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Commentary

Mendelian randomization in COVID-19: Applications for cardiovascular comorbidities and beyond

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The pandemic of Coronavirus Disease 2019 (COVID-19) is rapidly evolving as a major threat to global health. Cardiovascular and metabolic comorbidities including hypertension, diabetes, coronary artery disease (CAD) are common among COVID-19 patients, and are associated with increased mortality and adverse outcomes in COVID-19 [1]. However, clinical or physiological evidence is lacking regarding the causal relationship between cardiovascular diseases and the severity of COVID-19, and whether management of cardiovascular risk factors would benefit the outcome of COVID-19.

Mendelian randomization (MR) is a recently emerged strategy for assessing the causality between a disease and intermediate risk factors utilizing genetic variants as instrumental variables [2]. If the intermediate risk factor is indeed causal for the disease, the genetic variants specifically associated with the risk factor will also be associated with the disease of interest. Although MR can be conducted in a retrospective way, it is conceptually similar to prospective randomized controlled trials (RCT) (Fig. 1). Since the genetically determined risk factors occur prior to the disease onset, MR avoids the potential bias of reverse causation in retrospective studies, and the risk of confounding is also reduced by applying genetic instruments unassociated with known confounders of the disease through pleiotropic effects [2].

A potential important application of MR is to investigate whether cardiovascular risk factors such as hypertension, hyperlipidemia and diabetes are contributing causally to the poor outcome of COVID-19, by applying the instruments validated in previous MR studies [3]. Once the causal risk factors are identified, the interventions against these risk factors such as anti-hypertensive drugs, lipid-lowering drugs such as statins, and blood glucose control agents may be effective to ameliorate the disease progression of COVID-19. Notably, the causal estimates derived from MR may reflect the lifetime effects of the risk factors. It has been shown that the CAD protection effects of genetically lower low-density lipoprotein (LDL) and blood pressure are substantially greater than what has been observed in short-term RCTs of statin and antihypertensive drugs [4]. Therefore, the results of MR may not recapitulate exactly the same degree of effects for short-term treatment during the acute phase of infection, but rather the effects of prevention and long-term treatment of the cardiovascular risk factors on the disease outcome. Importantly, most clinical trials currently ongoing are directed at treatment strategies and are not addressing the prevention of COVID-19 disease progression [5]. If the control of cardiovascular risk factors is effective to reduce the risk of severe disease of COVID-19, the strengthened management of these risk factors and cardiovascular comorbidities in the area of high incidence of COVID-19 may protect those with underlying cardiovascular diseases from becoming severely ill once they are infected. Ultimately, these measures can be applicable for altering the incidence of severe cases and death rate of COVID-19 in the coming months and future.

Another potential application of MR is to address controversies regarding the use of certain drugs in COVID-19 patients, including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) [6]. Preclinical studies suggested that ACEI/ARB may increase expression of ACE2, the functional receptor to SARS-CoV-2, which may in turn increase the susceptibility of the patients to the virus [6]. Several recent retrospective observational cohort studies showed that the continued use of ACEI/ARB is unlikely to be harmful or may even be beneficial to COVID-19 patients with hypertension, but the effects of ACEI/ARB on the disease outcome await prospective studies to confirm [7]. This question can be investigated through MR in a more straightforward way, since MR is also able to predict the long-term therapeutic and side effects of a drug in human by manipulating the genetic variants of the drug-targeted proteins. Genetic variants of *ACE* and *AGTR1*, the genes encoding angiotensin-converting enzyme and angiotensin II receptor type 1, respectively, can be carefully selected and applied to construct the instrumental variables that mimic the effects of ACEI and ARB. Evaluating the phenotypes of the COVID-19 patients with genetically lowered

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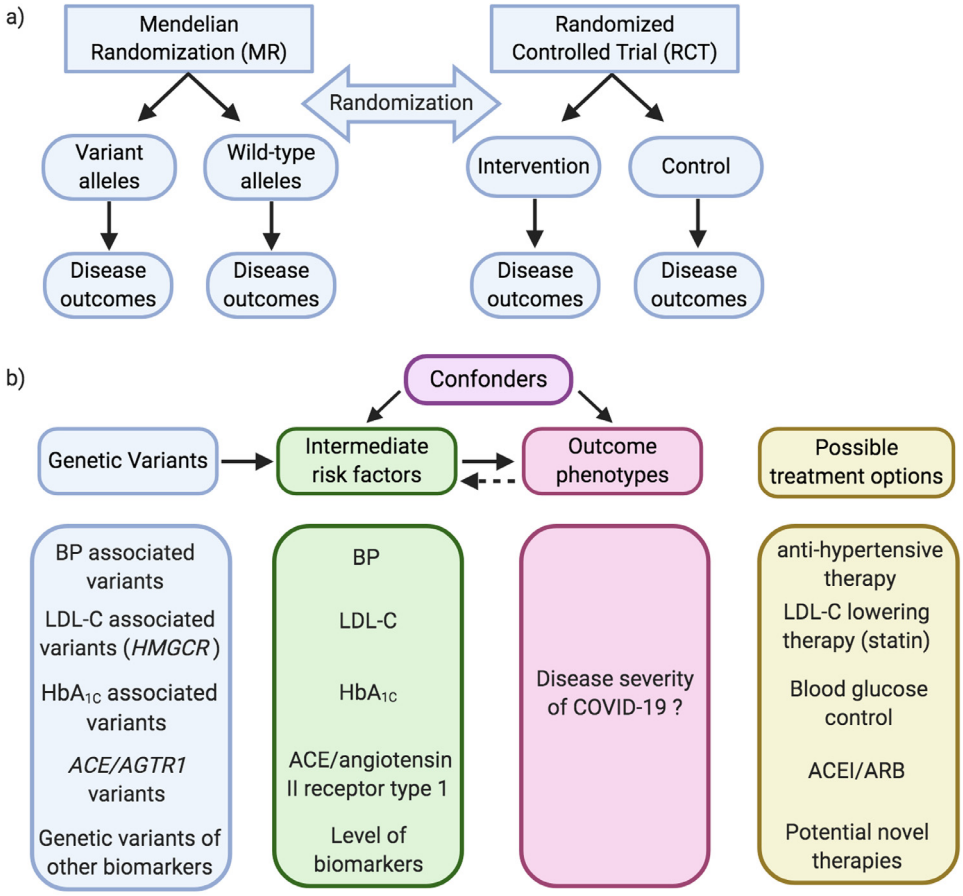

Fig. 1. Mendelian randomization to identify causal risk factors and potential treatment options to severe disease of COVID-19. a) Similarities between the design of MR and RCT. b) The causation pathway in MR from genetic variants to intermediate risk factors and the subsequent outcome phenotypes (Dash line: reverse causation). Examples of MR design on COVID-19 that mimic possible treatment options are also listed. BP: Blood Pressure, LDL-C: Low Density Lipoprotein Cholesterol, HMGCR: HMG-CoA Reductase, HbA_{1C}: glycated haemoglobin, ACE: Angiotensin-Converting Enzyme, AGTR1: Angiotensin II Receptor type 1, COVID-19: Coronavirus Disease 2019.

expression of *ACE* or *AGTR1* may shed light on the effects of long-term treatments of ACEI/ARB on the outcome of COVID-19.

The power of MR can be extended to explore other host-modulated therapies that have defined genetic targets in human. In 2018, an MR study screened the association between the genetic determinants of 227 biomarkers and CAD, and identified serum CSF1 and CXCL12 as novel causal mediators of CAD [8]. Since CSF1 is known to be upregulated by IL-1β, this causal association is consistent with the protective effect of IL-1β antagonist canakinumab on CAD in the CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study) [8]. Such a comprehensive screening approach could also be applied in COVID-19 patients to identify the biomarkers causally associated with disease severity, which may elucidate potential therapies for COVID-19. Interestingly, a recent MR study found tentative causal contributions of diabetes-related traits as well as several druggable blood proteins on increased *ACE2* expression in lung tissue [9]. Since the increased lung *ACE2* expression is not equivalent to the susceptibility or disease severity of COVID-19, future MR studies on COVID-19 patients with well-defined phenotypes of disease outcomes will be more directly informative to prioritize treatment candidates. Finally, it has to be noted that it may be challenging in MR studies to choose the correct genetic instruments to model the effects of certain drugs, especially for drugs with multiple targets or mechanisms not fully known.

The retrospective design but prospective nature of MR renders its unique advantage during pandemic, which has the potential to dramatically accelerate the translation of epidemiological studies into insights of pathophysiology and targeted therapies in COVID-19. Besides, the advances in genetics provides additional opportunities to promote disease risk prediction through genetic risk scores (GRS), which have been shown effective for CAD risk prediction [4]. Recently, collaborative sequencing projects have been launched to search for human genetic variants that associate with the diverse clinical outcomes of COVID-19 [10], which may contribute to genetic risk prediction of disease severity and exploration of potential drug targets of COVID-19 in the future. Genetics studies hold promise to provide advanced tools in our battle against the COVID-19 pandemic.

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Author Contributions

YT and SZ conceived the commentary. YT did the literature search and wrote the first draft. JX helped with literature search and revised the manuscript. YZ, ZL, and SZ provided critical revision to the manuscript. All authors have read and approved the manuscript. SZ made the full decision to publish the manuscript in its current form.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

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