LETTERS TO THE EDITORS

Letter: Mendelian randomisation to investigate moderate alcohol consumption in nonalcoholic fatty liver disease; modest effects need large numbers

SIRS, Mendelian randomisation is a method of using variation in genes of known function to examine the causal effect of a modifiable expo- sure on disease. Since allocation to genetic variation is random, this elegant study design is less susceptible to confounding. In addition, because allocation of the polymorphism occurs at conception, Mendelian randomisation is less vulnerable to reverse causation. Sookoian et al.[1] performed a Mendelian randomisation study to investigate a potential beneficial effect of moderate alcohol consumption on the severity of nonalcoholic fatty liver disease (NAFLD). The validated variant rs1229984 (G> A) was used as an instrument variable. Carriers of the A allele are at low risk of alcohol dependence, and consume much lower levels of alcohol (~17% less), since the variant is associated with rapid oxidation of ethanol to alcohol dehydrogenase, leading to unpleasant side-effects (eg flushing, headaches).[2,3]

Taylor et al.[2] have recently developed a polygenic risk score for alcohol consumption; a score (PGRS) comprising of 49 single nucleotide polymorphisms (snps) which included rs1229984 explained only 0.003 of the variance of overall alcohol consumption within a (women only) population; this is partly due to the fact that the risk allele is relatively uncommon (mean allele frequency = 0.07). With such a modest overall variance explained, the authors conclude that very large sizes (often in the hundreds of thousands), from large multi-study consortia, will be required for the PGRS, and in consequences1229984 to be used in an Mendelian randomisation framework. Indeed, Holmes et al. validated rs1229984 as a genetic instrument in a sample of 261 991 participants.[3]

Based on the above results, we used a validated online tool (http://cnsgenomics.com/shiny/mRnd/) to perform a power calculation for the study published above.[4]

For a 31% protective effect against NAFLD (odds ratio (OR) = 0.69) expected by the authors, a sample of 75141 at the very least would be required for the study to be adequately powered (variance = 0.003, a 1:1 case-control ratio, 80% power, alpha = 0.05). For a 50% protective effect (OR = 0.5) against non-alcoholic steatohepatitis (NASH), a sample of 20931 would be required. In fact, the sample size required is likely to be greater than the results estimated here, since rs1229984 was just 1 of 49 snps used to achieve a variance of 0.3 %.

In summary, the negative study above (n = 466) is under-powered. Mendelian randomisation studies frequently require huge sample sizes, and should provide a power calculation. Conclusions with regards to the benefits of light to moderate drinking of alcohol in NAFLD cannot be reached; much larger studies are required.