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Assumptions for Mendelian Randomisation Studies with Multiple Instruments

Abstract: Mendelian randomisation (MR) refers to situations where a genetic predisposition can be exploited as an instrumental variable (IV) to estimate the causal effect of a modifiable risk factor or exposure on an outcome of interest. For example, the ALDH2 gene is associated with alcohol consumption, and has therefore successfully been used as an IV to estimate the causal effect of alcohol on outcomes related to coronary heart disease. MR analyses have become very popular recently with the increased availability of GWAS data. This gives rise to a number of challenges, especially around the topic of multiple IVs: it is common that several SNPs are found to be associated with an exposure of interest. However, the validity of such multiple IVs can often not be established in a convincing way and numerous methods that claim to allow for multiple - but partially invalid - IVs have been put forward in the last few years.

In this talk I will propose and investigate a formal notion of "valid IV" in the context of multiple and potentially invalid IVs - this has been neglected by all of the previous literature but turns out to be crucial to assess the plausibility of various suggested methods. Using graphical models and the formal properties linking marginal and conditional independencies is especially useful to clarify some of the misunderstandings in the field. Amongst others, it can be shown that a notion of marginal validity of multiple IVs is not implied by nor implies a notion of joint validity and hence care has to be taken with typical analyses based on GWAS data.