The J-shaped curve-conceptual and methodological challenges

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Abstract

Purpose – *The purpose of this paper is to review the conceptual and methodological challenges of a J-shaped association between alcohol consumption (AC), coronary heart disease (CHD) and all-cause mortality. In associated papers in this journal, Skovenborg* et al.*, 2021 reviews the evidence for the J-shaped curve, and Ellison* et al.*, 2021 examines the advantages and drawbacks of Mendelian randomization studies of the J-shaped curve.*

Design/methodology/approach – *A number of methodological problems are common in observational research in general, and some of the methodological problems suggested for the J-shaped alcohol-CHD-associations are discussed. The extent of the methodological problems in studies of the J-shaped curve is reviewed, and the possibility that the J-shaped curve is an artifact created by reverse causality and residual confounding is discussed. Further, the issue of interaction with drinking pattern and type of alcohol is discussed.*

Findings – *Imprecise categorization of alcohol intake information seems to have had little effect on the J-shaped alcohol-CHD-associations, nor has it affected the ability of these studies to show increasing mortality from a range of causes with increasing AC. The problem of "sick quitters" has been resolved by large studies using lifelong abstainers or infrequent drinkers as reference group. Many studies lack information on drinking patterns with regard to regular, moderate consumption versus binge drinking. Stratified analyses by important risk factors for CHD have not significantly changed the J-shaped association observed in most epidemiologic studies.*

Originality/value – *Potential biases and residual confounding probably do not overcome the J-shaped alcohol-CDH-association observed in most epidemiologic studies; however, the existence of a J-shaped curve is challenged by some degree of uncertainty. The actual review together with the associated papers by Skovenborg* et al.*, 2021 and Ellison* et al.*, 2021 offers a possibility to "update your priors" and achieve greater certainty when giving your patients information on the pros and cons of alcohol intake.*

Keywords *Alcohol drinking, Information bias, Abstainer misclassification, Drinking pattern, Confounding factors*

Paper type *General review*

Introduction

Many risk factors, such as alcohol consumption (AC), exhibit a J-shaped association when plotting health effects like mortality on the vertical axis against the magnitude of the risk factor on the horizontal axis: light drinking is associated with lower mortality than non-drinking and heavy drinking. The J-shaped alcohol-coronary heart disease (CHD)-association has been examined intensely for conceptual and methodological challenges that may bring the validity of the J-shaped curve into question. Methodological flaws suggested are, e.g. bias in self-reported AC with misclassification of alcohol intake, confounding bias, AC being linked to certain socio-economic and lifestyle characteristics known to affect cardio-vascular events; the sick quitters' fallacy leading to a reverse causality bias, residual confounding bias, and the question whether drinking pattern and/or type of alcohol may influence the J-shaped association.

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Misclassification of alcohol intake

Moderate use of alcohol is in itself an inaccurate term but is frequently considered to be up to 1 drink per day for women and up to two drinks per day for men. The quantity of AC expressed in alcohol g/day has become a standardized and widely used measure. The limits of moderate consumption are around 30 g/day for men and 15 g/day for women. The intrinsically imprecise categorization, ambiguously defined and self-reported information about amount of alcohol intake, often based on one single measure of alcohol, is an important methodological challenge for observational studies. However, while the methods of assessing AC vary widely in the different studies, this seems to have had little effect on the results for the associated risk of CHD, nor has it affected the ability of these studies to show that increasing AC is associated with increasing mortality from a range of causes. The relation of alcohol intake to CHD may in this respect be analogous to the relation of randomly collected measurements of blood pressure to the risk of CHD. Even though there is huge variability in the way blood pressure is measured, the net result is that blood pressure, however measured, turns out to be an important risk factor for CHD. Boffetta and Garfinkel (1990) argue that if alcohol histories in the American Cancer Society study were correct they would expect to see alcohol associated with mortality from cancer of the oral cavity and esophagus, liver cirrhosis, suicide and accidents. This is, in fact, what they found.

Reporting bias and changes in alcohol intake over the life span might introduce misclassification of AC. Non-differential misclassification means that some of the subjects, randomly misclassified into intake-groups, are classified differently than their "true" intake with the result that the effect of alcohol on mortality would be diluted, and this would lead us to observe a lower than true relative risk of abstinence and heavy drinking. Differential misclassification means that the errors in reporting have a certain direction of which the most likely is some underreporting intake in all groups and underreporting predominantly among heavy drinkers. An analysis of a total of 1 876 046 participants in 40 cohort studies from 18 countries on alcohol use and all-cause mortality (Stockwell *et al.*, 2018) found mean coverages of age 15+ per capita alcohol intake of 61.71% ranging from 29.19% for Russia and 55.35% for western European countries to 66.22% for the USA and 96.53% for Japan.

If underreporting is equal at all levels, the true risk function would be at a higher level of intake which means that many studies would overestimate the risk of dying from given levels of alcohol intake in the higher alcohol intake groups and the nadir of the J-curve would also be at a higher level. Preferential underreporting by heavy drinkers is a source of bias against apparent benefit by moderate intake. The presumed effect is to systematically reclassify some true "heavy" drinkers as apparent "light-moderate" drinkers and thereby distorting alcohol-health curves. If the true relation of a harmful effect has a threshold (i.e. no effect at light drinking but increasing harm at heavier intake), underreporting lowers or obliterates the threshold. With a J-curve-association, underreporting lessens the apparent benefit of light-moderate drinking. Klatsky and Udaltsova (2007) tried to identify a group of persons among moderate drinkers that was more likely to be underreporters including persons who, on another occasion, indicated intake of three or more drinks per day or who ever had a diagnosis of an alcohol-related condition. The supposed underreporters were about twice as likely to have high aspartate aminotransferase levels, a fact indirectly pointing to probable heavy drinking. 27% of persons reporting one–two drinks per day fell into this more likely underreporter group, and the reduced mortality risk associated with moderate alcohol intake was concentrated in those unlikely to be underreporters, whereas the suspected underreporters showed little if any apparent mortality benefit.

Most current AC categories share a common denominator in that they are ex-ante classifications. In being a priori defined groupings, they may exhibit a few non-negligible weaknesses: the existence of categories is assumed and cannot be tested; cutoff points are often arbitrary; the assignment of a subject to a certain category is

deterministic (absolute certainty) instead of probabilistic; and they create fixed group boundaries that fail to capture gradual or rapid AC changes over time. In most studies, AC is measured over short time frames. Longitudinal studies are scarce and usually do not take into account changes over time, using baseline measures as predictors of future cardiovascular risk. The inability to account for within-person variability of AC, especially throughout life, presents a major impediment to identifying alcohol's potential cardio-protective role. Passos *et al.* (2017) applied a Group Based Trajectory Model (GBTM) to extract distinct progressions of AC over time, and the GBTM analysis laid bare the heterogeneity of AC dynamics over the life-course. However, AC showed relative stability in middle-age and elderly years and the findings elicited supportive evidence for a J-shaped association of AC and CHD.

Urinary ethyl glucuronide (EtG) is an alcohol metabolite and validated biomarker for recent AC. A study of 5,676 participants of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study cohort aimed to examine and compare the associations of self-reported AC and EtG with cardiovascular disease (CVD) and all-cause mortality (Van de Luitgaarden *et al.*, 2020). EtG was measured in 24-h urine samples and AC questionnaires were administered. Follow-up times differed for CVD (8 years; 385 CVD events) and all-cause mortality (14 years; 724 deaths). For both self-reported AC and EtG, nonsignificant trends were found toward J-shaped associations between AC and CVD, while neither self-report nor EtG was associated with all-cause mortality. Comparable associations with CVD events and all-cause mortality were found for self-report and EtG. This argues for the validity of self-reported AC in epidemiologic research.

Misclassification of abstainers

In a study of nondrinkers' reported reasons for abstinence having no interest in drinking and disliking the effects of alcohol were the most salient categories of reasons for lifelong abstainers; having no interest in drinking and health reasons were the most salient categories of reasons for current abstainers and health reasons were the most salient category of reasons for former problem-drinkers (Rosansky and Rosenberg, 2020). The "Sick quitters" fallacy leading to a reverse causality bias was proposed as explanation for the U-shaped curve by Shaper *et al.* (1988). In a prospective study of 7,735 middle-aged British men, 504 of whom died in a follow-up period of 7.5 years, there was a U-shaped relationship between alcohol intake and total mortality and an inverse relationship with cardiovascular mortality, even after adjustment for age, cigarette smoking and social class. However, the U-shaped alcohol-mortality relationships were present only in men with cardiovascular or cardiovascular-related doctor-diagnosed illnesses at initial examination. The data suggested that the observed alcohol-mortality relationships are produced by preexisting disease and by the movement of men with such disease into nondrinking or occasional-drinking categories. The Lancet used the occasion to bury the U-shaped curve as a myth (Editorial, 1988) disregarding studies like the Honolulu Heart study (Kagan *et al.*, 1981), where the six-year CHD incidence rate in true never drinkers was 45% higher than in current drinkers. The journal had long suspected that "there is more to the U-shaped alcohol-mortality curve than meets the eye" and expressed worry that the drinks industry had been quick to latch on to the good news that moderate levels of AC have a protective effect on especially cardiovascular mortality. The observation that "men who do not drink" include a considerable proportion of ex-drinkers who have a high prevalence of ill health made it "abundantly clear" to Wannamethee and Shaper (1988) "that the general category of nondrinkers, which includes a large proportion of ex-drinkers, should not be used as a baseline against which to measure the effects of alcohol consumption".

Doll and Peto (1995) did not agree that nondrinkers were an inappropriate reference group:

> In our prospective study of mortality in relation to use of alcohol 12 000 British male doctors, who had been born in 1900-1930, were asked in 1978 what they then drank, and over the next

13 years one third of them died of various causes. After standardisation for age and smoking the mortality from ischaemic heart disease was about one third lower among those who had said that they usually had a few drinks a day than among those who had said that they did not drink at all ($P < 0.0001$). The higher mortality from ischaemic heart disease among the self-reported non-drinkers cannot be attributed to the inclusion of some heavy drinkers, or former heavy drinkers, among them because even the highest category of alcohol use was not associated with any material increase in cardiac mortality. Moreover, for the reasons discussed in our paper, among the "non-drinkers" the proportion thus misclassified is likely to be only a few per cent.

In a report of 23 years' observation of the 12,000 male British doctors (Doll *et al.*, 2005) overall mortality during the past decade of the study (1991-2001) was significantly higher in the 239 recent ex-drinkers (men who had been current drinkers in 1978) than in the never-drinkers or current drinkers, while the mortality of long-term ex-drinkers (men who were ex-drinkers in 1978 as well) was similar to that of never-drinkers. Thus the effect of "reverse causality," that is, a tendency for some drinkers who have developed a life-threatening disease to become ex-drinkers because of the disease, seems to wear off within a decade.

In a comment on the problem that some earlier studies had failed to separate former drinkers including "sick quitters" from lifelong abstainers Klatsky (2008) reported on a proposition to use infrequent drinkers as an alternative to lifelong abstainers as referent category. Lifelong abstainers were defined as noncurrent drinkers who reported having "no alcoholic beverages during the past year" and "never or almost never before the past year". A current infrequent drinker category was created by the option "less than 1 (drink) per month (special occasions only)." Among 56,926 men, 7.2% were lifelong abstainers, 4.2% former drinkers and 14.2% infrequent drinkers; among 72,008 women, these proportions were 15.8% lifelong abstainers, 2.5% former drinkers and 26.8% infrequent drinkers. In analyses of various outcomes, including total mortality, Klatsky found no or trivial differences in risk between persons classified as infrequent drinkers and those classified as lifelong abstainers: adjusted hazard ratios for total mortality (vs "lifelong abstainers") were 1.19 (95% CI 1.10–1.27) for former drinkers and 0.98 (0.93–1.02) for infrequent drinkers. The trivial difference between infrequent drinkers and abstainers provides no support for the suggestion that lifelong abstainers have a spuriously increased risk related to inclusion of some actual past drinkers.

The same pattern was found in an analysis of data from National Health Interview Surveys (Mukamal *et al.*, 2010). Compared with lifetime abstainers, summary relative risks were 0.95 (95% CI 0.88–1.02) among lifetime infrequent drinkers, 1.02 (0.94–1.11) among former drinkers, 0.69 (0.59–0.82) among light drinkers, 0.62 (0.50–0.77) among moderate drinkers and 0.95 (0.82–1.10) among heavy drinkers.

Systematic misclassification of abstainers

Reasonable fear of problems consequent to encouragement of moderate drinking contributes to reluctance to accept any benefit from alcohol. Skepticism is fueled by the failure of some studies to separate ex-drinkers from lifelong abstainers in the referent group, and Fillmore *et al.* (2006) used "rigorous operational definitions" based on Shaper *et al.*'s "sick quitter" hypothesis to examine 54 prospective studies evaluating alcohol's association with all-cause mortality (including 35 studies evaluating CHD mortality) for systematic misclassification error by including as "abstainers" many people who had reduced or stopped drinking – a phenomenon associated with aging and ill health. Two errors were evaluated: the inclusion of former drinkers and of occasional drinkers in the abstainer category. Studies without either error did not show abstainers to be at higher risk of all-cause mortality (n = seven studies) and CHD mortality (n = two studies) than were "light" or "moderate" drinkers. The results suggested that the protective effect of alcohol for CHD may have been exaggerated by systemic misclassification of abstainers in most epidemiological studies to date.

An example of the "rigorous operational definitions" used by Fillmore *et al.* to exclude studies owing to misclassification error is the word "never" or "almost never." In some occasions abstainers were defined, in part, as never or almost never drinking. Fillmore *et al.* regarded "Almost never" as highly subjective, suggesting that very infrequent drinkers might have been included in the abstainer group. As referred earlier Klatsky (2008) found no or trivial differences in risk between persons classified as infrequent drinkers and those classified as lifelong abstainers, whereas Mukamal *et al.* (2010) found similar risk of CVD mortality among lifelong abstainers, lifelong rare drinkers and former drinkers. At a panel discussion (Panel Discussion I, 2007) chaired by R. Curtis Ellison as part of an international symposium on the harms and benefits of moderate drinking, the following points were made as response to Fillmore's hypothesis of abstainer misclassification:

- Mittleman said that most of the harmful effects from moderate drinking that Fillmore demonstrated were related to cancer and that, in fact, prospective studies also show such adverse effects.
- Ellison pointed out that in analyses among the generally light drinkers in the Framingham Heart Study (where there are repeated assessments of alcohol intake), similar results are usually found regardless of whether one uses alcohol data assessed at baseline, average data over time, or the most recent updated data prior to the occurrence of CHD as the exposure variable.
- Wannamethee stated that heavier drinkers are more likely than others to stop drinking completely at some point in their drinking career; as people age, many of them become light drinkers.
- Klatsky commented: "We all agree that 'sick quitters' are inappropriate as controls; but I am not concerned about including occasional drinkers in the referent group. Our own studies find that about 20% of the drinkers consume alcohol infrequently, perhaps once a month, and we have consistently found that these infrequent drinkers have essentially the same risk as lifetime abstainers."
- Rimm said that his own studies had found that using light drinkers (rather than abstainers) as the referent group still yielded a dose-response curve of increasing protection against CHD with increasing AC.

The conclusion of the panel discussion was that the "rigorous" criteria used by Fillmore *et al.* had inappropriately excluded many solid studies. Ten years later, Stockwell *et al.* (2016) extended the exploration of presence of misclassifying of former and occasional drinkers as abstainers and other potentially confounding study characteristics to 87 studies with a total population of 3,998,626 individuals among whom 367,103 deaths were recorded. Without adjustment, meta-analysis of all 87 included studies replicated the classic J-shaped curve, with low-volume drinkers (1.3–24.9 g ethanol per day) having reduced mortality risk: RR = 0.86 (95% CI 0.83–0.90). Occasional drinkers (<1.3 g per day) had similar mortality risk: RR = 0.84 (0.79–0.89), and former drinkers had elevated risk: RR = 1.22 (1.14 – 1.31). After adjustment for abstainer biases and quality-related study characteristics, no significant reduction in mortality risk was observed for low-volume drinkers: RR = 0.97 (0.88 – 1.07). Of the 87 studies, only 13 strictly coded lifetime abstainers (and not quitters) as the reference group. An analysis of these studies did not find a statistically significant difference comparing lifetime abstainers with everyday drinkers, and only those who drank at least 65 grams of alcohol a day had an increased risk of death. Stockwell *et al.* refined their model further, excluding "lesser quality studies," to consider only seven studies: the results were unchanged. They then excluded one more study that had results heavily favoring alcohol; the remaining six studies suggested that people who drank 2–3 drinks a day had a slightly elevated risk of death, whereas those who drank 1–2, or 3–4.5 drinks a day, did not.

If the results of that analysis were valid you might drink up to just below 65 grams of alcohol a day and still have the same mortality risk as a nondrinker – a conclusion that is hardly plausible. Stockwell *et al.* used the same selection criteria as Fillmore *et al.*, demonstrated earlier to be invalid and did not acknowledge that the "errors" that had been proposed in 2006 have been adjusted for in most recent reputable investigations without changing overall results (Barrett-Connor *et al.*, 2016). Stockwell *et al.* had identified 2,575 studies on the subject and analyzed only 87; however, even so they found reasons to exclude almost all of these 87 studies and reached the conclusion of no significant protection for low-volume drinkers based on a very small number of publications. In some of their analyses, only six or seven studies remained after exclusions were made. Stockwell *et al.* also ignores an immense amount of experimental data that have described the mechanisms by which light/moderate alcohol intake decreases the risk of CVD and mortality.

A variant of the "sick quitter" argument is that abstainers may have a greater burden of ill health than moderate drinkers, regardless of their previous drinking status. However, most longitudinal studies exclude people who have evidence of illness at the time they are enrolled into the study (Marmot and Brunner, 1991). Among the 276,802 men enrolled in the American Cancer Society cohort and followed up for 12 years, 33% were classified as sick at enrollment by using a very broad definition of ill health (Boffetta and Garfinkel, 1990). Among the healthy remainder, the higher incidence of CHD in nondrinkers compared with moderate drinkers was clear as was the conclusion by the authors:

> The hypothesis that the U- or J-shaped relation between alcohol drinking and total and CHD mortality is caused by the inclusion of diseased subjects into the nondrinker category was refuted by the present study.

The hypothesis that never-drinkers might differ systematically from drinkers in ways that are difficult to measure, but which might be relevant to disease causation, was used by Wood *et al.* (2018) in an extreme variant of abstainer misclassification: they amputated the left rising arm of the J-shaped curve by eliminating nondrinkers from their analysis. The stated reason for eliminating nondrinkers were notable differences in baseline characteristics compared with current drinkers. It is questionable, however, whether trivial differences like the approximate 3% difference in diabetes status between never-drinkers and drinkers will affect the outcomes, and it is possible to adjust for these confounders, as was already done for the analyses among drinkers (Astrup *et al.*, 2018). The reader has to turn to page 31 of the study's appendix to locate graphs where the J-shaped association has been restored for cardiovascular events and all-cause mortality: with nondrinkers included the study by Wood *et al.* is in accordance with existing evidence, as they found that the mortality risk of nondrinkers is 20% higher than those who drink 100 g alcohol per week and similar to the risk of those who drink 330 g per week. Wood *et al.* also concludes that all-cause mortality is higher in people consuming 100–200 g alcohol per week than in people consuming 0–100 g alcohol per week. However, the data and graphs on page 38 of the appendix suggest that this is only true for people who either consume alcohol twice a week or less or who are binge-drinkers or prefer beer or spirits. For those who consume alcohol more often than two days per week or drink wine or do not engage in binge drinking, consuming up to 200 g alcohol per week does not seem to increase mortality compared to nondrinkers.

Aspects of drinking patterns

Many cohort studies examining the effects of alcohol lack information on drinking patterns with regard to frequency of drinking (regular moderate versus binge drinking), beverage type (wine, beer or spirits) and drinking with or without meals. The results of the Whitehall II Cohort Study confirmed a U-shaped relationship between volume of alcohol consumed per week and outcome (Britton and Marmot, 2004): compared to those who drank moderately (10–80 g alcohol/week), nondrinkers and those drinking more than 248 g/week had

approximately a twofold increased risk of mortality. The optimal frequency of drinking was between once or twice a week and daily, after adjustment for average volume consumed per week. The Male Health Professionals Study (Mukamal *et al.*, 2003) found that cardioprotection seemed more strongly related to frequency of intake than to amount of alcohol ingested. As compared with men who consumed alcohol less than once per week, men who consumed alcohol three–four or five–seven days per week had decreased risks of myocardial infarction (MI): multivariate relative risk, 0.68 (95% CI 0.55–0.84) and 0.63 (0.54–0.74), respectively. The risk was similar among men who consumed less than 10 g of alcohol per drinking day and those who consumed 30 g or more. In Finland, drinking six or more bottles of beer in one session was associated with a more than twofold increased risk of cardiovascular mortality compared to drinking less than three beers in one session, adjusted for total volume (Kauhanen *et al.*, 1997). Analyses from the large Danish Diaries and Health Study (Tolstrup *et al.*, 2004, 2006) found large differences in all-cause mortality and CHD as a consequence of drinking pattern with large advantages of a steady intake compared to a binge like intake, even when the total weekly amount of alcohol was the same, in both men and women.

In a quantitative meta-analysis, Roerecke and Rehm (2014) found a clearly J-shaped relationship of average AC and CHD with lifetime abstainers as the reference group. Drinkers with average intake of $<$30 g alcohol/day and no episodic heavy drinking had the lowest CHD risk: RR 0.64 (95% CI 0.53–0.71). A meta-analysis (Roerecke and Rehm, 2010) examining drinking patterns among current drinkers (excluding those with average total alcohol intake of $\geq$60 g/day) found a significant higher risk for episodic heavy drinkers compared with moderate regular drinkers: a pooled RR = 1.45 (95% CI 1.24–1.70). It may be concluded that average AC is not sufficient to describe the risk relation between AC and IHD; it is essential to evaluate the pattern of drinking as well.

In the Mediterranean alcohol-drinking pattern wine is drunk in modest amounts as an accompaniment to food (Boban *et al.*, 2016). Jones *et al.* (1997) found that drinking ethanol (0.30 g per kg) after eating a meal, regardless of the nutritional composition, caused a pronounced lowering of the peak blood alcohol concentration and a marked decrease in area under the curve compared with drinking on an empty stomach. The rate of disposal of ethanol was boosted when there was food in the stomach: the time required to eliminate ethanol from the blood was shortened by 1–2 h compared with drinking on an empty stomach.

In exploring the French Paradox, it has been suggested that wine may have beneficial effects additional to that of ethanol. Correlational studies suggested that there may be different effects of the different types of alcoholic beverages, by showing that mortality from coronary heart disease was lower in countries where wine was the predominant type of alcohol (St Leger *et al.*, 1979), than in countries where beer or spirits were the beverages mainly ingested. A number of cohort studies have supported the beneficial effect of a preferential wine drinking pattern by showing that wine drinkers were at lower mortality than beer and spirits drinkers. In the Copenhagen City Heart Study (CCHS), the risk of death from cardio- and cerebrovascular disease was lower amongst drinkers of three–five glasses of wine per day: RR = 0.4 (95% CI 0.2–0.8) than amongst non-wine drinkers (1.0). Drinking three – five beers per day implied a relative risk of 0.7 (0.6–0.9) as related to not drinking beer (Grønbæk *et al.*, 2000). Wine intake was positively correlated with social class variables in the CCHS but the apparent protective effect of wine, with regard to mortality, was not significantly weakened when controlling for this factor.

Diet may be a substantial confounder in CCHS as Danish wine drinkers have a healthier diet than beer drinkers (Johansen *et al.*, 2006). Grønbæk and Sørensen (2002) have quantitatively assessed in a theoretical sensitivity analysis whether diet is a plausible confounder of the relation between wine intake and mortality by applying the method to previously reported CCHS-data (Grønbæk *et al.*, 1995). In the present analysis, the

unadjusted odds ratio for the 50 deaths among the 257 exposed (*i.e.* those who had a daily intake of wine) and the 780 deaths among the 2,553 unexposed (non-wine drinkers) was estimated as 0.6. The odds ratios for the relation between wine intake and mortality, adjusted for a hypothetical confounder, have been calculated for various scenarios and it appears that even a very strong confounder (odds ratio = 0.3 or 0.1) would have to exhibit a very uneven distribution among wine drinkers and non-wine drinkers to fully explain the findings noted previously.

A meta-analysis on the relationship between wine, beer or spirit consumption and vascular events evidence from 16 studies confirmed a J-shaped relationship between wine intake and vascular risk (Costanzo *et al.*, 2011). A significant J-shaped relationship was apparent for wine: maximal protection 31% (95% CI 19–42%) observed at 21 g alcohol/day, and from 13 studies, a J-shaped relationship was found for beer: maximal protection: 42% (19–58%) at 43 g alcohol/day. In the ten studies on spirit consumption and vascular risk, no J-shaped relationship was found. The ethanol content in a serving of wine is similar to that in a serving of beer, and results from metabolic studies suggest that the effects of these beverages on lipid and hemostatic factors are similar. Thus, if this apparent difference in beverage-specific relative risks is true, then components in wine other than ethanol must confer substantial additional benefit. An alternative explanation might be that beer and wine have the same physiological effect, but differences in the risk factor patterns among beer and wine drinkers might create the appearance of a difference in coronary heart disease risk (Rimm and Stampfer, 2002).

Confounding

Alcohol is one of the most investigated risk factors for CHD (Mente *et al.*, 2009) and concerns about the explanation of the lower risk of CHD in alcohol drinkers have been expressed from the beginning; few epidemiologic observations have been scrutinized for bias as thoroughly as the apparent CHD benefit from alcohol. Confounding is often a concern when risks vary by less than two-fold: an important epidemiologic principle is that weak associations can often be explained by one or more confounding variables (Doll, 2002). Many risk factors for CHD have been identified, e.g. age, smoking, BMI, education, physical activity, energy intake and intake of saturated fat and cholesterol. Cigarette smoking is correlated positively with both lighter and heavier drinking in most populations (Klatsky *et al.*, 1974); in the case of CHD, it is likely that residual confounding from smoking diminishes apparent benefit of moderate AC. Inclusion of potential confounders had little influence on the pooled risk estimates from meta-analyses examining drinking versus non-drinking status (Ronksley *et al.*, 2011), and most alcohol epidemiology studies have found that when models are controlled for confounding, the resulting changes in relative risk estimates were small when compared to models that did not control for confounding (Rehm, 2000). The difference between control for confounding and the consequence of effect modification is illustrated by large studies with data that allow stratification on, e.g. sex or age (Hvidtfeldt *et al.*, 2010).

Aside from adjustment for confounding, many studies have reported stratified analyses by important risk factors for CHD. Pedersen *et al.* (2008) investigated fatal CHD in the Copenhagen City Heart Study and found an inverse relationship for both physical activity level and average AC in a low consumption cohort. Within each level of physical activity, nondrinkers had the highest hazard rate (HR) of fatal CHD, and within each category of weekly alcohol intake, the physically inactive had the highest HR of fatal CHD. Thus, the lowest HR of fatal CHD was observed among the physically active moderate or heavy drinkers (range 0.50–0.56) and the highest HR among the physically inactive nondrinkers (reference group). Likewise, the lowest HR of all-cause mortality was observed among the physically active moderate drinkers and the highest HR among the physically inactive nondrinkers and heavy drinkers.

Socioeconomic position (SEP) is relevant to behaviors, exposures and susceptibilities that may influence health, such as social support, financial resources or the knowledge, awareness and determination required to actively follow a healthy lifestyle or consult a physician if needed. An analysis of Norwegian population-based health surveys found that moderately frequent consumers of alcohol had a lower risk of CVD mortality compared with infrequent consumers, and Degerud *et al.* (2018) observed that this association was more pronounced among participants with higher SEP throughout their life course. Frequent binge drinking was associated with a higher risk of CVD mortality, but it was more uncertain whether the risk differed by life course SEP. It was unclear if these findings reflect differential confounding of AC with health-protective or damaging exposures, or differing effects of alcohol on health across socioeconomic groups. A prospective multicohort study including 116,043 people free of major disease at baseline was performed to estimate the association between healthy lifestyle and the number of disease-free life-years (Nyberg *et al.*, 2020). Four baseline lifestyle factors (smoking, body mass index, physical activity and AC) were each allocated a score based on risk status: optimal (2 points), intermediate (1 point) or poor (0 points) resulting in an aggregated lifestyle score ranging from 0 (worst) to 8 (best). There was a linear association between overall healthy lifestyle score and the number of disease-free years, and findings did not support a synergistic role for any specific combination of lifestyle factors; rather, a normal BMI, never smoking, physical activity, and moderate AC appear to be associated with healthy life expectancy in a way that is consistent with an additive effect. Confounding by socioeconomic influences was an unlikely explanation for the findings, as the results were replicable across socioeconomic hierarchy.

Moderate alcohol intake is related to self-perception of good health (Poikolainen *et al.*, 1996) and there is some evidence that healthy behaviors tend to cluster making moderate, sensible drinkers more likely to adopt a sensible lifestyle. A meta-analysis of 15 cohort studies comprising 531,804 people found that the number of healthy lifestyle behaviors, which people adopt, is inversely related to the risk of all-cause mortality (Loef and Walach, 2012). Compared with individuals who have an unhealthy lifestyle (smoking, no or excessive AC, no physical exercise, unhealthy diet, obese), those with four or more healthy behaviors have an overall risk of mortality that is lower by 66%. Even in men (8,867 participants of the Health Professionals Follow-Up study free of major illness at baseline) already at low risk on the basis of body mass index, physical activity, smoking and diet, moderate alcohol intake is associated with a further lowering of risk for MI (Mukamal *et al.*, 2006). In their study, compared with abstention, the hazard ratios for MI were 0.98 (95% CI 0.55–1.74) for alcohol intake of 0.1 to 4.9 g/d, 0.59 (0.33–1.07) for 5.0 to 14.9 g/d, 0.38 (0.16–0.89) for 15.0 to 29.9 g/d and 0.86 (0.36–2.05) for 30.0 g/d or more.

While several possible confounders have been controlled for in comparisons of life-long abstainers and light drinkers, there still remains the possibility that the risk difference between abstainers and light drinkers could be explained by some as yet uncontrolled factor. Psychosocial factors, such as emotional support, negative affect, hostility and work satisfaction, have been found to vary by alcohol intake (Roberts *et al.*, 1995) and nondrinkers (no alcohol in past 12 months) have been found to be more likely to have current financial hardships, poor social support, recent stressful life events, lower scores of extraversion, lower fun-seeking scores and lower drive (Rodgers *et al.*, 2000). To find possible candidates for an unknown confounder, Poikolainen *et al.* (2005) compared the prevalence of several putative coronary heart disease risk factors between never-drinkers and light drinkers in a large working-age sample from Finland. Moderate drinking is an important part of the cultural norm in most western societies and the overall prevalence of abstainers in the study was small (4.1%) but similar to what has been found typically in many European populations. Because the prevalence was low, one could suspect that never-drinkers were more deviant from the general population in Finland; however, of the 16 comparisons under study, only 7 showed significant differences between never-drinkers

and light drinkers (≤1 drink a day). Five of the differences favored never-drinkers and only two showed a disadvantage: very low BMI and low leisure-time physical activity. In contrast, smoking, sleep disturbances, trait anxiety, effort–reward imbalance and dependent life events were less common among never-drinkers than among light drinkers. Compared with never-drinkers, the lowest relative risk of CHD has been found to be 0.78 at the level of 29 g/day according to a meta-analysis of 51 high-quality studies (Corrao *et al.*, 2000). If an unknown factor explained the lower CHD risk among moderate drinkers compared with never-drinkers, it should be strong and highly unevenly distributed between the two groups. To observe a risk ratio of 0.78 because of an unknown confounder, if alcohol intake had no real effect, the unknown factor should, for example, increase the CHD risk twofold and its prevalence should be 35% among light drinkers and 75% among never-drinkers. None of the risk factors studied by Poikolainen *et al.* was a likely candidate for such an unknown confounder.

Conclusion: confounding or causality?

Methodological problems such as imprecise categorization of alcohol intake, the composition of reference group, potential biases, residual confounding and reverse causation do not seem to overcome the J-shaped alcohol-CDH-association observed in most epidemiologic studies. The observational evidence – used when randomized controlled trials may be infeasible or raise ethical concerns – indicates a casual association in accordance with the conclusion in favor of causality drawn by Doll *et al.* (1997). He concurred with the expert advisors to the European Office of the World Health Organization that "drinking moderate amounts of alcoholic beverages is likely to reduce the risk of CHD for some populations" (Edwards *et al.*, 1994), and in his Fisher Memorial Lecture, given at Oxford on 29 October 2001, Sir Richard Doll offered a plausible explanation of how the benefit might be produced (Doll, 2002):

> [...] the experimental finding that ethanol by mouth increases the blood level of high-density lipoprotein and lipoproteins A1 and A2, reduces slightly the blood levels of low-density lipoprotein and fibrinogen, and reduces the aggregability of platelets – you could hardly ask any antithrombotic drug to do more [...] That the inverse relationship between ischemic heart disease and the consumption of small or moderate amounts of alcohol is, for the most part, causal should, I believe, now be regarded as proved.

However, for a number of reasons meta-analyses of studies involving alcohol use and all-cause mortality which are based on the usual large cohorts will give risk curves which are not representative for the general population of any country (Rehm, 2019). Gold-standard evidence by which to judge the health effects of limited AC remains elusive, introducing serious difficulty in considering the safety of AC. To do so, physicians and policymakers must consider the population, dose and context of AC and the end-point of interest. The need for large-scale randomized trials to clarify the causal relation and to give greater insight into the health effects of population-wide AC has recently been argued by Mukamal (2020).

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