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RISK FACTORS

Reducing alcohol intake improves heart health

The association between excess alcohol consumption and increased cardiovascular risk is well established. By contrast, numerous observational studies have reported that light-to-moderate alcohol intake, compared with no intake, is beneficial for cardiovascular health. According to Caroline Dale and colleagues, who recently authored a paper on this topic,"observational studies often suffer from the limitation that the group of nondrinkers contain people who have quit drinking in response to ill-health, including cardiovascular disease. In addition, light-to-moderate drinkers display a range of healthy behaviours, such as better diet and more physical activity." Determining if light-to-moderate drinking is indeed linked to reduced cardiovascular risk, therefore, necessitates the removal of these confounding factors.

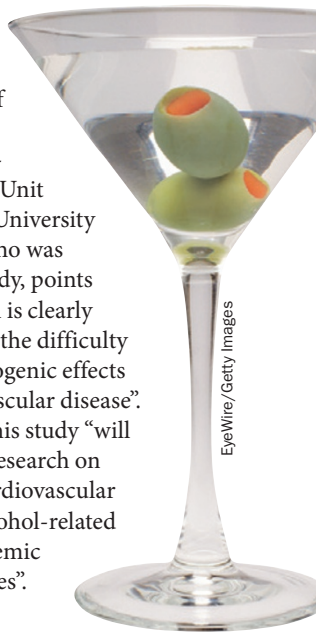
Caroline Dale, Michael Holmes and colleagues performed a Mendelian randomization meta-analysis of 56 epidemiological studies to investigate the causal role of alcohol in cardiovascular disease. Mendelian randomization analyses, made possible by the increasing number of genotyped cohorts in epidemiological studies, can avoid many limitations of observational studies because the allocation of genetic variants is a random process, and not modifiable by external influences. Carriers of the rs1229984 A-allele gene variant in the alcohol dehydrogenase 1B gene (*ADH1B*) exhibit faster alcohol metabolism compared to non-carriers, which can cause unfavourable symptoms including nausea and facial flushing. The *ADH1B* rs1229984 variant might, therefore, be associated with reduced alcohol consumption, and was used by Holmes *et al*. to examine the link between alcohol and cardiovascular risk. The primary end point was the incidence and prevalence of coronary heart disease.

Over 260,000 participants of European ancestry from 56 studies were included in the analysis. From questionnaire data, carriers of the rs1229984 A-allele were found to consume fewer units of alcohol per week, were less likely to participate in binge drinking, and were more inclined to abstain from alcohol than noncarriers. These behaviours were associated with more favourable indicators of cardiovascular health, including lower systolic blood pressure, BMI, and concentration of non-HDL cholesterol, compared with noncarriers. Levels of IL-6 and C-reactive protein were also significantly lower in carriers of the rs1229984 A-allele than in noncarriers. No association between the rs1229984 A-allele and HDL-cholesterol level was apparent. The investigators describe this finding as "unexpected", because researchers in previous studies have attributed the cardioprotective effect of alcohol to its ability to increase the level of HDL cholesterol.

Importantly, and in contrast to previous observational and experimental studies, the investigators reported that "individuals with a genetic predisposition to consume less alcohol had lower, not higher, odds of developing coronary heart disease regardless of whether they were light, moderate, or heavy drinkers". Specifically, carriers of the rs1229984 A-allele had a 10% lower risk of coronary heart disease (OR 0.90, 95% CI 0.84–0.96). In patients whose alcohol intake was light (0–6 units/week), moderate (7–20 units/week), or heavy (≥21 units/week), the rs1229984 A-allele conferred the same protective effect. These results indicate that no difference in the risk of coronary heart disease exists between carriers of the rs1229984 A-allele and noncarriers across all levels of alcohol intake. Individuals with the rs1229984 A-allele also had a reduced likelihood of experiencing an ischaemic stroke (OR 0.83, 95% CI 0.72–0.95); however, no association was found with combined stroke subtypes or type 2 diabetes mellitus.

The findings from this study challenge the 'U-shaped association' between alcohol intake and coronary heart disease established in previous observational studies, which suggests that light-to-moderate drinkers have a diminished cardiovascular risk, whereas heavy drinkers experience an increased risk, compared with nondrinkers. By contrast, the study investigators conclude that "individuals with a genetic variant associated with nondrinking and lower alcohol consumption had a more favourable cardiovascular profile and reduced risk of coronary heart disease than those without the genetic variant", suggesting that reducing alcohol intake benefits cardiovascular health, even in low-to-moderate drinkers.

Holmes *et al*. have expressed the need to expand their research across larger population studies, such as UK Biobank and the China Kadoorie Biobank study. Such a study "will help to minimize potential measurement error in alcohol exposure and provide sufficiently large numbers of coronary heart disease events to enable replication of our findings".



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Joaquim Fernandez-Solà from the Alcohol Unit Hospital Clinic at the University of Barcelona, Spain, who was not involved in the study, points out that "such research is clearly necessary considering the difficulty in evaluating the pathogenic effects of alcohol on cardiovascular disease". He also believes that this study "will clearly impact future research on how alcohol affects cardiovascular diseases, including alcohol-related hypertension and systemic inflammatory responses".

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Original article Holmes, M. V. *et al*. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ* **349**, g4164 (2014)