

## Editorial



# Lipid and Ischemic Heart Disease Revisited: Mendelian Randomization Analysis

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Evidence of causal effects of certain biomarker comes from researches utilizing various methodology, among which randomized controlled trials (RCTs) provide evidences with the highest scientific rigor. A well-known representative example is the relationship between low-density lipoprotein (LDL)-cholesterol and ischemic heart disease (IHD).<sup>1)</sup> However, there are research questions which are very difficult or practically impossible to be solved by RCT's. Unlike the causal relationship between LDL-cholesterol and ischemic heart disease which were proven by RCT's using statin therapy, an effective intervention to modify the biomarker in question may be absent. In case of high-density lipoprotein (HDL)-cholesterol, the cholesteryl ester transfer protein inhibitors, HDL-cholesterol raising agents that had been apparently promising, resulted in failure and left us with the lack of effective modifying agents.<sup>2)</sup> Life style risk factors such as diet, exercise, smoking, alcohol, etc., are notoriously hard to address with RCT's because of the difficulty in strict control of exposure to the 'treatment'. With these difficulties, we have to rely on observational studies ranging from cross-sectional to longitudinal cohort studies.

But observational studies, even well-designed and carefully done large-scale prospective cohort studies, cannot be completely free from the most problematic flaw: unmeasured confounding bias. This is the point where we need some breakthrough and Mendelian randomization (MR) is emerging as a helpful analytical method that uses genetic variants as instrumental variables for modifiable risk factors, which is considered to be a 'randomization at birth'.<sup>3)</sup> One good example of this approach is the studies on the relationship between alcohol intake and the incidence of hypertension, which are prone to be confounded by other behavioral and sociodemographic factors while clinical trials are difficult to implement. There have been studies using aldehyde dehydrogenase 2 (ALDH2) as a surrogate for the amount of alcohol consumption. A variant in the ALDH2 gene (A allele) compared to wild-type G allele slows the metabolism of acetaldehyde, which causes a flush response and other adverse responses to alcohol, thus those who are carrying AA type assumedly associated with less alcohol consumption than those with GG type or heterozygotes. A meta-analysis of eight such studies showed greater odds of being hypertensive in those carrying A allele(s).<sup>4)</sup>

The proliferation of studies including large-scale genetic data has had a profound impact upon cardiovascular disease related research, resulted in the emergence of MR approaches.<sup>5)</sup>

In the current issue of the *Korean Circulation Journal*, Lee et al.<sup>6)</sup> reported that high levels of LDL-cholesterol and triglyceride (TG) were causally associated with increased IHD risk in a Korean population, inferred from 2-sample Mendelian randomization analysis.<sup>6)</sup> Genetic variants significantly associated with lipid concentrations were obtained from the Korean Genome and Epidemiology Study (n=35,000), and the association between the genetic variants and outcomes (IHD) were obtained from the Korean Cancer Prevention Study-II (n=13,855). Strength of the two-sample study is that statistical power is usually much higher.<sup>7)</sup> The authors provided a summary of the three basic assumptions for MR analysis in the 'Methods' section and elaborately applied the methods to overcome the possible violation of these assumptions, such as MR-Egger method for pleiotropy of genetic variants.<sup>8)</sup>

As clinical implications, 1) the result of the study that HDL-cholesterol did not show causal association with IHD supports the recent trend of pursuing HDL function and not just HDL-cholesterol level as a potential treatment target,<sup>2)</sup> and 2) another TG-modifying clinical trial may be needed to improve the cardiovascular outcomes. One weakness of this study is that the outcome included is only 'non-fatal' IHD events, which regrettably does not seem to be negligible and should be considered in generalization of the study results.

## REFERENCES

1. Jun JE. Cholesterol lowering therapy in coronary artery disease: with particular reference to statins. *Korean Circ J* 2001;31:849-56.  
[CROSSREF](#)
2. Sung J. The long and winding road: to the proper understanding of high-density lipoprotein. *Korean Circ J* 2020;50:248-9.  
[PUBMED](#) | [CROSSREF](#)
3. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018;362:k601.  
[PUBMED](#) | [CROSSREF](#)
4. Chen L, Smith GD, Harbord RM, Lewis SJ. Alcohol intake and blood pressure: a systematic review implementing a Mendelian randomization approach. *PLoS Med* 2008;5:e52.  
[PUBMED](#) | [CROSSREF](#)
5. Spiller W, Jung KJ, Lee JY, Jee SH. Precision medicine and cardiovascular health: insights from mendelian randomization analyses. *Korean Circ J* 2020;50:91-111.  
[PUBMED](#) | [CROSSREF](#)
6. Lee SH, Lee JY, Kim GH, et al. Two-sample mendelian randomization study of lipid levels and ischemic heart disease. *Korean Circ J* 2020;50:940-8.  
[CROSSREF](#)
7. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. *Am J Epidemiol* 2013;178:1177-84.  
[PUBMED](#) | [CROSSREF](#)
8. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015;44:512-25.  
[PUBMED](#) | [CROSSREF](#)