The use of Mendelian randomization in alcohol research

To date, there have been no systematic reviews or meta-analysis of Mendelian-randomization-based alcohol research on all-cause mortality, cardiovascular disease, and total cancer. This document reflects IARD's initial work to synthesize published research in this area but should not be considered a comprehensive review.

WHAT IS MENDELIAN RANDOMIZATION?
Mendelian randomization (MR) is an emerging research method that uses genetic proxies to test if certain behaviors such as alcohol consumption are linked to health outcomes such as cardiovascular disease (CVD) or cancer.

WHAT HAVE RESEARCHERS SAID ABOUT THE APPLICABILITY OF MR TO ALCOHOL AND HEALTH RESEARCH?
MR has been promoted by some researchers as an alternative method able to establish causal relationships between drinking and health outcomes and to challenge the wider body of scientific evidence that finds a nonlinear relationship between alcohol and all-cause mortality and cardiovascular disease [1, 2].

However, other researchers have challenged the use of MR in alcohol research [3-7]. Stated concerns have included that results from recent MR studies have been inconsistent [5, 8] or have not met at least one of the core assumptions [3, 6, 7].

Researchers have also suggested a range of possible approaches to integrate the results of MR studies with the wider research literature [9, 10], including:

- conducting large randomized controlled trials [11]

- combining findings of MR with other research designs [3]

- giving precedence to observational and experimental research methods where results conflict with MR methods, due to the current unknowns associated with MR research design [6].

ARE RESULTS OF MR STUDIES CONSISTENT WITH THE WIDER EVIDENCE ON DRINKING AND HEALTH OUTCOMES?
Several MR studies have produced results that are inconsistent with the wider body of scientific evidence on the association between alcohol consumption and risk of cardiovascular disease, breast cancer, ovarian cancer, and cognitive decline [2, 12, 13].

Consistent experimental evidence that alcohol causally affects some types of cholesterol [14] has not been replicated in some MR studies [1].

To date, there has been a lack of systematic reviews or meta-analyses of MR-based alcohol research on CVD, all-cause mortality or total cancer. This may reflect the newness of the approach, the limited number of studies applying this methodology, and the difficulty of comparing results across different genetic proxies and outcomes.

WHAT ARE THE POTENTIAL STRENGTHS OF AN MR APPROACH?
Its proponents suggest that a Mendelian randomization approach may avoid some of the challenges of observational research methods, such as:

- **Reporting errors:** Individuals may estimate their current or past alcohol consumption in a biased manner, which may result in erroneous conclusions.

- **Confounding bias:** Genetic proxies are not subject to many of the confounding factors that can affect both alcohol consumption and disease risk, and can obscure the true relationship between drinking and health outcomes. However, it may not address environmental or epigenetic factors, which may introduce other potential confounding factors.

WHAT ARE THE LIMITATIONS OF AN MR APPROACH TO ALCOHOL RESEARCH?
An important general limitation is that multiple dimensions of drinking behaviors (frequency of drinking, average drinking volume, heavy episodic drinking (HED), and alcohol use disorders) often are not, but need to be, assessed. Some researchers have stated that current MR methodology cannot adequately assess the risk of low-volume consumption as it does not distinguish HED from total consumption [4, 5], which independently affects overall CVD and cancer risk [15, 16].

In addition, MR depends on several assumptions [17, 18], some of which are specific to alcohol research. The plausibility of some of these assumptions have been challenged:

- **Strong and reliable association with an exposure or behavior:** Some genetic variants used in alcohol-

related MR research have been reported to have limited associations with drinking behavior [5-7, 19].

- **No evidence of pleiotropy** (the outcome cannot be affected by the genetic proxy through any other mechanism): Some researchers have identified evidence of pleiotropy in alcohol-related MR studies. For example:

  ◊ Certain genetic variants may modify the relationship between alcohol consumption and cancer risk, violating a core condition of MR [3, 5], and extrapolating this risk for carriers of the genetic variant to non-carriers would breach guidelines for conducting MR research [20].

  ◊ Non-drinking carriers of a specific genetic variant were found to be more likely to have lower body mass index (BMI), lower blood pressure, and higher levels of education [1] – which all affect CVD risk - compared with non-drinkers without the genetic variant, which challenge the applicability of the MR method [3, 6, 7].

- **Sufficient sample size**: Very large sample sizes are needed in MR to detect modest effects on health outcomes among the subset of a population who carry specific genetic variants [16, 21]. Consequently, researchers acknowledge it may not be possible to detect small causal effects of alcohol on disease outcomes [13, 15, 21].

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