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Editorial

Mendelian Randomization—Let's Prevent Common Mistakes

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Mendelian randomization (MR) is increasingly used in epidemiology, including in gerontological research. MR uses genetic variants associated with the exposure, for example, as identified in genome-wide association studies, as instrumental variables for the purpose of causal inference between exposure and outcome (1). Using MR, progress has been made in multiple areas of medicine without the use of expensive and time-consuming randomized-controlled clinical trials. Most illustrative, MR showed that high genetically influenced high-density lipoprotein (HDL) cholesterol concentration was not associated with the risk of cardiovascular disease (2), already suggesting the expected limited effectiveness of pharmacological interventions targeting HDL cholesterol concentrations. As not feasible to investigate in clinical trials, using MR, the effect of educational attainment on human longevity was demonstrated and evidence for the potential mediators was described (3).

Due to the free and open access to large-scale summary-level data from (published) genome-wide association studies and the introduction of streamlined analytical pipelines (ie, the R-based TwoSampleMR package (4)) to harmonize data and to perform the statistical (sensitivity) analyses, MR has become a widely used statistical tool used by many research groups. Despite the significant increase in use, the general quality of the published MR studies is moderate at most, and the clinical meaning of most obtained study results is minimal, despite the attempt to harmonize and improve publication guidelines by developing the STROBE guidelines for MR studies (5,6). As translational research (ie, drug target discovery, medical guidelines development) increasingly relies on the results derived from MR studies, the quality of the presentation, interpretation, and publication needs to be improved to allow proper follow-up of the study results. Although most of the MR studies currently being conducted consider the risk of pleiotropy and perform appropriate sensitivity analyses to meet all necessary MR assumptions (7), I here list some common issues identified frequently in published MR studies and/or those received for consideration for publication.

Overinterpretation of the results from MR. MR is a tool to approximate a causal association between an exposure and outcome, under the condition of specific assumptions (1,7), and therefore does not prove the presence of causality. Causal inference in etiological research is increasingly seen as the triangulation of the same observation in different settings and using different study designs, including conventional confounder-adjusted epidemiological cohort studies, genetic studies including MR, and experimental designs (ie, animal experiment or human intervention) (8). Although it is mostly unreasonable to combine all 3 designs in a single research paper, the hypothesis being tested in an MR study would benefit from significant backup from other studies, an aspect that is frequently lacking. MR should be considered only as a useful tool to identify risk factors of potential interest for further translation into clinical practice, and not as the highest obtainable level of evidence for causal inference.

Absence of evidence is not the same as evidence for absence. Frequently, MR studies have been published claiming a specific relationship between exposure and outcome as noncausal, although this can be easily argued based on the data presented in the paper. MR studies frequently only rely on the level of statistical significance to conclude whether an association is present or not. A clear (and correct) interpretation of the effect sizes with confidence limits is frequently lacking causing misinterpretation of the data being presented. MR studies are frequently limited by low statistical power either caused by a limited number of (valid) genetic instruments strongly associated with the exposure and/or by a lower statistical power in the outcome dataset (notably, low sample size, low number of cases, or a combination of both) (9). Although most published MR studies still rely on single cohort designs, the increased open availability of genetic association summary data from large biobanks (ie, UK Biobank, FinnGen, and Biobank Japan) in combination with published summary-level data from large genomics consortia allows:

1) testing for between-cohort variation of approximated causal estimates for the purpose of validation, and
2) increase the statistical power to the highest possible with current available data.

For example, we previously performed an MR study to examine the association between dietary-derived antioxidant levels and atherosclerotic cardiovascular disease. By combining the summary-level data from 3 different and independent

genetic association studies through meta-analyses, we were able to more convincingly show the lack of evidence for a causal association despite limited statistical power present for some of the traits (10). An assessment of the statistical power in an MR study in combination with an assessment of the minimal obtainable reasonable effect size of the approximated causal effect (ie, through https://shiny.cnsgenomics.com/mRnd/) allows further interpretation of the research finding, especially in the case of a negative finding (ie, lack of evidence for a causal association).

The assumption of linearity of the approximated causal effect is difficult to challenge. Where classical MR assumed a linear association between exposure and outcome, it is reasonable that some of these associations between exposure and outcome show a nonlinear trend. However, currently available methodology can introduce specific forms of bias and therefore invalid results, which are difficult to fully rule out (11). Until unbiased analytical pipelines or guidelines are available, researchers should be cautious to perform nonlinear MR analyses.

Bias in MR, a particular issue of causal inference in gerontology. Although frequently neglected given that most MR studies are considered to be conducted in a representative sample of the general population, selection bias (or also referred to as a collider stratification bias or survival bias) can cause serious issues in the interpretation of the results (12). These issues especially arise when investigating late-onset disease, including dementia and stroke. For example, examining the association between cardiovascular risk or disease and vascular dementia using MR might be biased given that people with cardiovascular disease are at an increased propensity for mortality, and therefore less likely to reach the age at which late-life diseases like stroke and dementia are developed. The interpretation of MR studies on old-age diseases should therefore be done with caution in the light of these limitations, until solid solutions are developed. Furthermore, there is increasing interest to perform stratified MR analyses to assess subgroup effects. However, the interpretation of the results derived from such analyses might be challenging given the potential introduction of collider stratification bias, which refers to a form of selection bias in which the selection could introduce spurious associations between exposure and outcome (see example in Figure 1), although now additional methodology for corrections is available (13). Indeed, we found that classical risk factors for atherosclerotic cardiovascular disease have age-specific effects (14), and a higher genetically influenced body mass index showed stronger effect estimates to atherosclerotic cardiovascular disease in people with low socioeconomic status (15).

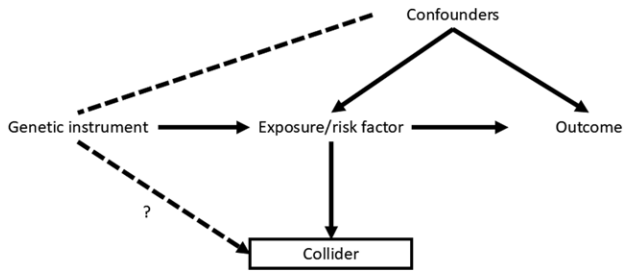

Figure 1. Directed acyclic graph (DAG) illustrating the concept of collider bias. When the genetic instrument and the collider are directly linked, stratification (or conditioning) can introduce selection bias and a direct link between the exposure and the collider.

Not all exposures are clearly genetically influenced. With more MR studies being done, also less clear genetically influenced exposures are more frequently investigated to approximate causal effects, including exposures such as physical activity and nutritional intake. As the exposures are also clearly linked to compensatory behavior (ie, in the case of obesity), multivariable-adjusted MR approaches are required to provide clear evidence of the potential direct causal effects, if present, to produce results with the correct interpretation.

MR remains a powerful research tool to facilitate the translation of observational findings to clinical practice. However, to facilitate the gerontological research field requires researchers to perform studies in the best way possible, considering the assumptions and limitations, and to interpret the study results as such.

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Conflict of Interest

None.

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