Arteriosclerosis, Thrombosis, and Vascular Biology

EDITORIAL

Circulating Lipids and COVID-19: Insights From Mendelian Randomization

Michael G. Levin

At a population level, dyslipidemia is both highly prevalent and undertreated, representing an important modifiable cardiometabolic risk factor from a public health perspective.[1,2] Early observational studies of individuals with coronavirus disease 2019 (COVID-19) highlighted dyslipidemia and blood lipids as potential risk factors for disease.[3–5] At a molecular level, several putative mechanisms link cholesterol/lipid metabolism to severe acute respiratory syndrome coronavirus 2 infection.[6] For example, the SRB1 (scavenger receptor class B type 1), involved in trafficking HDL (high-density lipoprotein)-cholesterol, has been identified as a binding partner for severe acute respiratory syndrome coronavirus 2 proteins.[7] Cholesterol-enriched lipid rafts within cellular membranes play important roles in severe acute respiratory syndrome coronavirus 2 binding, activation, internalization, and cell-cell spread.[8] Cholesterol metabolism may also have immunomodulatory consequences, influencing the proliferation of regulatory T cells and activating inflammatory pathways via the NLRP3 (NLR family pyrin domain-containing 3) inflammasome.[9,10] Thus, understanding the relationship between lipids and COVID-19 has important implications for both risk assessment and therapeutics.

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Mendelian randomization (MR) is a clever framework for inferring causal relationships between risk factors and outcomes from observational data. The MR framework represents a specific application of instrumental variable analysis, a technique first described in the econometrics literature nearly a century ago.[11] Within the MR framework, genetic variants are used as instrumental variables to overcome some of the biases that may limit traditional observational study designs. Due to the nature of genetic inheritance, genetic variants are randomly and independently passed from parents to offspring (Mendel's laws of segregation and independent assortment). This scenario provides a natural experiment, which under certain assumptions mimics allocation within a randomized clinical trial. For genetic variants to serve as valid instrumental variables, they must satisfy 3 main assumptions (Figure). First, genetic variants must strongly associate with the risk factor of interest. Second, the variants should not be associated with confounders of the risk factor-outcome relationship. Finally, these variants must influence the outcome only through their effects on the risk factor of interest. Provided these assumptions, the MR framework permits the estimation of the lifelong effects of a risk factor on an outcome of interest. Because genetic variants are fixed at conception, before health outcomes occur, results from MR studies are less susceptible to reverse causality than traditional observational study designs.[12] Furthermore, due to the random assortment of genetic variants, estimates are less susceptible to bias from residual/unmeasured confounding, the main limitation of some traditional observational designs.[12] Interpreted within the context of evidence from other study designs, results of MR studies provide support for causal relationships between risk factors and outcomes.[12] The increasing public availability of data from genetic association studies has facilitated the widespread application of the MR study design.

Key Words: Editorials ■ cholesterol ■ COVID-19 ■ dyslipidemias ■ population ■ public health ■ risk factors

Correspondence to: Michael G. Levin, MD, Division of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania Perelman School of Medicine, 3400 Civic Center Blvd, 11-South, Philadelphia, PA 19104. Email michael.levin@pennmedicine.upenn.edu
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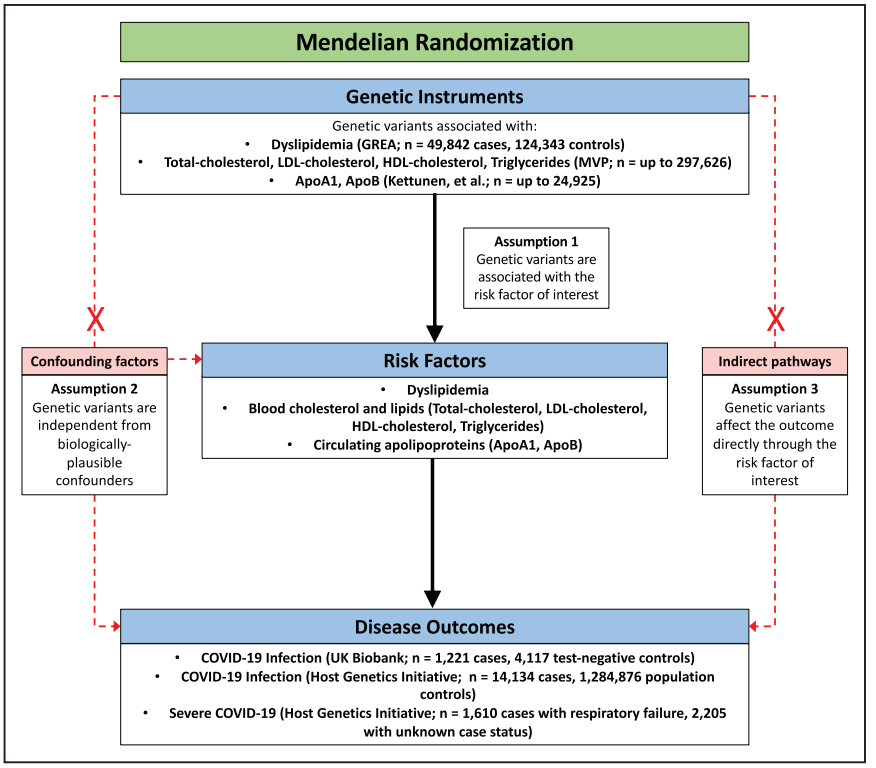

Figure. Mendelian randomization (MR) uses genetic variants as instrumental variable (genetic proxies) for risk factors, enabling the inference of causal effects of risk factors on disease outcomes.
Assuming (1) genetic variants associate with the risk factor of interest (typically associations are derived from large genome-wide association studies); (2) genetic variants are independent from biologically plausible confounders; and (3) genetic variants affect the outcome directly through the risk factor of interest (rather than via alternative pathways), then MR provides causal effect estimates that are less susceptible to confounding or reverse causality in comparison to traditional observational study designs. Genetic instruments, risk factors, and disease outcomes for the study by Zhang et al[13] are highlighted as an example. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Zhang et al[13] apply the MR framework to investigate the relationship between circulating lipids and risk of COVID-19.[13] The authors constructed genetic instruments for dyslipidemia, total cholesterol, LDL (low-density lipoprotein)-cholesterol, HDL-cholesterol, triglycerides, ApoA1 (apolipoprotein-A1), and ApoB (apolipoprotein-B) from large publicly available genome-wide association studies (GWAS) of these traits. Using a 2-sample MR design, the authors estimated the effect of these traits on (1) risk of COVID-19 infection (UK Biobank [UKB], Host Genetics Initiative [HGI]) and (2) severe COVID-19 (HGI), based on separate GWAS of these traits. The authors identified significant associations with dyslipidemia, total cholesterol, and ApoB with risk of COVID-19 infection (UKB) after accounting for multiple testing. They further identified a nominal association between LDL-cholesterol and COVID-19. These effects were consistent across alternative MR methods which make different assumptions about the presence of directional pleiotropy and invalid genetic instruments. When considering an alternative COVID-19 infection outcome from the larger HGI GWAS (14 134 cases and 1 284 876 controls), the authors identified nominally significant ($P<0.05$) associations with ApoB, total cholesterol, and triglycerides. However, the associations between ApoB and total cholesterol with risk of COVID-19 infection were substantially attenuated (ApoB odds ratio, 1.18 in UKB, 1.01 in HGI; total cholesterol odds ratio, 1.19 in UKB, 1.01 in HGI). The authors detected no significant associations between lipid traits and risk of severe COVID-19.

Overall, the results of this study should be interpreted cautiously. The UKB COVID-19 infection outcome GWAS used in this study was limited to participants from relatively early in the COVID-19 pandemic, when availability of testing was not universal. UKB participants who underwent COVID-19 testing at this time were substantially enriched for a range of factors, including demographic, cardiovascular, anthropometric, and genetic traits, potentially introducing a source of selection/collider bias.[14] It is also worth noting the discrepant magnitude of associations between the UKB and HGI analyses which may be due to differences in the COVID-19 case/control definitions (cases in the UKB GWAS were compared with controls who had undergone negative testing, while controls in the HGI analysis were from the remaining population at large and could have unknown COVID-19 status), or differences in sample size (1221 cases in UKB versus 14 134 cases in HGI), and timing of each GWAS with respect to the onset of the pandemic (June 5, 2020, for UKB, October 20, 2020, for HGI release 4). Finally, the genetic instruments in the current study serve as proxies of lifelong changes in circulating lipids and may not reflect the efficacy of shorter-term pharmacological interventions on the circulating lipid profile.

Despite this caution, there is a reason for optimism. MR has been applied to COVID-19 more broadly, successfully anticipating the benefits of targeting the interleukin-6 pathway (ultimately validated as a target in randomized clinical trials), and prioritizing medications for drug repurposing.[15,16] Given the rapid pace of the early COVID-19 pandemic, and the logistical challenges of

designing and implementing large-scale adaptive clinical trials to test causal hypotheses, MR represents an important methodological tool to infer putative causal relationships to prioritize for further evaluation. A broad literature of both observational and MR studies has identified links between circulating lipids and COVID-19, and several plausible biological mechanisms exist to support these associations.[17–21] For example, 2 recently published propensity-matched cohort studies of 1296 and 922 hospitalized patients with COVID-19 identified a substantially reduced risk of mortality among individuals taking statins.[18,19] Similarly, a recent systematic review and meta-analysis including 110 078 hospitalized COVID-19 patients across thirteen retrospective cohorts found statin administration after diagnosis was associated with decreased mortality, particularly among individuals not requiring intensive care.[20] In contrast to the current study, which found a reduced risk of COVID-19 infection but not severity, observational studies have largely focused on the effects of statin treatment on COVID-19 outcomes rather than infection. The current MR study thus complements the published literature, which in sum suggests that therapies modifying circulating cholesterol and ApoB levels may have beneficial effects on COVID-19 infection and severity. Several randomized clinical trials of lipid-modifying medications are underway to evaluate their role in the prevention or treatment of COVID-19. A recent systematic review identified 40 ongoing randomized clinical trials for medications including statins, fibrates, omega-3 fatty acids, niacin, and dalcetrapib.[22] Ultimately, while randomized clinical trials remain the gold-standard for identifying causal relationships between traits, MR represents an important technique to synthesize causal insights from observational data.

ARTICLE INFORMATION

Affiliation

Division of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia.

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