Mendelian randomisation meta-analysis sheds doubt on protective associations between ‘moderate’ alcohol consumption and coronary heart disease

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Context
A protective association between low-dose alcohol and risk of coronary heart disease (CHD) has been suggested by meta-analyses of observational studies and experimental studies. Observational studies are, however, vulnerable to residual confounding and selection bias. Compared with observational studies, the Mendelian randomisation (MR) approach can mitigate confounding, is immune to reverse causation, and is consistent with intention-to-treat principles since ‘quitting’ a genotype is impossible.

Methods
The MR approach relies on the random assignment of genetic variants (genotypes) at meiosis to randomly allocate participants to exposures (eg, alcohol consumption) known to be affected by those genotypes. Holmes and colleagues applied an MR meta-analysis design to data from 56 studies, including 260 000 participants of European ancestry. A variant genotype of the alcohol dehydrogenase 1B gene (rs1229984 A-allele), which is associated with unpleasant side effects after drinking, and therefore associated with less drinking compared with those without the variant genotype, served as a proxy for reduced alcohol consumption. Carriers of the variant genotype were compared with non-carriers to examine risk of fatal and non-fatal CHD events (primary outcome), and stroke and diabetes (secondary outcomes).

Findings
Owing to the unpleasant side effects of alcohol use among rs1229984 A-allele carriers, and as expected given results obtained from past studies, participants with the variant genotype drank less alcohol, were less likely to binge drink and were more likely to abstain. The key findings for CHD were that, compared with non-carriers, risk of CHD among those with the variant genotype was significantly lower among all participants (OR=0.90; 95% CI 0.84 to 0.96) and drinkers (OR=0.86; 95% CI 0.78 to 0.94), but not among non-drinkers (OR=0.98; 95% CI 0.88 to 1.10). Among drinkers, protection from the variant genotype was consistent across consumption categories, including those consuming relatively low amounts of alcohol (0–210 g weekly).

Commentary
This meta-analysis is a critical new addition to our understanding of the relationship between alcohol and CHD. It suggests that alcohol consumption increases CHD events among all drinkers, including those who drink ‘moderately’. We concur with the authors’ conclusion that their findings challenge the concept that low-dose alcohol is cardioprotective. Although it is possible that the variant genotype could differentially associate with confounders, have an effect on CHD independent of alcohol, or have close genetic linkage to other genes with such effects, the fact that the variant genotype had no association with CHD among non-drinkers argues against these possibilities. Although no single study, genetic instrumental variable or scientific method is definitive in its own right, this adds to evidence suggesting the protective association between low-dose alcohol and CHD typically identified in observational studies may not exist.

Along these lines, the MR approach has been applied to other CVD-related conditions including hypertension, myocardial infarction and cognitive function, and to children’s academic achievement and balance. Contrary to observational studies, most (but not all) of these studies do not find protective effects for low-dose alcohol. Furthermore, research using the MR approach casts doubt on whether associations between CHD and various biomarkers such as high-density lipoprotein cholesterol, C reactive protein and fibrinogen are in fact causal. This is important because short-term experimental studies demonstrate that exposure to alcohol can affect those biomarkers in a way that is thought to be protective for CHD. In addition, non-MR studies find only a linear association between alcohol consumption and more proximate indicators of vascular risk than serum biomarkers, including coronary calcification and carotid intima-media thickness.

When assumptions are valid, MR studies are comparable with randomised controlled trials with an intention-to-treat approach. Most cohort studies work against an intention-to-treat approach by systematically excluding ex-drinkers from their true drinker groups. Since ex-drinkers may suffer more ill-health, this biases towards the selective retention of healthier drinkers. When an intention-to-treat approach has been simulated using data from large-scale observational studies, evidence for low-dose health protection is substantially reduced. Other systematic biases operate across the life course because unhealthy individuals are less likely to participate in cohort studies. The upshot is that the research literature suggesting cardioprotection is largely based on studies of healthy survivors who have not died from other competing causes.

In conclusion, the cardioprotective hypothesis for ‘moderate’ alcohol consumption is plagued by confounding, selection bias and increasingly implausible biological mechanisms, and the scientific pillars on which it is based appear increasingly shaky indeed.

Competing interests None.

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References
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