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Commentary

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Commentary: One size fits all: are there standard rules for the use of genetic instruments in Mendelian randomization?

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As a tool for the epidemiologist and a translational extension for the geneticist, Mendelian randomization (MR) has been exemplary and has been able to unify otherwise disconnected research specialties and show the genuine utility of genetic association studies. With this, the demand for and development of MR have of course brought with them a smoothing or facilitation of existing analytical process. What was once the reserved analytical space of a limited number of experts is now a burgeoning, semi-automated, plug-and-play approach to causal inference. This of course is to be praised in that applied methods are being used and accessed by many researchers and, with this, pertinent questions are being addressed. However, what is also true is that as we learn more about the source of genetic association signals and the complicating effects that our own favourite complex phenotypes might impart, the more we need to advise caution in inference. This does not mean that we should remove applied genetic epidemiology from the quiver of the analyst, rather that in the era of proliferation of genetic analysis we should remain critical and not allow the success of MR to become its own worst enemy.

Into this context Swerdlow *et al.*[1] have delivered a much needed examination of the factors which need to be considered when embarking on an MR study. Their paper 'Selecting genetic tools for Mendelian randomization in the wake of genome-wide association studies' discusses a series of important considerations when forming an MR study if working from the now substantial pools of genome-wide association study (GWAS) results that are available for causal pathway breakdown. Until relatively recently, MR studies have generally focused on a limited number of intermediate phenotypes. Recent applications of 'omic' technologies into large-scale population-based studies present new opportunities for identifying predictive biomarkers and causal links between established phenotypes and disease outcomes.[2–5] Whereas there is no guarantee that use of multi-omic phenotype data will avoid any of the problems encountered in observational epidemiology, in combination with MR approaches there is an opportunity to undertake informative analyses which exploit genetically tractable intermediate phenotypes/biomarkers and to potentially identify novel predictive biomarkers and causal links between established phenotypes and disease outcomes.[4,6]

Swerdlow *et al.* focus on important factors when selecting genetic variants to act as proxy measures for exposures or intermediate phenotypes of interest. In contrast to direct measurement, germline genotypes reliably associated with risk factors can act in this role and offer several advantages: genotypes are relatively easy to measure, they are stable through time and between tissues (though their effects may not be), they are largely immutable and are not correlated with confounding factors as a result of the mechanisms of Mendelian inheritance.[7,8] Important issues considered when choosing genetic variation to employ in MR studies include the nature of the original GWAS signal

(including the frequency and effect size of the relevant mutation) and the specificity of the genetic effect which is being exploited to yield a causal estimate. The former of these is of course acknowledged as a function of the genetic architecture of any given exposure or intermediate phenotype; however, the authors appropriately note that non-specificity of genetic effect can be derived from a number of sources including horizontal pleiotropy, biological complexity and complex pathway or regulatory systems. In light of this, a guiding set of rules or advice is provided in efforts simultaneously both to make the potential MR analyst aware of the issues in question and also to offer support in the undertaking of this type of applied analysis.

The one area which remains important and perhaps should be highlighted even more is the potentially damaging impact of apparently informed instrument selection. If one thing was learned from the exciting era of GWAS, it was that the best conceived ideas about which loci would contribute specifically to health outcomes of interest were largely incorrect and that the hypothesis-free nature of GWAS was the master stroke. To this end, I would commend the efforts of the current paper for guiding MR analyses, but would encourage the authors to go further. It is unlikely that our current and limited appreciation of genetic architecture (i.e. the shape of the underlying genetic contribution to a phenotype of interest—here biomarkers for causal analysis) is going to reflect the complete and uncomplicated nature of genetic association. With this, the notion of being able to assign biological function and reliable labels or filters for pleiotropy or pathway effects is likely to be, at best, as reliable as our ability to measure complex biology. Marking the direction of travel for advanced MR analyses (highlighted by Swerdlow *et al.*), analysis methods which are aware of limitations and the likely invalidities of instrumentation (and which make no assumptions about being able to filter these out), are likely to be the way forward. A seminal paper published in this journal in June 2015 marked a real step forward and (outside the realm of defined functional biology) leaves a lasting message: standardized rules for instrument choice may bring awareness and sensible checks, but flexible and robust methods born of an understanding of our limitations may be the future for MR.[9]

Clearly, MR analyses are a positive contribution in this era of deep phenotyping and genetic association studies, but it is also important to state that they are not the only source of evidence. Combinatorial investigations incorporating multi-omic examination of patients, population-based analyses and interventions will be essential to the future breakdown and understanding of causal pathways. In this manner, triangulation of evidence remains the tried and tested gold standard, though guided and appropriate MR will offer a major contribution.

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