Obesity and COVID-19

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Actionable targets to reduce COVID-19 severity

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Identifying mechanistic pathways that link obesity with COVID-19 severity provides targets for interventions to reduce the high risk of severe outcomes owing to obesity. The authors of a recent study use genomics and proteomics to show that nephronectin could be involved in one of these pathways.

The COVID-19 pandemic, which began in December 2019, is a major global health crisis that has led to more than 6.6 million deaths as of December 2022. Although traditional herd immunity is not likely to be the pathway to successfully ending this pandemic[1], many epidemiological studies have been conducted to explore factors that contribute to COVID-19 susceptibility and severity. However, these studies have primarily been observational and are therefore difficult to interpret, owing to confounding, selection bias and reverse causation[2]. These biases may have also contributed to paradoxical findings such as the inverse association between smoking and COVID-19 severity[2], which has confused policy formulation and public health messages that aim to mitigate the associated disease burden. Subsequent studies, including Mendelian randomization studies, have clarified factors that are likely to be relevant to COVID-19 risk — notably, obesity and smoking[3]. Mendelian randomization studies use genetics to investigate the causal role of exposures in health outcomes. As genetic variants are randomly allocated at conception, this resembles the randomization process used in randomized controlled trials and makes Mendelian randomization studies less vulnerable to confounding, as compared to conventional observational studies[4]. However, few studies have assessed the mechanistic pathways that link these exposures to COVID-19 severity. Understanding these pathways may help identify targets for interventions that aim to mitigate the associated risk among people who are predisposed to elevated risks of severe COVID-19, especially if the exposure is difficult to change. In the current issue of *Nature Metabolism*, Yoshiji et al. investigated the proteomic pathways that link obesity with COVID-19 severity, using primarily Mendelian randomization[5].

In their study, a two-step Mendelian randomization design was used to assess mediation by proteins. In brief, the authors initially assessed the association of body mass index (BMI) with plasma proteins and identified around 1,200 proteins that are strongly associated with BMI (step 1)[5]. Then, they assessed the association of shortlisted proteins with severity outcomes for COVID-19 (step 2) (Fig. 1). They showed that nephronectin (NPNT) and hydroxysteroid 17-β dehydrogenase 14 (HSD17B14) are associated with severity outcomes for COVID-19. To validate the putative causal association, the authors also included colocalization; used other adiposity measurements that correlate better with body fat accumulation (for example, body fat percentage); and performed fine-mapping, single-cell RNA sequencing analysis and observational association studies. They concluded that NPNT — but not HSD17B14 — partially mediated the association of obesity with severity outcomes for COVID-19 (ref. [5]).

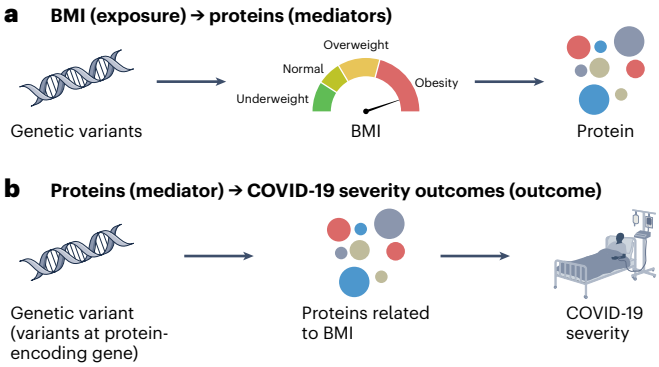

Fig. 1 | Use of two-step Mendelian randomization to explore the mechanistic pathway that links obesity with severity outcomes for COVID-19. In this study[5], the authors explored the mechanistic pathway that links obesity with severity outcomes for COVID-19 using a design known as two-step Mendelian randomization. Mendelian randomization makes use of genetics randomly allocated at conception, and hence resembles the randomization process in randomized controlled trials. As such, findings from Mendelian randomization are less vulnerable to confounding than conventional observational studies. **a**, In this study, the first step assessed the association of BMI with 4,907 proteins using Mendelian randomization. **b**, The second step assessed the association of shortlisted proteins related to BMI with severity outcome for COVID-19 using Mendelian randomization. Image credit (protein structure): Unnaugan/Alamy Stock Photo.

On the basis of their study, NPNT is likely to be an actionable target to reduce the elevated risk of COVID-19 severity due to obesity, and the authors further proposed the use of interventions that may improve weight loss, such as the use of glucagon-like peptide 1 (GLP-1) receptor agonists[5]. Apart from the NPNT pathway, there are probably other pathways that could explain the increased risk of severe COVID-19 due to obesity as only 11–14% of the total effect of BMI with severity outcomes for COVID-19 was mediated by NPNT. Another Mendelian randomization study[6] has suggested that plasma angiotensin-converting enzyme 2 (ACE2) may also mediate part of the pathway that links obesity and severity outcomes for COVID-19. ACE2 is potentially modifiable as a preclinical study[7] has suggested that an off-patent medication (ursodeoxycholic acid) could downregulate ACE2 and thus reduce SARS-CoV-2 infection. Additional follow-up studies on the putative pathways — such as using different protein quantification technologies with varying precision, accuracy and breadth[8] — will improve our search for approved or well-studied drugs to be repurposed for reducing the severity of COVID-19 in patients with obesity. This approach is likely to be more efficient and practical than developing a new medication, and to have a lower development cost, faster development timeline and better information on safety profile[9].

An important highlight of this study is its design, which is mainly based on Mendelian randomization with publicly available summary

statistics from large genome-wide association studies (GWAS). Although (as with all epidemiological designs) Mendelian randomization has its own assumptions (relevance, independence and exclusion restriction)[4], a properly conducted Mendelian randomization study tends to give findings that are consistent with randomized controlled trials[10]. Mendelian randomization studies have also clarified previous paradoxical findings concerning smoking and COVID-19 risk in observational studies[11], which were probably due to selection bias.

Before the COVID-19 pandemic, Mendelian randomization studies were often used to address questions related to noncommunicable diseases[10], but Mendelian randomization studies in infectious diseases are rare. One likely reason is the lack of corresponding large GWAS datasets of infectious diseases. For example, the majority of GWAS have focused on noncommunicable diseases (for example, coronary artery disease and type 2 diabetes)[12,13]. Conversely, GWAS on infectious diseases were much smaller in sample size and limited in disease phenotypes until the COVID-19 Host Genetics Initiative (COVID-19 HGI), which involves collaborations from numerous studies across the globe with constant updates on summary statistics, was established in 2020[14,15]. In fact, a systematic review of Mendelian randomization studies related to COVID-19 has also shown that the data from COVID-19 HGI were used in most of the Mendelian randomization studies of COVID-19 (ref. [3]). This highlights the importance of large GWAS on infectious diseases of global health importance, such as viral hepatitis and tuberculosis, as these data (if available) will probably improve overall understandings of the effect of exposures on the risk of these diseases using Mendelian randomization as well as improve our ability to search for medication to reduce the severity of infectious diseases.

In conclusion, the study by Yoshiji et al. demonstrates that NPNT is an actionable target that mediates the relationship between obesity and COVID-19 severity, although it is likely that there are additional unexplored pathways[5]. Using the same approach in exploring other domains within the exposomes (for example, metabolomics and microbiome) may help to identify additional actionable targets and thus to devise corresponding interventions to mitigate elevated risk of severe COVID-19, which is particularly important for individuals with obesity who have an elevated risk of severe COVID-19 but may not respond well to weight loss interventions. Furthermore, Mendelian randomization studies can also be applied to address questions related to other infectious diseases, subject to the availability of GWAS of infectious diseases. COVID-19 HGI has already demonstrated the effect that this can bring about in infectious disease research.

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Competing interests

The authors declare no competing interests.