

Editorial

Mendelian randomization studies: A unique research design

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Mendelian randomization (MR) studies are a method used in epidemiology to investigate causal relationships between modifiable risk factors and outcomes, such as diseases, by leveraging genetic variants as instrumental variables. Essentially, they use the random assignment of genes at conception to mimic a randomized controlled trial (RCT), thus helping to overcome limitations such as confounding and reverse causation inherent in observational studies.

The main idea behind MR studies is the principle that genes are randomly inherited from parents, meaning that genetic variants associated with a particular exposure are effectively randomly assigned at conception. This random assignment allows researchers to examine the causal effect of that exposure on an outcome, like how a RCT would work.

The desire to establish causality through observational studies, coupled with the increasing number of large-scale genome-wide association studies (GWASs) that contain genetic markers in addition to variables such as demographic and clinical data as in typical observational studies has given rise to the concept of MR. The idea is to let MR in GWASs play the role that randomization does in RCTs so that we can assess the causal effects of certain exposures, including genetic markers.

STEPWISE PROTOCOL

Identifying genetic variants

First, scientists look for genetic variations (also known as single-nucleotide polymorphisms, or SNPs) that are closely linked to the exposure of interest.

Instrumental variable

As instrumental factors, these genetic variations are linked to the exposure but are not directly affected by the result or other variables.

Analyzing associations

The relationship between these genetic variations and the

desired result is then examined by researchers. Finding a substantial correlation suggests that the exposure may have a causal impact on the result.

ADVANTAGES OF USING MR METHODOLOGY

Overcoming confounding

Confounding is a common problem in observational research, where a third variable affects both the exposure and the result, producing false positives. By employing genetic variants as exposure proxies that are less susceptible to confounding factors, MR can help to counteract this.

Addressing reverse causation

Sometimes it's hard to tell if the exposure leads to the result or the other way around. By utilizing the fact that genetic variants are predetermined at conception and are therefore unlikely to be impacted by the outcome, MR can assist in addressing this problem.

Causal inference

Understanding the genesis of diseases and creating successful interventions depend on the ability to draw conclusions about the causal link between exposures and outcomes, which MR offers.

There are three fundamental presumptions that underlie MR: (i) the genetic variant is linked to the exposure; (ii) the genetic variant exclusively influences the outcome through the exposure (exclusion restriction); and (iii) the genetic variant is unaffected by confounders.

There are various methodological challenges for this kind of research. First, large sample sizes are frequently needed for MR research to obtain sufficient statistical power, particularly when working with weak genetic connections. Since genetic characteristics cannot be changed, MR can only predict how interventions might affect exposure rather than the direct impact of a particular intervention.

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Applying MR to complex features that are impacted by several genes and environmental factors might be difficult. In MR studies, binary outcomes (yes/no) can present certain issues. MR investigations can also be complicated by epigenetic modifications, which are variations in gene expression without alterations to the DNA sequence. Complex relationships can nevertheless make interpretation more difficult, even though MR seeks to lessen reverse causation. It might be challenging to interpret null results in MR investigations, particularly when there is little correlation between the exposure and the genetic variant. MR study results might not necessarily apply to different groups or environments. Multiple comparisons can raise the possibility of false positives when working with high-throughput data. There may not always be genetic variants that are appropriate for a given environment.

We can address these limitations by undertaking certain measures. Statistical methods to identify and account for pleiotropy, several statistical techniques are available, such as MR-Egger and mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO). It is essential to conduct sensitivity assessments to evaluate how resilient the results are to assumptions being broken. Multiple genetic variants can be used to decrease bias and boost statistical power. Meaningful causal inference requires the selection of suitable exposures and outcomes. Researchers can improve MR studies' validity and reliability by being aware of these constraints and using the right techniques.

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