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Has the leaning tower of presumed health benefits from 'moderate' alcohol use finally collapsed?

The evolving epidemiological literature, including improved methodology for assessing causality in observational studies, is raising doubts about whether moderate alcohol consumption has a protective effect on health.

For several decades, most epidemiologists have agreed that 'moderate' (i.e. low average volume) alcohol consumption is protective against cardiovascular disease. Indeed, estimates of protective effects for prevalent chronic conditions such as heart disease, stroke and type 2 diabetes have been built into the international burden of disease estimates, including the Global Burden of Disease [World Health Organization (WHO)] project. In some countries, the assumption has also been incorporated into national drinking guidelines and economic estimates of the cost of alcohol use to communities [1]. It has led several authors to argue that alcohol may have a role as a potential therapeutic agent for some patients (e.g. [2,3]).

However, the evolving epidemiological literature and emerging new methodologies have raised serious doubts about the veracity of health benefits of low-dose consumption found in observational studies. That the observed protective associations may not be causal is suggested by the diverse and unlikely conditions for which such relationships have been identified (e.g. liver cirrhosis, fetal effects, the common cold) [4]. Other emerging evidence is also pointing increasingly to confounding [4,5] and selection bias [6,7] as important contributors to the J-shaped alcohol–health curve.

Fillmore *et al.* [7] grouped longitudinal studies on alcohol and health according to how 'an abstainer' was defined, as this is the key reference group to which all drinkers are typically compared. They found that studies excluding former and occasional drinkers from the abstainer reference did not show significant protection from moderate alcohol consumption. The theory is that as people age and become unwell they are more likely to quit or substantially reduce their alcohol consumption, leading to an exaggeration of the already poor pre-existing health profiles of life-long 'abstainers'. Liang & Chikritzhs applied a kind of 'intention-to-treat' principle in which former and current drinkers were combined, and both were compared with life-long abstainers to address selection bias. When the intention-to-treat adjustment was combined with adjustment for confounding, the observed disparity in health status between abstainers and low-dose drinkers was eliminated [8]

Mendelian randomization (MR) is a method in which genetic variation that could have no plausible association with typical confounding factors, but is associated reliably with exposure to a putative causal factor, can test the relationship between that causal factor and the outcome. The assumption is that the genotype itself has no direct effect on the outcome and no role in the outcome apart from a mediating effect via the causal factor. If the genetic variation turns out to be associated with the outcome, there is a reasonable presumption that this is through the putative cause.

An MR meta-analysis by Holmes *et al.* found that drinkers with a genetic variant linked with lower consumption among those consuming $<=21$ g of ethanol daily had a *decreased* risk of cardiovascular events, with the protective relationship between the allele and cardiovascular events found only among drinkers, not among non-drinkers [9]. As the MR approach relies upon the random assignment of genes at meiosis to simulate the random allocation of participants to exposure, it resembles more closely a randomized controlled trial (RCT) than traditional observational studies. It is less susceptible to confounding, misclassification and reverse causation than prospective cohort studies, and has the added benefit of 'randomizing' subjects at birth to assess effects more effectively across the life-course.

Other MR studies have similarly contradicted findings from previous observational studies relevant to alcohol use, including outcomes as diverse as cognitive function [10], children's academic achievement [11], balance [12] and blood pressure [13], all finding no protective effect from low-dose alcohol.

MR studies have also suggested that putative biomarkers of coronary heart disease (CHD) found to be improved by low doses of alcohol in experimental studies, including increased high-density lipoprotein cholesterol, reduced C-reactive protein and reduced fibrinogen, may not in fact be causally related to CHD [14–16]. Moreover, more proximate indicators of vascular risk than serum biomarkers, such as coronary calcification and carotid intima-media thickness, have demonstrated only positive associations with alcohol at all levels of consumption [17,18]. If CHD is not related causally to these biomarkers, then they cannot explain plausibly the apparent protective effect of low-dose alcohol exposure on all-cause mortality, as any positive mortality effect is driven by cardiovascular outcomes.

Added to the mix is a recent RCT which found a health benefit from the 'Mediterranean diet' [19]. Because this trial was not randomized with respect to alcohol consumption, this suggests that the 'French Paradox' may not be due to wine consumption, but rather a constellation of dietary components.

The foundations of the hypothesis for protective effects of low-dose alcohol have now been so undermined that in our opinion the field is due for a major repositioning of the status of moderate alcohol consumption as protective. Because alcohol is a leading cause of health problems, social responsibility demands adoption of the precautionary principle, particularly in the absence of randomized studies (Mendelian or clinical) that support any protective effects.

We recommend that future estimates of the alcohol-related burden of disease and national drinking guidelines should no longer assume any protective effects from low dose consumption. We include in this the Global Burden of Disease estimates, as these can play a major role in either perpetuating the *status quo* or reforming the field. Guidelines should discourage drinking for health-related reasons. Health professionals should not recommend moderate alcohol consumption as a means of reducing cardiovascular risk for patients. At the policy level, the hypothesis of health benefits from moderate drinking should no longer play a role in decision making.

Declaration of interests

None.

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