

HERE'S TO YOUR HEALTH! THE BENEFITS OF MODERATE ALCOHOL USE ON VASCULAR DISEASE

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INTRODUCTION

Alcohol has played an integral role in society, with use possibly dating back to cultures as early as the Neolithic period circa 10,000 BC. There is even evidence of wine drinking based on artifacts found from ancient Egypt and China. Although initially used for religious purposes in these cultures, the abuse of alcohol and the effects of this abuse on all of the systems of the body have contributed to much of its negative attention. There is now a growing body of data showing that light-to-moderate use of alcohol does not seem to lead to the same negative health consequences as heavier drinking. To the contrary, studies have shown that there is a mortality benefit to this degree of intake. This idea was initially proposed in 1926, based on research done by Raymond Pearl.¹ Since this was released during prohibition, however, it had been largely ignored. The decline in overall mortality is felt to be mainly related to a reduction of cardiovascular disease.^{2-6, 35-40}

ALCOHOL AND MORTALITY

The effect of alcohol on total mortality is described as a J-, or U-shaped relationship.³ As an individual's alcohol intake increases, mortality from all causes initially drops, but after a given point of intake, the mortality rises again to an eventual relative risk greater than 1.0. A significant amount of research has focused on this improvement in mortality (relative risk less than 1.0) that has been shown to be attributed to a decline in myocardial infarctions. Although the exact amount of alcohol varies from study to study, this corresponds to light-to-moderate use, or approximately one to two drinks daily (10-15g of alcohol per drink). The rise in mortality when alcohol intake is approximately greater than two drinks daily has been shown to be secondary to an increased prevalence of conditions such as cirrhosis, traumatic injuries, cardiomyopathy, cancers of the mouth, esophagus, pharynx, larynx, liver, and breast cancer in women.^{3,6,39-}

⁴⁰ Most of these population-based prospective cohort studies use individual questionnaires to gather information on self-reported alcohol use. Participants are asked to quantify how much they drink on a daily or weekly basis and what type of beverage they most frequently imbibe (beer, wine, or spirits). The reliability of information taken from these self-surveys has been questioned, assuming that participants would not be honest, especially in estimating their total alcohol intake. It has been determined, however, that this is a trustworthy mechanism.⁷ A variety of other health and lifestyle factors are often asked about, including, but not limited to: age, body mass index, tobacco use, physical activity, diet, blood pressure, cholesterol, income, education, and even personality type. These are all confounders that have been adjusted for in recent analyses. In most large studies, the majority of participants are light-to-moderate drinkers, and thus it is more difficult to make conclusions about heavier use.

In work by Gaziano *et al.*³, data from the Physicians' Health Study was used to evaluate the relationship of alcohol on mortality. This was a study of 89,299 middle-aged male physicians in the United States. The causes of 3,216 deaths were evaluated over 5.5 years of follow-up. Figure 1 shows the relative risk of total mortality, cardiovascular disease mortality, cancer mortality, and other mortality by alcohol consumption. This study highlights the J- or U-shaped mortality curve of light-to-moderate alcohol use, and also specifically shows that, for deaths from cardiovascular disease including myocardial infarctions, stroke, and "other," the relative risk reached a nadir at 0.74, corresponding to an alcohol intake of one drink per day.

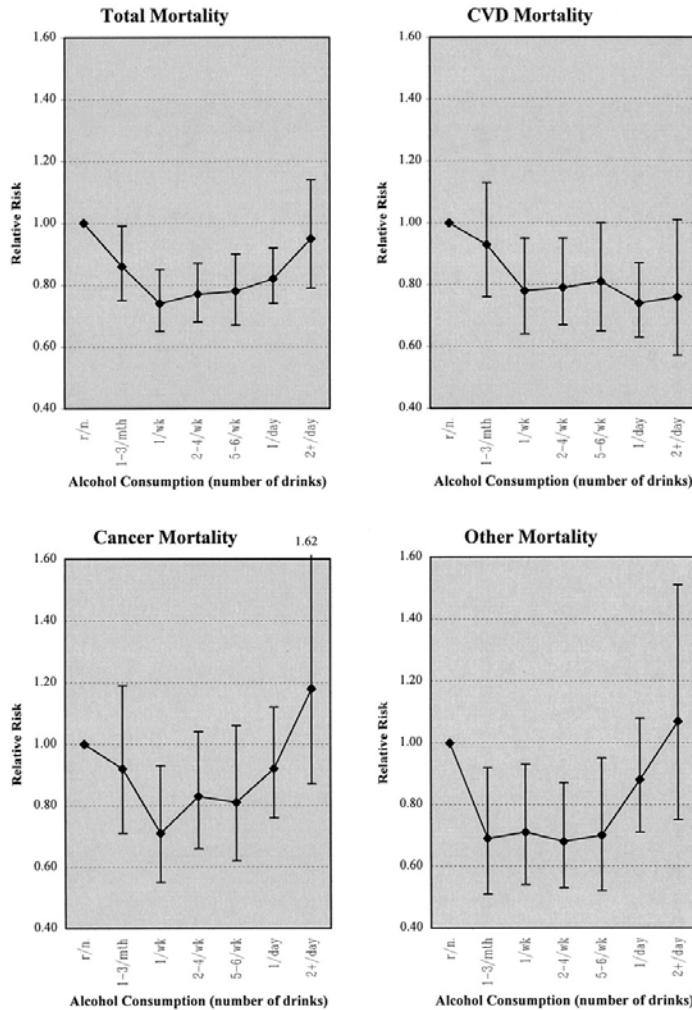


Figure 1 A. Relative risk of total mortality by alcohol consumption category after multivariate adjustment. B. Relative risk of CVD mortality by alcohol consumption category after multivariate adjustment. C. Relative risk of cancer mortality by alcohol consumption category after multivariate adjustment. D. Relative risk of other mortality by alcohol consumption category after multivariate adjustment. *J Am Coll Cardiol* 2000;35:96-105.³

CARDIOVASCULAR DISEASE AND RISK FACTORS

Sex and Age

Although the demographic features of study participants are controlled for in order to solely determine the effect of alcohol use on mortality, many of these are known risk factors of cardiovascular disease, including age, sex, tobacco use, and prior history of cardiovascular events. When comparing the effects of alcohol consumption on each of these individual groups (men to women, age 30-59 to 60-79, low cardiovascular risk to high risk), some patterns to the mortality benefit can be identified. Specifically, the population that exhibited the greatest statistically significant reduction in mortality with consumption of up to four drinks per day was elderly men and women with a preexisting cardiovascular condition (RR 0.8 [0.7-0.8]). But in younger participants as well as older participants who had a low cardiovascular risk, drinking one alcoholic beverage daily led to the lowest overall mortality rates.⁵

Data from the Nurses Health Study was used to examine the relationship of alcohol to mortality in women and showed that it fit the same J-shaped curve. The largest benefit in mortality occurred at one to three drinks weekly, with a relative risk of 0.83 for all causes of death, and 0.57 for deaths from cardiovascular disease. Women consuming approximately three or more drinks daily exhibited an increased death rate from noncardiovascular causes such as cirrhosis and breast cancer. Light-to-moderate alcohol use was most protective in older, postmenopausal women (>50 years) with one or more cardiovascular risk factors.⁶

Drinking frequency and its inverse association to coronary heart disease was found to be different for men and women in a Danish population-based study. In women, alcohol intake was associated with a lower risk of coronary heart disease, regardless of whether individuals drank one day each week or seven days per week (hazard ratio of 0.64 and 0.65, respectively). For men, an increase in drinking frequency from once weekly to seven days per week demonstrated a steadily decreasing hazard ratio (0.93 and 0.59, respectively).⁴ It is possible that this observation is secondary to a lower number of women in this study, but also brings up questions related to how men and women may metabolize alcohol differently.

Hypertension

Despite the mortality benefit from cardiovascular disease, alcohol use is linked to a higher prevalence of hypertension.⁸⁻¹⁰ A study dating back to 1977 proposed that regularly drinking three or more alcoholic beverages daily was a risk factor for having a blood pressure of at least 160/95.⁸ Since this time, more recent data confirm the increased prevalence, but at the lower blood pressure measurements now labeled as being hypertensive. This has been shown in comparisons of current and noncurrent drinkers to lifetime abstainers, and also in studies of average alcohol intake. Daily drinkers demonstrated a higher prevalence, which increased more with the number of drinks per day. No amount of alcohol, pattern of drinking, or type of beverage (beer, wine, or spirits) has been shown to prevent hypertension with any statistical significance.⁹ The INTERSALT study¹⁰ also showed that alcohol intake was associated with hypertension, but results were significant at levels greater than 300mls of alcohol per week. Men who drank 300 to 499mls each week had a systolic/diastolic blood pressure 2.7/1.6 mm Hg

higher than nondrinkers, and women with this level of intake had blood pressures 3.9/3.1 mm Hg higher than nondrinkers. This occurred in across all ages and was independent of body mass intake, as well as urinary excretion of sodium and potassium.

There is still some speculation as to how alcohol causes hypertension. This is possibly through sympathetic activation of the central nervous system in addition to direct and acute vasoconstriction that is not felt to be centrally mediated.¹¹ It is also believed that heavy drinkers may have hypertension that is related to alcohol withdrawal at the time of blood pressure measurements, however, the INTERSALT trial documented that heavy drinkers had elevated blood pressures regardless of whether alcohol consumption had taken place in the 24 hours prior to measurement.¹⁰

Diabetes Mellitus

Diabetes is known to cause accelerated atherosclerosis throughout the body, and it is considered to be a coronary heart disease equivalent. In comparisons of populations of diabetic patients to those without diabetes, the same inverse association of light to moderate alcohol use and death from either ischemic heart disease or myocardial infarction was seen in both diabetic men^{12, 13} and women.¹⁴ Among diabetic men specifically, daily alcohol use seems to be more protective with a relative risk of 0.42 compared to nondiabetic men who had a relative risk of coronary heart disease of 0.61.¹² No statistically significant differences were noted among type of alcoholic beverage. Beer, wine and spirits each showed an inverse associated with coronary heart disease.¹³

Light to moderate alcohol improves insulin sensitivity and decreases post-glucose insulin levels, while heavy use precipitates insulin resistance.¹⁵ Hyperglycemia is known to cause oxidative stress to collagen in blood vessels by raising levels of advanced glycation end products. When ethanol is metabolized to acetaldehyde, this limits the formation of advanced glycation end products.¹⁶

STROKE

The effect of light-to-moderate alcohol intake on cerebrovascular disease is not as clear as the data on cardiovascular disease. Evidence from the Physicians' Health Study¹⁷ suggests that there is an L-shaped association of alcohol consumption on total strokes, with an insignificant trend with increasing categories of consumption (Figure 2). This implies that the benefits of alcohol are within a range of one to seven drinks weekly.

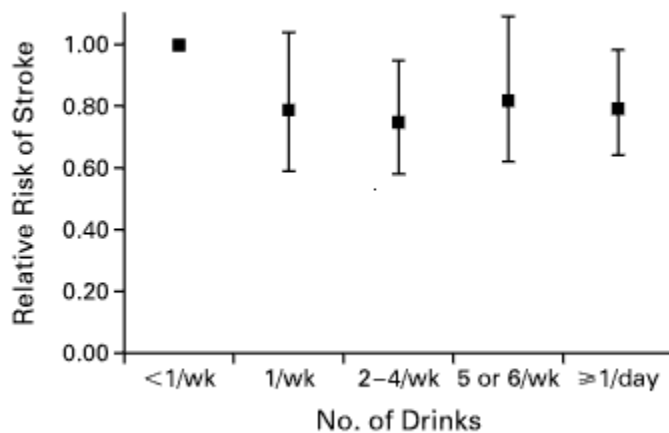


Figure 2. Relative risk of ischemic or hemorrhagic stroke (total stroke) according to alcohol consumption. The reference category of alcohol consumption was less than one drink a week. Bars denote 95 percent confidence intervals. (N Engl J Med 1999;341:1557-64)¹⁷

When total strokes are separated into subtypes of ischemic and hemorrhagic strokes, the relative risk of ischemic strokes drops to 0.77 with at least one drink weekly after multivariate adjustment. The relative risk of hemorrhagic stroke is 0.92, but statistically insignificant (Table 1), making the effect of this degree of alcohol intake controversial. Thus it seems likely that the net benefit seen in the reduction of total strokes can be attributed to the decrease in the incidence of ischemic strokes.¹⁸

Table 1. Relative risk of ischemic or hemorrhagic stroke (total stroke) and subtypes of stroke according to alcohol consumption. (N Engl J Med 1999;341:1557-64)¹⁷

ALCOHOL CONSUMPTION	TOTAL STROKE				ISCHEMIC STROKE				HEMORRHAGIC STROKE			
	NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)				
		<i>adjusted for age and treatment†</i>	<i>multivariate adjusted‡</i>		<i>adjusted for age and treatment†</i>	<i>multivariate adjusted‡</i>		<i>adjusted for age and treatment†</i>	<i>multivariate adjusted‡</i>			
<1 drink/wk	206	1.00	1.00	168	1.00	1.00	26	1.00	1.00			
≥1 drink/wk	473	0.83 (0.71–0.98)	0.79 (0.66–0.94)	389	0.84 (0.70–1.01)	0.77 (0.63–0.94)	62	0.84 (0.53–1.33)	0.92 (0.55–1.54)			

*The mean period of follow-up was 12.2 years. CI denotes confidence interval. Men who consumed less than one drink per week served as the reference category.

†Values have been adjusted for age (in years) and treatment assignment (aspirin, yes or no; beta carotene, yes or no).

‡Values have also been adjusted for systolic blood pressure (continuous values), current treatment for hypertension, smoking (four categories), history of diabetes (yes or no), body-mass index (in quartiles), and exercise (four categories).

PERIPHERAL ARTERIAL DISEASE

Although less studied in comparison to alcohol's effect on cardiovascular and cerebrovascular diseases, peripheral vascular disease is also improved by alcohol use. A diagnosis of peripheral arterial disease was defined by study participants having intermittent claudication or peripheral artery surgery. Analyses from data again taken from the Physicians' Health Study showed an inverse association that was significant only after controlling for smoking. The relative risk for physicians who drank at least seven drinks weekly was 0.68 [0.52-0.89].¹⁹

MECHANISMS

An increasing amount of research is supporting the notion that alcohol in moderation can be protective, not only against coronary heart disease, but also against cerebrovascular disease and peripheral vascular disease. Most significant for the mortality benefits is the prevention of cardiovascular damage, as described above. The physiological mechanisms which provide this protection are related to the prevention of atherosclerosis,^{20,21} antithrombotic properties,²²⁻²⁴ smooth muscle relaxation,²⁵⁻²⁹ and antioxidant properties.^{32,33} It is also important to mention psychological benefits. Moderate alcohol can act to reduce stress and anxiety.²

Alcohol increases serum levels of high density lipoprotein (HDL). HDL is known to protect against atherosclerosis by maintaining the vascular endothelium via transporting low density lipoprotein (LDL) to the liver. This means that less cholesterol is available for fatty streak atheroma formation.²⁰ In a comparison of patients from the general Boston population who had survived a myocardial infarction to those without a cardiac history, it was shown that levels of total HDL and the HDL₂ and HDL₃

subfractions were associated with alcohol consumption. Total HDL increased from 36.5 in subjects with less than one drink per month to 42.8 for those who had at least three drinks daily.²¹ As shown in Table 2, the trend for this association was statistically significant, where the trends for total cholesterol, triglycerides, and low density lipoproteins were not significant.

Table 2: Plasma lipid levels, adjusted for age and sex, according to alcohol consumption. (N Engl J Med 1993;329:1829-34)²¹

LIPID*	NO. OF DRINKS†				P FOR TREND
	<1/MO	≥1/MO BUT <1/DAY	≥1/DAY BUT <3/DAY	≥3/DAY	
	<i>milligrams/deciliter</i>				
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

*To convert cholesterol values to millimoles per liter, multiply by 0.02586; to convert triglyceride values to millimoles per liter, multiply by 0.01129.

†Values are means ±SD. One drink was defined as 13.2 g of ethanol.

‡Triglyceride values were used in logarithmic form for the multivariate analyses; for log(triglycerides), P = 0.651.

Several hemostatic variables are altered in relation to alcohol consumption. These effects are more transient, as evidenced by ex-drinkers who lose the protection after they stop drinking. There is an inverse association of the number of drinks per week to levels of fibrinogen, factor VII, and von Willebrand factor antigen for both men and women. Plasma viscosity demonstrated a U-shaped curve with increasing alcohol consumption, reaching a nadir at 4 drinks per week for women, and 5 drinks per week for men. At higher levels of alcohol intake where plasma viscosity begins to trend upward, the fibrinolytic potential of the blood declines as indicated in measurements of plasminogen-activator inhibitor antigen-1 and tissue plasminogen activator antigen.²² The initial increase fibrinolytic potential seen with light-to-moderate alcohol is independent of the lipid effects from alcohol.²³

Platelet aggregation, specifically secondary aggregation to adenosine diphosphate (ADP), is decreased with increasing alcohol intake. This is a mechanism similar to aspirin use. These results are seen even with less than weekly use. There is also an acute inhibitory effect on thrombin, followed by a rebound elevation in responsiveness, perhaps important in alcohol withdrawal.²⁴ Platelet inhibition is essential in the prevention of thrombosis in the setting of unstable plaque rupture.

Prevention of any vascular disease is directly related to the body's ability to prevent damage to the vascular endothelium. Nitric oxide (NO) release is a pivotal player in this process. Systemic administration of ethanol as well as other components such as polyphenolic compounds act to increase production of NO,^{25, 26} which will

acutely act as a vasodilator. NO has beneficial antiatherosclerotic properties. It is an inhibitor of platelet aggregation, leukocyte adhesion, smooth muscle cell proliferation, and expression of genes involved in atherogenesis.²⁷ Alcohol also acts to reduce levels of C-reactive protein²⁸, which is a known inhibitor of NO release and an upregulator of adhesion molecules.²⁰

Multiple studies have been done looking specifically at the components of red wine. They have attempted to answer the question, is ethanol itself is the sole factor lending to mortality benefits and improved vascular health, or are there other beneficial properties in particular alcoholic beverages? A large amount of attention has been directed to polyphenols, which are present in red, but not white wine. Of these, procyanidins are the most vasoactive,²⁹ are present in the highest concentration,³⁰ and are also found in raw chocolate, cranberries, tea, onions, and apples.³¹

With regard to NO activity, one study specifically looking at red wine has shown that the polyphenol component also acts to raise endothelial nitric oxide synthase (eNOS) activity and eNOS promoter activity.²⁵ Additionally, these polyphenols inhibit the oxidation of low density lipoprotein (LDL) and decrease plasma total peroxides. This has been shown in vitro with phenols isolated from red wine,³² and in vivo through comparisons of red and white wine. In a separate study, ingestion of grape juice for 14 days was shown to decrease the susceptibility of LDL to oxidation and to increase endothelium-dependent arterial vasodilation.³³ This helps to differentiate the benefits of alcohol alone from the role of phenolic compounds that are present in red wine (Figure 3). When LDL is oxidized, it gets taken up by macrophages. This results in the formation of foam cells, promoting plaque formation.²⁰ The exact mechanism of how polyphenols work is unclear, but they could potentially function by chelating trace elements.³⁰

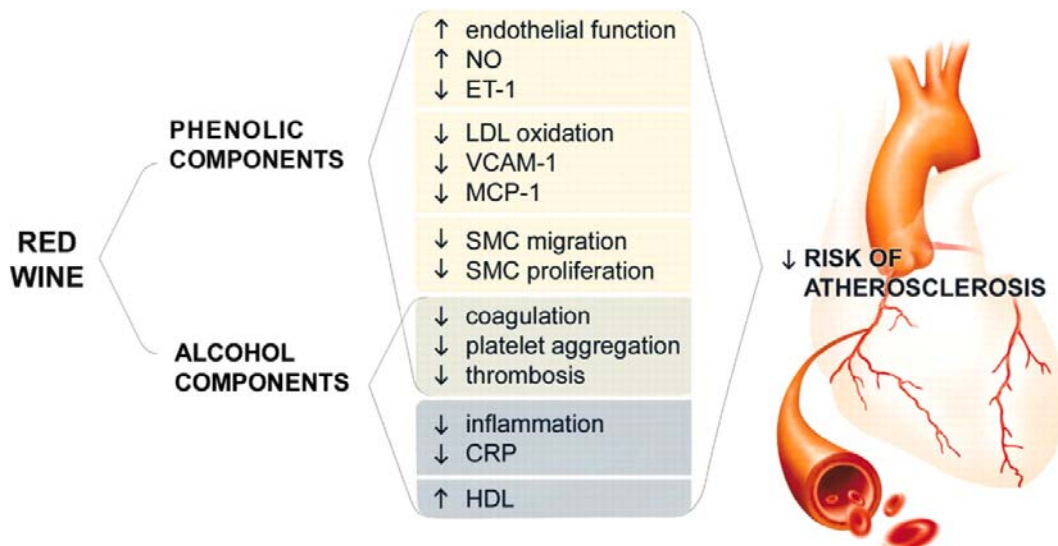


Figure 3. Both the alcohol and phenolic components found in red wine are believed to decrease the risk of atherosclerotic disease via several different mechanisms. NO, nitric oxide; ET-1, endothelin-1; LDL, low-density lipoprotein; VCAM-1, vascular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; SMC, smooth muscle cell; CRP, C-reactive protein; HDL, high-density lipoprotein.

BEER, WINE, OR SPIRITS?: THE FRENCH PARADOX

It has been recognized that the population of France has a lower incidence of coronary artery disease despite having a high intake of saturated fats when compared to other countries with similar levels of fat intake, such as the United States, Germany, and the United Kingdom.³⁴ This concept is known as the “French paradox,” and it is believed to be secondary to the French population’s red wine consumption.^{25, 29, 34-37} Detailed studies have been carried out to relate regional variations in mortality in France to levels of polyphenols in red wine from that region.²⁹

Given the notion of the French paradox, there is a significant amount of speculation surrounding the issue of whether one type of alcohol is healthier than others, and a large portion of the results are inconclusive. When general population studies on alcohol intake have been separated by type of alcohol that participants document as usually drinking, no significant differences have been seen.^{6, 9, 13, 22, 36} In a review of ten prospective cohort studies to determine the effect of specific types of alcohol on coronary risk, Rimm *et al.*³⁸ determined that, while all found an inverse association between light to moderate intake of either beer, wine, or spirits on risk of heart disease, no consistent pattern supporting one type of drink was seen. This association was felt to be secondary to alcohol rather than from the additional components of each type of drink. The authors hypothesize that differences in mortality may be confounded by different drinking patterns or lifestyles related to the choice of alcohol. For example, in the United States, wine drinkers tend to be of a higher socioeconomic class that supports a healthier lifestyle and allows easier access to healthcare. More so, when one type of drink was suggested as being more protective than the others, this was determined to be in populations where that was the one predominant type of alcohol consumed.

To avoid this latter bias, Gronbaek *et al.*³⁹ used data from a Danish population where there was a substantial intake of all three types of alcohol. In comparing wine drinkers, to non-wine drinkers, the investigators determined that light drinkers who avoided wine had a relative risk for death from all causes of 0.90, while those who drank wine had a relative risk of 0.66. Non-wine drinkers had a relative risk for death from coronary heart disease of 0.76, compared to 0.58 in wine drinkers. This data supports a previous study by the same author where the relative risk of mortality with three to five glasses of wine daily was 0.51, compared with no benefit with this amount of daily beer, and an increased mortality with the same amount of spirits (Figure 4).⁴⁰ Although studies can be criticized for potential confounders related to differences between wine, beer, and spirit drinkers (diet, lifestyle, drinking pattern), there does seem to be sufficient evidence to support how the polyphenols included in red wine may provide a health advantage in addition to protection afforded by alcohol alone, especially with LDL oxidation. The question still remains as to whether beer or liquor contains similar protective components that have not yet been identified.

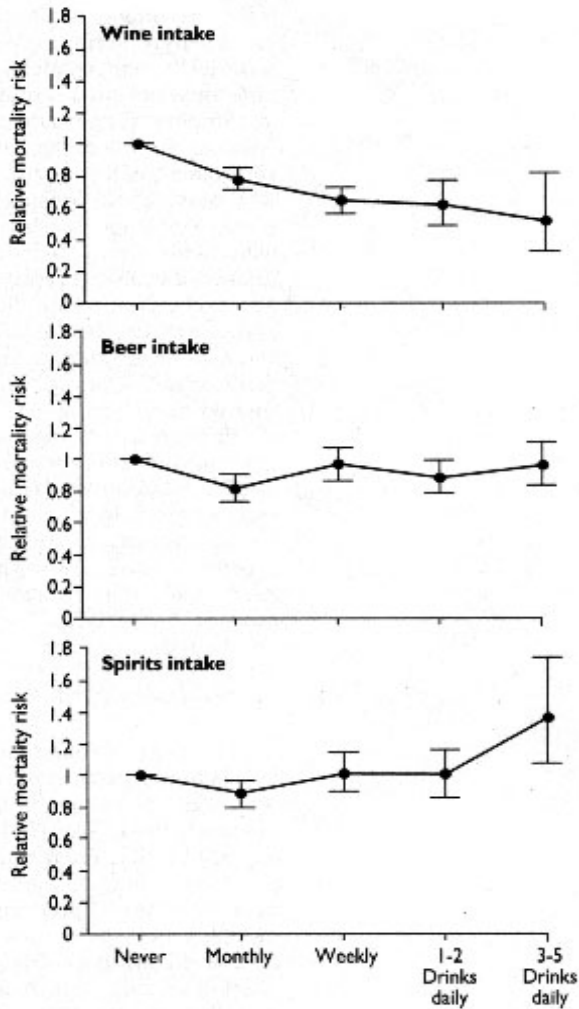


Figure 4. Relative risk, with confidence interval, of mortality in relation to intake of wine, beer, and spirits. The risk is set at 1.00 for subjects who never drank. (BMJ 1995;310:1165-1169)⁴⁰

CONCLUSIONS

Alcohol in moderation clearly has a protective effect on the vascular system. There are well studied mortality benefits, particularly against coronary artery disease. Yet it is still not apparent how this data can be appropriately used. At this time, there are no guidelines for physicians to recommend to their patients light-to-moderate intake of alcohol knowing that excess lends itself to so many negative health consequences, and since there is potential for abuse and dependency. In terms of cardiovascular disease, alcohol has mortality benefits, but is not the preventative therapy of choice when compared to the far less risky options of diet, exercise, and smoking cessation. Secondly, it is not the

treatment therapy of choice given the many highly effective medications for coronary artery disease, hypertension, hyperlipidemia, and diabetes. Given the available data, it seems reasonable that alcohol consumption for health purposes must be taken on a case by case basis. Individuals who will gain the most benefit are those at higher risk for vascular disease, including middle-aged/older men and post menopausal women with cardiovascular risk factors. Light drinkers need not change their habits for vascular reasons, while it is probably not necessary to recommend that lifelong abstainers start drinking. In the words of Voltaire, "Use, do not abuse; neither abstinence nor excess ever renders man happy."

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