Benefits and hazards of alcohol-the J-shaped curve and public health

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Abstract

Purpose – *The purpose of this paper is a review of updated evidence of a J-shaped association between alcohol consumption and the risk of coronary heart disease (CHD) and all-cause mortality in relation to public health issues to create a basis for sensible individual health deliberations.*

Design/methodology/approach – *A review of the evidence from the first observation of a J-shaped association between a moderate alcohol intake and CHD in 1926 to recent studies of the effect of healthy lifestyles (including moderate alcohol intake) on life expectancy free of cardiovascular disease (CVD), cancer and Type 2 diabetes. An update on the biological plausibility of the J-shaped association with focus on recent findings of the association of alcohol intake and blood lipid levels.*

Findings – *Plausible J-shaped relations between light to moderate alcohol consumption and the risk of CHD, CVD mortality and all-cause mortality have been found in a large number of robust epidemiological studies. Among the potential mechanisms underlying the proposed protective effects are higher levels of high-density lipoprotein lacking apolipoprotein C3, reduced platelet aggregability, increased level of endothelial cell fibrinolysis, increased insulin sensitivity and decreased inflammation.*

Originality/value – *The existence of a J-shaped association between alcohol consumption and the risk of CHD and all-cause mortality is based on observational evidence and accordingly challenged by a degree of uncertainty leading some public health circles to state: ''there is no safe level of alcohol consumption.'' The authors propose that communication on the pros and cons of alcohol intake should emphasize the nadir of a J-shaped curve as a healthy range for the general population while advice regarding the consumption of alcohol should be adjusted to factor in the risks and potential benefits for each individual patient considering age, sex, family history, personal drinking history and specific medical history.*

Keywords *Alcohol drinking, Coronary heart disease risk factors, All-cause mortality, J-shaped dose-response-relationship*

Paper type *General review*

Introduction

The first data suggesting a J-shaped relationship between alcohol consumption and mortality was presented by Raymond Pearl, a chief proponent of biostatistics (Pearl, 1926). His interest arose from observations of fowls, which lived longer if maintained for hours on end, day after day, in an atmosphere containing ethanol than control birds who were not exposed. Pearl also calculated actuarial survival curves for people with different drinking habits from data he had obtained in a study of the family health of two groups of 5,248 individuals. His findings for men showed that heavy drinking was harmful throughout life, but moderate drinking was associated with a slightly better survival than abstention over about 65 years of age; he defined moderate drinking as small amounts at any one time, never leading to intoxication, but including the consumption of a "daily pint or two of beer, a bottle of claret or a few glasses of whisky and soda." For women, there was no category of heavy drinking, but moderate drinking was associated with longer expectation of survival throughout life. Pearl's conclusion that moderate alcohol consumption was not harmful gave rise to great controversy at the time when prohibition was on the public's mind; however,

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after his continued studies showed that smoking decreases longevity but drinking does not Pearl announced that he was going to stop smoking and drink more than ever (Goldman, 2002).

From epidemiologic science to political science

While Pearl's observations on alcohol, tobacco and longevity were forgotten, the results of Carl C. Seltzer's studies on alcohol and tobacco met very different fates (Seltzer, 1997). Inspired by the 1964 Report of the Advisory Committee to the Surgeon General on Tobacco and Health, where he wrote a chapter on the morphologic constitution of smokers, Seltzer in 1972 began examining the smoking – coronary heart disease (CHD) relationship in the original "coded" data from the Framingham Heart Study where information on such possible confounders as alcohol usage, personality, constitutional factors, pertinent blood tests, occupation, race and marital status were available. Seltzer found that after 16 years of follow-up, the Framingham men who habitually consumed moderate amounts of alcohol showed a lesser risk of developing CHD than those who refrained from alcohol drinking. The risk of CHD also showed a "dose-response curve," i.e. a regularly diminishing gradient proportional to the amount of alcohol consumed. To his knowledge, this result was the first time this phenomenon had been observed in CHD research and he drafted a manuscript entitled "The relation of alcohol consumption to the development of coronary heart disease. The Framingham Study".

Much to Seltzer's surprise, when the manuscript was sent for the necessary government approval, Dr William Zukel, Associate Director, National Heart & Lung Institute, refused to allow the alcohol/CHD manuscript to be submitted for publication. The main stated reason was that:

> An article which openly invites the encouragement of undertaking drinking with the implication of prevention of coronary heart disease would be scientifically misleading and socially undesirable in view of the major health problem of alcoholism that already exists in the country.

Dr Zukel added that it would not be appropriate "to have such a manuscript with these unsupportable conclusions co-authored from the staff of the NHLI." He urged that an article be produced maintaining the "conclusion of no significant relationship of alcohol intake to incidence of coronary heart disease." The results would be based on earlier data showing no association between alcohol consumption and CHD.

When the lid in this way was put on the surprising Framingham findings on the relation of alcohol consumption to the development of CHD, the initiative passed into the hands of Gary D. Friedman of the Kaiser Permanente Medical center in Oakland. Dr Friedman's novel idea was to use computers to unearth unknown predictors of heart attacks and they soon spit out a surprising discovery: abstinence from alcohol was associated with a higher risk of heart attack (Klatsky, 2003). Thus, Klatsky, Friedman and Siegelaub (Klatsky *et al.*, 1974) became the first to publish findings of a larger proportion of teetotalers among those who had a myocardial infarction (MI), as well as a smaller proportion of moderate (<2 drinks/day) and heavy (3+ drinks/day) drinkers. Ten years later The Framingham Study turned from political to epidemiologic science with a paper (Gordon and Kannel, 1984) concluding that:

> [. . .] unlike what is reported from most other prospective studies, men who drank had lower mortality than men who did not, the lowest mortality being for light drinkers. Even men drinking 60 ounces of alcohol per month or more had no greater mortality than nondrinkers.

Convincing strength of existing evidence

In a review on moderate alcohol consumption and CHD 12 years after Klatsky *et al.*'s "first-mover" study, Moore and Pearson (1986) were able to present many studies from all over

the world (Framingham, Chicago, CA, Honolulu and Puerto Rico [USA], Busselton [Western Australia], North Karelia [Finland], Belfast [Northern Ireland] and Yugoslavia), that had examined the relationship between alcohol use and CHD and found a negative correlation in all but one study (Belfast). Overall the data showed an inverse dose-response relationship or a U-shaped (three studies) or J-shaped (one study) association. Dilated cardiomyopathy, hypertensive heart disease, dysrhythmias, cirrhosis of the liver, certain forms of cancer and hemorrhagic stroke accounted for some of the deaths in the right up-sloping portion of the U-shaped mortality curve. "Overall, the evidence indicates that a potentially protective level of alcohol consumption exists between the extremes of abstention and drinking in excess of 3–4 drinks per day." Regarding strength of association Moore and Pearson concluded:

> In both the case-control and cohort studies, the relative risk of CAD from moderate alcohol consumption compared with no consumption ranges from 0.4 to 0.7. Generally, this was significantly different from 1.0 and implies a moderately strong association.
>
> Although it is possible that a confounding factor could explain the association, it would be necessary for that factor to be present twice as frequently among moderate as among heavier drinkers to account for this strong inverse association. It is unlikely that a confounding factor could have consistently remained unidentified in multiple studies.

Moore and Pearson found the strength of existing evidence so convincing that they thought that new and expensive population-based studies of the association of alcohol consumption and CHD were unnecessary. However, their hint to the scientific community was not taken and the evidence with respect to the J-shaped curve is now overwhelming. A meta-analysis of 34 prospective studies, pooling findings from more than one million individuals and almost 100,000 deaths, showed a J-shaped relationship between alcohol intake and total mortality (Di Castelnuovo *et al.*, 2006). Consumption of up to 2 drinks/day (25 g alcohol/d) in women and 4 drinks/day (42 g/day) in men was associated with lower mortality than zero consumption, with one-half drink per day (6 g/day) associated with the lowest mortality risk. A more recent systematic review and meta-analysis included 84 of 4,235 studies reviewed for eligibility (Ronksley *et al.*, 2011). The pooled adjusted relative risks for alcohol drinkers relative to non-drinkers in random effects models for the outcomes of interest were 0.75 (95% CI 0.70–0.80) for CVD mortality (21 studies), 0.71 (0.66–0.77) for incident CHD (29 studies), 0.75 (0.68–0.81) for CHD mortality (31 studies), 0.98 (0.91–1.06) for incident stroke (17 studies) and 1.06 (0.91–1.23) for stroke mortality (10 studies). Compared with no alcohol, 2.5–14.9 g alcohol (up to about 1 drink) per day was protective for all five outcomes. The lowest risk of CHD occurred with 1–2 drinks/day, but for stroke mortality it occurred with $\leq$1 drink/day. Secondary analysis of mortality from all causes showed lower risk for drinkers compared with non-drinkers: relative risk 0.87 (0.83–0.92).

The J-shaped curve in different populations

Nature and nurture

The NHLBI twin study found an inverse overall and within-pair relation between alcohol intake and 41-year CHD mortality risk (Dai *et al.*, 2015). The within-pair adjusted hazard ratios for a twin with 10-g higher daily alcohol consumption than his co-twin were 0.90 (95% CI 0.84–0.97) for CHD and 0.95 (0.90–1.00) for CVD mortality independent of genetic makeup, early life environment and adulthood experience shared by twins.

Competing risks

Competing risks could make a non-existing association look like a beneficial association (Glynn and Rosner, 2005). In a Norwegian study on acute myocardial infarction (AMI) in a population with low average alcohol consumption in which abstaining from alcohol is not

socially stigmatized, the authors controlled for a multitude of life-style factors and demographic variables (Gemes *et al.*, 2016). After adjusting for major cardiovascular disease (CVD) risk factors, the hazard ratio for a one-drink increment in daily consumption was 0.72 (95% CI 0.62–0.86). Accounting for competing risks, former drinking or comorbidities had almost no impact on the association, however, frequency of alcohol consumption was more strongly associated with lower AMI risk than overall quantity consumed. The down-slope part of the J-curve is exemplified in the linear reduction in AMI risk with increasing alcohol intake in a population with low average alcohol intake and extremely rare excessive consumption (Figure 1).

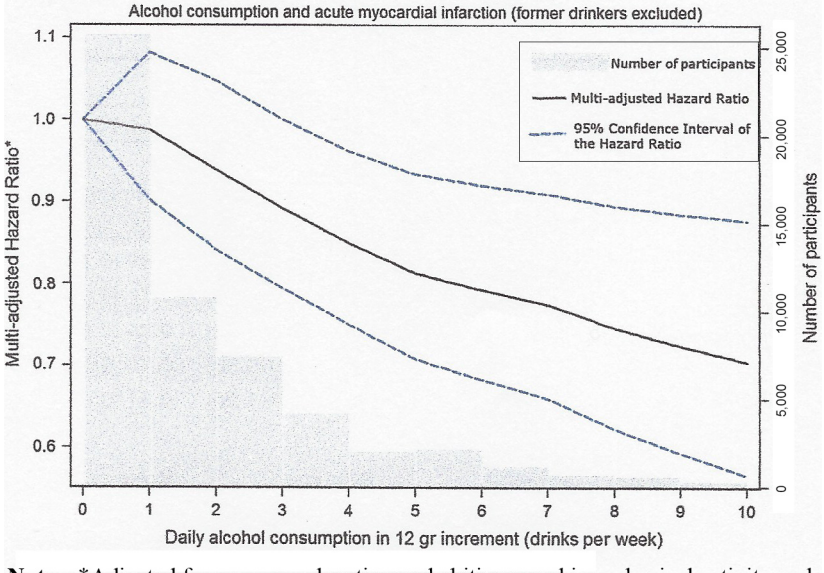
Older adults

A population-based cohort study using data from 99,654 adults aged 55–74 years found positive linear associations between lifetime alcohol consumption and cancer-related mortality and J-shaped associations between lifetime alcohol consumption and cardiovascular-related mortality and all-cause mortality (Kunzmann *et al.*, 2018). These findings support a J-shaped association between lifetime alcohol use and mortality in older adults (Figure 2) with an increased overall mortality in lifetime never drinkers and infrequent drinkers (<1 drink/week), as well as heavy (2–<3 drinks/day) and very heavy drinkers (3+ drinks/day).

Adults ≥18 years of age

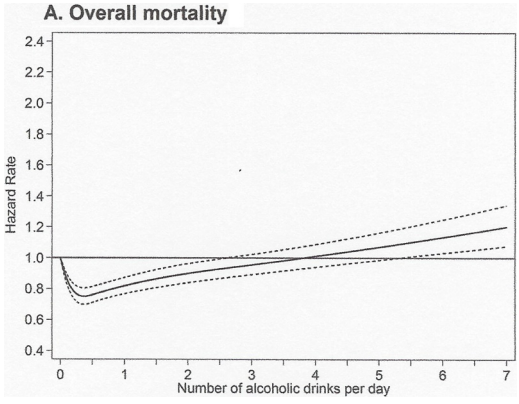
Data obtained by linking 13 waves of the National Health Interview Surveys 1997–2009 (including 333,247 participants ≥18 years of age) to the National Death Index records through December 31, 2011 found light or moderate alcohol consumers at a reduced risk of mortality for all causes: light alcohol consumers: HR 0.79 (95% CI: 0.76–0.82); moderate alcohol consumers: HR 0.78 (95% CI: 0.74–0.82) compared with lifetime abstainers (Xi *et al.*, 2017). In contrast, there was a significantly increased risk of mortality for all causes in

Figure 1 Alcohol consumption and acute myocardial infarction. Reprinted with permission from Gémes *et al.* © The Association for the Publication of the *Journal of Internal Medicine*



Notes: *Adjusted for age, sex,education. cohabiting, smoking, physical activity and body mass index

Figure 2 Lifetime alcohol consumption and all-cause mortality. Reprinted from Kunzmann *et al.* with permission from PLoS Medicine



adults with heavy alcohol consumption: HR 1.11 (95% CI: 1.04–1.19) and binge drinking ≥1 day/week: HR 1.13 (95% CI: 1.04–1.23) (Figure 3).

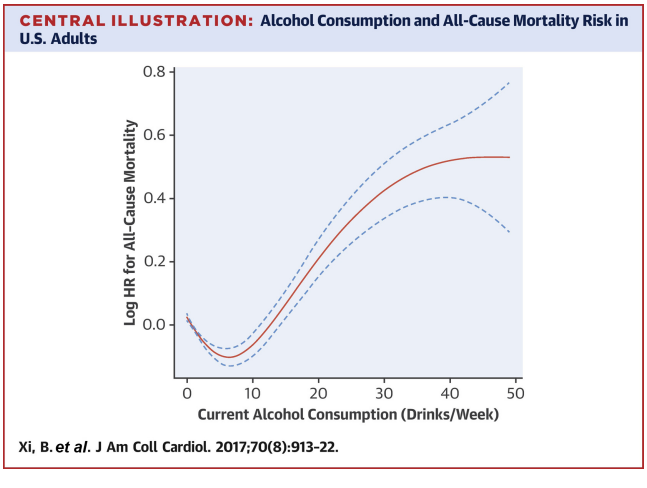
Adults with chronic diseases

A J-shaped association with light and moderate drinking associated with lower risk of mortality and CHD has also been found in type 2 diabetic patients (Koppes *et al.*, 2006), in hypertensive men (Britton *et al.*, 2009) and in individuals with established CVD (Costanzo *et al.*, 2010).

Biological plausibility of the J-shaped association

A review of data from 44 interventional studies found intake of alcohol associated with

Figure 3 Alcohol consumption and all-cause mortality risk in US adults. Reprinted from Xi *et al.* with permission from Elsevier



favorable changes in several cardiovascular biomarkers (Brien *et al.*, 2011). Alcohol significantly increased levels of high density lipoprotein cholesterol (HDL-C): mean difference 0.094 mmol/L (95% CI 0.064–0.123), apolipoprotein A1 (apoA1) 0.101 g/L (0.073–0.129) and adiponectin 0.56 mg/L (0.39–0.72). Alcohol decreased fibrinogen levels: −0.20 g/L (−0.29 to −0.11) but did not affect triglyceride levels. Analyses were also stratified by beverage type (wine, beer, spirits) and the results were similar to the combined analyses of all beverage types. Nested case-control studies of participants from the Nurses' Health Study and the Health Professionals Follow-Up Study found alcohol intake at least 3–4 days/week associated with a lower risk of MI among women and men, an association attributable to the relationship of alcohol with HDL-C, fibrinogen and hemoglobin A1c (HbA1c). Among women HDL-C accounted for 36% of this association and HbA1c alone accounted for a similar proportion. Among men half of the inverse association was attributable to HDL-C and adjustment for the combination of HDL-C, fibrinogen and HbA1c fully attenuated the regression coefficient in men (Mukamal *et al.*, 2005).

High density lipoprotein cholesterol

While an increasing total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio is a powerful predictor of CHD risk in men and women (Calling *et al.*, 2019), randomized trials of HDL-C modifying drugs have not shown the anticipated benefit (Riaz *et al.*, 2019) and results of Mendelian randomization (MR) analyses also challenge the concept that raising plasma HDL-C will translate into reductions in risk of MI (Voight *et al.*, 2012). However, high density lipoprotein (HDL) is not simply a carrier of cholesterol taken from cells for redistribution and removal from the body; HDL is a complex constellation of many proteins and phospholipids organized into HDL subspecies with diverse physiochemical properties and metabolic actions. The main protein on HDL is apoA1 that lends structural stability to the particle and stimulates efflux of cholesterol from cells to HDL, enlarging the particles. However, ongoing research has focused on apolipoprotein C3 (apoC3) as a potentially important protein that may modulate HDL function. ApoC3 is present on 6% to 15% of HDL, and several cohort studies found HDL that contains apoC3 associated with a higher risk of CHD: pooled relative risk per standard deviation, 1.09 (95% CI 1.01–1.18), whereas HDL that lacks apoC3 was associated with lower risk: relative risk 0.76 (0.70–0.83) (Jensen *et al.*, 2018).

HDL containing apoC3 is associated with metabolic risk factors, such as diabetes mellitus, obesity and blood glucose. In contrast, HDL lacking apoC3 is associated with favorable levels of these risk factors. Regarding lifestyle, HDL containing apoC3 levels were 0.9% lower (95% CI: –1.7, –0.1) per each 20 MET h/week higher physical activity while HDL not containing apoC3 levels were 1.6% (0.8–2.3) higher per 15 g/day higher alcohol consumption (Koch *et al.*, 2017). The MR approach, having thus far focused on HDL cholesterol or apoA1 levels, may not capture the functional properties of HDL that play a role in the disease pathology (Sacks and Jensen, 2018).

Apolipoprotein B

Each apolipoprotein B (apoB)-containing lipoprotein [very-low-density lipoprotein (VLDL), VLDL remnant particle and low-density lipoprotein (LDL)] has a single apoB molecule. Therefore, plasma apoB concentration is a direct measure of the total number of circulating atherogenic apoB particles that can become trapped in the artery wall (Ference *et al.*, 2020). A recent MR study using UK Biobank data found the effects of low-density lipoprotein cholesterol (LDL-C), triglycerides and apoB consistent with a higher risk of CHD when assessed individually, while in a multivariable MR, only apoB: OR 1.92 (95% CI 1.31–2.81) retained a robust effect (Richardson *et al.*, 2020). The apoB/apoA1 ratio has been suggested to be a powerful and more accurate predictor of future CVD risk than the TC/HDL-C ratio (Tognon *et al.*, 2012). In the Swedish INTERGENE study of 2,907

individuals, body mass index (BMI) showed a very strong positive association with the apoB/apoA1 ratio and consumption of alcohol was the only dietary factor that appreciably attenuated the association (Tognon *et al.*, 2012). Cross-sectional analyses within a Swedish cohort of 24,984 individuals found high alcohol consumption, high physical activity, non-smoking, a low BMI and intake of fermented dairy products the main determinants of high apoA1 concentrations while the main determinants of high apoB concentrations were smoking, a high BMI and a diet high in sugar (Frondelius *et al.*, 2017). MR analyses in three Japanese populations using the aldehyde dehydrogenase 2 genotype in an attempt to clarify a causal role of alcohol on circulating cholesterol levels and lipoprotein particle numbers supports a causal role of alcohol consumption in lowering LDL-C levels and particle numbers (Tabara *et al.*, 2016).

Thrombosis and fibrinolysis

Normal hemostasis is maintained through a delicate balance between the coagulation and fibrinolytic systems. Studies on healthy individuals have indicated that the primary hemostasis is impaired in man after ingestion of moderate amounts of alcohol (Elmer *et al.*, 1984). Platelet aggregation, which is related to CHD, is inhibited significantly by alcohol at levels of intake associated with reduced risk of CHD (Renaud and de Lorgeril, 1992). Consumption of red wine may reduce platelet aggregability partly due to ethanol and partly due to the polyphenolic components of wine. In fasted animals administered alcohol or wine, platelet aggregation to thrombin was inhibited by more than 60%. However, a rebound phenomenon of hyperaggregability that was observed after 18 h of alcohol/wine deprivation was not observed in animals given red wine (Ruf, 2004).

Moderate and frequent (daily) consumption of low levels of alcohol will maintain an increased level of alcohol-induced endothelial cell fibrinolysis, as compared with non-consumers of alcohol and thus reduce the risk for thrombosis and MI (Booyse *et al.*, 1999). The relation between alcohol and blood coagulation might be complex, with light alcohol consumption ($\leq$2 drinks/day) promoting less coagulation and heavy alcohol consumption ($>$3 drinks/day) promoting both impaired blood coagulation and also impaired fibrinolysis (Engström *et al.*, 2006). As a result, heavy alcohol consumption is expected to increase the risk of both ischemic and bleeding events (Askgaard *et al.*, 2020).

Insulin sensitivity

Light and moderate alcohol consumption is associated with a lower risk of type 2 diabetes (Li *et al.*, 2016). Results from the Danish Health Examination Survey indicate that frequent consumption of alcohol is associated with the lowest risk of diabetes, even after taking average weekly alcohol consumption into account (Holst *et al.*, 2017). A meta-analysis of 13 prospective cohort studies that assessed the effects of specific types of alcoholic beverage on the risk of type 2 diabetes found that wine was associated with a more significant decreased risk of type 2 diabetes compared with beer or spirits (Huang *et al.*, 2017).

C-reactive protein (CRP) – marker of inflammation

Atherosclerosis is now understood to be a chronic, low grade inflammatory disease of the arterial wall and increased levels of inflammatory markers have been associated with risk of CVD. Large cross-sectional surveys have found lower CRP concentrations associated with moderate alcohol consumption compared with no alcohol in Germany (Imhof *et al.*, 2001) and the USA (Albert *et al.*, 2003). In a diet-controlled intervention study, as compared to no-alcohol beer consumption, fibrinogen levels were decreased by 12.4% and plasma CRP was decreased by 35% after 3 weeks' consumption of beer (Sierksma *et al.*, 2002).

Allostatic load

Among 1,255 middle-aged adults in the MIDUS biomarker substudy current alcohol use was associated cross-sectionally with a favorable multisystem physiologic score (Allostatic load), known to be associated with better long-term health outcomes, providing evidence in support of long-term health benefits related to alcohol consumption (Goldwater *et al.*, 2019).

From press releases to headlines

"Alcohol has no health benefits after all" the Times told it is readers in 2015. However, the headline was without serious foundation and through no fault of the journalists. The headline was based on a study by Knott *et al.* (2015) published in BMJ which used data from over 18,000 people aged over 50 who took part in the Health Survey of England between 1998 and 2008 to investigate the protective effect of low consumption of alcohol. However, despite the press release and the claim in the abstract that "Compared with never drinkers, age stratified analyses suggest that beneficial dose-response relations between alcohol consumption and all-cause mortality may be largely specific to women drinkers aged 65 years or more, with little to no protection present in other age-sex groups," the findings of the study were actually in broad agreement with the J-shaped association between alcohol intake and all-cause mortality found in other studies. In the words of professor David Spiegelhalter, Winton Professor of Public Understanding of Risk, University of Cambridge (Spiegelhalter, 2015):

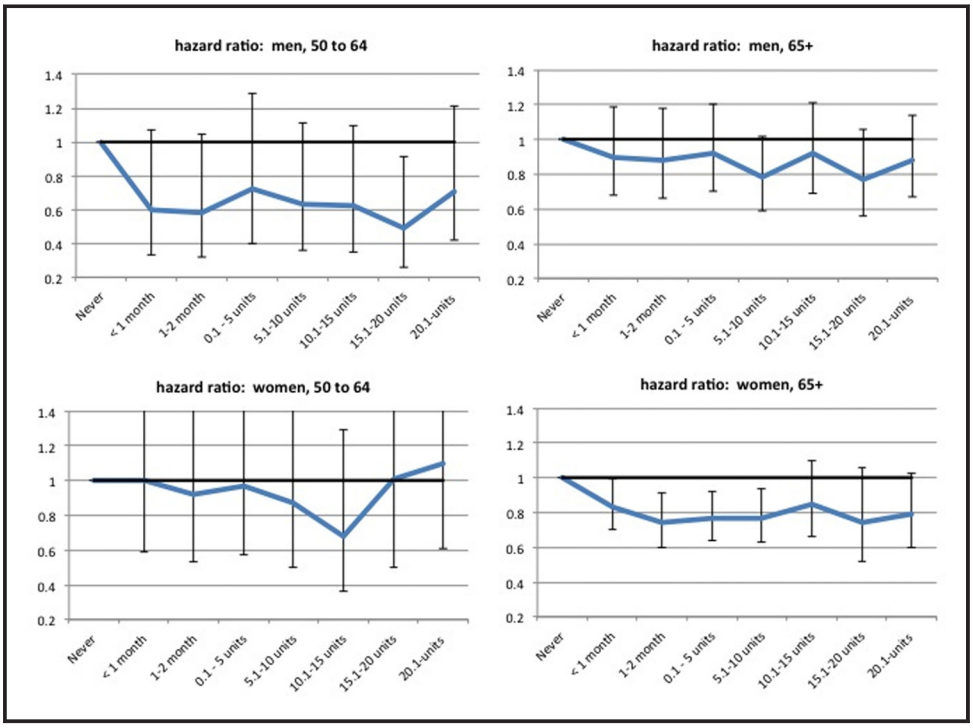
> The study is grossly underpowered to convincingly prove a plausible protection, and the authors have committed the cardinal sin of saying that non-significance is the same as "no effect" in a study lacking sufficient events, in this case, deaths in non-drinkers.

A casual look at the graph of observed hazard ratios, derived by professor Spiegelhalter from the data provided in the study tables (Figure 4), confirms that the observed data are compatible with the kind of 10–20% protection that has been previously suggested. The problem is the very wide confidence intervals. This is because there were few teetotalers and not many deaths – for example, the entire comparison for 50–64 year-olds is based on 17 deaths in the male baseline group and 19 deaths in the females. This is completely inadequate to draw any firm conclusions, as there is large uncertainty about what the true underlying relative risks are. This is a classic statistical error and poor use of statistics.

A Lancet paper claiming to be the definitive study on the benefits and dangers of drinking (GBD 2016 Alcohol Collaborators, 2018) was covered in the news media with headlines like "There's No Safe Amount of Alcohol." In a systematic analysis of data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 for 195 countries and territories, 1990–2016, the authors found alcohol use the seventh leading risk factor for both deaths and disability-adjusted life-years (DALYs), accounting for 2.2% (1.5–3.0) of female deaths and 6.8% (5.8–8.0) of male deaths. Tuberculosis was the primary cause of lost DALYs attributable to alcohol among individuals up to age 50 and among all individuals in low-income countries. The GBD Study, founded on a large and complex statistical model from a vast range of data sources, concluded that while moderate alcohol consumption may be preventive for some conditions such as CHD and diabetes, when combined with increasing risk of cancers and other outcomes there is a steadily increasing harm from alcohol consumption. However, the authors ignore the pattern of drinking in their analyses and the uncertainty interval of the weighted relative risk of alcohol for all attributable causes by standard drinks consumed per day does not start to exclude "no effect" until over one drink a day.

> In spite of the Lancet's own guidelines for meta-analyses saying 'For risk changes or effect sizes, give absolute values rather than relative changes', the paper did not report any absolute risks, meaning that readers couldn't tell how dangerous drinking alcohol really was for them, professor Spiegelhalter (2018) wrote in his blog post Aug. 24.

Figure 4 Reprinted from https://understandinguncertainty.org/misleading-conclusions-alcohol-protection-study



> "Fortunately this extraordinarily lax review process was countered by the Lancet press office who asked for absolute risk estimates from the authors. The press release reported that 'Specifically, comparing no drinks with one drink a day the risk of developing one of the 23 alcohol-related health problems was 0.5% higher – meaning 914 in 100,000 15–95 year olds would develop a condition in one year if they did not drink, but 918 people in 100,000 who drank one alcoholic drink a day would develop an alcohol-related health problem in a year. This increased to 7% in people who drank two drinks a day (for one year, 977 people in 100,000 who drank two alcoholic drinks a day would develop an alcohol-related health problem) and 37% in people who drank five drinks every day (for one year, 1,252 people in 100,000 who drank five alcoholic drinks a day would develop an alcohol-related health problem). So the information is now all there, but what does it actually mean for moderate drinkers? Let's consider one drink a day (10 g, 1.25 UK units) compared to none, for which the authors estimated an extra 4 (918–914) in 100,000 people would experience a (serious) alcohol-related condition. That means, to experience one extra problem, 25,000 people need to drink 10 g alcohol a day for a year, that's 3,650 g a year each. To put this in perspective, a standard 70 cl bottle of gin contains 224 g of alcohol, so 3,650 g a year is equivalent to around 16 bottles of gin per person. That's a total of 400,000 bottles of gin among 25,000 people, being associated with one extra health problem.

The Lancet paper gave rise to critique from several readers:

> The most reliable way to reach a definite conclusion is to analyze the association of alcohol with all-cause mortality. We were therefore surprised that the investigators did not consider total mortality as an outcome (Di Castelnuovo *et al.*, 2019).

> "Limitations in the methods have led to the unfounded conclusion that, at the individual level, no amount of alcohol consumption benefits health" (Shield and Rehm, 2019).

> The combination of data from widely divergent countries and marginal control for confounders might conceal substantial effects of social and cultural factors. The merged findings of the 23 investigated alcohol-related health issues cannot be interpreted at regional, let alone individual level. For example, for many individuals in high-income countries, the risk of heart disease and diabetes is much higher than the risk of tuberculosis (Astrup and Estruch, 2019).

J-shaped associations and public health

Evidence on the protective effect of drinking on coronary heart disease is conclusive at the level of association, highly suggestive at the level of causation, but not on present analysis significant at the policy level. Most of the achievable benefit is likely to be obtained at an alcohol intake between one drink every 2 days, and two drinks a day", was the verdict of "Alcohol Policy and the Public Good", a WHO report from 1994 (Edwards, 1997).

Roerecke and Rehm (2014), who have long been skeptical about this relationship, have now reached the following pertinent conclusion:

> For drinkers having one or two drinks per day without episodic heavy drinking, there is substantial and consistent evidence from epidemiological and short-term experimental studies for a beneficial association with ischaemic heart disease risk when compared to lifelong abstainers. The alcohol-IHD relationship fulfills all criteria for a causal association proposed by Hill.

In associated papers in this journal Grønbæk *et al.* review the methodological challenges that have brought the validity of the dose-dependent J-shaped association into question, and Ellison *et al.* examine the advantages and drawbacks of MR studies of the J-shaped curve.

Interventions that alter population-level risk exposure have yielded a number of improvements in public health. Tobacco taxes are an example of such population-based approaches to disease prevention. In the case of tobacco, the harms of shifting total population exposure through taxation are minimal, because there is no safe level of consumption. However, other risk factors do not exhibit the same linear relationship between exposure and mortality and therefore may introduce new complexities in communicating with individuals and the public (Chokshi *et al.*, 2015). Alcohol's association with health are analogous to the apocryphal "Strange Case of Dr Jekyll and Mr Hyde": prudent consumption of this dimorphic potion appears to improve cardiovascular health, but when consumed in excess, benefit transforms into detriment as alcohol unveils a deadly nature (O'Keefe *et al.*, 2018). Long-term consumption of large amounts of alcohol is harmful, leading to addiction and fatal or nonfatal injuries. Furthermore, excessive alcohol intake may cause serious harm to others. Concern about these dangers often leads to emotional denials that alcohol might have any benefits, particularly by those who have experienced or seen its bad effects (Friedman and Klatsky, 1993). First, however, health communication should emphasize the nadir of a J-shaped curve as a healthy range for the general population. Then conversations might focus on what is epidemiologically important, such as curbing excessive intake, rather than on theoretical risks to small subpopulations. When the evidence is clear, public health leaders should embrace the left side of the J-shaped curve to counter perception as "nannies" or prohibitionists and point out pursuit of the nadir as the goal.

Advice to the public regarding alcohol consumption should always include other important lifestyle factors that affect health: smoking, obesity, diet and exercise. Subjects in large observational studies who are non-smokers, are not obese, eat a Mediterranean-type diet and get regular exercise have lower risk of CVD and total mortality, whether or not they consume alcohol. However, regardless of other healthy lifestyle factors, the presence of light to moderate, regular alcohol consumption in subjects, when added to the analysis, provides significantly greater protection against CVD than seen for the adherence to all the

other lifestyle factors alone. A recent major study estimated the effect of five healthy lifestyles on life expectancy free of CVD, cancer and type 2 diabetes in the US population 50 years of age (Li *et al.*, 2020). One of these lifestyles was moderate alcohol intake (men 5–30 g/day; women 5–15 g/day). Compared with men with four healthy lifestyles (no smoking, high physical activity, ideal body mass index and healthy diet), those who were also drinking moderately had 0.8 years longer life expectancy. The respective increase for women was 3 years. Thus, unless contraindicated, our definition of a "healthy lifestyle" might include intake of small to moderate amounts of alcohol, especially when consumed on a regular (non-binge) basis and preferably with food (Trevisan *et al.*, 2004; Stranges *et al.*, 2004; Vieira *et al.*, 2016).

A study aimed to quantify alcohol-attributable and preventable mortality, totally and stratified on alcohol consumption in Denmark 2010, found that 1,373 deaths among women (5.0% of all deaths) and 2,522 deaths among men (9.5% of all deaths) were attributable to alcohol, while an estimated number of 765 (2.8%) and 583 (2.2%) deaths were prevented by alcohol (Eliasen *et al.*, 2014). Of the alcohol-attributable deaths, 73 and 81% occurred within the high alcohol consumption group (>14/21 drinks/week for women/men). A reduction of 50% in the alcohol consumption was associated with a decrease of 1,406 partly alcohol-attributable deaths (46%) and 37 alcohol-preventable deaths (3%). Total compliance with sensible drinking guidelines with a low risk limit (<7/14 drinks/week) and a high risk limit (<14/21 drinks/week) was associated with a reduction of 2,380 and 1,977 alcohol-attributable deaths, respectively. In summary, 5.0% of deaths among women and 9.5% of deaths among men were attributable to alcohol in Denmark 2010. The minority of Danish women and men had high alcohol consumption (16 and 26%). However, the majority of all alcohol-attributable deaths among women and men were caused by high consumption (73 and 81%).

Physicians and policymakers have asked for a randomized controlled trial for many years given the importance and prevalence of CHD, the potential benefits of alcohol use, the risks of alcohol abuse and the inherent limits of observational studies (Freiberg and Samet, 2005). On February 15, 2018, the recruitment of subjects for the moderate alcohol and cardiovascular health (MACH 15) trial began. The worldwide study was to include 7,800 participants, 50 years of age or older and at an above-average risk for CVD (Spiegelman *et al.*, 2020). After an average of six years' follow-up, those who were advised to consume one drink a day (15 g) were to be compared with abstainers in terms of the incidence of CVD and diabetes. The decision not to include cancer as an end point was deemed by critics of the study as evidence of methodological bias. Consequently because of the controversy sparked by the industry's funding and the study's design, the RCT was halted by The National Institutes of Health (NIH) after four months (Oppenheimer and Bayer, 2020). The NIH's decision to shut down MACH 15 has been criticized as scientifically unfounded and a disservice to alcohol consumers who need to know that the public health advisories they rely upon are supported by the best science possible (Dejong, 2020).

J-shaped associations and individual health

Addressing an Illinois temperance society in 1842, Abraham Lincoln offered an opinion about "intoxicating liquor" that probably got a frosty reception:

> It is true that many were greatly injured by it, but none seemed to think the injury arose from the use of a bad thing but from the abuse of a very good thing.

Alcohol has been widely consumed through the ages because of its perceived benefits as a social lubricant and for relaxation and sensory pleasure presuming a halcyon drinking style where a glass of wine improves people's meals and enhances their social life. With public knowledge of the J-shaped association of alcohol and CHD any clinician who has tried to counsel a patient about alcohol use has encountered the question: "But I thought a couple

of drinks a night is good for my health?" In this way, the strategies of preventive medicine – both individual and population based – that have proven quite successful for tobacco control may be less effective when confronting the epidemiologic and perceptional challenges presented by the J-shaped curve.

A sensible interpretation of the message of the J-shaped curve would be that consumption of more than a few drinks per day is undesirable for the standpoint of health for most people. Whether drinking low to moderate amounts may be desirable or undesirable depends on individual characteristics and any advice regarding the consumption of alcohol should be adjusted to factor in the risks and potential benefits for each individual patient considering age, sex, family history, personal drinking history and specific medical history. Instead of waiting for perfect evidentiary consensus, what is required is a synthesis of common sense and the best available scientific facts applied by a knowledgeable health professional to make a balanced judgment (Klatsky, 2010).

The Greek poet Eubulus (375 B.C.) voted for a wine dose of 3 Kylix cups (≈250 mL) and in one of his plays had Dionysus, the god of wine, say:

> Three bowls do I mix for the temperate: one to health, which they empty first, the second to love and pleasure, the third to sleep. When this bowl is drunk up, wise guests go home.

Eubulus's view comes close to current guidelines, however, all the official recommendations suffer from the fact that the thresholds of healthy moderation are population averages and do not necessarily reflect individual thresholds – indeed intestinal degradation, absorption, metabolism and blood clearance of ethanol are all subject to high interindividual variability (Fraser *et al.*, 1995). The Finnish epidemiologist Kari Poikolainen has the following advice for "perfect drinking":

> Virtue does not lie in following guidelines but in a judicious setting of your own rules. Rhythm and drinking speed play a major role. *Fruens tardius*. Drink slowly and enjoy, preferably around evening meals. Adjust your drinking so that you sleep well and feel good in the mornings. Avoid drinking that elevates your blood pressure and watch your body weight (Poikolainen, 2020).

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