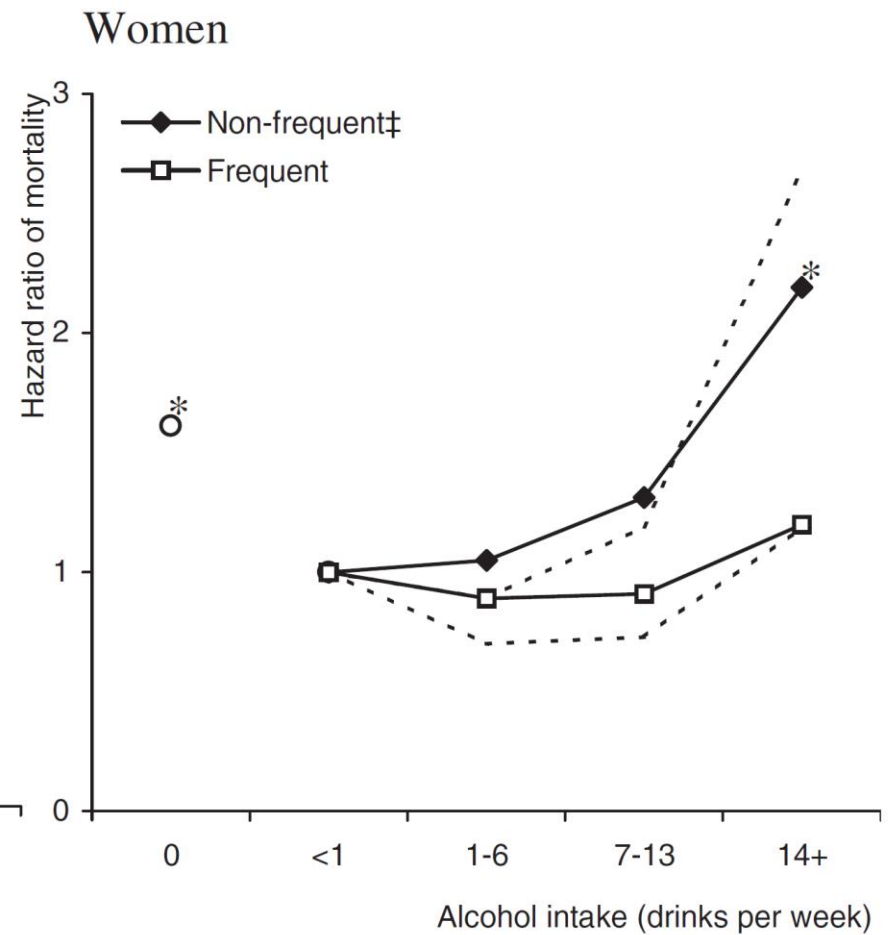
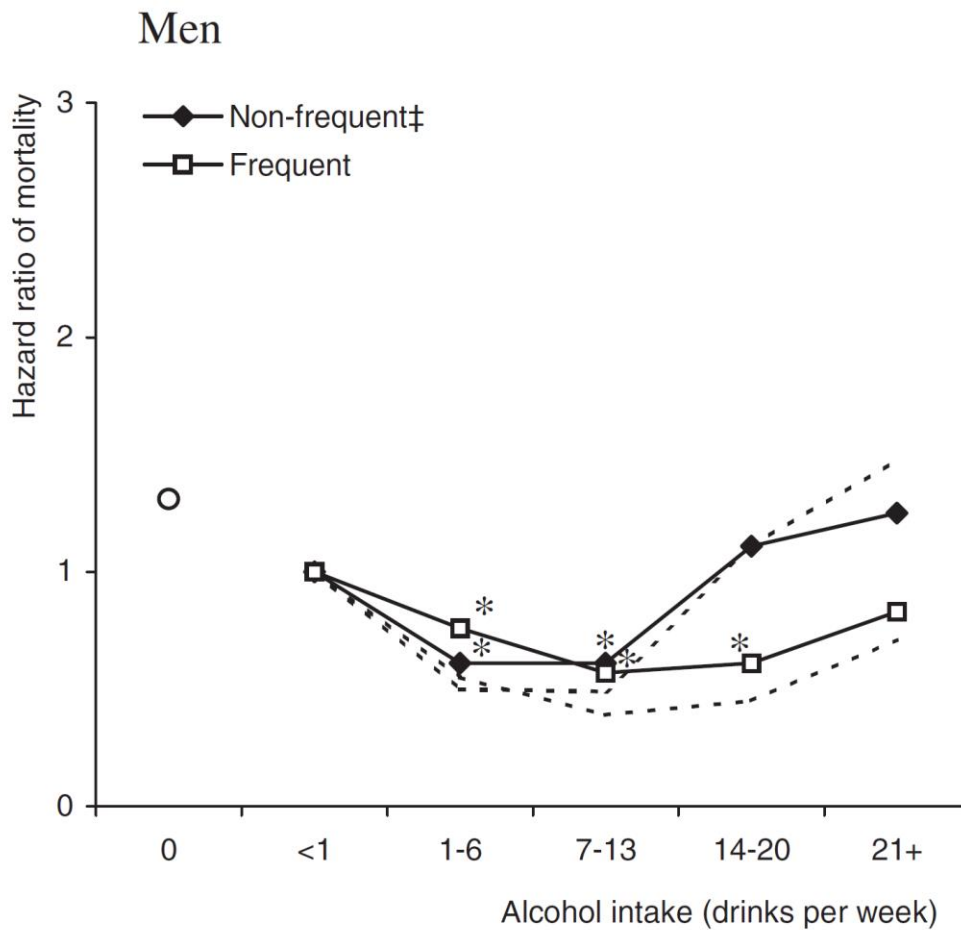
- Ethanol undergoes a first pass metabolism (FPM) in the stomach and liver. Gastric first pass metabolism of ethanol primarily depends on the activity of gastric alcohol dehydrogenase (ADH) which is larger in men.

**A woman will absorb about 30% more alcohol into her blood than a man of the same weight who has drunk an equal amount. For a woman of average size, one drink will have about the same effect as two for the average-size man.**





- With an equal dose of alcohol, Mediterranean habits may be associated with a lower risk of coronary heart disease:
  1. Drinking patterns may modify the shape of the dose-response function.
  2. Red wine may have a superior protective effect than other alcoholic beverages. *Addiction 2000;95:1505-23*



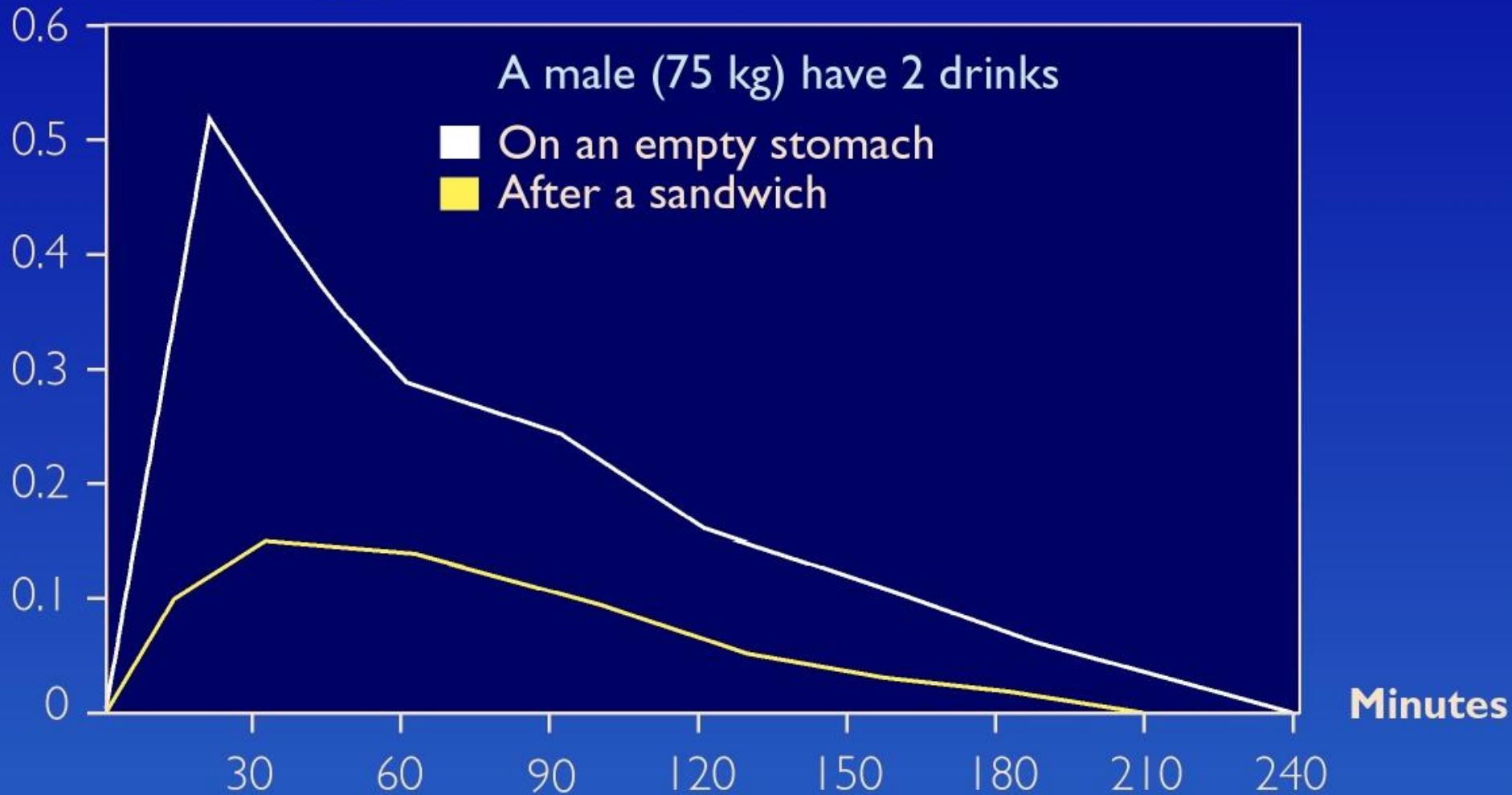
- For the same average consumption of alcohol, a non-frequent intake implied a higher risk of death than a frequent one. Public guidelines concerning sensible alcohol drinking should include messages about drinking pattern together with quantity of alcohol.

*Addiction 2004;99:323-30*



The intake of alcohol with food decreases the speed of gastric emptying (GE) and modulates both gastric and hepatic FPM of ethanol.

### Blood-ethanol (g/L)



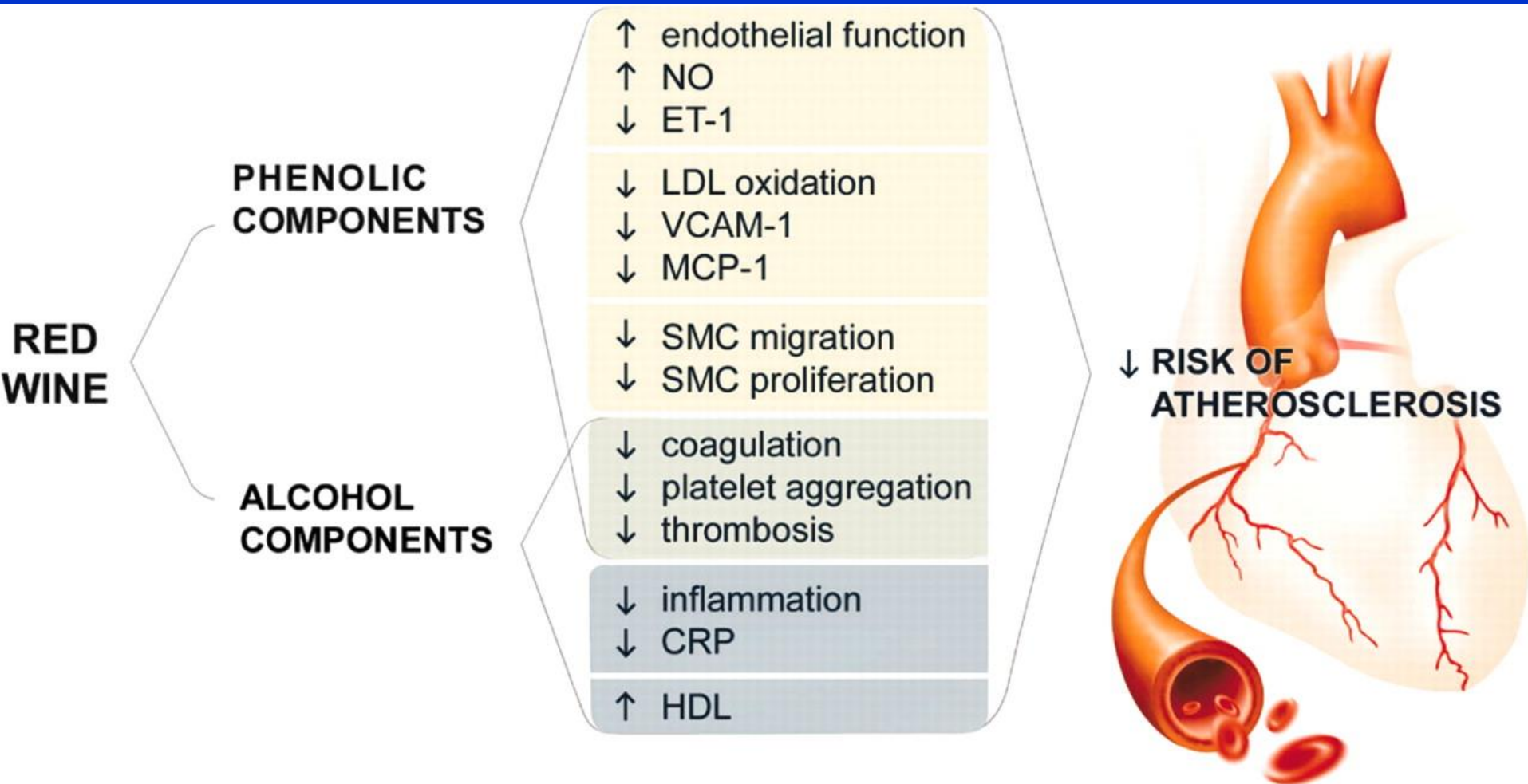
# The anatomy of the Mediterranean Diet

**Table 4** | Mortality ratios associated with two unit increment\* in Mediterranean diet score (MDS) and after alternate subtraction of each of its dietary components

Dietary variable	Mortality ratio† (95% CI)	P value	Reduction in apparent effect (%)‡
MDS overall	0.864 (0.802 to 0.932)	<0.001	0
MDS minus vegetables	0.886 (0.822 to 0.955)	0.002	16.2
MDS minus legumes	0.877 (0.815 to 0.944)	<0.001	9.7
MDS minus fruit and nuts	0.879 (0.818 to 0.946)	0.001	11.2
MDS minus cereals	0.872 (0.814 to 0.935)	<0.001	6.1
MDS minus monounsaturated/saturated lipids (ratio)	0.878 (0.806 to 0.957)	0.003	10.6
MDS minus dairy products	0.870 (0.806 to 0.939)	<0.001	4.5
MDS minus meat and meat products	0.887 (0.825 to 0.953)	0.001	16.6
MDS minus ethanol	0.896 (0.835 to 0.962)	0.002	23.5

- The Greek EPIC Study found a higher Mediterranean diet score associated with a significant reduction in total mortality.
- The contribution of the Mediterranean Diet components:  
Moderate alcohol consumption: **23,5%**. Less red meat: **16,6%**.  
A lot of vegetables: **16,2%**. Plenty of fruit and nuts: **11,2%**.  
Olive oil for cooking: **10,6%**. More legumes: **9,7%**. Only small effects of cereals and dairy products. **BMJ 2009;338:b2337**

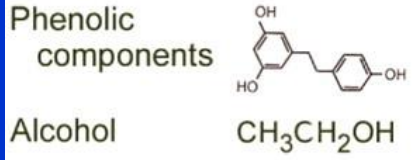
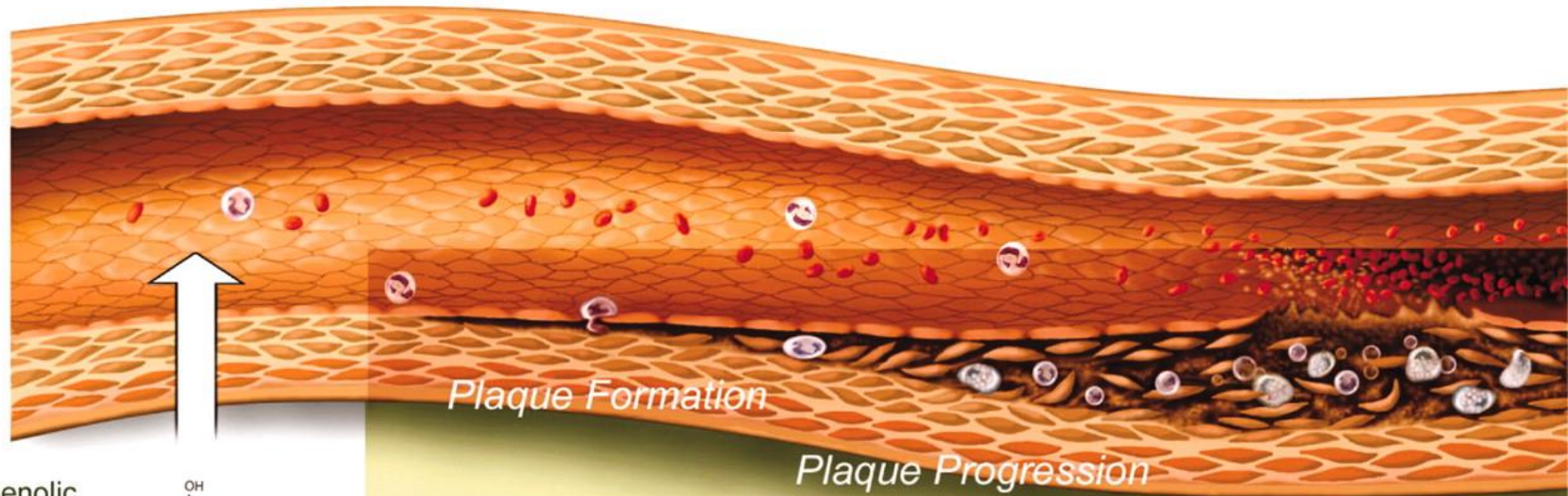
# The results from in vitro investigations in the laboratory and small clinical trials suggest that red wine polyphenols may reduce the risk of atherosclerosis





# Results from in vitro investigations and small clinical trials suggest that red wine polyphenols may reduce the risk of thrombosis

Endothelium Maintenance	Impairment of Plaque Formation	Impairment of Plaque Progression	Reduction of Thrombosis
<ul style="list-style-type: none"> <li>↑ HDL</li> <li>↑ NO</li> <li>↓ ET-1</li> <li>↓ CRP</li> </ul>	<ul style="list-style-type: none"> <li>↓ LDL oxidation</li> <li>↓ VCAM-1</li> <li>↓ MCP-1</li> <li>↓ Macrophage transmigration</li> <li>↓ NF-κB</li> </ul>	<ul style="list-style-type: none"> <li>↓ LDL oxidation</li> <li>↓ SMC migration</li> <li>↓ SMC proliferation</li> </ul>	<ul style="list-style-type: none"> <li>↓ TF, vWF, Factor VII</li> <li>↓ Fibrinogen, PAI</li> <li>↓ Platelet function &amp; aggregation</li> <li>↑ tPA</li> </ul>



Without Red Wine

- The red wine antioxidants: polyphenols
- The antioxidant content of red wine is believed to play a role in the health benefits derived from drinking in moderation.
- Antioxidants help counteract the harmful effects of free radicals. This is why moderate consumption of red wine and a healthy diet abundant in fresh fruit and vegetables can improve our health and increase longevity.

Feeling that Bond is slipping, M orders him to enroll in a health clinic in order to "eliminate all those free radicals and get back into shape".

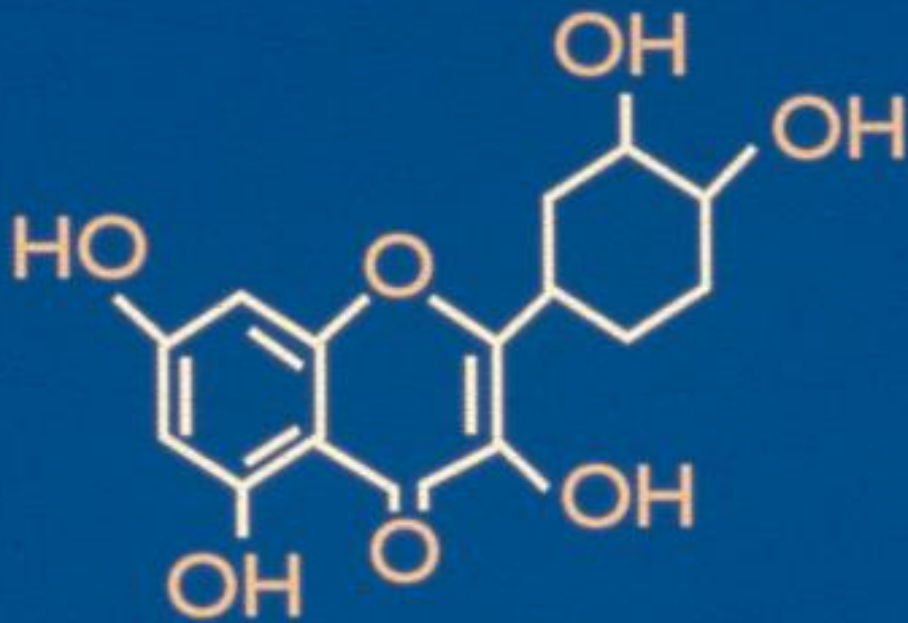
Bond: "Free radicals?"

M explains: "Toxins that destroy the brain and the body. Too much white bread, red meat, and too many dry Martinis."

Bond: "I'll cut down on the bread!"



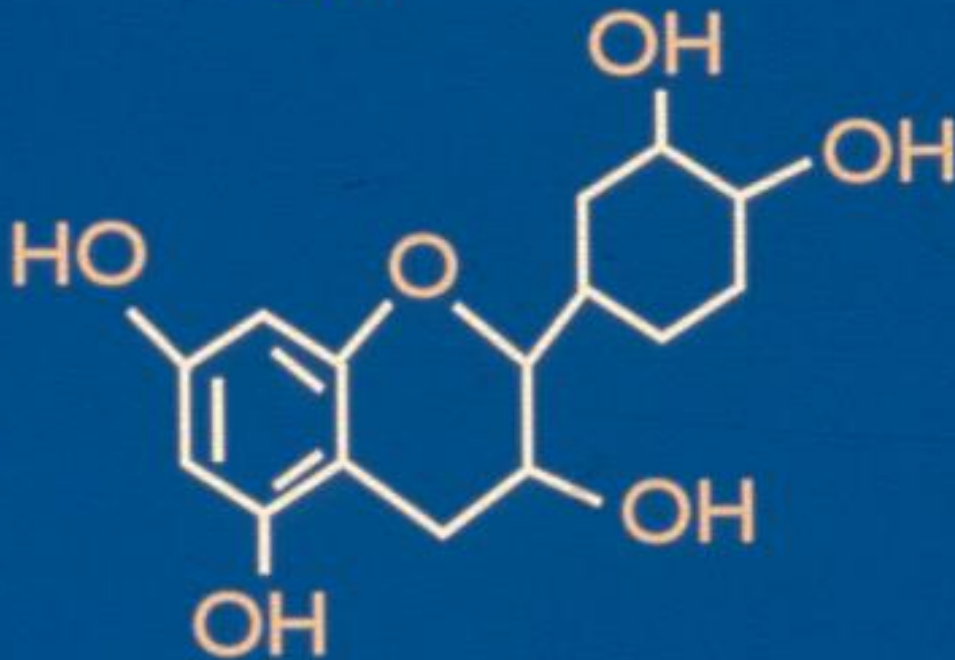




## Quercetin

*25 mg/L in red wine*

A word of warning: searching for your favourite polyphenol molecule in wine is a double-edged sword



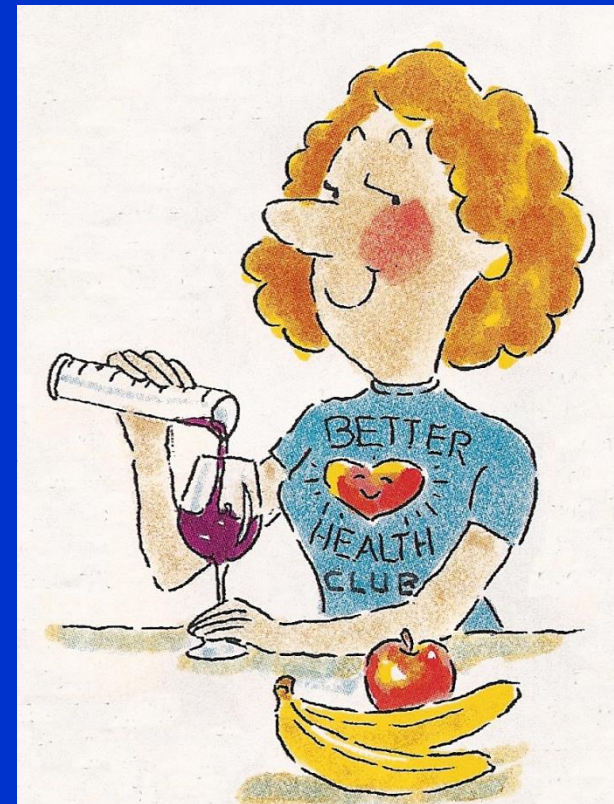
## Epicatechin

*15 mg/L in white wine*

*150 mg/L in red wine*

- Large uncertainties remain due to the lack of comprehensive data on the content of some of the main polyphenol classes in food & wine.
- Large variations among polyphenols and among individuals in bioavailability are observed. The maximum concentration in plasma rarely exceeds 1  $\mu\text{M}$  after the consumption of 10–100 mg of a single phenolic compound.
- The metabolites of polyphenols formed in the body's tissues or by the colonic microflora are still largely unknown and not accounted for.

*Journal of Nutrition.*  
2000;130:2073S-2085S



- Previous studies in humans have used doses of resveratrol between 10 to 2000 mg per day.
- Red wines typically contain between 2 and 12.5 mg of resveratrol per liter.
- A daily dose of 250 mg *trans*-resveratrol in the form of wine = 250 glasses of Pinot Noir.



# Not all resveratrol news are good news...

- At a dose of 22 mg/kg per day resveratrol mimicks the beneficial effects of Calorie Restriction and endurance training in obese mice.
- In a study of 8 weeks of exercise training with (14 men) or without (13 men) 250 mg *trans*-resveratrol resveratrol blunted the positive effects of exercise:

## Exercise without resveratrol:

- 45% increase in max. oxygen uptake
- 5 mmHg lower blood pressure
- 10% lower blood lipids

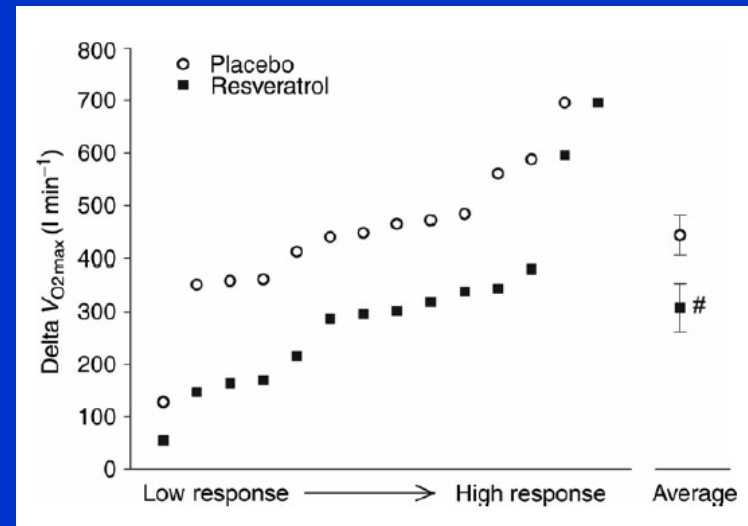
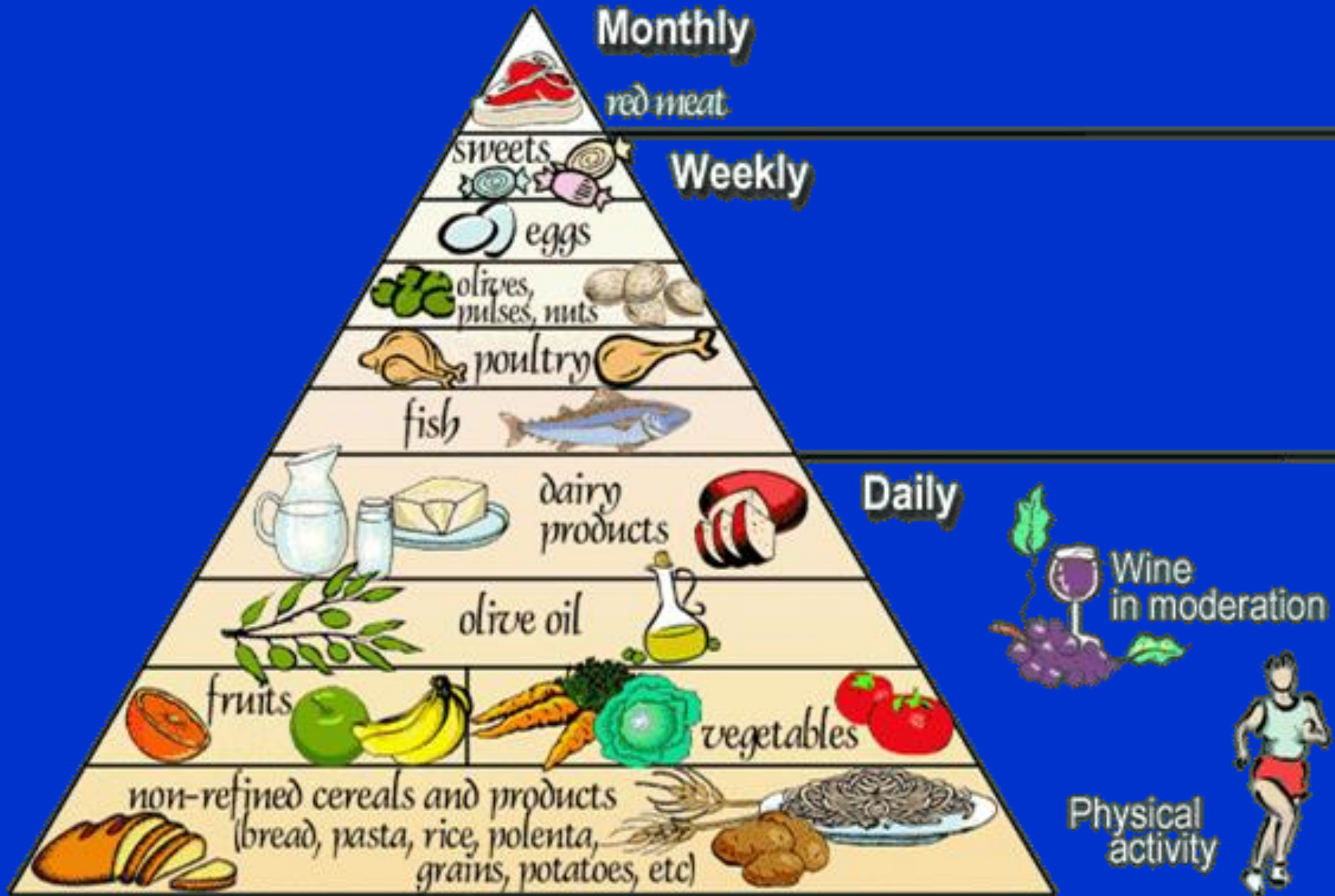


Figure 1. Absolute changes in maximal oxygen uptake from baseline to after a period of exercise training with or without resveratrol supplementation in aged men



# PYRAMID OF MEDITERRANEAN DIET



# Take home messages

- Healthy drinking habits is a balance of risks as well as benefits – a regular, moderate intake of alcohol – 1-2 drinks/day for women and 1-3 drinks/day for men – would be a sensible suggestion for responsible drinking guidelines.
- Healthy drinking excludes binge drinking and includes regular intake of some wine or beer with your meals.
- Focus on particular polyphenols in red wine is a dangerous pursuit that might result in success (followed by synthesis of the molecule as a drug) or failure (adverse effects when tested in human studies followed by damage to the image of red wine).
- A marketing drive based on quality instead of quantity with increased health consciousness may lead to health gains of the population along with improvement in the overall value of the wine industry.