In Vino Veritas: Alcohol and Heart Disease

Joseph A. Hill, MD, PhD

Departments of Internal Medicine and Molecular Biology,
University of Texas Southwestern Medical Center,
Dallas, TX

"When I read about the evils of drinking, I gave up reading."
Henny Youngman

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For centuries, society has struggled with whether alcohol is a good thing or a bad thing. Through history, consumption of alcoholic beverages has been socially regulated, either by government, by the Church, or by society at large. In the United States, morays have vacillated wildly between strict avoidance during Prohibition and the current media bombardments encouraging consumption.

During the past 30 years, biomedical research has suggested that alcohol consumption may afford significant health benefits. At the same time, the well known deleterious effects of excessive alcohol consumption take an enormous toll of life and wealth. Accordingly, the medical profession is charged with a unique dimension of regulatory oversight of this sharpest of double-edge swords; do we discourage alcohol consumption among our patients? do we recommend it? if so, to whom? and how much?

Historical Perspective

Today, alcohol is viewed variably as a social menace, party tool, sophisticated social lubricant, or enjoyable medicine. For the vast majority of the past 10,000 years, however, alcohol was viewed very differently. Indeed, for most of that time, alcoholic beverages may have been the only safe liquid to drink[1].

Ethanol is a by-product of the energy-producing metabolism of sugar by yeast. As such, accidental ingestion of ethanol in "spoiled" foods has undoubtedly occurred for millennia; indeed, at least trace amounts of ethanol can be found in many fruits and vegetables. The very existence of an alcohol dehydrogenase gene in man (and other mammals) suggests that our species evolved in the presence of alcohol, however unintentional the exposure may have been.[a]

For most of the past 10 millennia, when water supplies were largely contaminated and dangerous, alcoholic beverages may have been the most popular and common daily drinks[1]. The historical record – from Egyptian writings to the Bible – is filled with references to wine and beer as beverages for quotidian use with medicinal and psychogenic powers. Indeed, ancient writings, including ancient Greek texts and the Old and New Testaments are virtually devoid of references to water as a beverage. As recently as 200 years ago – a blink of the eye in historical terms – consumption of coffee in the West was questioned as a threat to our social order relative to the customary consumption of beer and wine[1]!

It is likely that intentional consumption of alcohol began approximately 10,000 years ago. With the advent of agriculture – and the attendant migration of people into communal living arrangements – an over-supply of food developed, and water quality deteriorated. Our early ancestors probably began farming not so much to grow food, which they could usually find easily, as to insure a steady supply of ingredients needed to make alcoholic beverages. Indeed, ancient records reveal that the cereal-based diets of peasant laborers was largely accompanied by fermented beverages vaguely reminiscent of modern-day beer.

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[a] Alcohol dehydrogenase exists as a family of isozymes encoded by at least 7 genes and comprised of 5 classes[2]. All are expressed at highest levels in the liver. In addition to alcohol, these enzymes recognize a number of substrates, including bile compounds, testosterone, retinol, and mevalonate, though the role of alcohol dehydrogenase in the metabolism of these substances is unclear.

Some ancient records include recipes for beer – replete with figures! Around 6000 B.C., cultivation of grapes for wine (viniculture) was emerging in present-day Armenia. By the third millennium B.C., Egyptians and Babylonians[b] were drinking barley- and wheat-based beer as a regular part of their diet (Fig 1). Early Egyptian writings urged mothers to send their children to school with plenty of bread and beer for their lunch!

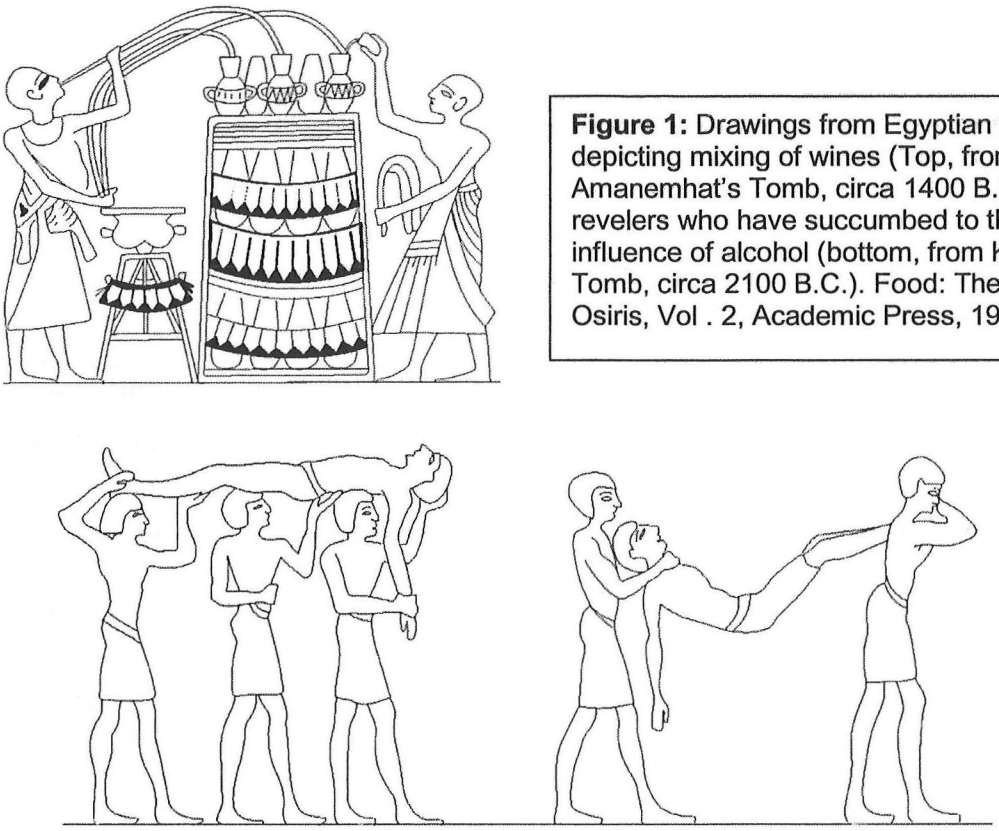

Figure 1: Drawings from Egyptian tombs depicting mixing of wines (Top, from Amanemhat's Tomb, circa 1400 B.C.) or revelers who have succumbed to the influence of alcohol (bottom, from Khety's Tomb, circa 2100 B.C.). Food: The Gift of Osiris, Vol . 2, Academic Press, 1977

It is interesting to note that long-range ocean voyages were possible only because of the antiseptic properties of alcohol-based beverages. Christopher Columbus crossed the Atlantic with a crew that quenched its thirst largely with wine, and the Pilgrims made their initial landing at Plymouth Rock only because they had run out of beer.

Around the beginning of the 17th century, nonalcoholic beverages made with boiled water – coffee, tea, and cocoa – became popular, breaking alcohol's monopoly on safety[c]. This was followed by a growing religious antagonism toward

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[b] In ancient Babylon, the bride's father would supply his son-in-law with all the mead (fermented honey beverage) he could drink for a month after the wedding. Because their calendar was lunar or moon-based, this period of free mead was called the "honey month," or what we now call the "honeymoon."

[c] In the East, boiled water-based beverages, such as tea, were commonplace. This, combined with genetic differences in alcohol metabolism in Asian peoples, contributed to the lack of emergence of alcohol-based drink as a central part of society in the Orient.

alcohol, especially among Quaker's and Methodists in Great Britain[d]. With the realization that microorganisms caused disease and the development of facilities to treat and store water, the role of alcoholic beverages began to change.

American society has vacillated wildly in its perceptions of alcoholic drink. In the early decades of the 19th century, Americans drank approximately 3 times as much alcohol as they do now[3] (Fig 2). In the late 18th century, Benjamin Rush, prominent physician and founder of the University of Pennsylvania, was a vocal proponent of limiting alcohol consumption to moderate levels. In the mid 19th century, a growing temperance movement led to passage of prohibition laws, such that by 1855 roughly a third of Americans lived under laws that prohibited the sale of alcohol. This culminated in the "Great Experiment" of Prohibition (1920-1933), banning alcohol entirely in the United States. Whereas rates of liver cirrhosis dropped to all-time lows, Prohibition fostered the development of organized crime rings and was an utter failure in convincing Americans to abstain.

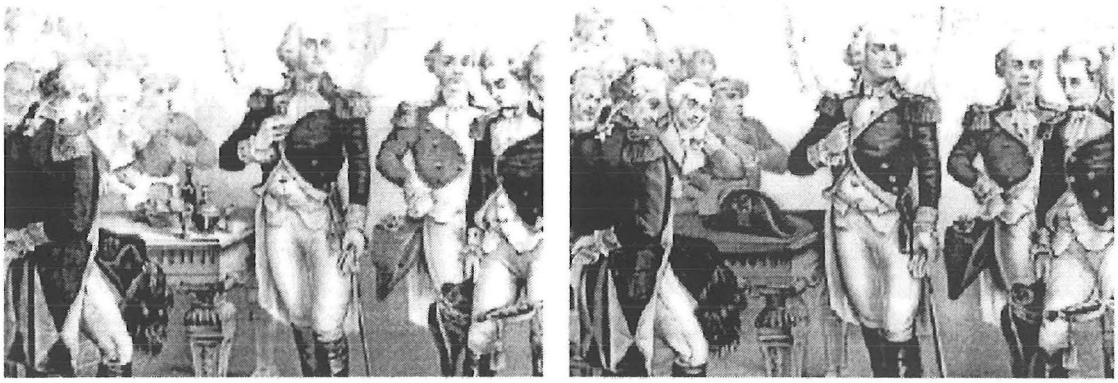

Figure 2: Lithographs depicting George Washington bidding farewell to his officers. In one dated 1848 (left), he is depicted toasting his men. In another dated 1876 (right), a period when alcohol consumption was relatively disfavored, the alcoholic beverages have been removed. Musto, 1996.

Early Suggestions of Health Benefits

References to wine and beer as medicines are commonplace in ancient texts, such as the Bible and records from Egypt and ancient Babylonia. Hippocrates recommended wine as remedy for a host of ailments, and alcohol as medicine was taught at the Alexandrian School of Medicine.

In the early part of the 20th century, potential impact of alcohol

[d] A host of English language expressions in common use trace back to practices related to alcohol. Before thermometers were invented, brewers would dip a thumb or finger into the liquid to determine the ideal temperature for adding yeast. From this we get the phrase "rule of thumb." In old England, a whistle was baked into the rim or handle of ceramic cups used for beer. When pub patrons wanted a refill, they used the whistle to get service ("wet your whistle"). Likewise, English bartenders would advise unruly customers to mind their own pints and quarts ("mind your P's and Q's").

consumption on coronary heart disease (CHD) was proposed. Pathologists noted that the large arteries of people who died of alcoholic liver cirrhosis were remarkably free of atherosclerosis. This led to a hypothesis that alcohol served as a nonspecific solvent that dissolved the crusty buildup inside arteries.

In the 1960's, the concept of "risk factors" for coronary heart disease began to emerge. Cigarette smoking, hypertension, high cholesterol, family history of CHD, and male gender emerged as predictors of development of CHD. In these epidemiologic studies, abstinence from alcohol was found to be associated with increased risk of myocardial infarction. These early studies were confounded, however, by the fact that alcohol drinkers often smoke. In the 1970's, investigators at Kaiser Permanente in California examined the role of moderate alcohol consumption in the absence of smoking[4]. These investigators examined the relation between consumption of alcoholic beverages and CHD, attempting to factor out the impact of concomitant tobacco abuse[5]. In so doing, they documented a clear inverse relation between alcohol consumption and CHD.

The possible role of alcohol consumption in prevention of CHD exploded on the national consciousness in the early 1990's. Two reports by Sixty Minutes (November 17, 1991 and November 5, 1995) highlighted the lower rate of cardiovascular disease in France (approximately ½) compared with its

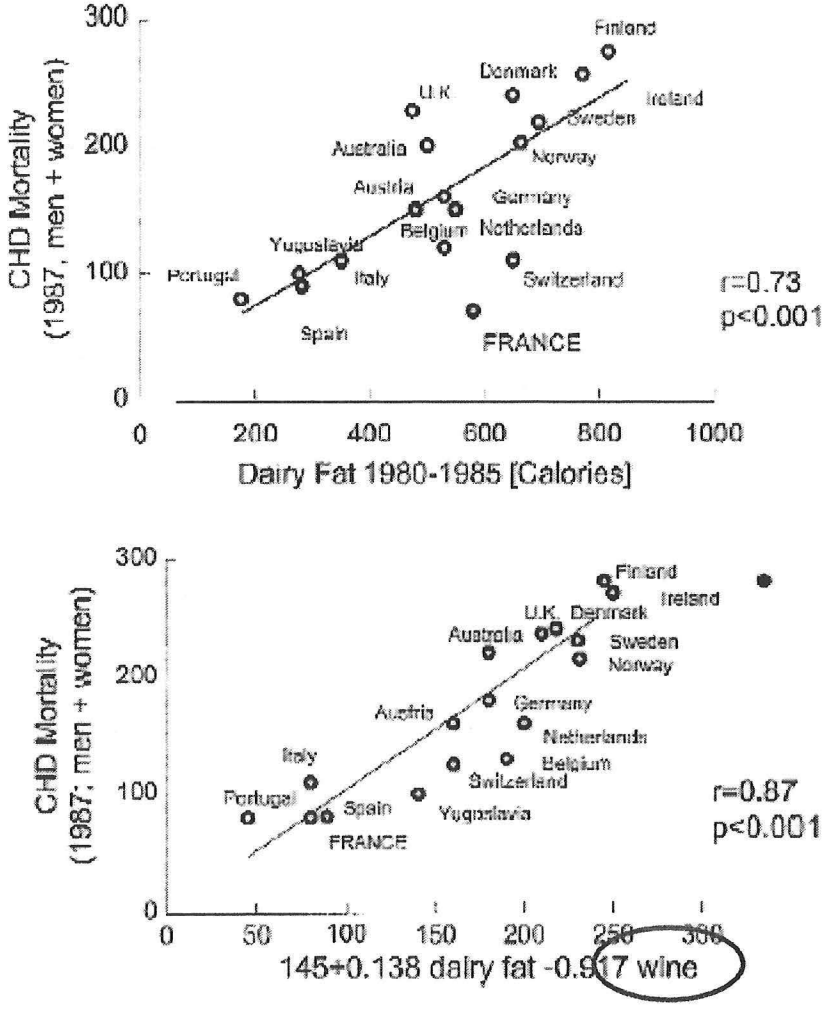

Figure 3: Top, CHD mortality as a function of dietary fat in different countries. Note discordance of France and Switzerland relative to neighboring countries to the North and the US. **Bottom,** regression analysis that includes wine consumption brings these 2 countries in line with others. Renaud et al., 1992.

neighboring countries to the north and with the US, despite the high intake of fat in France (Fig 3). This "French paradox" was attributed to the relatively high consumption of red wine[6], although subsequent large studies have not supported this hypothesis[7-9].

Epidemiologic Evidence of Association

Numerous epidemiological studies – numbering nearly 100 studies – have documented an inverse association between alcohol consumption and vascular risk. All-cause mortality has typically been depicted as a J-shaped function, where risk of CHD is lower at moderate levels of consumption and risk of cancer and cirrhosis are elevated at high levels of consumption.

As one example, in the recently published Health Professional Follow-up Study, patterns of alcohol consumption were followed for 12 years in 38,077 males free of cardiovascular disease or cancer at base line[9]. Consumption of alcohol 3-4 or 5-7 days per week was associated with decreased risk (32% and 37% respectively) of myocardial infarction (Fig 4). A 12.5-g increase in daily alcohol consumption over a 4-year follow-up period was associated with a relative risk of myocardial infarction of 0.78. No single type of beverage conferred additional benefit[9] (Fig 5).

Variable*	Alcohol Consumption†							P Value‡
	0 g/day	0.1–4.9 g/day	5.0–9.9 g/day	10.0–14.9 g/day	15.0–29.9 g/day	30.0–49.9 g/day	≥50.0 g/day	
Nonfatal myocardial infarction								
No. of cases	167	300	140	116	132	82	23	
Relative risk	1.00	1.03	0.82	0.69	0.76	0.64	0.55	<0.001
95% CI	—	0.85–1.25	0.65–1.02	0.54–0.88	0.60–0.96	0.48–0.85	0.35–0.85	
Multivariate relative risk	1.00	1.04	0.84	0.73	0.80	0.64	0.50	0.003
95% CI	—	0.86–1.26	0.67–1.05	0.57–0.93	0.63–1.02	0.48–0.84	0.31–0.79	
Fatal myocardial infarction								
No. of cases	93	142	73	57	61	57	15	
Relative risk	1.00	0.87	0.80	0.60	0.62	0.74	0.53	0.01
95% CI	—	0.67–1.14	0.59–1.08	0.43–0.84	0.44–0.86	0.53–1.05	0.29–0.96	
Multivariate relative risk	1.00	0.89	0.84	0.61	0.71	0.62	0.39	0.01
95% CI	—	0.67–1.17	0.61–1.15	0.43–0.87	0.50–1.01	0.43–0.89	0.21–0.71	

Figure 4: Relative risk of nonfatal or fatal myocardial infarction in 38,077 U.S. male health professionals according to alcohol consumption. Mukamal et al., NEJM 2003.

Variable*	0 g/day	0.1–9.9 g/day	10.0–14.9 g/day	≥15.0 g/day		P Value†
Red wine						
No. of cases of MI	814	560	36	8		
Person-yr	211,361	171,979	8,952	4,681		
Relative risk	1.00	0.94	1.14	0.48		0.14
95% CI	—	0.84–1.05	0.81–1.59	0.24–0.97		
Multivariate relative risk	1.00	1.06	1.48	0.64		0.34
95% CI	—	0.95–1.19	1.05–2.09	0.32–1.29		
White wine						
No. of cases of MI	671	709	26	12		
Person-yr	168,438	214,784	8,346	5,404		
Relative risk	1.00	0.93	0.82	0.62		0.04
95% CI	—	0.83–1.03	0.55–1.21	0.35–1.10		
Multivariate relative risk	1.00	1.04	0.98	0.74		0.87
95% CI	—	0.93–1.17	0.65–1.46	0.41–1.32		
	0 g/day	0.1–9.9 g/day	10.0–14.9 g/day	15.0–49.9 g/day	≥50.0 g/day	
Beer						
No. of cases of MI	747	574	72	21	4	
Person-yr	184,927	173,592	26,914	9,657	1883	
Relative risk	1.00	0.91	0.74	0.58	0.45	<0.001
95% CI	—	0.81–1.01	0.58–0.94	0.38–0.90	0.17–1.22	
Multivariate relative risk	1.00	0.93	0.78	0.57	0.34	<0.001
95% CI	—	0.83–1.04	0.61–1.01	0.37–0.89	0.12–0.92	
Liquor						
No. of cases of MI	646	515	156	87	14	
Person-yr	186,506	142,782	41,587	22,390	3706	
Relative risk	1.00	1.02	0.80	0.73	0.67	<0.001
95% CI	—	0.91–1.15	0.67–0.96	0.58–0.92	0.39–1.14	
Multivariate relative risk	1.00	1.03	0.79	0.67	0.54	<0.001
95% CI	—	0.91–1.16	0.66–0.95	0.53–0.84	0.31–0.92	

Figure 5: Relative risk of nonfatal or fatal myocardial infarction in 38,077 U.S. male health professionals according to type of alcoholic beverage consumed. Mukamal et al., NEJM 2003.

Meta-Analyses

Given the large number of studies documenting an inverse association between consumption of alcoholic beverages and CHD mortality and total mortality, recent work has emphasized meta-analytic approaches. Several large meta-analyses, incorporating many thousands of subjects, have been reported examining the relation between alcohol consumption and heart disease. Caution is warranted, however, as interpreting these data can be difficult if poorly controlled studies are included or if covariates are not treated equally across studies. Pooling relative risks from studies that do not equally account for risk factors, such as diet, exercise, and smoking, can exaggerate or mask differences.

In a large meta-analysis, Corrao et al examined 196 studies published between 1966 and 1998, eliminating several due to methodological problems or inadequacy of the data within the published study[10]. These authors report a consistent finding of a J-shaped relation between alcohol consumption and CHD (Figs 6, 7). In all included studies, statistically significant benefit (relative risk 0.75) peaked at 25 g of ethanol per day, which corresponds to approximately 2 drinks per day (Table I). With greater degrees of consumption, the benefit declined and ultimately, high levels of alcohol consumption proved harmful.

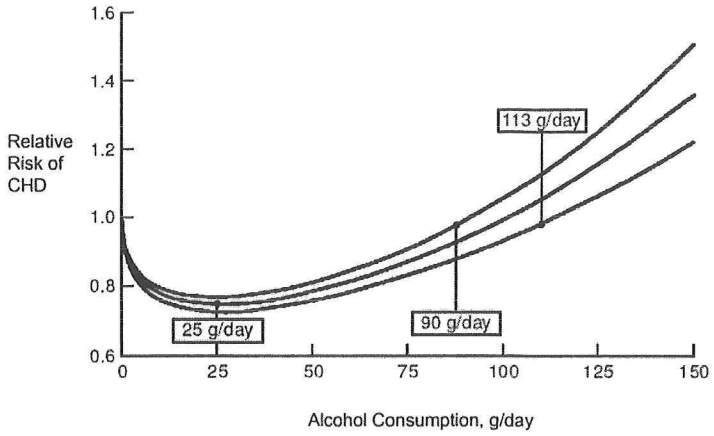

Figure 6: Meta-analysis of 51 studies modeled as functions ± 95% CI revealed a nadir in CHD risk at 25g of ethanol per day (approximately 2 drinks per day). The maximum dose revealing statistically significant benefit and the minimum dose showing statistical evidence of harm are indicated. Corrao et al., 2003

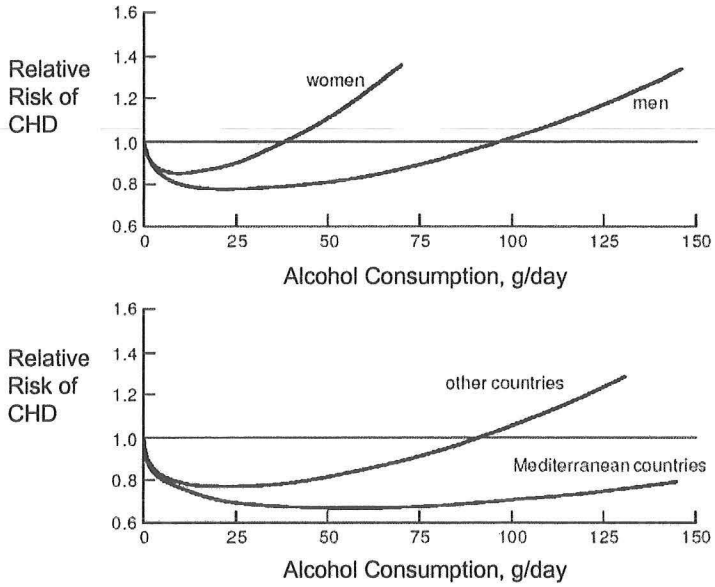

Figure 7: Meta-analysis of 51 studies revealed a nadir in CHD risk at 1 drink/day in women and 2 drinks/day in men (**top**). A significant rightward shift in the J-shaped relation was observed in Mediterranean countries, where wine with meals is the predominant form of alcohol consumption (**bottom**). Corrao et al 2003

Table I: Meta-analysis of 51 studies examining relation between alcohol consumption and coronary heart disease.

	maximum benefit	relative risk	95% confidence intervals	neutral benefit	harm
total	25 g/day	0.75	0.73 – 0.77	90 g/day	113 g/day
men	25 g/day	0.77	0.74 – 0.80	87 g/day	114 g/day
women	10 g/day	0.85	0.80 – 0.90	31 g/day	52 g/day
Mediterranean countries	53 g/day	0.67	0.51 – 0.88	ND	ND

ND: not detected

In women, a similar J-shaped relation was observed, but the maximum benefit occurred at much lower levels of alcohol consumption (10 g/day, or approximately 1 alcoholic beverage per day) (Fig 7, Table I)[10]. This leftward shift in the J-shaped curve in women has been reported previously, but the underlying mechanism is unknown. Pre-menopausal women are at lower risk of CHD and hence may benefit less from the protective effects of alcohol. This combined with smaller body size, slightly increased risk of breast cancer in alcohol consumers, and a possibly higher susceptibility to alcoholic cirrhosis may contribute.

DiCastelnuovo et al performed a meta-analysis of 26 studies on the relationship between wine or beer consumption and vascular risk[11]. They reported a relative risk of vascular disease associated with wine intake of 0.68 (95% confidence interval, 0.59 to 0.77) relative to nondrinkers. In studies where the quantity of alcohol consumption was documented, a J-shaped relationship between wine intake and vascular risk was observed (Fig 8). In studies of beer consumption, the overall relative risk in subjects who consumed moderate amounts of beer was 0.78 (95% confidence interval, 0.70 to 0.86)[11].

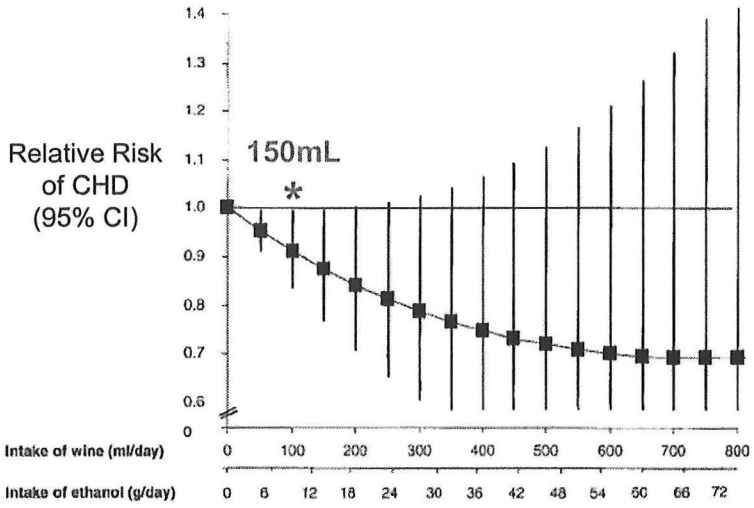

Figure 8: Best-fit model (± 95% CI) of association between CHD risk and ethanol consumption. Statistically significant benefit was noted only at 150mL wine/day. Di Castelnuovo et al., 2002

Some evidence suggests that the beneficial effects of alcohol in women are age-dependent (Table II). In a prospective study of 85,709 US nurses (Nurses' Health Study), the typical J-shaped curve was observed only in postmenopausal women[12]. In subgroups of women with increased risk of CHD, however, moderate alcohol consumption may be beneficial. In a study of 39,092 women with type 2 diabetes mellitus, alcohol consumption between 0.1 and 4.9 g per day was associated with a relative risk of fatal or nonfatal myocardial infarction of 0.74[13] (Fig 9). In those consuming more than 4.9 g daily, relative risk was 0.48[13] (Fig 9). These findings are consistent with a prior report from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), which documented a progressive reduction in risk of CHD death and overall mortality with increasing levels of alcohol consumption, within the mild to moderate range, in patients with type II diabetes.[14;15]

Table II: Effect of alcohol consumption on overall mortality in 85,709 women followed 12 years.[12]

Age	Alcohol Intake (g/day)			
	0	0.1 - 1.4	1.5 – 29.9	≥30
34 – 39yo	1.0	1.89	2.08	2.46
40 – 49yo	1.0	1.02	0.95	1.47
50 – 59yo	1.0	0.88	0.88	1.26
≥60yo	1.0	0.88	0.79	1.02

	Usual Daily Alcohol Intake, g			
	None	0.1–4.9	≥5	P_{trend}
Total CHD				
Cases, n	204	65	26	
Person-years	22 715	10 326	6051	
Age-adjusted RR (95% CI)	1.0	0.74 (0.56–0.98)	0.48 (0.32–0.72)	0.0001
Multivariate RR* (95% CI)	1.0	0.72 (0.54–0.96)	0.45 (0.29–0.68)	0.0003
Nonfatal CHD				
Cases, n	132	45	17	
Age adjusted RR (95% CI)	1.0	0.78 (0.56–1.09)	0.48 (0.29–0.80)	0.003
Multivariate RR* (95% CI)	1.0	0.79 (0.56–1.12)	0.47 (0.28–0.79)	0.005
Fatal CHD				
Cases, n	72	20	9	
Age adjusted RR (95% CI)	1.0	0.66 (0.40–1.08)	0.48 (0.24–0.95)	0.01
Multivariate RR* (95% CI)	1.0	0.60 (0.36–1.01)	0.43 (0.21–0.88)	0.03

Figure 9: Dose-dependent effects of alcohol consumption on CHD risk in type 2 diabetics in the Nurses' Health Study. Solomon et al, 2000.

Dementia

In a recent report from the Cardiovascular Health Study, Mukamal et al described an inverse relation between alcohol consumption and risk of dementia[16] (Fig 10). Compared with nondrinkers, the adjusted odds ratio for dementia among those whose weekly alcohol consumption was 1 to 6 drinks was 0.46 (95% confidence interval 0.27 to 0.77)[16]. A typical J-shaped relation was observed with increased risk noted at high levels of consumption. Intriguingly, the relations between alcohol use and both Alzheimer's disease and vascular dementia were similar; low-to-moderate levels of consumption were protective[16].

Variables	Weekly No. of Drinks					Linear *P* Value for Trend (Quadratic)	Former	Quitter
	None	<1	1-6	7-13	>14			
All-cause dementia								
No. of cases	151	53	33	25	24		35	52
No. of controls	123	73	72	32	18		22	33
Matching adjusted, OR (95% CI)*	1.00	0.59 (0.39-0.91)	0.37 (0.23-0.60)	0.64 (0.36-1.13)	1.09 (0.56-2.10)	.06 (<.001)	1.40 (0.77-2.53)	1.31 (0.80-2.16)
Fully adjusted, OR (95% CI)†	1.00	0.65 (0.41-1.02)	0.46 (0.27-0.77)	0.69 (0.37-1.31)	1.22 (0.60-2.49)	.45 (.001)	1.52 (0.81-2.83)	1.38 (0.81-2.35)
Alzheimer disease‡								
No. of cases	130	44	28	22	19		28	41
OR (95% CI)	1.00	0.59 (0.37-0.94)	0.43 (0.25-0.72)	0.65 (0.35-1.23)	0.95 (0.46-1.96)	.08 (.002)	1.47 (0.77-2.82)	1.18 (0.68-2.04)
Vascular dementia§								
No. of cases	36	17	9	7	4		11	14
OR (95% CI)	1.0	0.96 (0.49-1.91)	0.60 (0.26-1.37)	0.79 (0.30-2.10)	0.93 (0.29-3.05)	.46 (.48)	1.36 (0.55-3.40)	1.39 (0.63-3.08)

Figure 10: Dose-dependent effects of alcohol consumption on risk of dementia in 5,888 men and women (≥65yo) in the Cardiovascular Health Study. Mukamal et al, JAMA 2003.

Similar findings were reported earlier in the Rotterdam Study where risk of dementia was lowest among consumers of 1 to 3 drinks per day[17].

Epidemiologic Evidence: Association vs Causation

At present, there is virtual unanimity regarding the inverse association between moderate consumption of alcohol and CHD. Indeed, most authorities attribute a causal role to the relation: moderate alcohol consumption reduces risk of CHD. Current research, then, centers on the mechanistic underpinnings of this salutary effect and whether patterns of drinking are important. It is essential, however, to discuss briefly how epidemiological associations may (or may not) be used to infer mechanistic conclusions.

Documented now in a very large number of studies, there is a clear association between moderate alcohol use and diminished risk of fatal and nonfatal CHD. These studies have included both retrospective and prospective studies. However, epidemiological assessment of the risks and benefits on alcohol use are hampered by the following potential biases:

- dose-response relation is not linear, but rather J-shaped
- it is difficult to quantify consumption
- levels of consumption often change
- many "nondrinkers" are, in fact, former drinkers
- individual differences, such as gender and pattern of drinking
- publication bias

Epidemiological evidence can never pinpoint mechanism, but rather reveals associations. Balding could be identified as a risk factor for skin wrinkles, as the 2 are clearly associated (with aging). Aspirin treats both headaches and heart attacks, but that does not mean that headaches cause heart attacks (or vice versa)! It is often possible to adjust data to normalize for possible confounders (e.g. age), but subtle effects may remain, and it is impossible to eliminate confounders that are either not measured or unknown. Is it possible that

moderate consumption of alcohol is a *marker* for another feature that itself mediates the "cardioprotective" actions associated with alcohol?

Recent experience highlights the importance of this concern. Hormone replacement therapy (HRT) is strongly associated with diminished risk of CHD, but randomized clinical trials demonstrated the opposite! Ditto vitamin E and β-carotene; epidemiologic evidence of benefit was not supported in prospective trials. On the other hand, who among us is not convinced of the dangers of cigarette use, even though prospective, randomized data will never be available?

In the case of alcohol, we will likely never have "gold standard" evidence supported by randomized, prospective, double-blinded, placebo-controlled clinical trials. As physicians, each of us needs to make a decision based on epidemiological evidence of association.

Established criteria exist for attributing causality to associations identified in epidemiological studies[18]. To establish causality, studies documenting an association between alcoholic beverage consumption and decreased risk of CHD should achieve the following standards:

- consistent relation across multiple studies
- strength of the association
- plausible dose-response relation
- correct temporal sequence; specific behavior pattern is identified, after which health patterns are observed long-term
- biologically plausible mechanisms
- effects on specific types of health issues, not general protection against all illness

For example, an early hypothesis proposed that apparent benefit from alcohol consumption might derive from inclusion of sicker individuals among the nondrinkers ("sick quitter effect"), but this has largely been refuted by studies that excluded those with poor health at baseline or included only lifelong nondrinkers in the comparison group.

It should be pointed out that if there is a hidden confounder in epidemiological studies on alcohol – which number nearly 100 – it would need to be a trait present in both sexes, numerous countries and several racial groups. It is increasingly unlikely that such an unknown confounder exists. Indeed, most authorities in this field accept a causal role for alcoholic beverage consumption and diminished risk of CHD.

One important study (discussed on page 18) documented a strong interaction between alcohol intake and a common polymorphism in the gene for alcohol dehydrogenase[19]. These data argue strongly for a causal relation between alcohol intake and prevention of heart disease, because such a result cannot be attributed to confounding factors; no associations between alcohol dehydrogenase genotype and behavior patterns, education, socioeconomic status, etc, have been observed. Thus, most authorities agree that consumption of alcoholic beverages is causally linked to diminished risk of CHD, mediated mostly by the ethanol component of these beverages.

Biological Actions

The sequelae of alcohol use can be divided into 3 inter-relating phenomena: intoxication, dependence, and direct biological actions (Fig 11). The interplay among these actions ultimately evokes a complex pattern of biological and clinical phenotypes[20]. The biological actions can be divided into several categories (Table III).

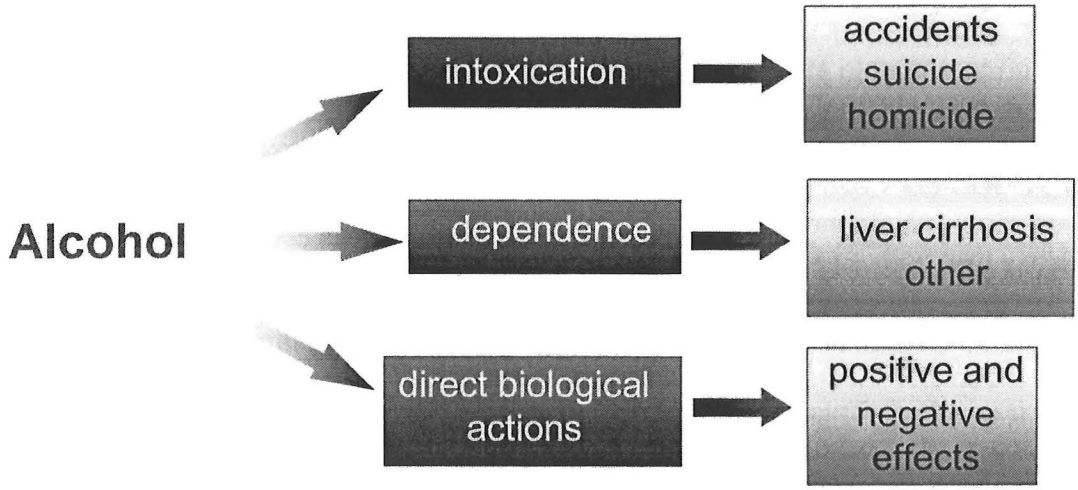

Figure 11: Schematic framework for effects of alcoholic beverage consumption.

Table III. Mechanisms purported to underlie the cardioprotective effects of moderate consumption of alcoholic beverages.

Mechanism	Biological Response	Strength of evidence
HDL raising	↓ atherosclerosis	I
Anti-platelet effects	↓ thrombosis	IIb
↑ insulin sensitivity[21-23]	↓ Type II DM	IIa
Anti-inflammatory effects	↓ CRP[24]	IIb
Anti-oxidant properties of other components of alcoholic beverages	↓ LDL oxidation[25] other effects?	III
↓ fibrinogen	↓ thrombosis	IIa
↓ psychological stress		III

In an attempt to quantify the "strength" of evidence supporting each proposed mechanism, I have utilized a standard ranking system (Class I – III)[e], based on my interpretation of the literature (Table III).

Serum HDL

Alcohol consumption is associated with 10-20% increases in high-density lipoprotein (HDL)[26;27], which has been estimated to account for 40-50% of the beneficial effects of alcohol on CHD[28]. Other evidence suggests that this figure may underestimate the impact of HDL raising[7;29], in other words, alcohol's effects on HDL may account for the majority of the beneficial effects of drinking.

Some studies suggest that alcohol may have a greater influence on HDL_3 rather than the isoform raised by exercise (HDL_2); more recent studies, however, have revealed alcohol-associated increases in both fractions[29;30]. In any case, it is likely that both species are protective.

In one case-control study of 340 post-myocardial infarction patients, integration of total HDL, HDL_2 and HDL_3 plasma levels into a multivariate analysis neutralized the inverse correlation between alcohol consumption and the risk of MI[29] (Fig 12) . This fact was used to support the notion that the HDL-raising properties of alcoholic beverages explain the majority of the cardioprotective effects of alcoholic beverages[29]. Little is known regarding mechanisms underlying alcohol's ability to raise HDL, though inhibitory effects on cholesteryl ester transfer protein (CETP) has been suggested.

	No. of Drinks†				P for Trend
	<1/mo	≥1/mo but <1/day	≥1/day but <3/day	≥3/day	
	milligrams/deciliter				
Total cholesterol	209.9±40.6	209.0±40.7	215.5±46.0	218.0±41.4	0.087
LDL	132.2±35.9	133.7±33.7	136.2±38.9	130.6±38.8	0.898
Triglycerides‡	150.6±83.7	149.4±94.6	144.0±95.8	185.7±176.7	0.099
VLDL	40.9±24.5	37.9±22.4	37.1±26.4	44.6±29.6	0.653
Total HDL	36.5±10.9	38.0±10.2	42.1±12.1	42.8±12.8	<0.001
HDL_2	13.4±9.2	14.2±8.3	17.2±8.8	16.3±9.1	<0.001
HDL_3	22.9±6.4	23.7±5.7	24.8±7.2	26.6±7.0	<0.001

Figure 12: Case-control study of 340 post-MI patients and an equal number of age- and sex-matched controls, revealing dose-dependent increases in total HDL, HDL_2, and HDL_3. Gaziano et al., NEJM 1993.

Antiplatelet Effects

Some evidence points to alcohol's ability to inhibit coagulation by inhibiting platelet activation. Landolfi and colleagues demonstrated in 1984 that alcohol

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[e] Class I: There is general agreement that this mechanism contributes to the cardioprotective effects of alcohol.
Class II: There is conflicting evidence regarding this mechanism
Class IIa: Weight of evidence supports this mechanism.
Class IIb: Mechanism is less well established
Class III: Mechanism is not well supported by scientific evidence.

increases platelet levels of prostacyclin relative to thromboxane[31;32]. Alcohol raises levels of plasminogen activator[33;34], and lowers levels of fibrinogen[30]. The mechanistic significance of these findings is not established.

Antioxidant Activity

Wine is a complex solution/suspension of >200 organic molecules of plant origin, many of which are biologically active (Figs 13, 14)[35]. Antioxidant capacity within a single glass of red wine is comparable to 7 glasses of orange juice and 20 glasses of apple juice (Fig 15). Quercetin (10μM), a polyphenolic compound present in red wine, totally inhibits the oxidation of low-density lipoproteins[25]. The relevance of this antioxidant activity is completely unknown.

Resveratrol is a polyphenolic compound present in several types of wine. Very recently, resveratrol received a great deal of press when it was shown to extend lifespan in yeast by up to 70% (Fig 16)[36].

Component	Concentration (g/100 ml)
Water	80–90
Carbohydrates[a]	
Glucose	0.05–0.1
Fructose	0.05–0.1
Pentoses	0.08–0.2
Arabinose, rhamnose, xylose[b]	
Pectin	Trace
Inositol	0.03–0.05
Fucose	0.0005
Alcohols	
Ethyl	8.0–15.0
Other	
Methyl, higher, 2,3-butylene glycol, acetoin[b]	0.3–0.19
Glycerol	0.30–1.40
Aldehyde	0.001–0.050
Organic acid	
Tartaric, lactic, succinic, acetic, *p*-hydroxy-glutaric, galacturonic, amino, malic, citric, fumaric, oxalic, α-ketoglutaric, aconic, citra-malic, malonic, pyrorocemic, pantothenic[b]	0.3–1.10
Nitrogenous compounds	
Amino, ammonia, amide, protein humin[b]	0.01–0.09
Mineral compounds	0.15–0.40
Potassium, magnesium, carbon dioxide, phosphate sulfate, calcium, chloride, silicic acid, fluoride, aluminum, manganese, sodium, iron, boron, iodine, copper, rubidium, oxygen[b]	

[a]Concentration is dependent on style of wine, that is, dry or sweet.

[b]Individual compounds are ranked in decreasing concentrations.

Figure 13: Components of wine excluding phenols. German et al., 2000.

Component	Concentration (mg/L) Red wine	White wine
Nonflavonoids	240–500	160–260
Hydroxybenzoic acids	0–260	0–100
p-Hydroxybenzoic acid	20	—
Gallic acid	116 (26–320)	1.4
Total gallates	40 (30–59)	7 (6.8, 7.0)
Salicylic acid	—	—
Syringic acid	5 (4.2–5.9)	—
Protocatechuric acid	88	—
Hydroxycinnamic acids	162 (62–334)	130–154
cis/trans-Coutaric	20 (16–24)	1.8
cis/trans-Caftaric	25 (11–47)	5 (3, 7)
Caffeic acid[b]	8.5 (3–18)	2.8
Coumaric acid[b]	12.6 (7.5–22)	1.5 (1–2)
Ferulic acid[b]	19	—
Stilbenes	12.3 (4–19)	1.8 (0.04–3.5)
trans-Resveratrol	1.0 (0.1–2.3)	0.22 (0.003–2.0)
Flavonoids	750–1060	25–30
Flavonols	98 (10–203)	Trace
Quercetin	18.8 (5–53)	0
Myricetin	16.2 (2–45)	0
Kamempferol	18	0
Rutin	6.8 (0.5–10.8)	0
Flavanols	168 (48–440)	15–30
Catechin	89 (27–191)	17.3 (3–35)
Epicatechin	57.3 (21.4–128)	13.6 (2, 18.9, 21)
Procyanidins	171 (29–333)	7.1 (5–10)
Anthocyanins	281 (20–500)	0
Delphinidin 3-monoglucoside[c, d]	22	0
Cyanidin 3-monoglucoside[c, d]	20 (2.8, 38)	0
Petunidin 3-monoglucoside[c, d]	18	0
Peonidin 3-monoglucoside[c, d]	32	0
Malvidin 3-monoglucoside[c, d]	93 (24–170)	1
Total phenolic acids and polyphenols	1200 (900–2500)	200 (190–290)

Figure 14: Phenolic components of wine. German et al, 2000.

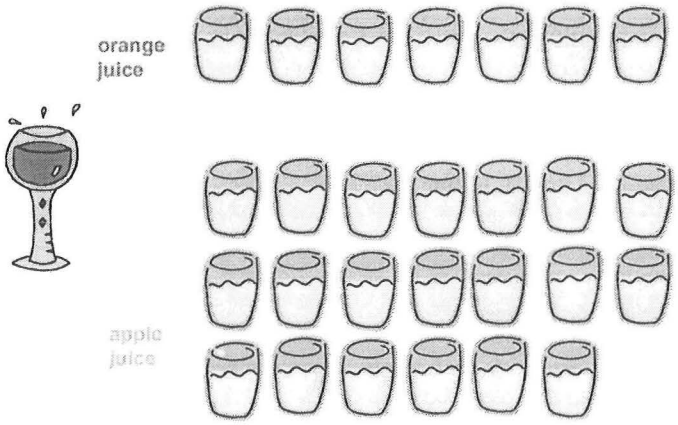

Figure 15: Relative proportions of antioxidant capacity of a single glass of red wine compared with that within orange juice or apple juice.

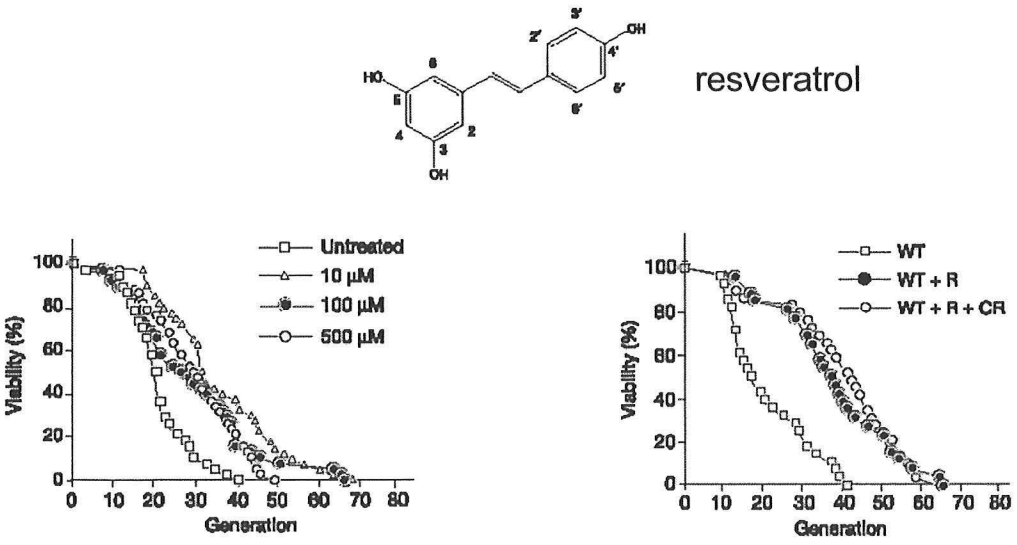

Figure 16: Resveratrol induced a dramatic, dose-dependent increase in lifespan in *Saccharomyces cerevisiae* (**left**) which was not additive to that induced by caloric restriction (**right**). Howitz et al., 2003.

Blood Pressure

Alcohol intake at levels of consumption greater than 4 drinks per day has been linked to increases in blood pressure[37;38]. At moderate levels of consumption, the link is less clear. Indeed, several prospective studies have revealed a J-shaped relation, suggesting a slight decrease in blood pressure among those who consume one drink a day[39].

Insulin Sensitivity

Alcohol intake (1-2 drinks per day) is associated with reduced risk for type 2 diabetes, reduced fasting insulin concentration, and improved insulin sensitivity[21-23]. These changes may reduce the risk of developing type 2 diabetes and thereby contribute to the beneficial effects of alcohol consumption on cardiovascular disease.

Other

Several studies have demonstrated increases in apolipoprotein A-I and A-II in proportion to alcohol consumption[29]. However, the degree to which these changes may be protective is unknown.

Rimm and colleagues attempted to summarize quantitatively the association of moderate alcohol intake with lipids and hemostatic factors (Fig 17)[30]. Then, on the basis of published association between these biomarkers and risk of CHD, they concluded that 30g of alcohol consumption daily would cause an estimated reduction of 24.7% in CHD risk, a number that corresponds closely to epidemiological findings.

Diminished Atherogenesis

In 2 studies, addition of alcohol to the diets of atherosclerosis-prone mice decreased atherosclerosis. Dai and coworkers fed LDL receptor knockout mice

an atherogenic liquid diet containing different amounts of alcohol (5%, 2.5%, 0% ethanol). These investigators reported a 70% reduction in fatty lesion size in the proximal aorta in mice fed 5% alcohol for 6 weeks[40]. Lesion size in the group fed 2.5% ethanol was not different compared with 0%[40]. Emerson and colleagues reported similar findings in C57BL/6 mice fed a high-fat diet; intake of ethanol inhibited the development of fatty streaks in a dose-dependent fashion[41].

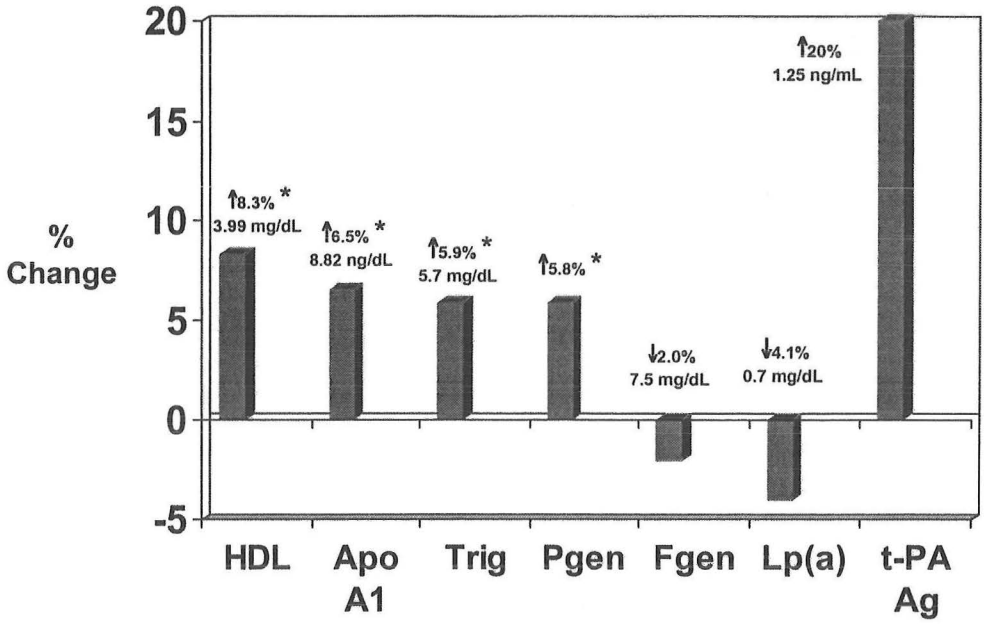

Figure 17: Quantitative summary of effects of 30g of alcohol consumption on serum lipids and hemostatic factors, based on 42 published studies. Adapted from Rimm et al., 1999.

Genetic Predispositions

In a case-control study based on data from the prospective Physicians' Health Study, Hines et al examined the relation between CHD and a polymorphism in the gene coding for alcohol dehydrogenase type 3 (ADH3)[19]. They studied a common polymorphism in *ADH3* that alters the maximal velocity of ethanol oxidation (γ_1, 2.5-fold increased rate relative to γ_2) in relation to alcohol consumption. Among men who were homozygous for the γ_1 allele (fast oxidizers), those who consumed at least one drink per day had a relative risk of myocardial infarction of 0.62 (95% confidence intervals, 0.34 to 1.13), as compared with men who consumed less than one drink per week (Fig 18). In men who consumed at least one drink per day and were homozygous for the γ_2 allele (slow oxidizers), relative risk for myocardial infarction was 0.14 (95% confidence interval 0.04 to 0.45). Presence of the γ_2 allele was associated with increased levels of HDL in consumers of alcohol, but not in nondrinkers. In the same report, these investigators confirmed the association between ADH3 genotype and HDL in an independent cohort of women derived from the Nurses' Health Study. Together these findings support the hypothesis that slower clearance of alcohol enhances the beneficial effect of moderate alcohol consumption on the risk of cardiovascular

disease. Further, these data point to the role of HDL elevation as a potential mechanism. Finally, these data argue against the notion that benefit from moderate consumption of alcoholic beverages derives from other associated factors (diet, exercise, socioeconomic status), as these factors were not associated with *ADH3* genotype[19].

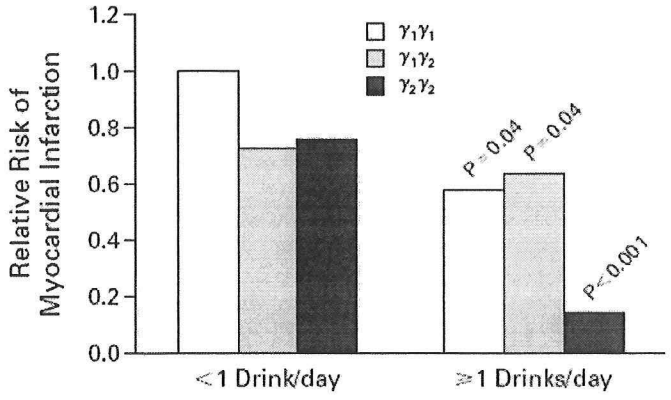

Figure 18: Relative risk of myocardial infarction in the Physicians' Health Study stratified by *ADH3* genotype and alcohol consumption. Hines et al., NEJM 2001

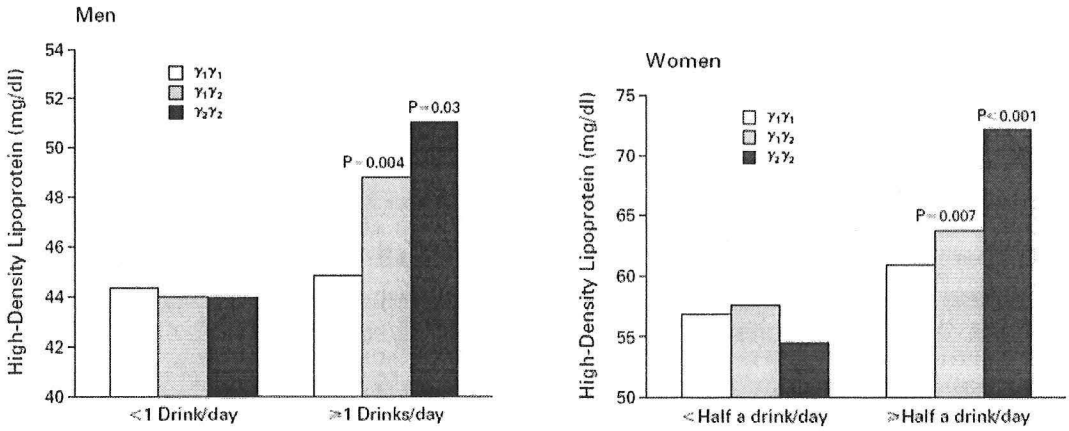

Figure 19: Serum HDL in the Physicians' Health Study stratified by ADH3 genotype and alcohol consumption. Hines et al., NEJM 2001.

Recent studies suggest that genetic factors other than alcohol dehydrogenase contribute to alcohol use patterns. The S (short) variant is a common polymorphism in the promoter region of the human serotonin transporter gene (*SLC6A4*); the S variant is associated with lower expression of serotonin transporter sites and reduced efficiency of serotonin re-uptake[42]. Strikingly, Caucasian college students homozygous for the S variant had a higher risk for purposefully engaging in alcohol consumption to induce intoxication (Fig 20)[43]. Some evidence suggests that individuals expressing the S variant have higher baseline levels of anxiety[42], handle stress poorly[44], and manifest greater levels of alcohol tolerance[45].

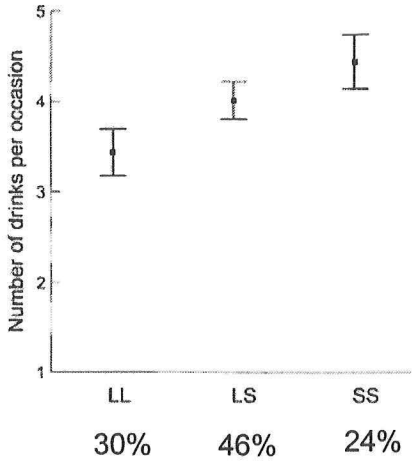

Figure 20: Alcohol consumption in 204 Caucasian college students stratified by genotype of the 5-HT transporter gene. Numbers on X-axis indicate proportion of subjects in each genotype category. Herman et al., 2003.

Does it matter *what* you drink?

With the observation that HDL levels are no higher in France than elsewhere, a search for other possible explanations ensued. Wine intake, in particular, was suggested as a possible explanation in one report[6]. However, this assertion has not withstood careful scrutiny.

It is difficult for epidemiological studies to tease out whether different types of alcoholic beverage differ in the beneficial properties. A large Danish study of 13,000 people followed for 12 years suggested that wine drinkers have lower death rates from CHD than do consumers of other types of other alcoholic beverages[46]. However, wine drinkers display numerous other differences in behavior pattern, including higher socioeconomic status and education level relative to drinkers of beer or liquor. Indeed, in some studies, wine consumption is associated with a healthier lifestyle compared with beer consumption. This observation has been used to support the notion, documented in several studies, that wine and beer consumption per se confer similar degrees of benefit[8]. Consumption of different alcoholic beverages is variably associated with differences in diet, physical activity, education, socioeconomic status, and other behavioral characteristics, any of which could be confounding.

A meta-analysis of cohort studies – examining data from more than 300,000 men and women followed for over 1.8 million person-years – concluded that if a particular type of alcoholic beverage afforded extra cardiovascular benefit apart from its alcohol content, the benefit is likely to be modest at best or possibly restricted to certain subpopulations[7].

In another careful study, Rimm et al found no important differences in lipids or hemostatic parameters across beverage types[30].

Red wine consumption was suggested early on as conferring special benefit, but careful study has revealed no clear evidence of protective effects beyond those of other alcoholic beverages[47]. Intriguingly, however, red wines strongly inhibit the synthesis of endothelin-1, a potent vasoconstrictor peptide, in proportion to their polyphenolic content (Fig 21) [48]. The IC_{50} for this response falls within the range of exposure expected from regular red wine consumption. Given that endothelin-1 has been implicated in the pathophysiology of coronary atherosclerosis[49] and that red wine extract can be antihypertensive[50], these observations may have clinical relevance.

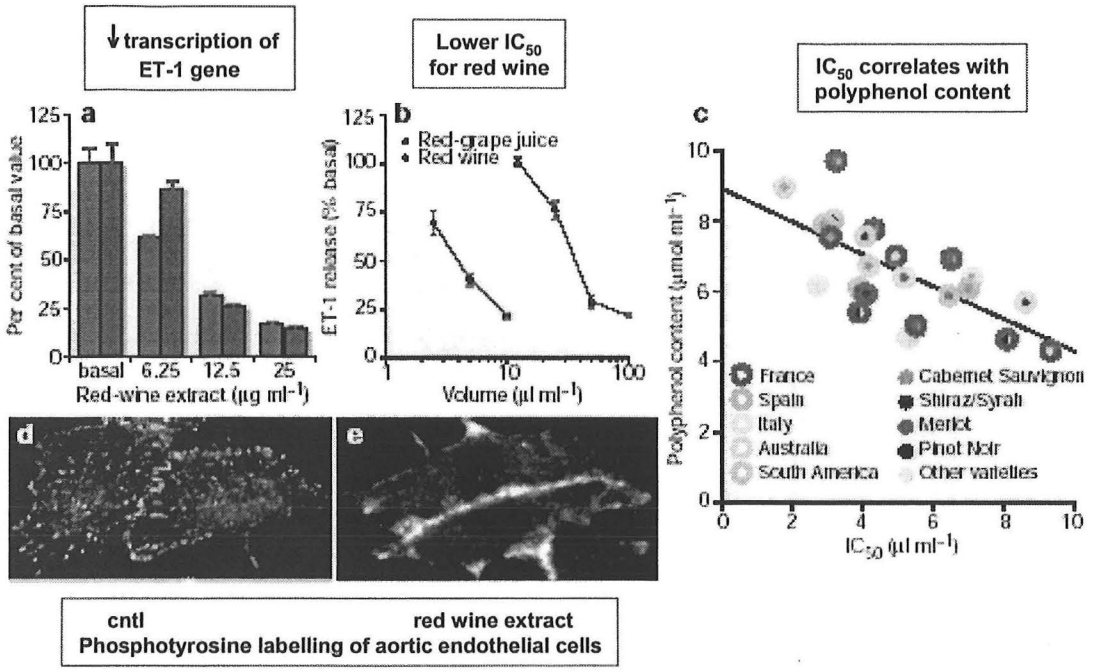

Figure 21: Transcription of the gene coding for endothelin-1 is suppressed by red-wine extract at an IC_{50} substantially lower than red grape juice. The IC_{50} correlates with polyphenolic content of various wines. Corder et al., Nature 2001.

Does it matter *how* you drink?

Recent investigation has focused on patterns of alcohol consumption. It has been known for some time that episodic binge consumption is linked to adverse cardiovascular events[51]. Only recently, however, have studies rigorously controlled for potential confounders, such as average volume and duration of consumption. Numerous recent studies have documented a protective effect for daily light-to-moderate consumption, but no benefit, or even detrimental effects, for people whose drinking patterns included heavy drinking occasions -- even if their usual pattern was moderate[52;53]. Plausible mechanisms include increased clotting and a reduced threshold for ventricular fibrillation after occasions of heavy drinking.

In some cultures, such as those found near the Mediterranean Sea, alcohol consumption tends to be regular, moderate, and with meals. In other societies, alcohol consumption tends to be more episodic, with intermittent periods of heavy consumption. Wine is typically consumed slowly with food, whereas beer and liquor often are not.

A small number of studies have examined the relation between alcohol and CHD based on different regions of the world. In Mediterranean countries, where alcohol is typically consumed in the form of wine accompanying meals throughout the day, a dramatic rightward shift in the J-shaped relation was observed (Fig 7, Table I). This contrasts with regions of the world where beer and spirits are more commonly consumed, and where episodic consumption outside of meals takes place.

Clinical Implications

When considering clinical implications, an obvious distinction must be made between light-to-moderate alcohol consumption and heavy consumption. Whereas a number of beneficial effects are associated with light-to-moderate consumption (Table IV), there are no benefits associated with heavy drinking (Table V).

Both low-to-moderate consumption and heavy consumption are associated with risk. In the case of moderate alcohol use, the potential for abuse is important, especially in individuals with prior history or family history of alcohol use disorders[54]. There is also evidence to support other possible deleterious actions, but these data are less well established (Table IV).

Table IV: Risks and benefits associated with light-to-moderate alcohol consumption.

Risks	Benefits
Alcohol use disorders	↓ risk of CHD
Breast ca?	↓ risk of ischemic stroke
Fetal damage?	↓ risk of gallstones
Bowel ca?	↓ risk of type II DM
hypertension	↓ risk of PVD

Table V: Risks and benefits associated with heavy alcohol consumption.

Risks	Benefits
hepatic cirrhosis	none
pancreatitis	
fetal damage	
cancers: mouth and oropharyngeal; esophageal; liver; breast	
hypertension	
accidents, homicide, suicide	
CNS degeneration	
cardiac arrhythmia	
hemorrhagic stroke	
cardiomyopathy[f]	

[f] Evidence pointing to a mechanistic link between excessive alcohol and cardiomyopathy, e.g. direct toxicity, is surprisingly weak. No good animal models exist. Thus, it is possible that the clearly established association between excessive alcohol intake and cardiomyopathy may stem from nutritional deficiencies or other associated behavioral or biochemical features.

Societal Impact

It is estimated that alcohol contributes to 100,000 deaths in the US annually, making it the 3rd leading cause of preventable mortality, after smoking and conditions related to poor diet and sedentary lifestyle. Heavy consumption of alcohol is dangerous to both the drinker and those around him/her (Table V)[53]. Numerous sequelae are associated with this pattern of alcohol use, and patients who consume heavily should be urged to abstain.

Highlighting the enormous impact of alcohol-induced disease, Rehm et al estimated that impact of alcohol use on chronic disease in the US, calculating alcohol-attributable fractions (the component of nationwide prevalence attributable to alcohol use) (Table VI)[53].

Table VI. Alcohol-attributable fractions for chronic diseases in the US

	male	female
CHD	-13%	-8%
ischemic stroke	2%	-27%
diabetes mellitus	-6%	-4%
liver cirrhosis	34%	61%
hemorrhagic stroke	23%	-13%
hypertension	29%	17%
breast cancer	NA	8%
liver cancer	34%	22%
esophageal cancer	40%	29%
mouth/oropharyngeal cancer	32%	22%

It is interesting to note that during the Gorbachev era in the Soviet Union, an aggressive anti-alcohol campaign was conducted. Between 1984 and 1987, a 25% reduction in estimated per-capita alcohol consumption was accompanied by decreases in the death rate from cardiovascular diseases of 9% for males and 6% for females[55].

Recommendations

Policy changes or recommendations to patients regarding alcohol consumption must take into account the complexity of the metabolic, physiological, and psychological effects of alcohol. The potential risks and benefits of alcohol consumption should be evaluated on a case-by-case basis. A balanced message should be tailored to the specifics of each individual. For those in whom alcohol consumption imposes increased risk, such as people with family or personal histories of alcoholism or pre-existing liver disease, reduction or abstention is advised. In young people, especially females, at low risk for CHD, the benefits of low-to-moderate alcohol consumption may not outweigh the risks. However, abstention based on a misconception that moderate alcohol

consumption is harmful is not appropriate either. Rather, a balanced, objective set of recommendations should be tailored to each person. For a select segment of the population, it is likely possible to define a clear, safe limit for alcohol consumption that would offer probable benefit. Of course, recommendations regarding diet, exercise, weight loss pertain, as well, especially as these interventions impose little risk compared with those attributable to alcohol (Tables IV, V, VI). Effective treatment of hyperlipidemia, hypertension and diabetes is essential.

In women, alcohol consumption has been linked to increased risk of breast cancer. For young women, who are generally at low short-term risk of CHD and therefore may not benefit greatly from alcohol's positive cardiovascular effects, the slightly increased risk of breast cancer may be more significant. In general, the upper limit of moderate drinking in women is 1 drink per day.

It has been pointed out that most nondrinkers abstain for a reason, such as religion, prior medical conditions or family history of alcohol use disorder; these individuals should not be urged to start drinking[56]. On the other hand, light-to-moderate alcohol consumption can be considered part of a healthy lifestyle for those who choose to consume, a position promulgated by the American Heart Association[47]. The well established risks of excessive consumption should be emphasized and moderation recommended to those who consume excessively.

Summary

The preponderance of evidence supports an independent beneficial effect of alcoholic beverage consumption on risk of CHD. However, it is important to remember that observational data cannot prove causation; unmeasured or incompletely controlled confounding cannot be excluded. That said, the consistency of the relation across numerous cohorts and hundreds of thousands of subjects demonstrate that light-to-moderate alcohol consumption can be considered part of a healthy lifestyle for those who choose to consume.

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