

Coffee consumption and gout: a Mendelian randomisation study

I have read with great interest the article by Larsson and Carlström¹ regarding coffee consumption and gout. This Mendelian randomisation (MR) analysis demonstrates that coffee consumption may lower the risk of gout. When a randomised controlled trial is lacking because of an unethical or infeasible issue, MR studies may help address the causal relationship. However, it has some methodological issues. The primary concern relates to whether the MR study has adequate statistical power to detect an association. An increase in the variance in the trait of interest explained by the genetic instrument leads to improvement in the power of the MR analysis. However, most genetic variants for an exposure may only explain a small proportion of variance in that exposure. As genetic variants typically explain a small proportion of the variance in an exposure, the statistical power to detect an association between the variant and the outcome in an MR analysis can be limited or low.² I wonder how much amount of the variance in coffee consumption is explained by the five single nucleotide polymorphisms (SNP) in the sample. A second concern relates to whether the causal effect in the MR study remained significant in the sensitivity tests. As all the variants used in MR may not be the valid instruments, methods for sensitivity analysis including MR-Egger regression and the weighted median approach have been developed.^{3 4} The use of both methods is recommended when multiple genetic variants must be assessed for robustness of any causal finding to different sets of assumptions.⁵ MR-Egger regression has been proposed to test for directional pleiotropy and provides an estimate of the causal effect adjusted for its presence, and has been shown to be robust against invalid instruments.³ MR-Egger regression provides a useful additional sensitivity analysis to the standard inverse variance weighted approach that assumes that all variants are valid instruments. Although MR-Egger regression revealed that directional pleiotropy was unlikely to have biased the result, this study did not show the data on the causal effect adjusted for pleiotropy by MR-Egger analysis. A 'leave-one-out'

analysis may also be needed to evaluate if the causal association by MR estimate is driven or biased by a unique SNP that might have a particularly large horizontal pleiotropic effect. Thus, I believe that the findings of this MR study should be interpreted by taking the aforementioned methodological concerns into consideration.

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