Network Mendelian Randomization Study Design to Assess Factors Mediating the Causal Link Between Telomere Length and Heart Disease

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Mendelian randomization study designs represent new powerful tools available to researchers that enable causal inferences to be made about the effects of risk factors in health and disease outcomes in the context of a prospective observational study. These study designs involve estimating the association between a genetically modifiable risk factor and health and disease outcomes. If individuals with genetically lower or higher levels of a risk factor of interest are at greater or lesser risk of an outcome, then it can be inferred that the risk factor has a causal relationship to that outcome. Provided that a chosen genetic variant is strongly associated with the risk factor of interest, it is not associated with other factors that might affect the risk factor, and imparts its influence on a given outcome exclusively through its link to the risk factor, these causal inferences are considered to be robust.

Mendelian randomization study designs have become increasingly popular among epidemiologists in recent years as recently completed genome-wide association and genome sequencing studies have substantially increased our knowledge of the genetic factors associated with health and disease. Using Mendelian randomization techniques allows researchers to conduct studies that can make the kinds of causal inferences that are typically only attainable from randomized controlled trials, thus avoiding much of the expense, difficulty, and ethical issues that often arise with such trials. Furthermore, as demonstrated in an exciting recent publication in Circulation Research, titled Exploring the Causal Pathway from Telomere Length to Coronary Heart Disease: A Network Mendelian Randomization Study by Zhan et al., these study designs allow assessment of the influence of risk factors that are impossible to manipulate in humans, like telomere length, on disease outcomes and the complex network of factors that mediate this influence.

Although Mendelian randomization techniques can involve fairly computationally intensive analyses, the fundamental principles that guide these study designs are straightforward and if understood clearly should make articles that describe such techniques accessible to the average consumer of scientific literature. Thus, I would like to very briefly describe some of these principles before discussing the value of the article by Zhan at al as an example of the ability of Mendelian randomization designs to address the complex biological relationships that exist between risk factors like telomere length and disease outcomes.

The basic premise behind these study designs lies in the fact that genetic variants recombine and randomly segregate during meiosis, such that their frequencies become randomly distributed within a population. This phenomenon creates a kind of natural randomized controlled trial, whereby risk alleles and normal control alleles are randomized within a population. Thus, when risk factor levels are linked to known genetic variants that can be measured and used to stratify study participants into risk allele and control allele groups, the confounding influence of all known and unknown factors on the association between the risk factor and a given outcome is minimized or excluded outright (a stepwise comparison with randomized controlled trials is depicted in the Figure). What is more, Mendelian randomization effectively rules out the influence of reverse causality on the relationship between a risk factor and the observed outcome, as no outcome can selectively influence the segregation of alleles before conception.

Thus, Mendelian randomization allows researchers to avoid many of the biases encountered in traditional observational studies that limit or prohibit inferences about causality and directionality. The idea to design these natural experiments was first proposed in a 1986 article by Katan as a way to assess the causal link between low-density lipoprotein (LDL) and cancer risk. Observational studies at the time had established an association between lower LDL levels and higher cancer risk; however, it was impossible to conclude if LDL levels truly mediated cancer onset, if some unknown confounding factor both reduced LDL levels and increased cancer risk, or if cancer onset reduced LDL levels. The proposed Mendelian randomization study was not conducted until 2009, when Trompet et al concluded that individuals with a genetic variant of apolipoprotein E that caused chronic reductions in LDL levels had no increased risk for cancer compared with individuals harboring a normal control variant.

Recently, basic Mendelian randomization designs have been expanded to allow assessment of networks of factors that mediate the causal relationships between risk factors of interest and a given outcome. This modified Mendelian
References


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