Possible Mechanisms in Prevention by Moderate Alcohol Intake

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Conflict of Interest Statement

- I have no financial conflicts of interest to disclose.
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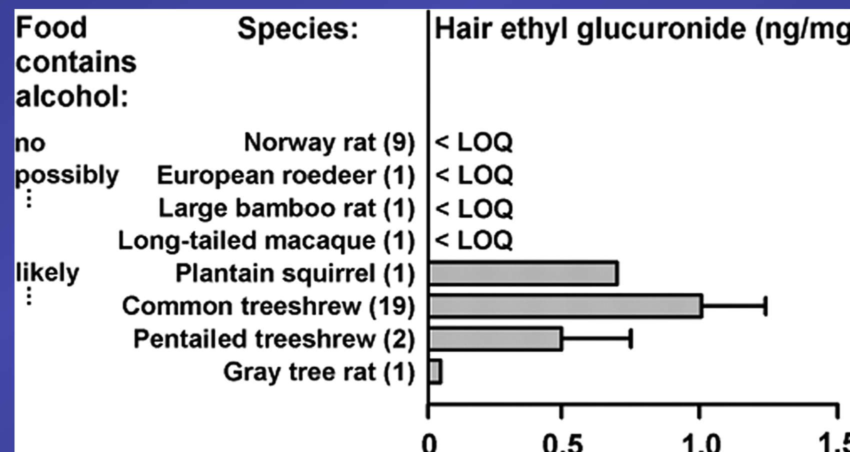
A Very Old Habit



Malaysian pen-tailed treeshrew

Ethyl glucuronide levels

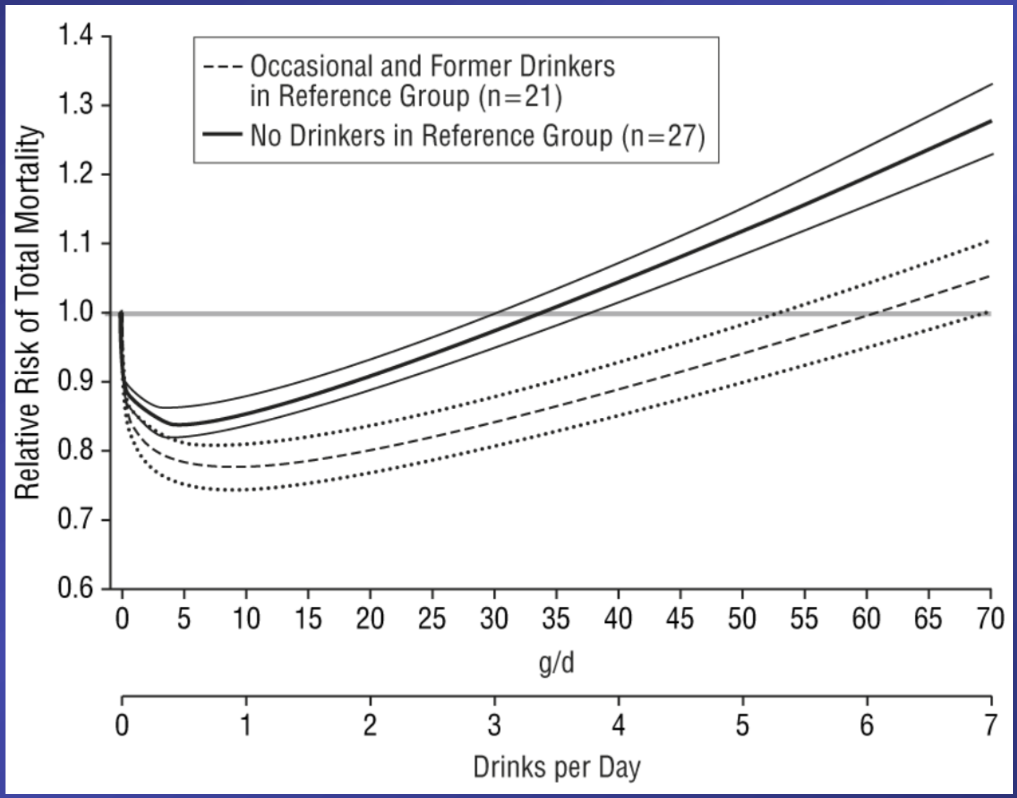
Wiens et al., PNAS 2008

A Pretty Old Observation

"My personal experience…has indicated alcohol was not only not a cause of arteriosclerosis, but, so far as one could judge, was in many cases a preventative."

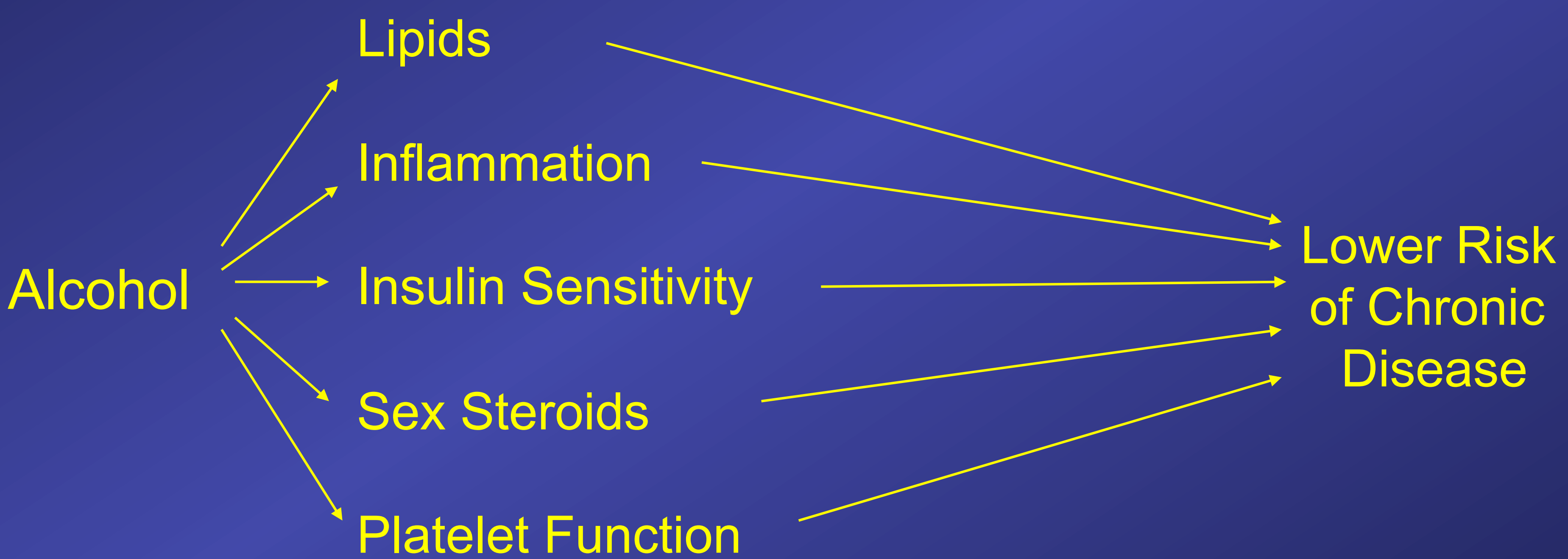
Timothy Leary, NEJM 1931

Alcohol Consumption and Mortality:
Systematic Review of 48 Dose-Response Curves



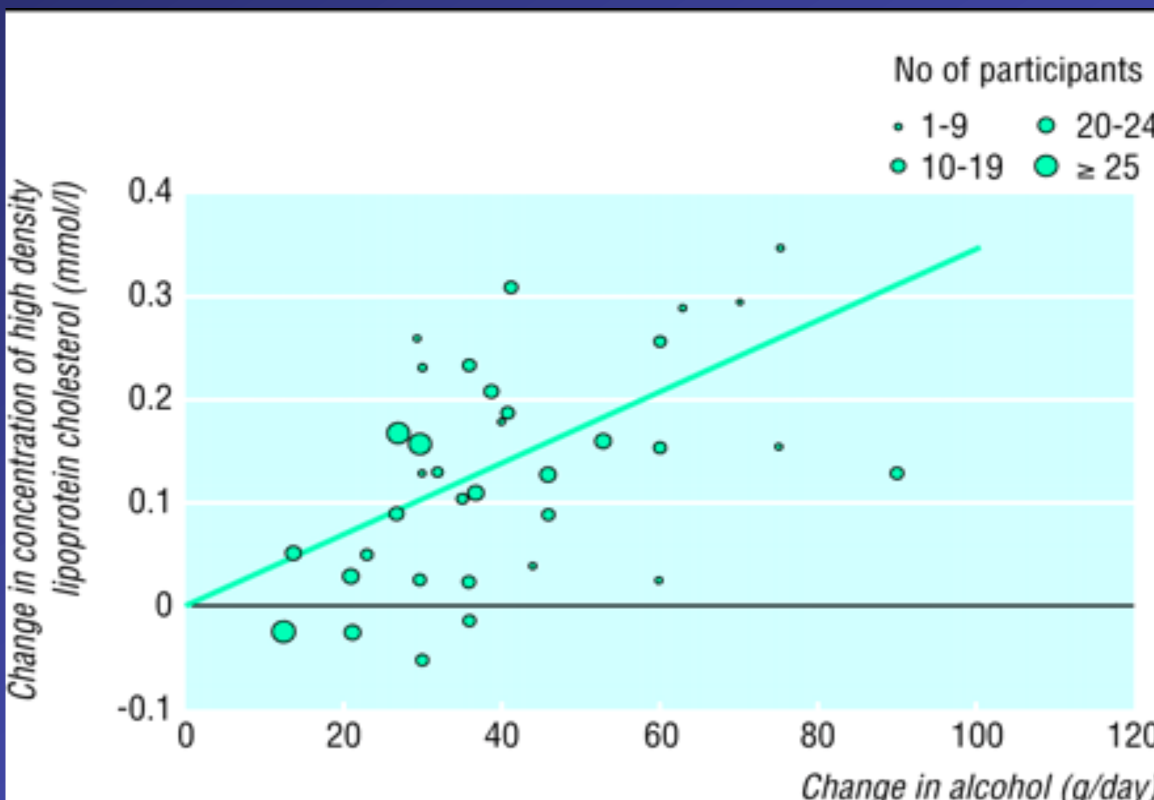
Di Castelnuovo et al, Arch Intern Med 2006

Alcohol and the J-Shaped Curve:
Potential Mechanisms



Alcohol Intake and HDL-C:

Meta-Analysis of 36 Randomized Trials

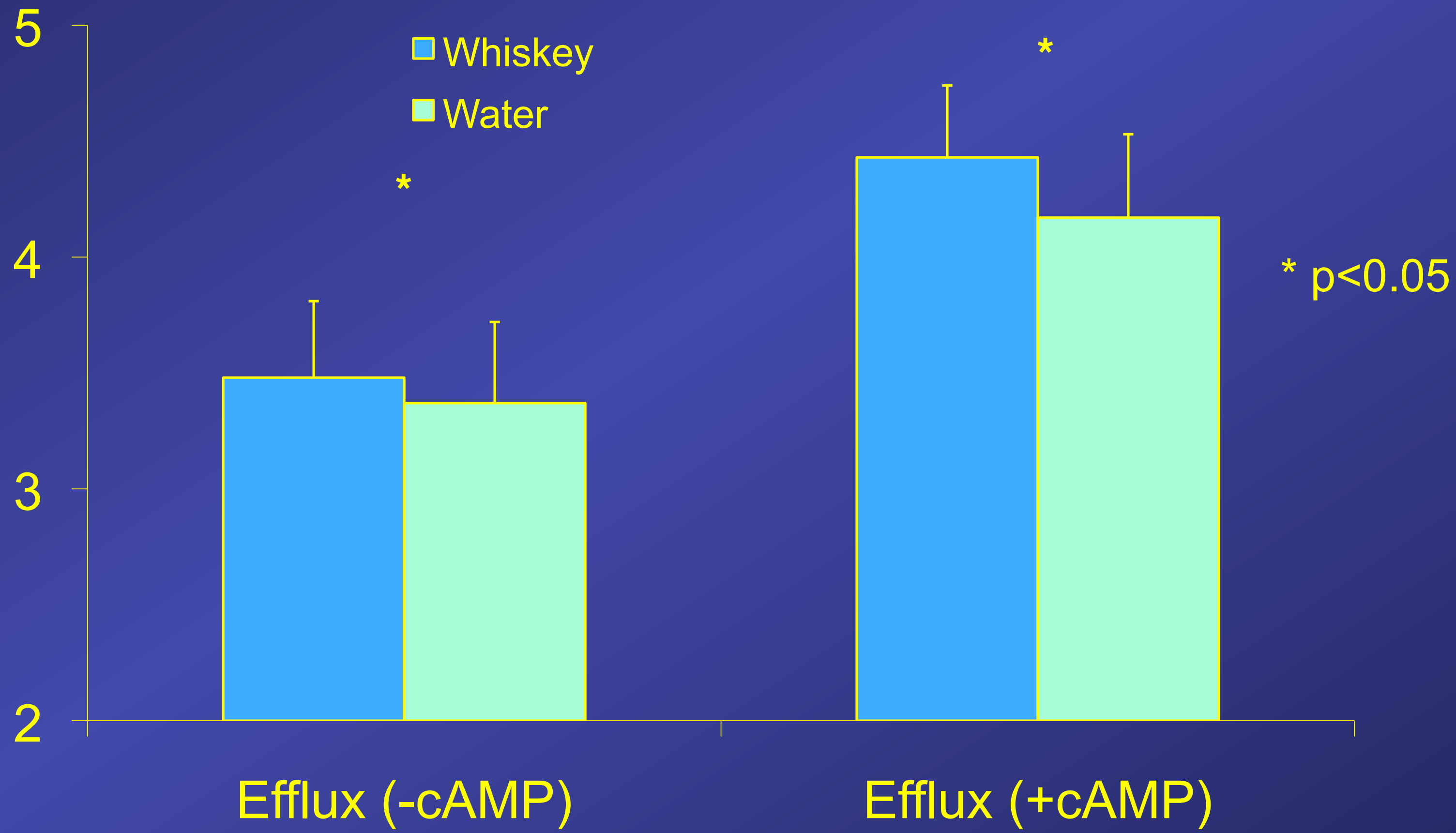


Effect 25% larger if baseline HDL-C <40 than if >48 mg/dl
P=0.04

Rimm et al, BMJ 1999

Alcohol & Macrophage Cholesterol Efflux:

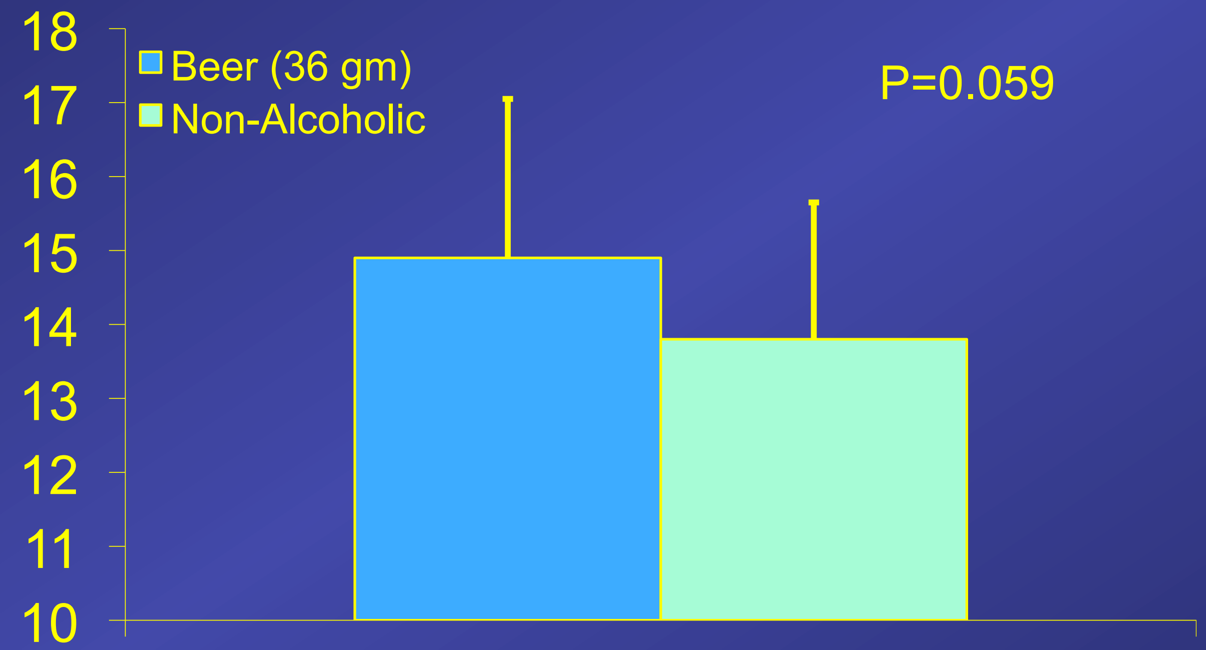
34-day crossover trial of 23 men



Beulens et al, J Lipid Res 2004

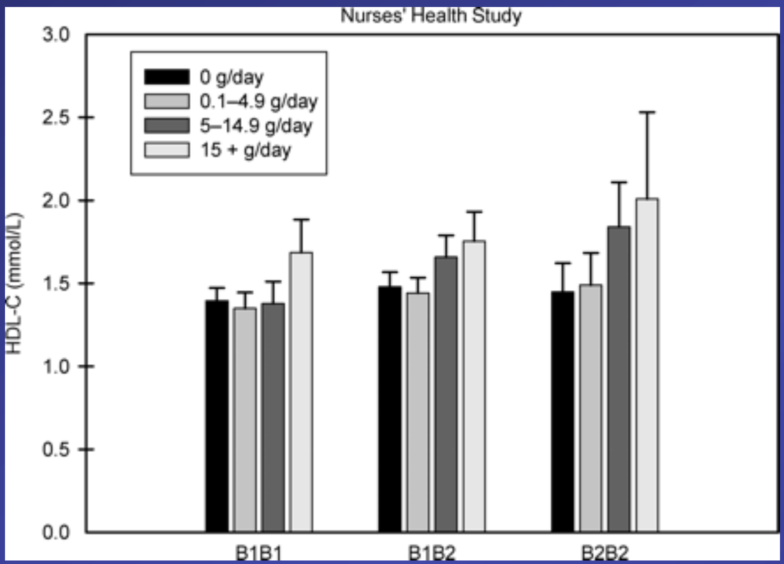
Alcohol & Macrophage Cholesterol Efflux:

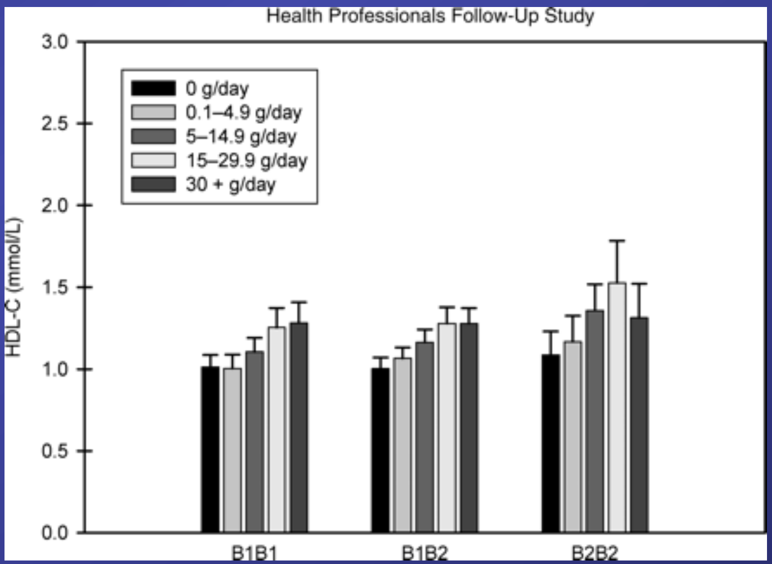
28-day crossover trial of 13 men



Králová Lesná et al, Physiol Res 2010

Alcohol, *CETP* Variation, and HDL-C:
Gene x Alcohol Interaction in Men and Women

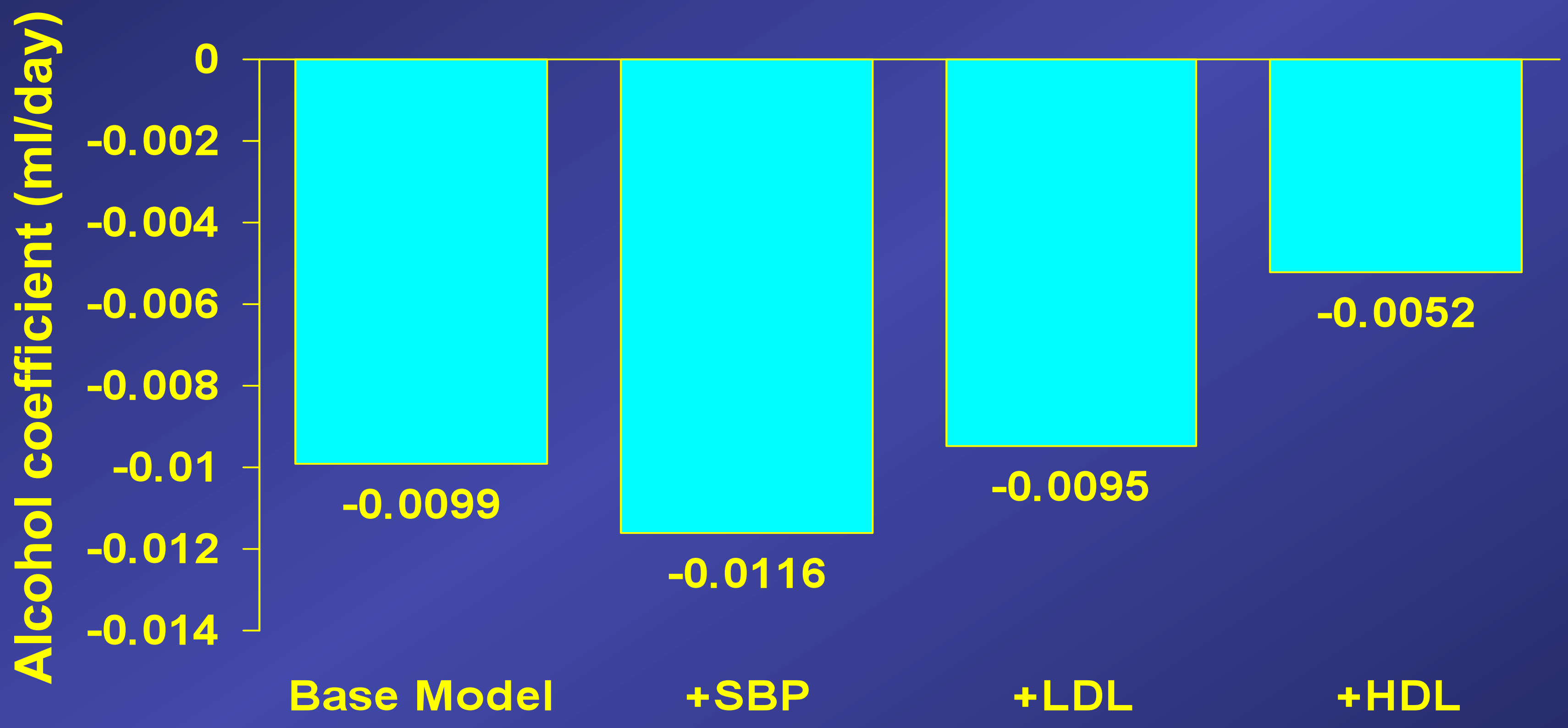




Jensen et al, Eur Heart J 2008

Mediating Effects on CHD Risk:

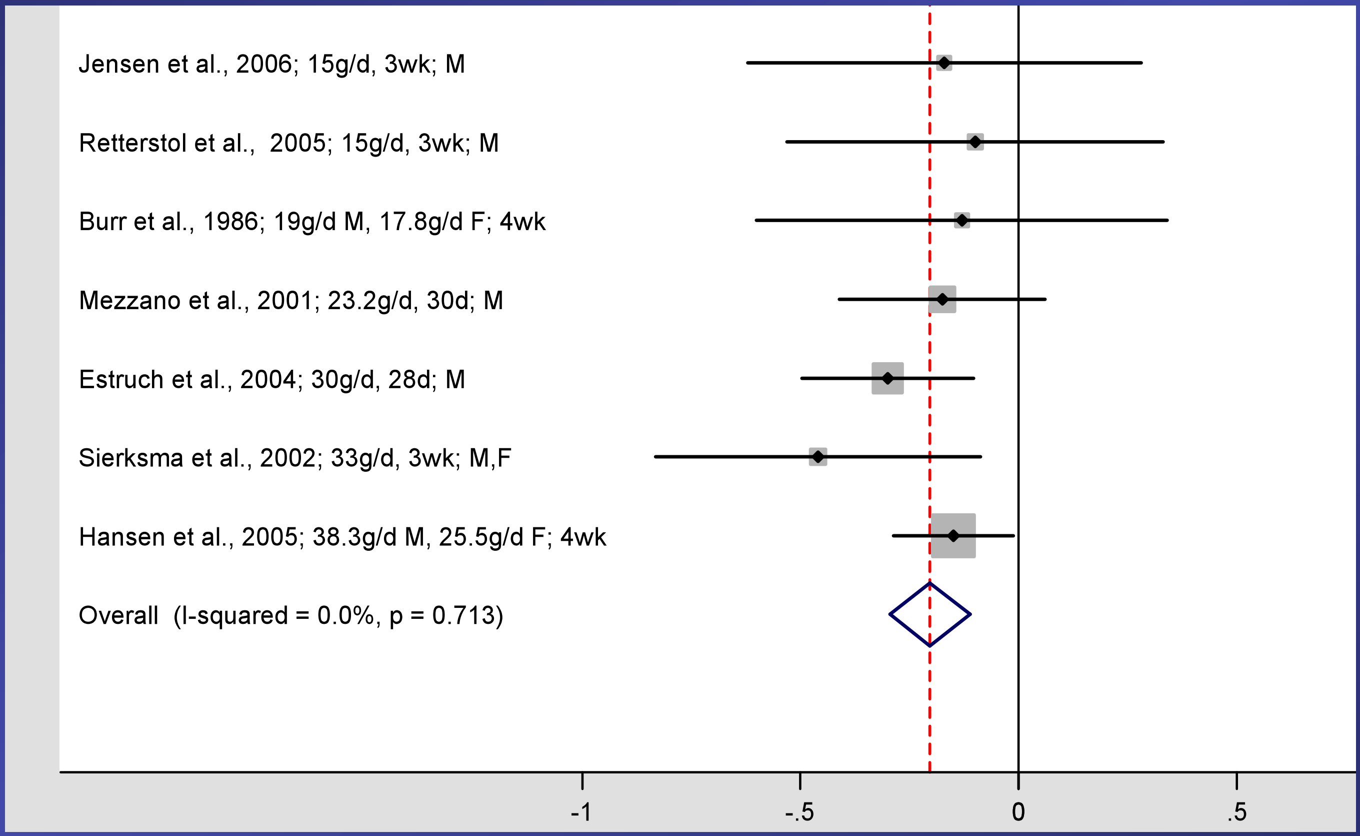
Honolulu Heart Program Lipoprotein Cohort



Langer et al, Circulation 1992

Alcohol Use and Fibrinogen:

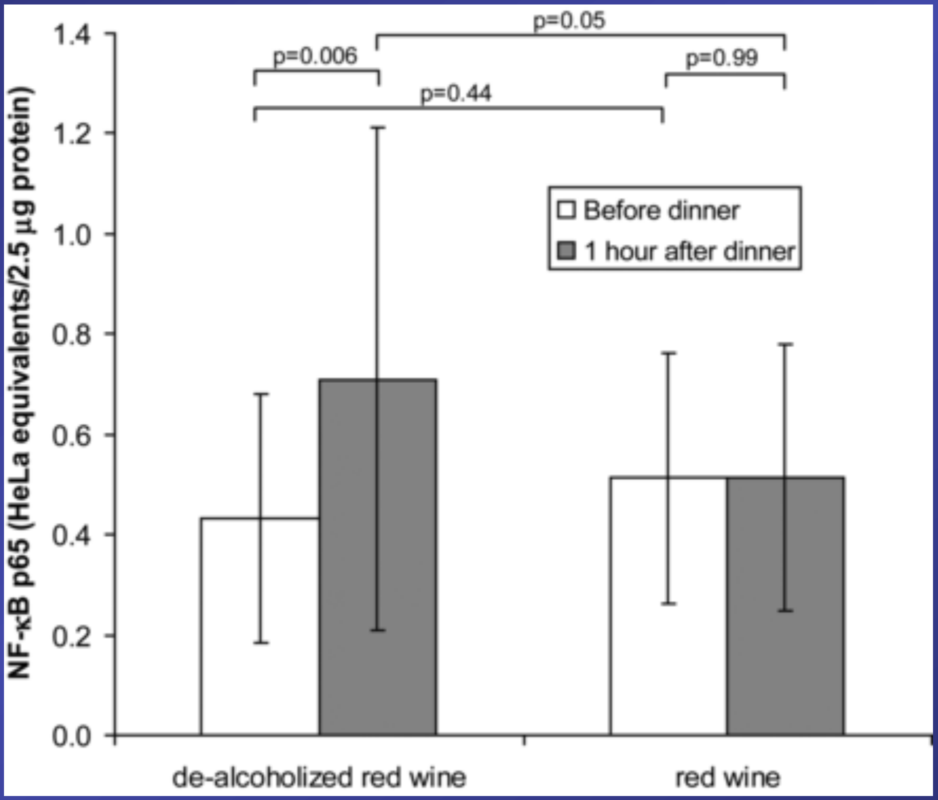
Meta-analysis of 7 clinical trials



Brien et al, BMJ 2011

Alcohol and PBMC NF-κB Activity:

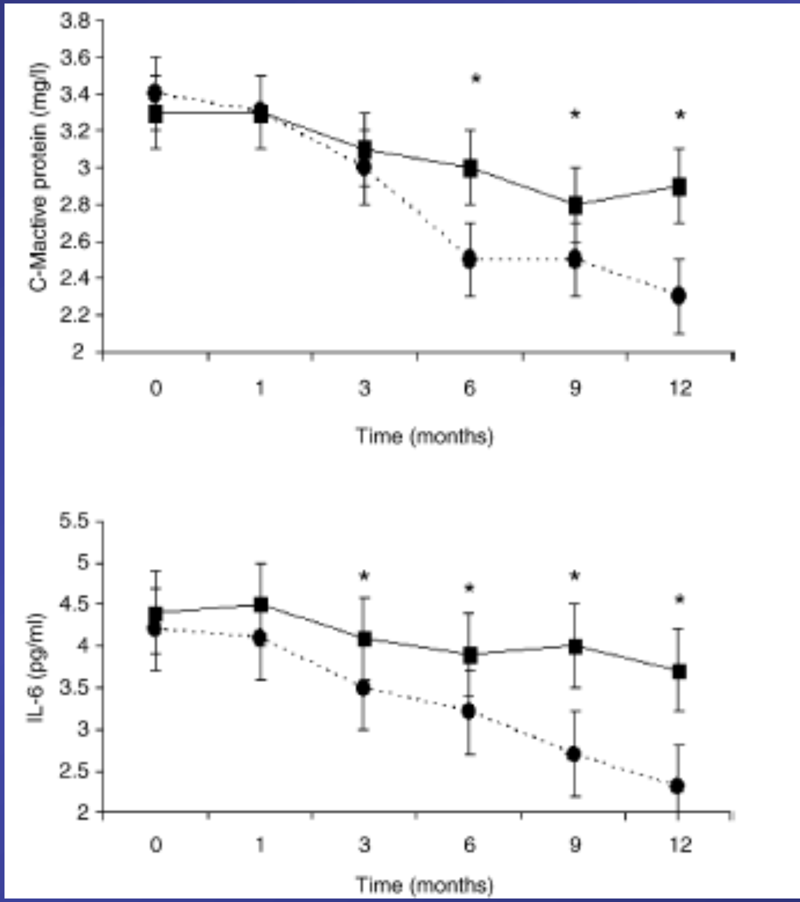
4-week crossover trial of 19 men



Schrieks et al, Alcohol Alcohol 2013

Red Wine in Patients with DM & MI:

1-year parallel RCT of advice to drink in 115 patients



CRP

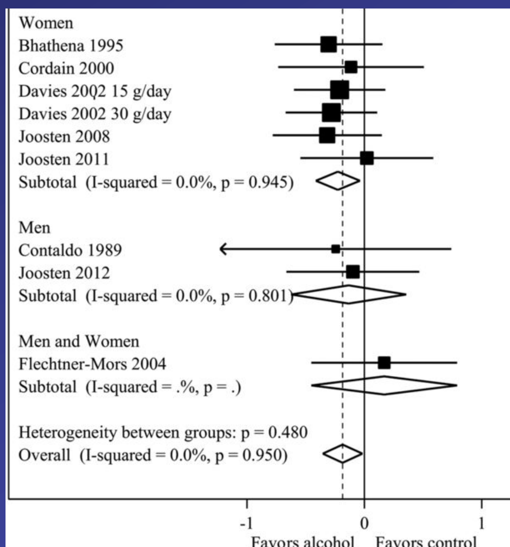
IL-6

Marfella et al, Diabet Med 2006

Alcohol Intake and Glycemia:

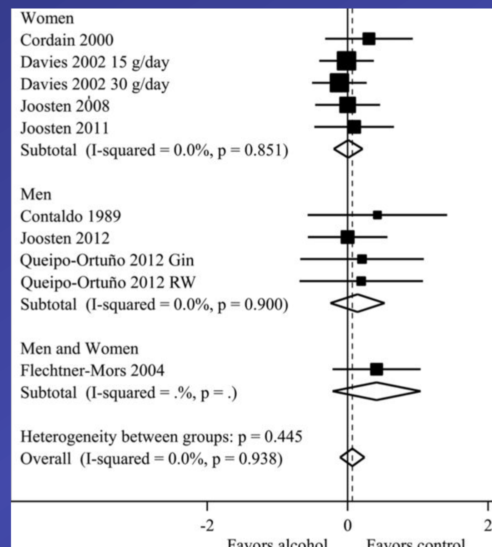
Meta-analyses of insulin, glucose and HbA_{1c}

Insulin



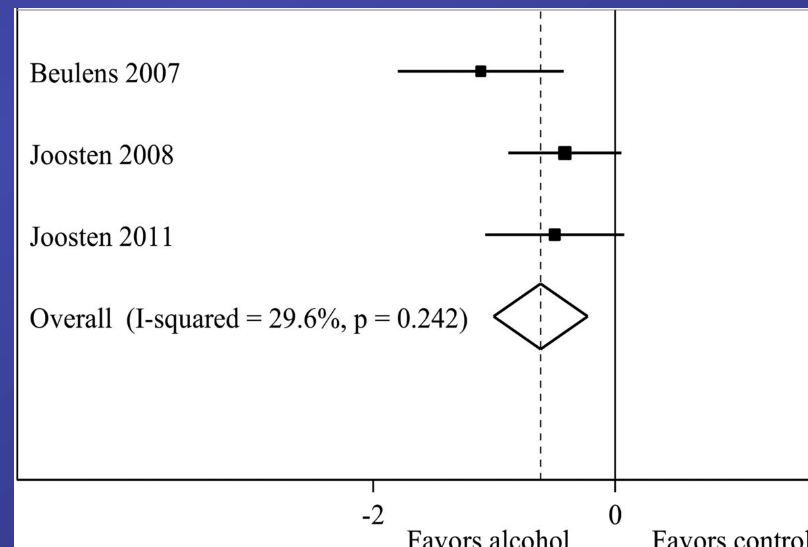
−0.19 (P=0.03)

Glucose



+0.07 (P=0.45)

Hemoglobin A_{1c}

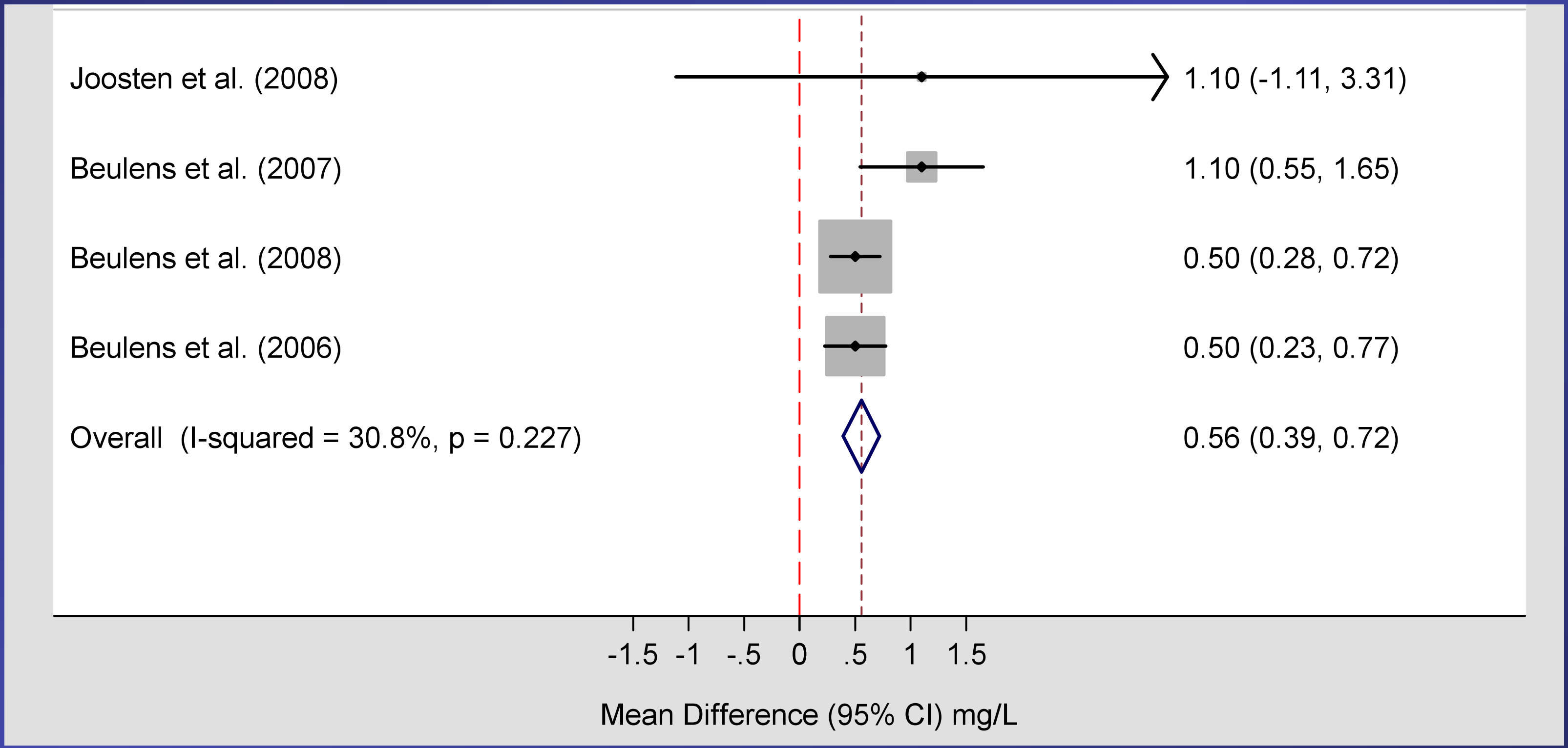


−0.62 (P<0.01)

Schrieks et al, Diabetes Care 2015

Alcohol Use and Adiponectin:

Meta-analysis of 4 clinical trials



Brien et al, BMJ 2011

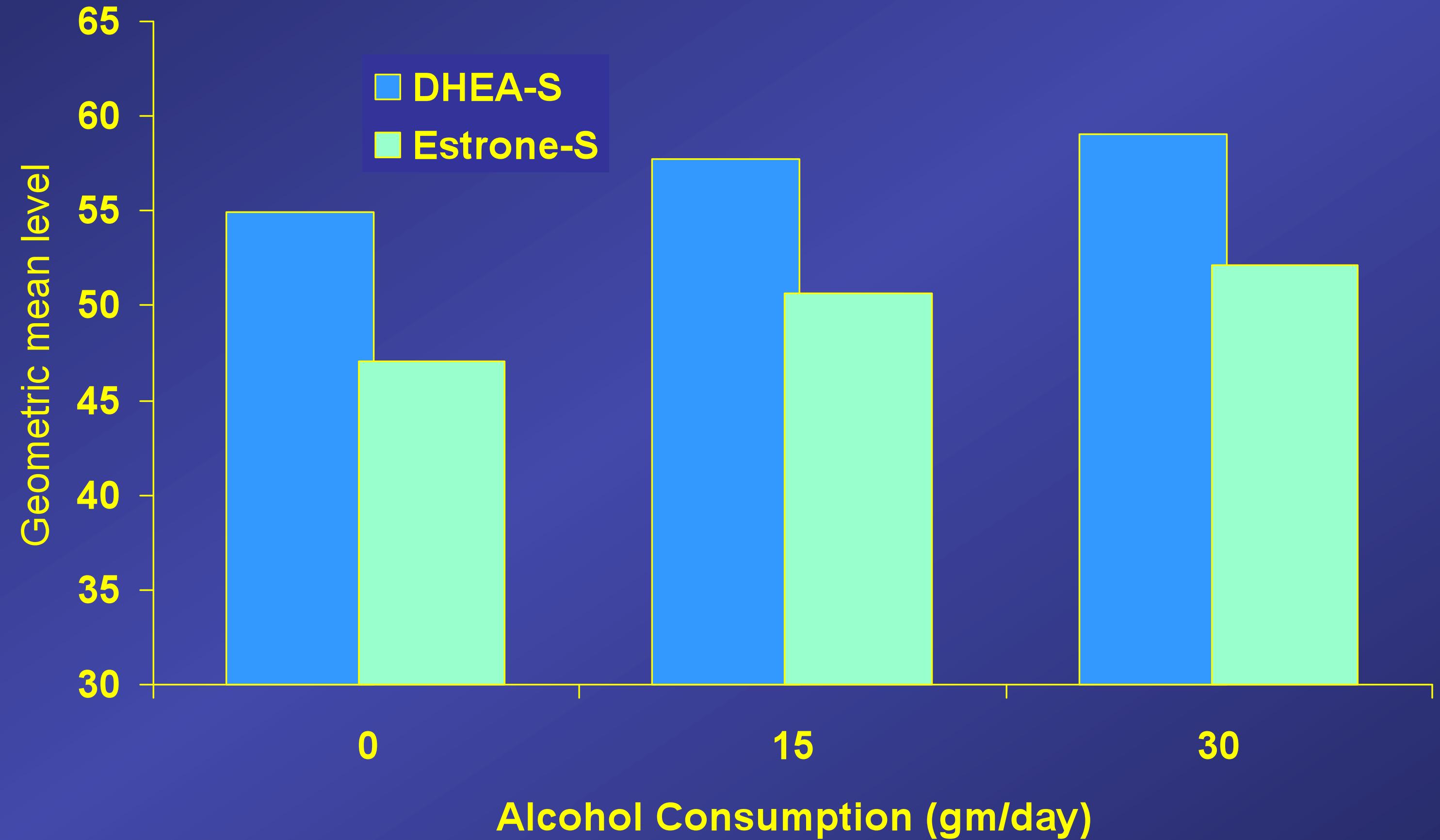
Alcohol & Adiponectin Expression:
6-week crossover trial of 36 women

Variable	Grape juice	White wine	*p* value
Insulin sensitivity			
HOMA-IR	1.64±0.13	1.42±0.13	0.02
Fasting insulin (pmol/l)	46.5±3.4	40.0±3.4	<0.01
Fasting glucose (mmol/l)	5.4±0.1	5.4±0.1	0.72
HbA_{1c} (%)	6.0±0.04	5.9±0.04	0.09
Fasting NEFA (mmol/l)	0.43± 0.04	0.44±0.04	0.67
Body weight (kg)	70.4±1.7	71.1±1.7	<0.001
Adiponectin			
ADIPOQ/ARBP mRNA (arbitrary units)	0.98±0.15	1.09±0.15	0.04
PPARG/ARBP mRNA (arbitrary units)	0.67±0.09	0.73±0.09	0.13
Fasting total adiponectin (µg/ml)	12.0±0.8	13.1±0.8	<0.001
Fasting HMW adiponectin (µg/ml)	8.8±1.2	9.9±1.2	0.02
Lipid profile			
Fasting triacylglycerol (mmol/l)	1.18±0.08	1.03±0.08	0.04
HDL-cholesterol (mmol/l)	1.57±0.04	1.68±0.04	<0.0001
LDL-cholesterol (mmol/l)	3.84±0.12	3.51±0.12	<0.0001

Joosten et al, Diabetologia 2008

Alcohol and Serum Sex Steroids:

8-week crossover trial of 51 postmenopausal women



Dorgan et al, JNCI 2001

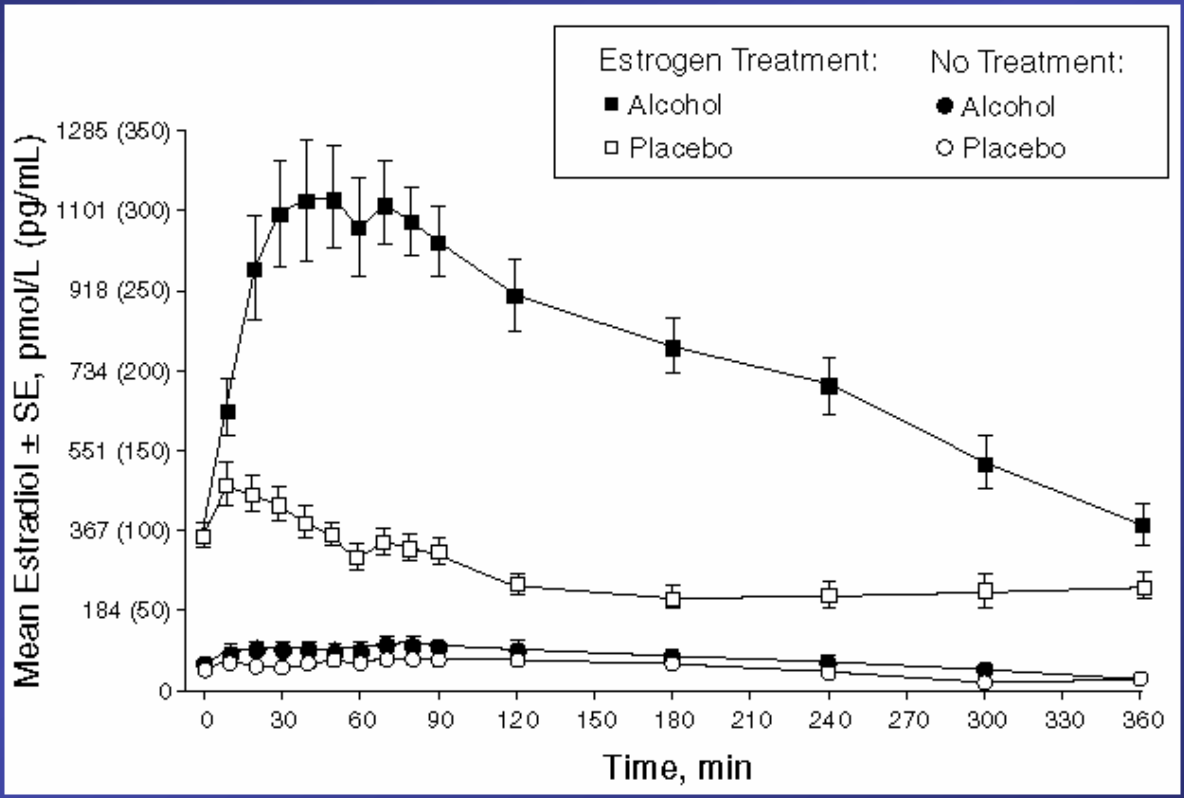
Alcohol and Plasma Sex Steroids:

3-week crossover trial of 9 women, 10 men

	Men (n = 10)		Women (n = 9)	
	Beer	No-alcohol beer	Beer	No-alcohol beer
HDL cholesterol (mmol/liter)	1.34 (0.24)*	1.18 (0.16)	1.70 (0.33)*	1.55 (0.32)
DHEAS (micromol/liter)	4.0 (1.8)#	3.5 (1.7)	3.9 (2.7)	3.3 (2.2)
Testosterone (nmol/liter)	15.3 (3.6)*	16.4 (2.9)	1.1 (0.6)	1.1 (0.6)
Estradiol (pmol/liter)	66.6 (11.7)	65.2 (8.9)	28.2 (16.3)	28.0 (13.0)

Sierksma et al, ACER 2004

Alcohol and Estradiol Levels:
Acute effects in 24 postmenopausal women



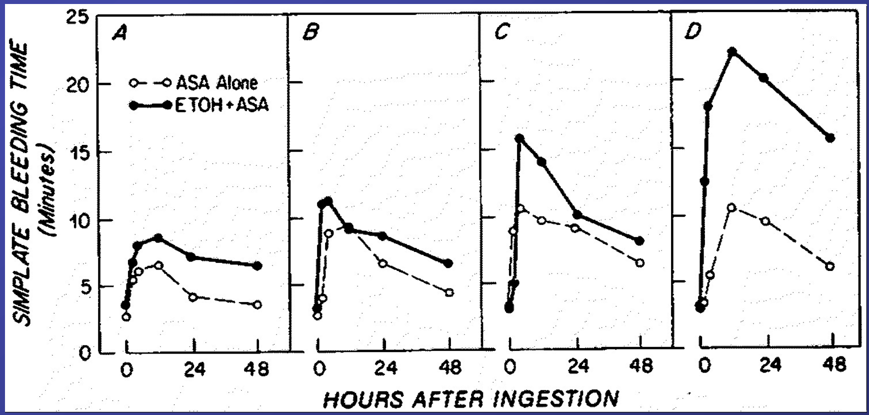
Ginsburg et al, JAMA 1996

Alcohol, Aspirin, and Bleeding Time:
Crossover trial among 9 men and women

Table 1. Response of Bleeding Time to Aspirin (325 mg), Ethanol (50 g), or Both Together.

Hours after Ingestion	Aspirin	Ethanol	Aspirin + Ethanol
	bleeding time (minutes) *		
0	3.3±0.2	3.0±0.1	3.1±0.1
2	5.1±0.2 †	3.5±0.2	7.3±0.9 ‡
4	6.4±0.7 ‡	3.7±0.3	10.4±1.2 §
12	7.2±0.8 ‡	3.3±0.1	11.0±1.5 §
24	5.8±0.8 †	3.4±0.1	9.1±1.5 ‡
48	4.3±0.5	3.2±0.1	7.1±1.2 ‡
72	3.4±0.2	3.3±0.1	5.6±0.7 ‡
96	3.2±0.1	3.2±0.1	4.2±0.3 ‡
120	3.2±0.2	3.1±0.1	3.3±0.1

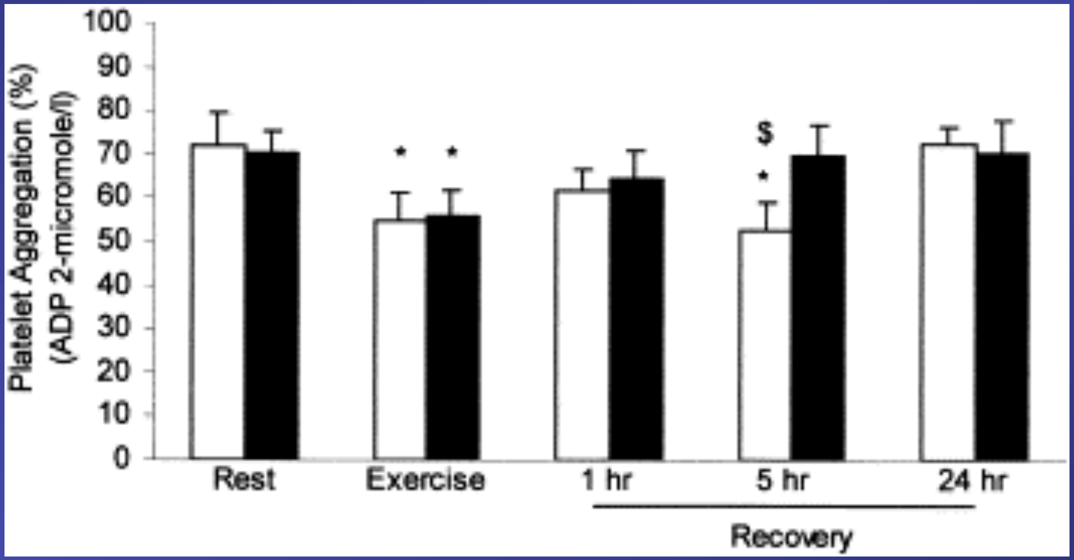
*Mean ±S.E.M. in nine subjects. †P<0.05 as compared with 0 hours.
‡P<0.01 as compared with 0 hours. §P<0.001 as compared with 0 hours.



Deykin D et al, N Engl J Med 1982

Alcohol and Platelet Aggregation after Exercise:

Crossover trial among 19 men and women

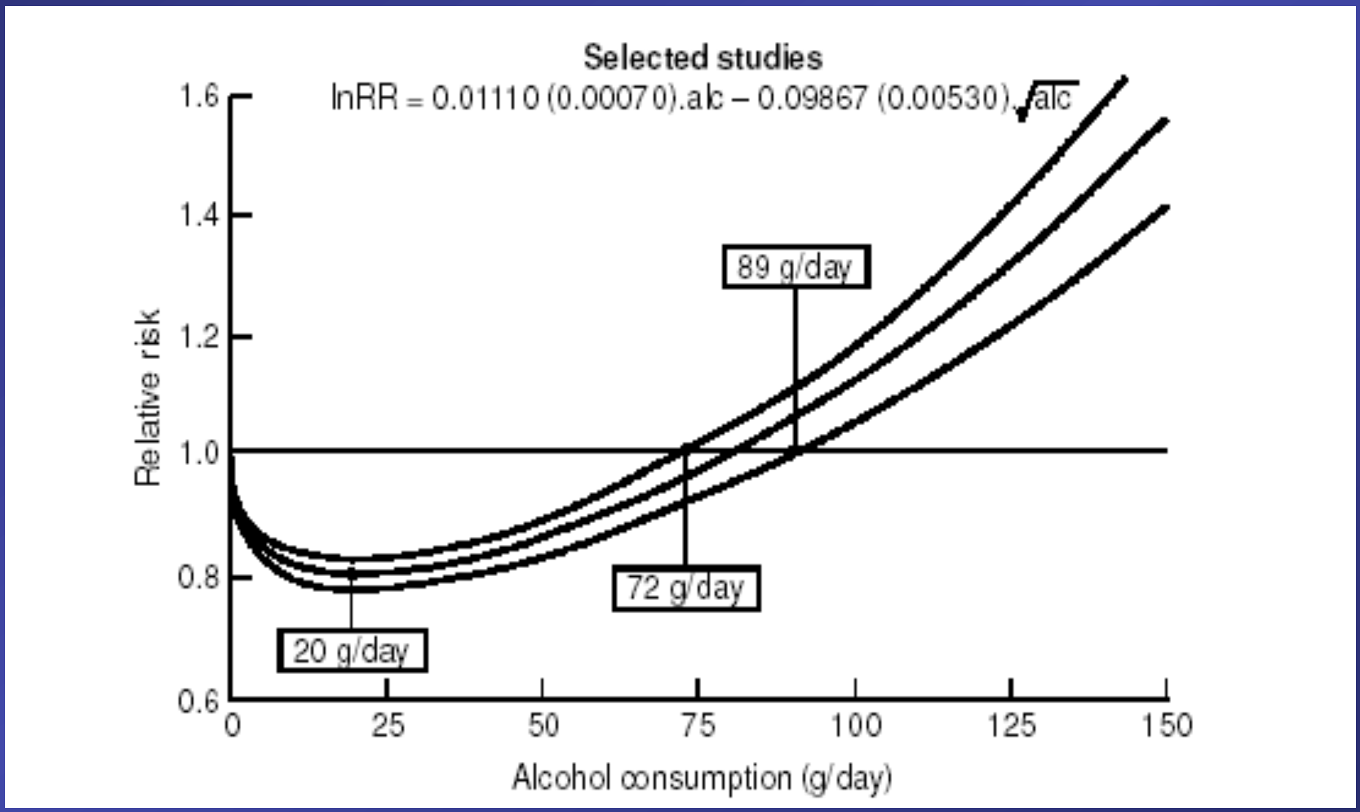


El-Sayed, Thromb Res 2002

Summary:
Existing Trials

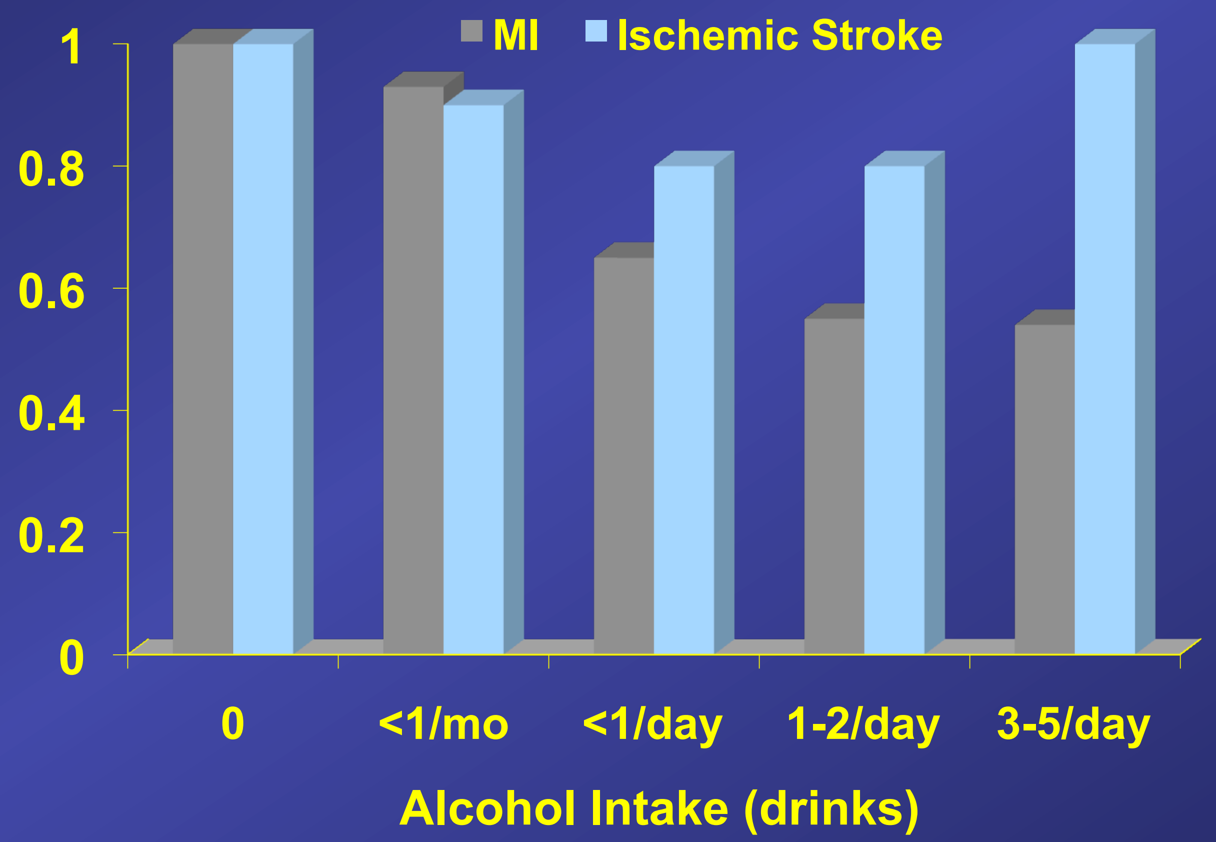
- In feeding studies, alcohol:
  - Raises HDL-C and cholesterol efflux
  - Lowers fibrinogen and possibly other markers of inflammation
  - Lowers fasting insulin and HbA_{1c}
  - Raises DHEA and estrone sulfate
  - Prolongs bleeding time and variably reduces platelet aggregability

Alcohol Use and Risk of CHD:
Meta-analysis of 28 cohort studies



Corrao et al, Addiction 2000

Alcohol & Risk of MI/Ischemic Stroke:
Kaiser Permanente cohort

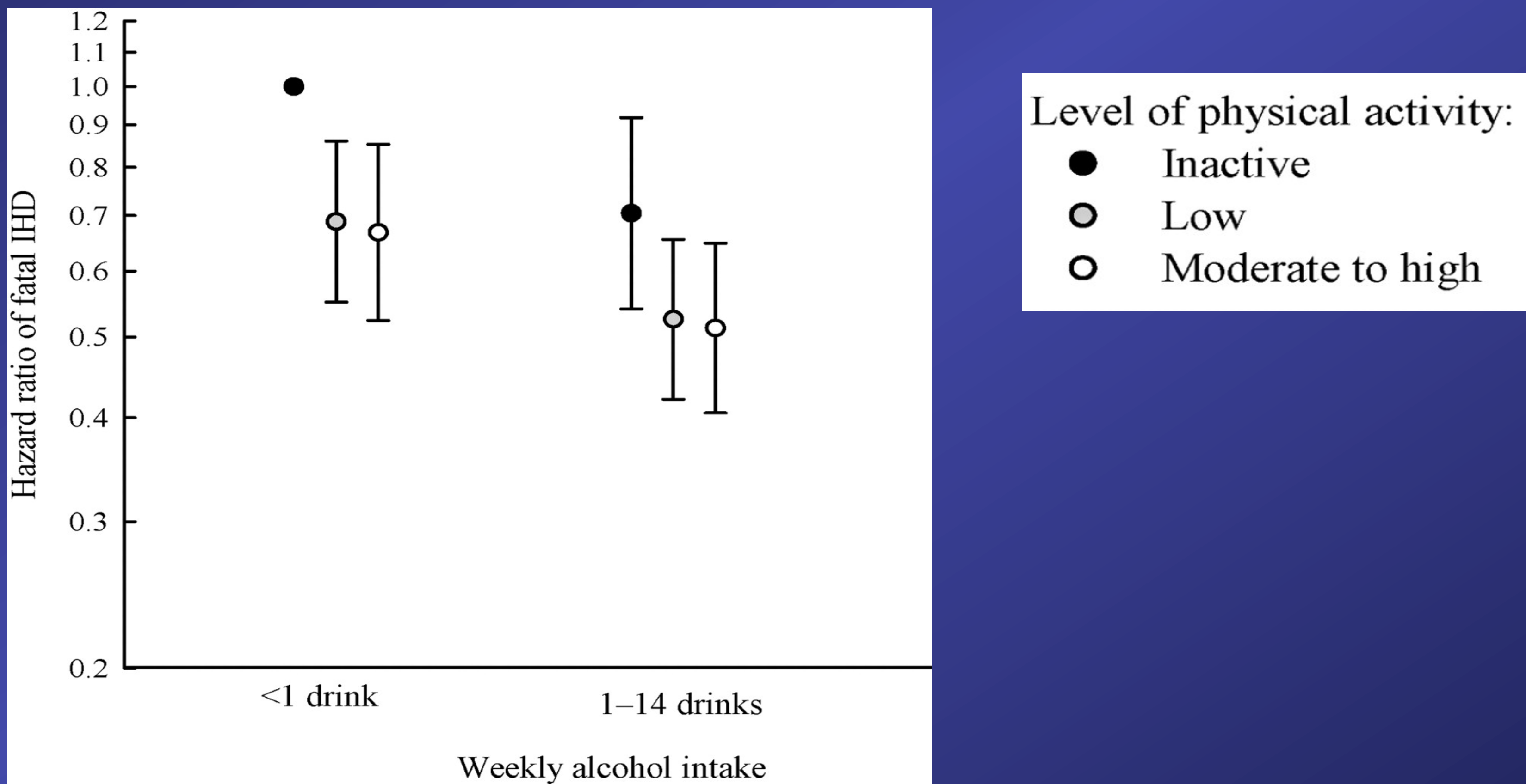


N=85000 KP members

Klatsky et al, Am J Cardiol 1986, 2001

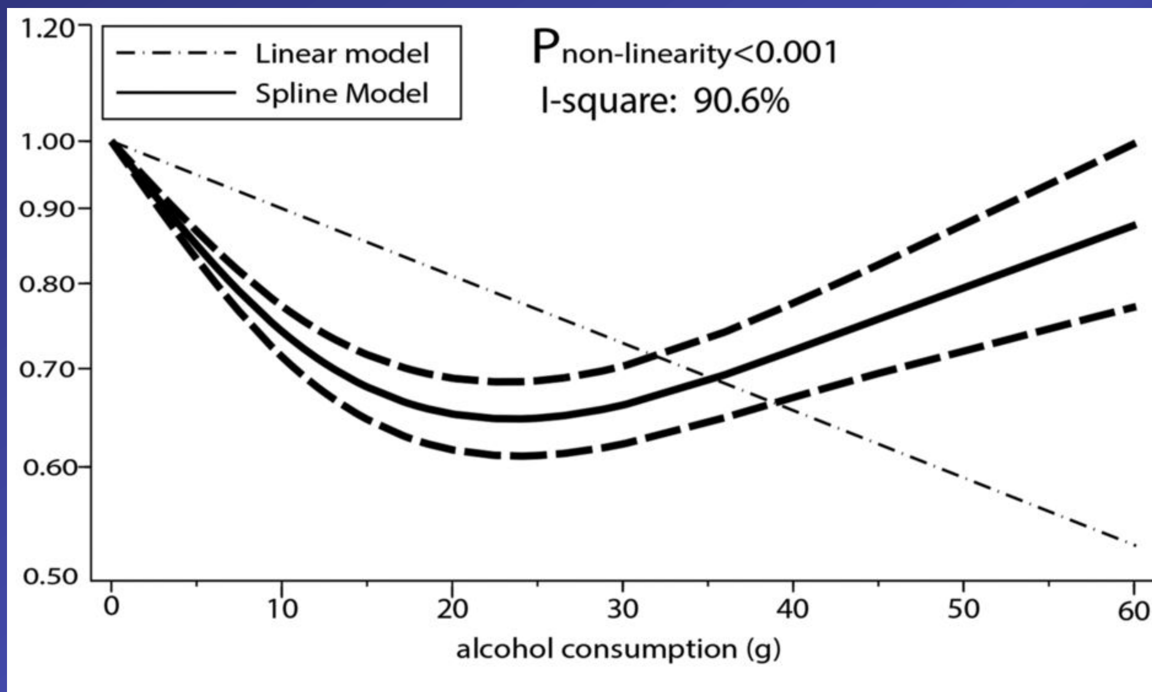
Alcohol, Physical Activity, and CHD

Copenhagen City Heart Study



Pedersen et al, Eur Heart J 2008

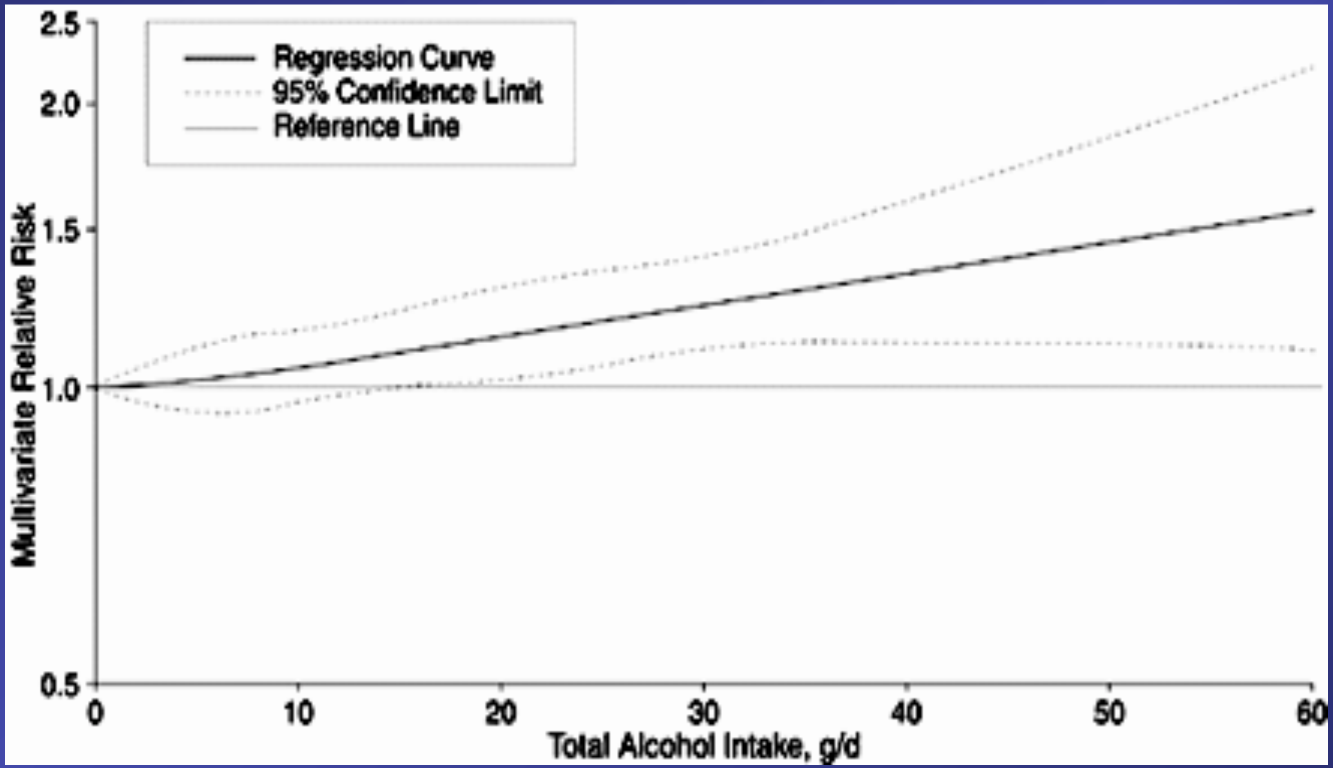
Alcohol Intake and Risk of Diabetes:
Meta-analysis of 26 cohort studies



Li et al., Am J Clin Nutr 2016

Alcohol Use and Risk of Breast Cancer:

7 Pooled Cohort Studies of Women



N=322647 women

Smith-Warner et al, JAMA 1998

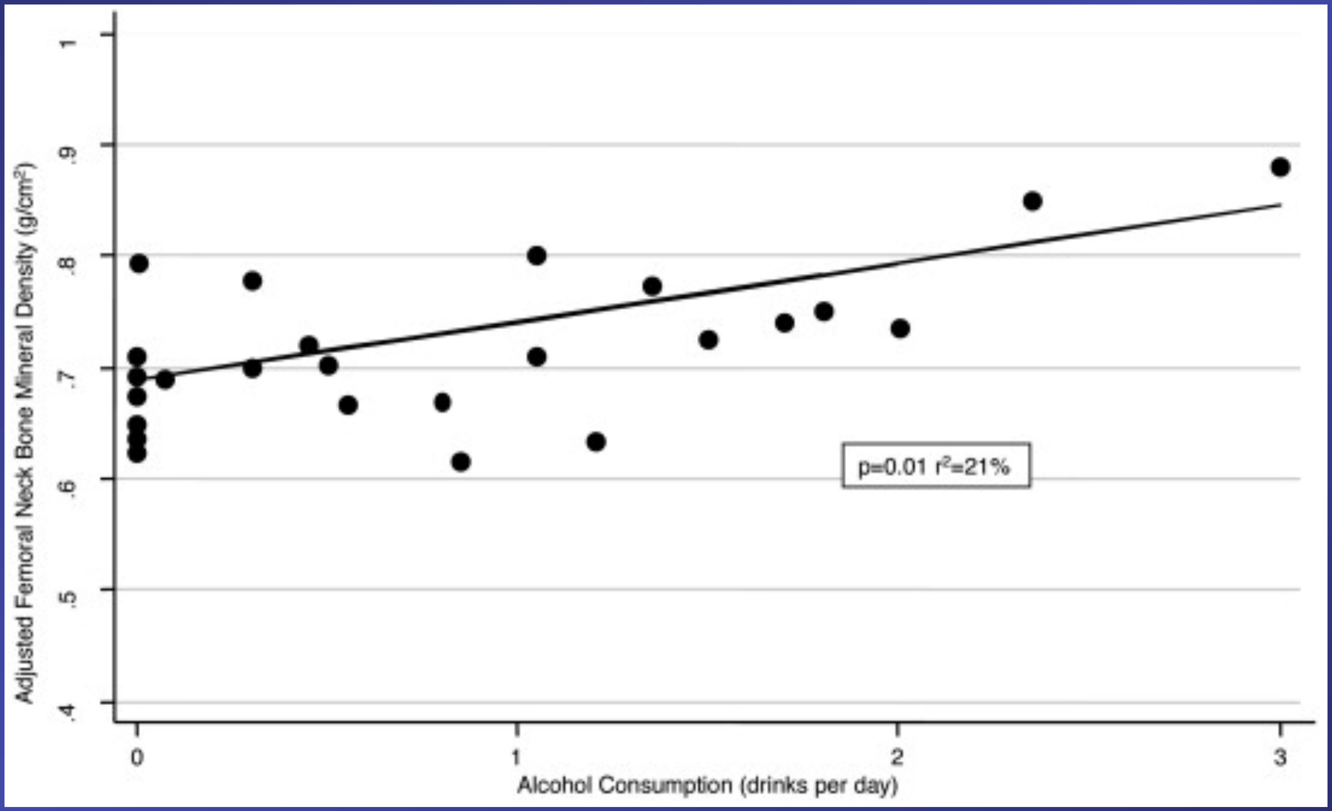
Alcohol and Breast Cancer:

Receptor Status in the PLCO Trial

Alcohol Consumption, by Hormone Receptor Status	No. of Cases[a]	Multivariate HR[b]	95% CI
ER+			
Never	175	1.00	Referent
Former	235	1.14	0.93, 1.4
Current, drinks/week			
<0.5	341	1.15	0.95, 1.39
0.5–<1	158	1.29	1.03, 1.61
1–<7	397	1.29	1.07, 1.56
≥7	219	1.48	1.19, 1.83
P_{trend}[c]		0.0039	
ER–			
Never	33	1.00	Referent
Former	50	1.10	0.70, 1.73
Current, drinks/week			
<0.5	60	0.98	0.63, 1.51
0.5–<1	29	1.08	0.65, 1.81
1–<7	68	1.05	0.68, 1.62
≥7	26	0.84	0.49, 1.44
P_{trend}[c]		0.24	

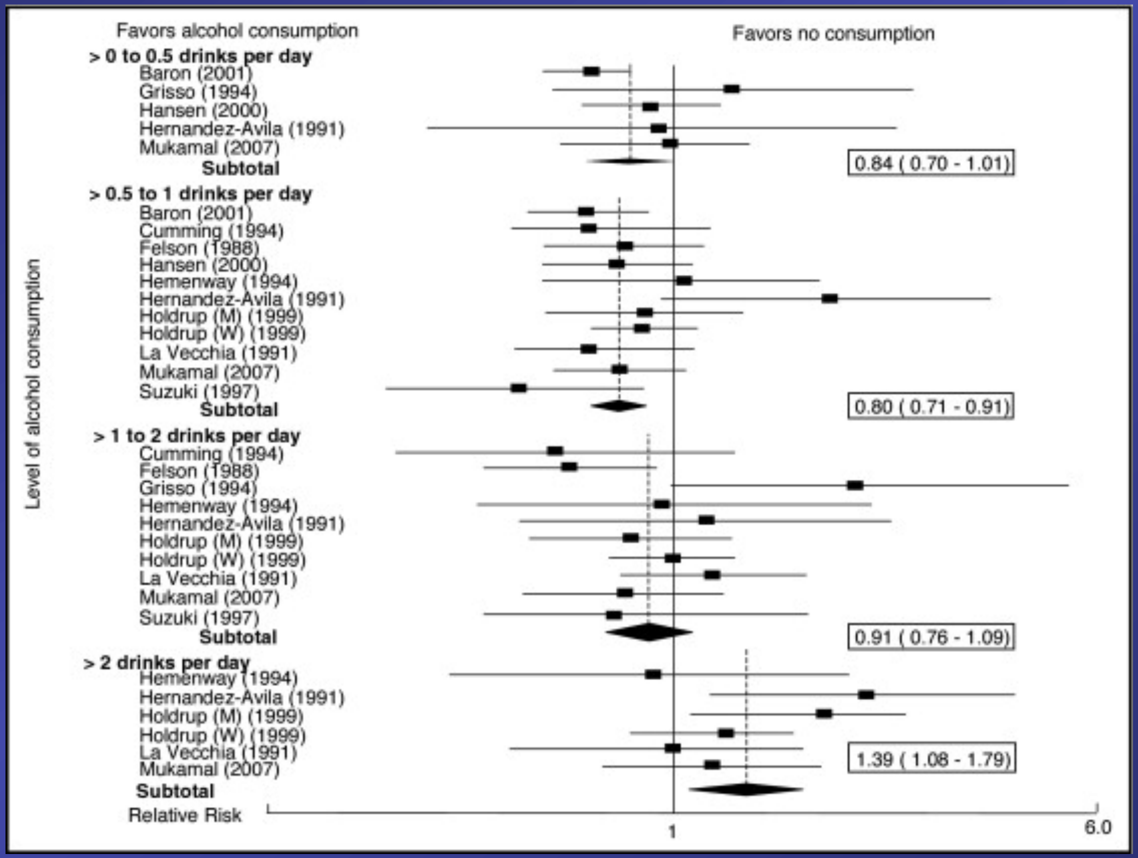
Falk et al, Am J Epidemiol 2014

Alcohol and Femoral Neck BMD:
Four Cohort Studies



Berg et al, Am J Med 2008

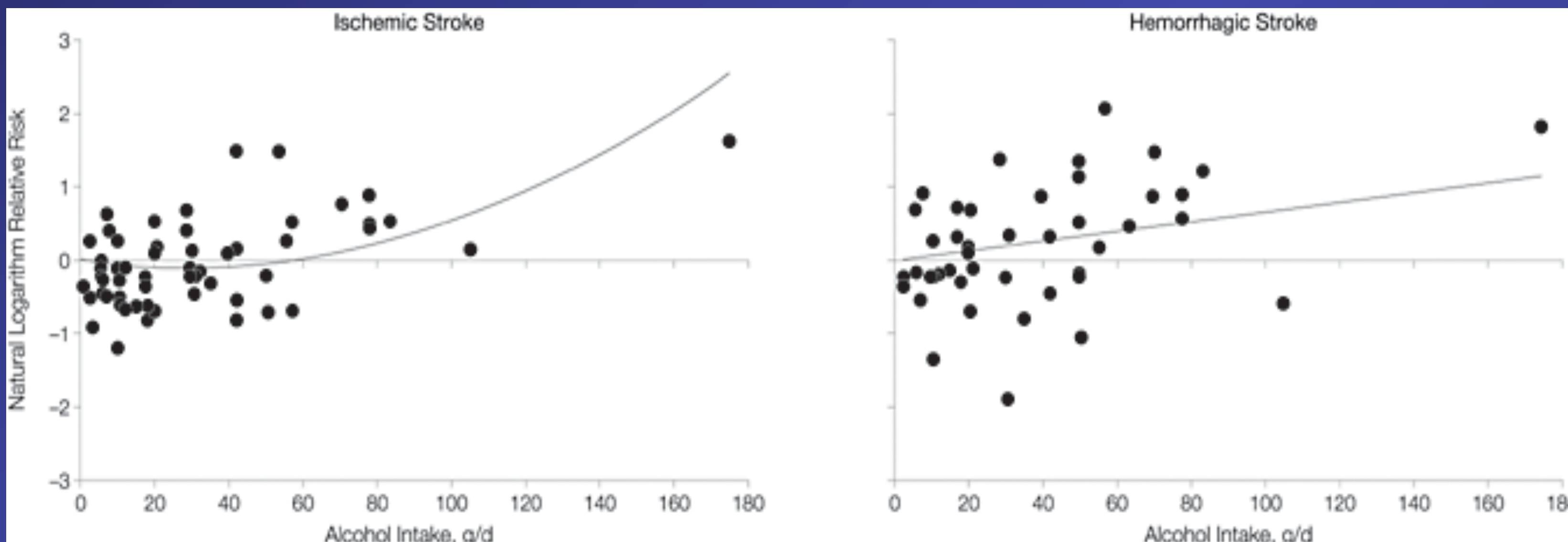
Alcohol and Hip Fracture:
Case-Control and Cohort Studies



Berg et al, Am J Med 2008

Meta-regression of Alcohol and Stroke:

Meta-Analysis of 24 Studies



Reynolds et al, JAMA 2003

Alcohol Use and Upper GI Bleeding:
1224 Cases and 2945 Controls in US and Sweden

Kaufman et al, Am J Gastroenterol 1999

Summary:
Observational Studies

- Lower risk of CHD
- Lower risk of ischemic stroke, less pronounced than for CHD
- Lower risk of diabetes
- Higher risk of estrogen-sensitive breast cancer
- Higher bone density
- Higher risk of hemorrhagic stroke
- Higher risk of GI bleeding

Returning to Alcohol Metabolism

Ethanol —(Alcohol Dehydrogenase)→ Acetaldehyde —(Aldehyde Dehydrogenase)→ Acetate

- 7 *ADH* genes on chromosome 4
- *ADH1A, ADH1B, ADH1C* have greatest affinity
- Common polymorphisms in *ADH1B* in African (B3) and Middle Eastern (B2) populations
- Common polymorphism in *ADH1C* in whites
- Common polymorphism in *ALDH2* in East Asians

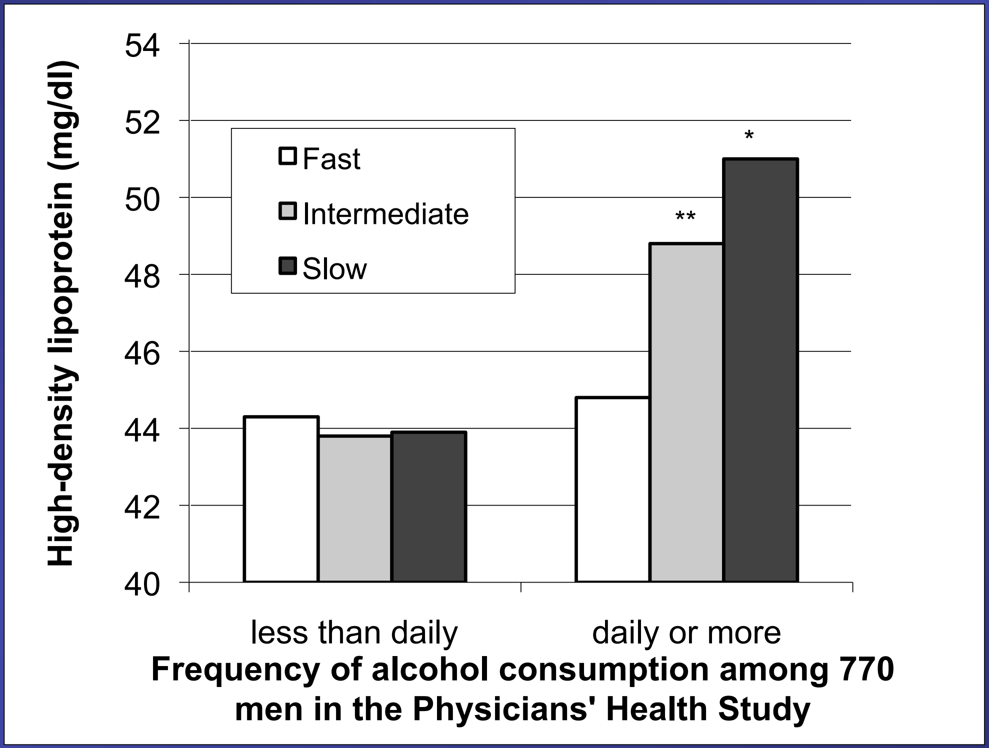
Kinetic Activity of ADH Alleles

	ADH1B			*ADH1C*	
	$\beta_1\beta_1$	$\beta_2\beta_2$	$\beta_3\beta_3$	$\gamma_1\gamma_1$	$\gamma_2\gamma_2$
V_{max}, min $^{-1}$	9.2	400	270	87	35

Bosron et al, Mol Aspects Med 1988

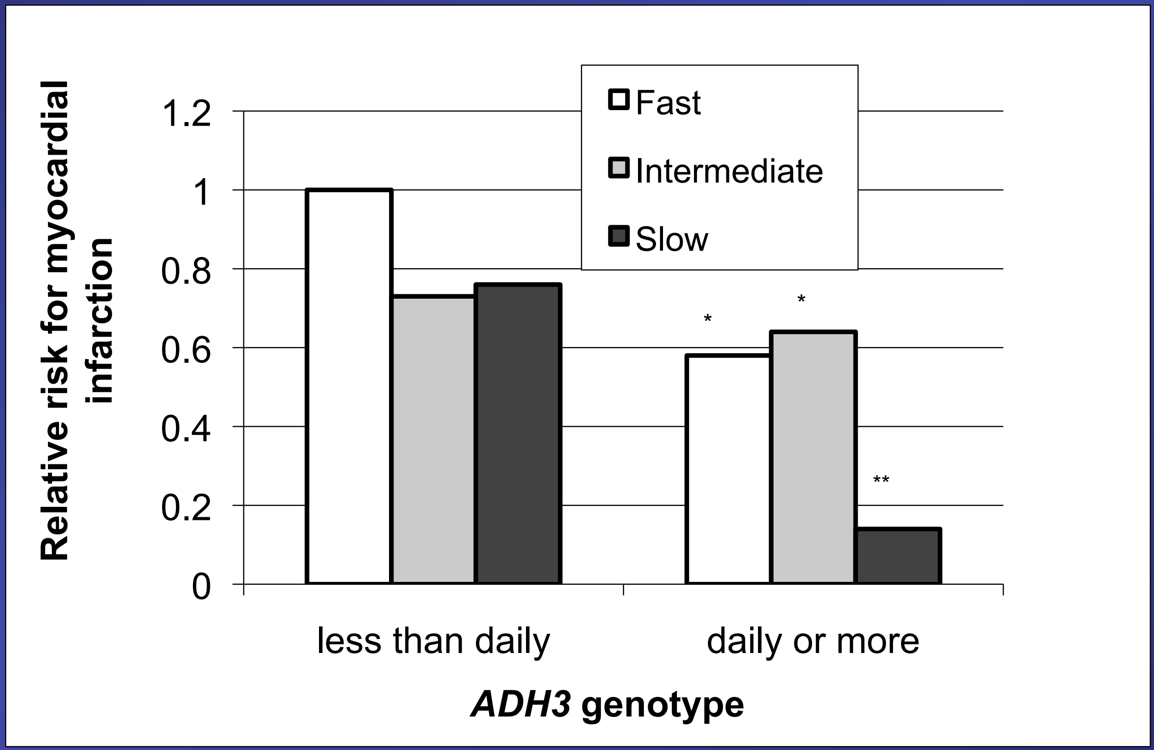
ADH1C, Alcohol, and HDL-C:

The Physicians' Health Study



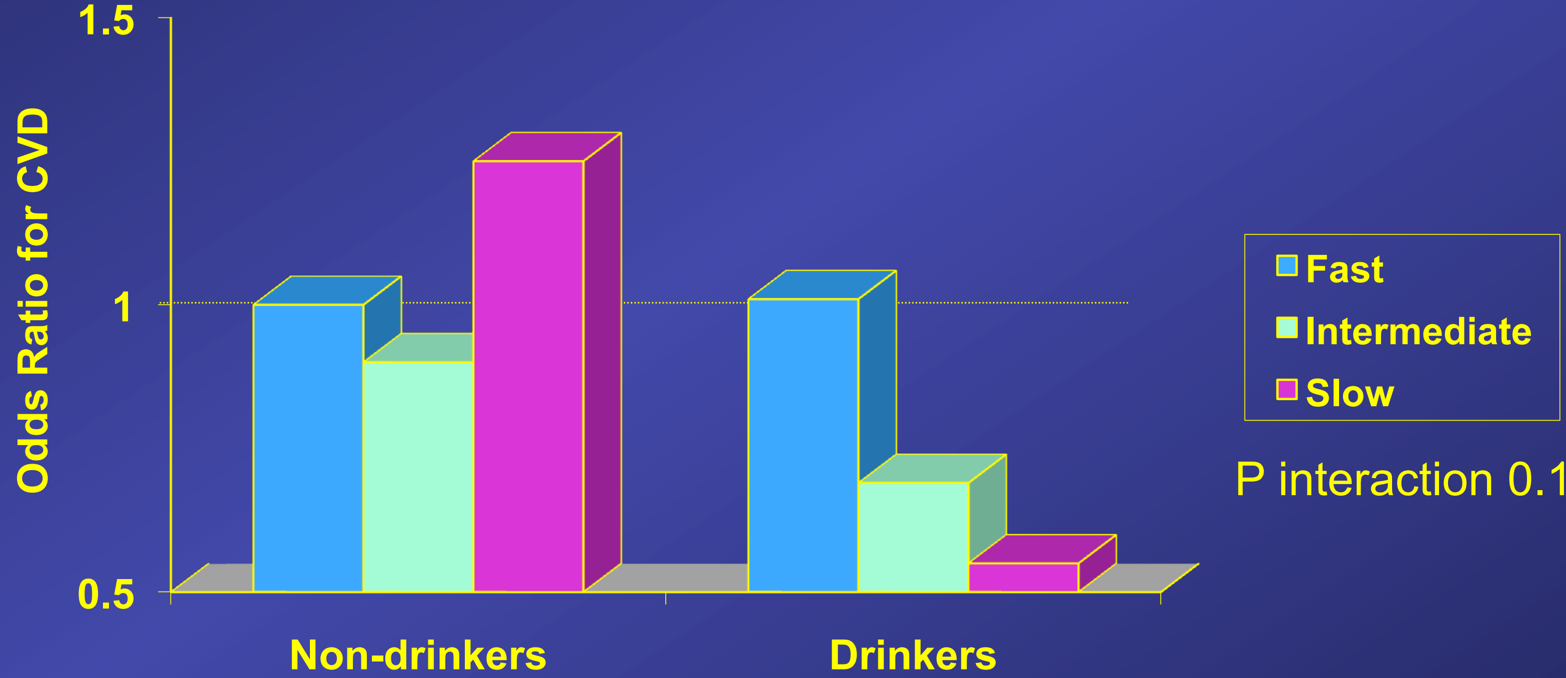
Hines et al, NEJM 2001

ADH1C, Alcohol, and Risk of CHD:
The Physicians' Health Study



Hines et al, NEJM 2001

ADH1C, Alcohol, and Prevalent CVD:
The Framingham Offspring Study



P interaction 0.16

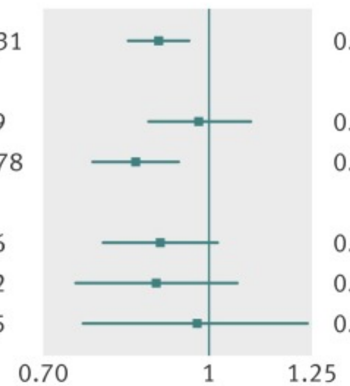
Djousse et al, Am J Cardiol 2005

*ADH1B*2* and Risk of CHD:

Meta-analysis of 46 observational studies

- Known population stratification (median MAF~5%)
- Associated with education
- Not associated with HDL-C
- Strong instrument for binge drinking

Category for coronary heart disease outcome	No of studies	No of cases/ individuals	Odds ratio (95% CI)	Odds ratio (95% CI)	P value
Overall (all individuals)	46	20 259/168 731		0.90 (0.84 to 0.96)	0.001
Any or no alcohol intake					
Non-drinkers	31	5883/43 029		0.98 (0.88 to 1.10)	0.095*
Drinkers only	40	10 130/107 478		0.86 (0.78 to 0.94)	
Drinkers subgroup (units/week)					
Light (>0 to <7)	32	4686/47 246		0.90 (0.79 to 1.02)	0.828*
Moderate (≥7 to <21)	32	3222/33 772		0.89 (0.75 to 1.06)	
Heavy (≥21)	29	1919/16 225		0.97 (0.76 to 1.24)	

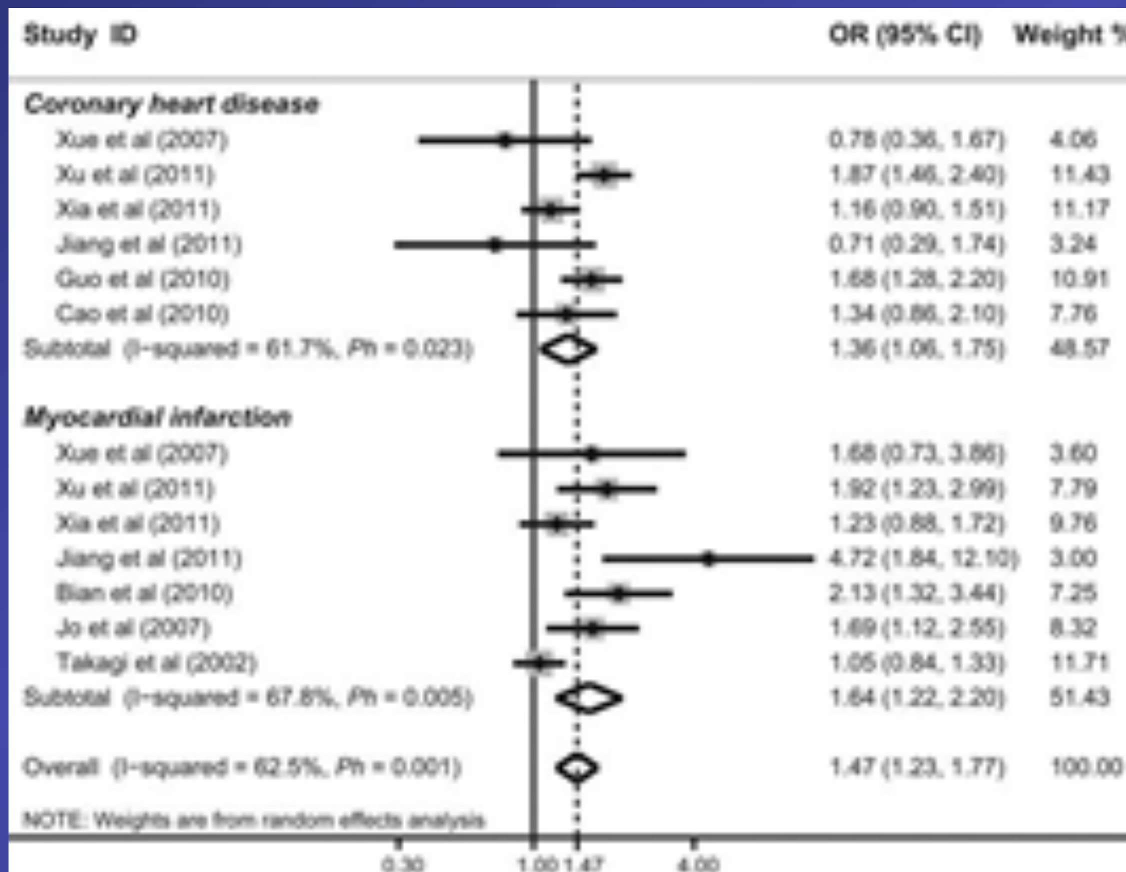


* P value for heterogeneity obtained from test for trend using meta-regression

Holmes et al, BMJ 2014

ALDH2 rs671 and Risk of CHD:

Meta-analysis of 9 case-control studies



Wang et al, DNA & Cell Biology 2013

Summary:
Genetic Studies

- Lower risk of CHD most pronounced in *CETP* Taq1B carriers
- Lower risk of CHD most pronounced in *ADH1C* slow metabolizers of ethanol
- Effects of variants associated with alcohol consumption *per se* mixed
  - Lower risk among *ADH1B**2 carriers
  - Higher risk *ALDH2**Lys carriers
- Dozens of other candidate gene studies mixed