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Alcohol consumption and cardiovascular disease: a two-sample Mendelian randomization study with multivariable adjustment for smoking and body mass index

Genetic instruments for alcohol consumption tested against seven cardiovascular outcomes, with multivariable adjustment for smoking and BMI.

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ABSTRACT

Background. Observational studies of the association between alcohol consumption and cardiovascular disease may be confounded by correlated lifestyle factors. We used Mendelian randomization (MR) to assess the causal relationship between alcohol consumption and cardiovascular disease.

Methods. We conducted a two-sample MR using 35 genetic variants strongly associated ($p < 5\times10^{-8}$) with alcohol consumption from the GSCAN consortium, assessing seven cardiovascular outcomes: coronary artery disease (CAD), myocardial infarction (MI), atrial fibrillation (AF) and four stroke subtypes. Inverse-variance-weighted (IVW) MR with MR-Egger, weighted-median and weighted-mode sensitivity analyses was the primary analysis; multivariable MR (MVMR) was adjusted for smoking initiation and body mass index (BMI).

Results. The 35 instruments had a mean F-statistic of 76.2 (minimum 29.8), indicating strong instruments. Genetically predicted alcohol consumption showed borderline associations with CAD (OR 1.27, 95% CI 0.97–1.67, p = 0.079) and large-artery stroke (OR 1.61, 95% CI 0.96–2.71, p = 0.071) in univariate MR; CAD sensitivity analyses were significant for the weighted-median (OR 1.48, p < 0.001) and weighted-mode (OR 1.46, p < 0.001) methods. Substantial heterogeneity was detected (CAD: Q = 84.3, p < 0.001), the MR-Egger intercept indicated pleiotropy for MI (p = 0.045), and leave-one-out analysis identified rs1229984 (ADH1B) as highly influential. In MVMR using SNPs available for all three exposures (n = 28 for CAD, n = 30 for large-artery stroke), associations were attenuated for both CAD (OR 1.20, 95% CI 0.82–1.75, p = 0.355) and large-artery stroke (OR 1.26, 95% CI 0.69–2.30, p = 0.464).

Conclusions. After accounting for smoking and BMI, we found no evidence for independent causal effects of alcohol consumption on cardiovascular outcomes, despite robust associations in some sensitivity analyses. Observational associations may be explained by confounding from correlated lifestyle factors, consistent with the heterogeneity and pleiotropy seen in univariate analyses and the attenuation in MVMR.

KEY WORDS Mendelian randomization; alcohol consumption; cardiovascular disease; stroke; multivariable analysis; causal inference

> After multivariable adjustment for smoking and BMI, borderline univariate associations of alcohol with CAD (OR 1.27) and large-artery stroke (OR 1.61) were attenuated to the null.
>
> Two-sample MR · 35 GSCAN instruments · seven outcomes

Introduction

The relationship between alcohol consumption and cardiovascular disease (CVD) remains one of the most debated issues in public-health epidemiology. Observational studies have repeatedly reported J- or U-shaped associations, suggesting cardioprotective effects of moderate alcohol consumption alongside harm at higher levels [1, 2], but these associations are vulnerable to confounding by socioeconomic and lifestyle factors and to reverse causation [3].

Mendelian randomization (MR) investigates causality using genetic variants as instrumental variables [4]: because variants are randomly allocated at conception and generally unaffected by environmental confounders or disease status, they can provide causal evidence under three assumptions — relevance, independence of confounders, and exclusion restriction [5]. Previous MR studies of alcohol and CVD have been mixed [6, 7, 8, 9], partly reflecting differences in instrument selection, outcome definitions and handling of horizontal pleiotropy. A key limitation of univariate MR is its inability to account for correlated lifestyle factors such as smoking and adiposity, which we address here with multivariable MR.

Methods

We performed a two-sample MR using 35 genetic variants strongly associated ($p < 5\times10^{-8}$) with alcohol consumption from the GSCAN consortium as instruments, and assessed seven cardiovascular outcomes (CAD, MI, AF and four stroke subtypes) using publicly available summary statistics. Inverse-variance-weighted (IVW) MR was the primary analysis, with MR-Egger, weighted-median and weighted-mode sensitivity analyses; between-study heterogeneity was assessed with Cochran's Q and pleiotropy with the MR-Egger intercept (using the t-distribution for inference), and influential variants were identified by leave-one-out analysis. Multivariable MR adjusted for smoking initiation and body mass index (BMI), using the variants available for all three exposures. Instrument strength was summarized by the F-statistic.

Results

Instrument strength. The 35 instruments had a mean F-statistic of 76.2 (minimum 29.8), indicating strong instruments.

Univariate MR. Genetically predicted alcohol consumption showed borderline associations with CAD (OR 1.27, 95% CI 0.97–1.67, p = 0.079) and large-artery stroke (OR 1.61, 95% CI 0.96–2.71, p = 0.071); the other outcomes were null. For CAD, the weighted-median (OR 1.48, p < 0.001) and weighted-mode (OR 1.46, p < 0.001) estimates were significant (Table 1; Figure 1).

Heterogeneity, pleiotropy and influence. Substantial heterogeneity was detected for CAD (Q = 84.3, p < 0.001), the MR-Egger intercept indicated pleiotropy for MI (p = 0.045), and leave-one-out analysis identified rs1229984 (ADH1B) as highly influential.

Multivariable MR. Adjusting for smoking and BMI (n = 28 variants for CAD, n = 30 for large-artery stroke), the associations were attenuated towards the null for both CAD (OR 1.20, 95% CI 0.82–1.75, p = 0.355) and large-artery stroke (OR 1.26, 95% CI 0.69–2.30, p = 0.464).

Table 1. Primary two-sample MR and multivariable MR (MVMR) results for the two outcomes with borderline univariate associations.

Outcome	Method	OR (95% CI)	P
Coronary artery disease	IVW	1.27 (0.97–1.67)	0.079
	Weighted median	1.48 (1.20–1.81)	<0.001
	MVMR (adj. smoking, BMI)	1.20 (0.82–1.75)	0.355
Large-artery stroke	IVW	1.61 (0.96–2.71)	0.071
	MVMR (adj. smoking, BMI)	1.26 (0.69–2.30)	0.464

Figure S2. Two-sample MR estimates by method and outcome
(IVW, MR-Egger, weighted median, weighted mode)

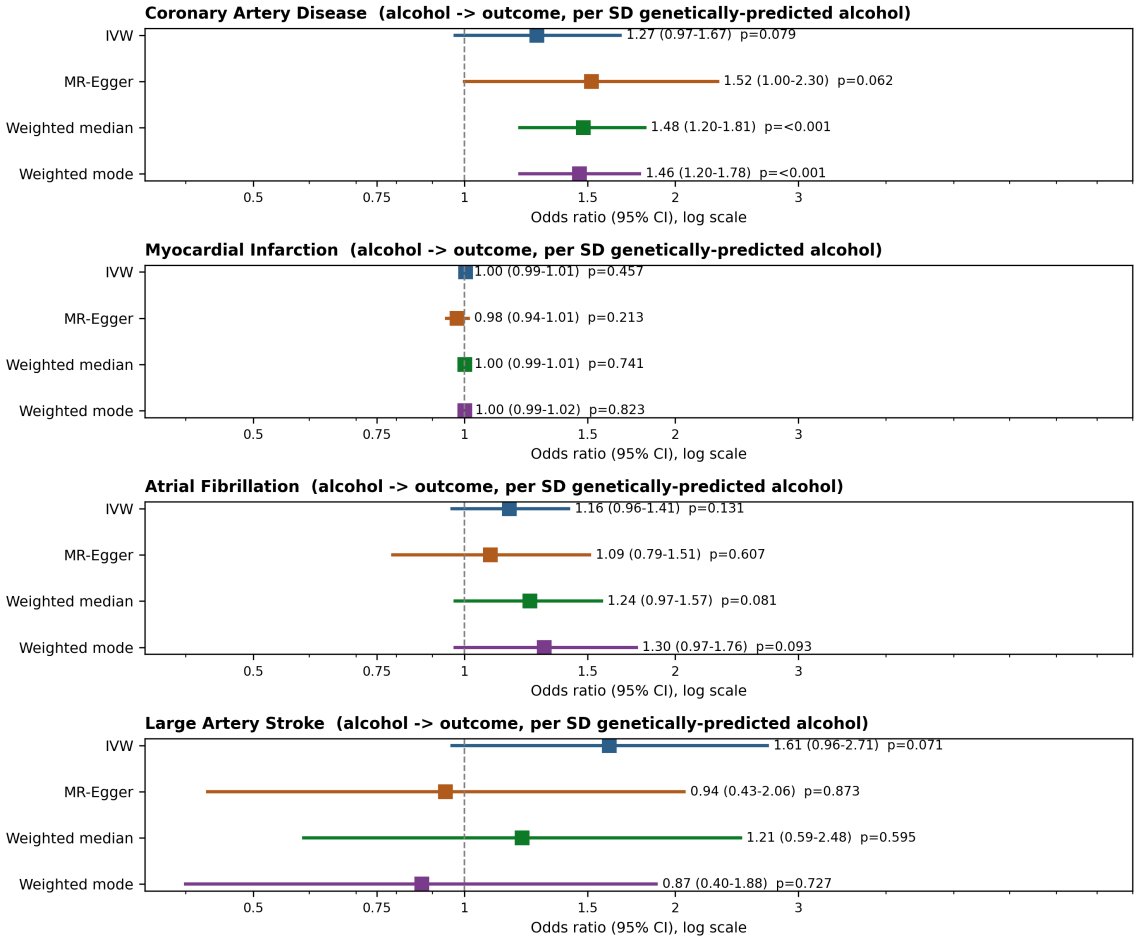

Figure 1. MR estimates by method. Forest plot of MR estimates (IVW, MR-Egger, weighted median and weighted mode) for each cardiovascular outcome.

Discussion

After multivariable adjustment for smoking and BMI, the borderline univariate associations of alcohol consumption with CAD and large-artery stroke were attenuated to the null, and we found no evidence for independent causal effects of alcohol on cardiovascular outcomes. The significant weighted-median and weighted-mode estimates for CAD, together with substantial heterogeneity, MI pleiotropy and the strong influence of the ADH1B variant rs1229984, indicate that the univariate signals are vulnerable to pleiotropy and confounding by correlated lifestyle factors.

Limitations. The analysis relies on summary statistics of predominantly European ancestry, binary-outcome MR rests on additional assumptions, and the exclusion-restriction assumption cannot be fully verified; residual pleiotropy may remain despite multivariable adjustment.

Conclusion. Genetic evidence does not support an independent causal effect of alcohol consumption on cardiovascular disease once smoking and BMI are accounted for, and the observational associations are most plausibly explained by confounding from correlated lifestyle factors.

Data availability

All analyses used publicly available genome-wide association summary statistics (GSCAN consortium for alcohol consumption; published outcome GWAS accessed via the IEU OpenGWAS database). No dedicated code repository is associated with this study; the analysis code is available from the authors on request.

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