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Physicians' prescription for lifetime abstainers aged 40 to 50 to take a drink a day are not yet justified

Thomas K. Greenfield and William C. Kerr

Professor Rubin's commentary (Rubin, this issue) concludes in effect that allowing for individual contraindications, based on overwhelming evidence of beneficial effects of moderate drinking "physicians should counsel lifelong non-drinkers at about 40 to 50 years of age to relax and take a drink a day, preferably with dinner." We wish to briefly present a number of reasons to be cautious in adopting this prescription at this stage. Rubin assembles an extensive, well-cited list of conditions such as cardiovascular disease (CVD) that epidemiological studies suggest may be reduced by 'moderate alcohol use.' However, this is a somewhat selective review that does not take up the matter of possible methodological issues that may introduce biases affecting the nadir seen in many observational studies. Notable among these is work spearheaded by Shaper and colleagues (Shaper et al., 1988) and later Fillmore (Fillmore et al., 2006). In a prospective study by Fillmore and colleagues (Fillmore et al., 2003) using NHANES I panel survivors between 1971–74 (then aged 22–49 and 50+) and 1982–84 whose death records were then followed 10 years to 1993, a key finding was that new drinkers who formerly abstained did not improve their chances for longevity (although not directly assessing the proposed 1 drink per day recommendation of Professor Rubin). Fillmore et al. (2006) conducted a meta-analysis of 54 published studies examining the degree to which systematic misclassification errors were present such as including as 'abstainers' many people who had reduced or stopped drinking, potentially due to ageing and ill health. Studies judged to be free of such errors found no significant all-cause or cardiac protection, suggesting alcohol's cardiac protection may have been over-estimated in observational studies. The authors noted limitations to their meta-analysis and stated that it was "only suggestive because [observational studies] cannot meet precise operational specification required to settle the matter of the potential existence of a cardiac-protective effect" (p 11). This only serves to emphasize the problem of taking as "overwhelming" the evidence from numerous epidemiological studies of a positive health benefit due to apparent reductions from moderate drinking via all-cause mortality, CVD, and other conditions. This line of work has been extended using scenario analysis with Canadian and Australian data, again finding no cardio-protective effects for the few studies deemed error free (Stockwell et al., 2007). Uncertainty regarding the relationship of alcohol use patterns and CVD has continued to be raised (Hansel et al., 2010).

Corresponding Author: Thomas K. Greenfield, Ph.D., Public Health Institute, Alcohol Research Group, 6475 Christie Ave., Suite 400, Emeryville, CA 94608, (510)597-3440, tgreenfield@arg.org.

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Recently, a new technique of “Mendelian randomization” has been employed to examine the causal role of alcohol in CVD taking the alcohol dehydrogenase 1B gene (*ADH1B*) and proposed as an unbiased approach to examine the effects of alcohol consumption in a study undertaken by a large consortium of genetic study groups (Holmes et al., 2014). This large-scale study involved 261,991 individuals of European descent in a meta-analysis of 56 epidemiological studies with over 20,000 coronary heart disease cases, over 10,000 stroke events (more than 4,000 ischaemic strokes), and over 14,500 diabetes type 2 cases. The authors noted the potential problems of abstainers including those with underlying poor health (Shaper et al., 1988) or other confounds involving light to moderate drinking and proposed the use of the *ADH1B* rs1229984 A-allele (directly genotyped in all samples) as the instrument. Data on carriers of either one or two copies of this allele (7% of sample) were compared to G-allele homozygotes as the reference. The A-allele carriers showed 17% less mean alcohol-intake volume based on self-reported consumption, lower odds of binge drinking, and greater odds of abstaining. No differential effect of *ADH1B* variation on lifestyle factors such as smoking was observed after stratifying by intake. Importantly, subdivision of drinkers into light (>0 to <55 g ethanol/week), moderate (55 to <166 g/week) and heavy (>166 g/week) showed the same CVD protective effect of the variant across all volumes, interpreted as suggesting no difference between rs1229984 A-allele carriers and non-carriers across levels in drinkers. A-allele carriers had lower odds of ischaemic stroke but no relationship was seen for Type 2 diabetes. The authors note the counterfactual that, given the U (or J) shaped associations in many observational studies, one would have expected the 17% reduction in intake below the typical nadir of 95 to 198 g ethanol intake/week to result in a small *increase* in risk (and above this a reduction), but instead the reductions were even across the whole drinking range. We argue, as did the authors, that Mendelian randomization design is less prone to a number of biases that have been identified in observational studies; the null results call into question the relevance of a cardio-protective effect of light-to-moderate drinking (Holmes et al., 2014). We note, however, that since the A-allele of *ADH1B* rs1229984 generates an alcohol dehydrogenase that is 40-times more active than the enzyme coded by the G-allele of *ADH1B* rs1229984, the mechanism by which the more active enzyme leads to overall reductions in ethanol intake also involves metabolic differences increasing acetaldehyde that could also influence cardiovascular disease (Israel, 2014).

Regardless of specific evaluations of particular CVD and all-cause mortality studies, we believe that Rubin’s commentary (Rubin, this issue) takes a too selective approach to the literature, one that emphasizes health benefits and minimizes harms and methodological challenges. It is well documented that even the report of being a lifetime abstainer may change in panel studies from one time to another (Rehm et al., 2008), making ascertainment difficult for researchers, let alone physicians. There are many reasons that underlie a patient’s choice not to drink, which may not be fully revealed to their physicians. Considering the quality of the evidence marshalled in the commentary, life-course drinker status misclassification issues are a major problem in the literature. Former drinkers are often combined with lifetime abstainers and many drinkers change patterns (and change reports of lifetime alcohol use behaviors) over time. In observational studies, even if former drinkers are separated, their removal from the drinker pool may still bias results on which

the protective effects are largely based if they abstain in response to health issues; similarly, lifetime abstainers cannot be considered a unitary category for a number of reasons. Although in the best studies, such as the Holmes et al. (2014) research, where cardiovascular biomarkers were included, in general, despite every effort being made to control for confounds, drinking status and patterns, as well as beverage preferences, are associated with many other health-related behaviors. Thus, all of the possible confounds cannot be fully addressed in observational studies.

As regards the commentary's cancer risk appraisal, it is again our concern that the review is selective. As a single example that is suggestive of effects at lower levels of consumption, we participated in a study based on two large datasets that indicated that daily consumption of 20 g ethanol (< 1.5 standard 14 g drinks) accounted for 26–35% of alcohol-attributable cancer deaths (estimated at 18,200 to 21,300 cancer deaths annually or 3.2 to 3.7% of all cancer deaths) in the United States (Nelson et al., 2013). To be sure, beginning drinking in later life would likely not contribute much to cumulative exposure, but it is important that effects at lower consumption levels may not be negligible. Thus, we disagree with the commentary's conclusion in relation to cancer that “all cause cancer mortality is not increased by light to moderate alcohol ingestion” (Rubin, this issue).

A caution also worth mentioning is the unintended consequences that a physician's recommendation could result in heavy drinking (despite the commentary's assertion that people would follow the one-drink-per-day recommendation, if given). For a long time it has been known that in the US population very few, even with a low overall volume of consumption, are regular light drinkers (Knupfer, 1987). This applies to older people too: among patients 60 and over in a large multisite primary care study, 15% of men regularly drank > 14 drinks/week and 12% of women > 7 drinks/week (Adams et al., 1996). Though fewer older women than men drink at all, or drink much, substantial proportions of both genders engage in drinking beyond the low-risk levels. Can one be sure that those abstainers in the targeted age groups who might begin to drink will follow low-risk drinking guidelines since they are likely to be in social milieus where other older adults may drink to excess? We believe simple recommendations might lead to unwanted outcomes. For example, we know that the ethanol content of drinks poured at home compared with on-premise establishments varies significantly, such that “one drink” could easily be two or three standard drinks, particularly for spirits and wine (Kerr et al., 2005; Kerr et al., 2008).

Lifetime abstainers are a diverse group and many abstain on religious grounds (Hilton, 1986; Michalak et al., 2007); these individuals may not be responsive to low-risk drinking recommendations and, further, might not appreciate receiving them from their doctors. Even among college students, a substantial number cite “upbringing” as a reason for not drinking or limiting drinking, e.g., “I was brought up not to drink”; “my religion discourages or is against drinking” (Greenfield et al., 1989). Lifetime abstainers later in life are likely to include a fairly large proportion of such individuals, a good number of the rest being likely to include those who believe their health or cognitive abilities would be adversely affected if they drank or resumed drinking. Should doctors dissuade them of this perhaps protective fallacy? Moreover, many older people are known to be prescribed multiple medications involving known or unknown interactions with alcohol (Satre et al., 2007)—often by

multiple specialists. Further current study is needed of the reasons for abstaining and ways to rapidly assess in the medical encounter all relevant contraindications, before moving ahead with the Rubin (this issue) proposal.

We are aware that advice from medical experts is often amplified and disseminated by commercial stakeholders in ways not easily anticipated or controlled. An example of evidence of the alcohol industry being alert for opportunities to promote its products by focusing consumers on alcohol's health benefits is the wine producers' application at the turn of the millennium to the Bureau of Alcohol, Tobacco and Firearms to include on bottles positive health messages (in addition to the federally mandated warning label). This led to hearings in several locations, including San Francisco (ATF Hearing, Notice 884, May 24, 2000). In this instance, subsequent to the hearings, the ATF decided that positive health messages would need to be fully disclosing of caveats and the state of the science behind them. Thus, to our knowledge, no simple positive health messages on containers were attempted thereafter. Recognizing, however, the potential for the diffusion of misinformation, we believe that advice for older, lifetime abstainers to drink daily could be taken by many enthusiastic drinkers to imply that it is healthy to expand their regular heavy drinking pattern to additional days.

In conclusion, we respectfully urge caution in prescribing drinking to abstainers, even lifetime abstainers, over 40 years of age. Because the recommendation to drink small amounts of alcohol regularly is for medical purposes, is proposed to be medically implemented, and involves a pharmacological intervention, it is our perspective that controlled, randomized trials should precede serious consideration of such a policy (Feinberg and Samet, 2005).

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