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Editorial Commentary: Alcohol consumption and cardiovascular health: The challenges of complexity

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As Rehm and Roerecke [1] allude to in their brief, focused review, the effects of alcohol when consumed within generally established limits (up to 7 drinks per week among women and up to 14 drinks per week among men) have been studied in formal epidemiological studies for roughly a century [2]. These studies have generally shown that excessive alcohol consumption is harmful and associated with increased incidence of several different diseases and all-cause mortality, while light-to-moderate consumption is associated with reduced risk of cardiovascular diseases and, as a consequence, of all-cause mortality—the J-shaped curve [3–5]. Despite this remarkably long and extensive track record of studies, now buttressed with dozens of short-term physiological experiments, the nature of the J-shaped curve continues to spur discussion and interest.

Following from the authors, we offer a few bits of perspective on chronic heavy, irregular heavy, and nonheavy drinking. To borrow from convention, and for brevity, we term these heavy, binge, and moderate drinking.

The cardiovascular effects of heavy drinking are widely agreed upon, even if they rest upon a smaller body of evidence than do those of moderate drinking. The hallmark cardiovascular consequence of heavy drinking is alcoholic cardiomyopathy, now thought to be a direct consequence of alcoholic cytotoxicity. However, the prevalence of alcoholic cardiomyopathy among individuals with even severe alcohol use disorders (AUD) is far from 100% (13% using a cut-off left ventricular ejection fraction of 50% in one well-done series) [6], and virtually no long-term prospective studies to establish its incidence exist. As a result, the co-factors that lead only some individuals with AUD to develop cardiomyopathy remain unclear; while absolute dose of alcohol is clearly associated with cardiac impairment, case–control studies implicate genetic predisposition as well [7]. Perhaps most interestingly in the context of heavy and moderate drinking, cardiac function can improve in patients with alcoholic cardiomyopathy not only with abstention, but even with a return to moderate drinking [8].

Rehm and Roerecke [1] also cite the potential adverse cardiovascular effects of binge drinking, although these have been far less well studied than those of moderate drinking. As the authors note, this form of drinking has been associated with adverse events both as an acute trigger and in longitudinal studies, but neither form of evidence is without nuance. In acute triggering studies, dose and timing both matter; even moderate drinking appears to increase risk of triggering an acute ischemic event within the following hour, but moderate doses lower risk in the ensuing day while heavy doses increase risk [9]. Because many of these studies use case-crossover methodology that compares exposed and unexposed time within an individual, and hence are immune to confounding by stable risk factors like age, sex, socioeconomic status, or chronic disease [10], they provide strong evidence that moderate and heavy drinking may well have

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directionally opposite effects on ischemic cardiovascular disease—a different form of the J-shaped curve.

The authors make several important observations about the evidence for a J-shaped curve on long-term risk of cardiovascular disease [1]. In particular, they cogently describe the difficulty of using instrumental variable analyses (Mendelian randomization) when those instruments (specifically genetic polymorphisms that alter the metabolism of ethanol) affect both episodes of binge drinking and usual alcohol consumption [11]. Of note, genetic analyses are also prone to their own forms of confounding when specific genetic variants tend to track with specific subpopulations (e.g., the *ADH1B* rs1229984 variant with individuals of East Asian and Middle-Eastern descent) [12]; this type of confounding can only be statistically addressed if genetic substructure is characterized in sufficient detail to identify the carriers of interest, which only variably occurs in most cohort studies.

Rehm and Roerecke also quite reasonably describe the classic controversies related to the choice of control groups and the sick-quitter hypothesis in studying moderate drinking. Of note, skeptics of the J-shaped curve have themselves been unable to agree on the most appropriate reference group, raising the spectre that no observational study could ever satisfy all objections simply because they are mutually incompatible [13,14].

The authors express the opinion that methodological biases tend to exaggerate the protective effect of moderate drinking, a point that bears some consideration. It neglects the profound association of even moderate drinking with prevalence and intensity of smoking, which is rarely sufficiently controlled in epidemiological studies. The authors also make one important simplification in their tabular review of moderate drinking, which suggests that most studies have specifically evaluated moderate drinking free of binging ("On average light-to-moderate drinking without heavy drinking occasions"). This is, unfortunately, not completely accurate and introduces a bias against moderate drinking. Since most binge drinking episodes occur among otherwise moderate drinkers [15], the observed effect of moderate drinking in most cohort studies represents the aggregated effect of both patterns despite their very different expected consequences.

Ultimately, the authors consider it impossible to determine causality of a protective effect of (moderate) alcohol on ischemic disease based on classic epidemiological research, a position that quite reasonably accords epidemiology a lower place in the hierarchy of causal inference than truly experimental research. The authors then strongly discourage not only any form of heavy drinking but also the initiation of (moderate) alcohol drinking because a safe alcohol consumption level, they argue, does not exist. We would agree that, even if low-moderate alcohol consumption reduces the risk of cardiovascular disease, life-long abstaining adults should not begin drinking for health reasons, simply because that scenario has not been assessed even in observational studies. A "safe" level of consumption seems, however, to be a quixotic target to meet as the authors have defined it, as they seem to require that moderate drinking be at least neutral for every health consequence, however rare, to be considered safe. In that respect, it is unclear if any dietary constituent could be considered safe. Additionally, they conclude that beneficial effects on cardiovascular risk could similarly be achieved with other lifestyle modifications, although moderate drinking has been associated with lower risk of myocardial infarction even among individuals who practice a healthy lifestyle [16].

At this time, while physicians and public policymakers wait for a long-term clinical trial to finally provide solid answers to the controversies surrounding moderate alcohol intake, and considering the currently available epidemiological evidence, we reiterate four key messages: (1) the choice to consume alcohol should be made on an individual basis, taking into account both its influence on health and individual's specific risk profile; (2) the hazards of even occasional binge drinking should be repeatedly highlighted and reinforced; (3) moderate drinking should only occur in the context of an otherwise healthy lifestyle and at appropriate occasions, such as with meals and after activities that require dexterity are complete; and (4) lifelong abstainers should not adopt drinking to improve their health. As Rehm and Roerecke note, alcohol consumption has a major but complex impact on cardiovascular diseases; alas, this complexity precludes any simple messages apt to be consistently true for all individuals.

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