Recent Efforts to Dissect the Genetic Basis of Alcohol Use and Abuse

Supplemental Information

Note 1

Genetic correlation and PRS analyses have shown that alcohol use has a shared genetic basis with many other complex traits; however, it is not clear if pleiotropy underlies these associations (i.e. same genes/biological processes influencing multiple traits) or whether there are causal relationships between alcohol use and health outcomes. Mendelian Randomization (MR, (1, 2)) can help to determine whether causal relationships exist by using genetic variants as instrumental variables. Because genetic variants are randomly “assigned” to the offspring during meiosis, they should be unrelated to confounding factors. As numerous variants have now been associated with alcohol use, they can be utilized as proxies for exposure to alcohol to probe causal relationships with various outcomes.

As reviewed in the main text, one striking observation from several independent GWAS has been that alcohol consumption is genetically correlated with *positive* health and lifestyle outcomes. This is supported by epidemiological studies showing that better health is associated with alcohol consumption at light to moderate intake levels, particularly for heart disease (3) and stroke (4). There is still debate as to whether these associations arise from unmeasured confounders and the misclassification of former drinkers (5), as there is also epidemiological evidence showing that even minimal alcohol drinking is detrimental for health (6). It is also unclear why AUD and alcohol consumption show different patterns of association with health outcomes, even at the genetic level. Epidemiologists have observed the 'alcohol harm paradox' whereby wealthier and more educated individuals consume alcohol more frequently whereas the burden of alcohol-related ill health is borne by individuals living in socially deprived regions (7). These patterns of alcohol use are likely to influence GWAS results. MR, along with sensitivity analyses in non-drinkers, will be an important tool to test the causal pathways underlying these observed correlations.

MR studies do not generally support the notion that alcohol consumption provides health benefits. For example, a MR analysis of vascular disease did not identify that genetic liability for alcohol use decreased risk for stroke or myocardial infarction (8), although the low rate of myocardial infarction in the Chinese biobank used in this study is a limitation of this analysis. In

addition, MR studies do not show that alcohol consumption provides educational advantage, contrary to the positive genetic association between educational attainment and alcohol consumption. In fact, Rosoff and colleagues recently showed that genetic liability for low educational attainment increased frequency of drinking, preference for various alcoholic beverages (beer, cider, and spirits), and risk for AUD (9).

MR has also been used to understand the positive genetic correlations between alcohol use behaviors and other substance use behaviors, such as smoking. To date, there is no compelling evidence for a causal effect of genetically instrumented alcohol consumption on smoking initiation (10, 11), which is in disagreement with previous observations suggesting that reduction of alcohol use could prevent smoking. There is also considerable co-morbidity between AUD and psychiatric disorders and evidence of shared genetic liability between these traits (12). For example, the significant co-morbidity between MDD and AD indicates a potential causal relationship, with a recent study suggesting that genetic liability for MDD increases risk for AD (13). In addition, although individuals with childhood ADHD showed increased risk for developing AD in an epidemiological study (14), a recent MR study did not find evidence that genetic liability for ADHD increased risk for alcohol consumption or AD (15). These important findings would not have been possible without the large GWAS studies of AUD and alcohol consumption, which discovered robustly associated genetic variants for use in MR analyses.

Note 2

The lack of genetic studies in large non-European samples is a concern for many complex traits, but particularly pressing for studies of AUD. For example, rs671, which explains a large amount of variation in alcohol consumption in East Asian populations, is not polymorphic in Europeans. The ADH1B locus has also proven to be more complicated than previously believed as rs2066702, and not rs1229984, seems to be the main signal of association in AA. The majority of downstream PRS analyses to date have been performed on European individuals and we do not as yet know their applicability to non-European populations.

Supplemental References

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