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RESEARCH LETTER

Cardiometabolic Traits, Sepsis, and Severe COVID-19

A Mendelian Randomization Investigation

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current coronavirus disease 2019 (COVID-19) pandemic. Many patients with severe COVID-19 develop sepsis. Cardiometabolic traits have been associated with increased risk of severe COVID-19 and sepsis; however, it is difficult to infer causal effects from observational studies because of the possibility that any identified associations may be attributable to confounding. Here, we leverage data from large-scale genetic association studies to identify genetic proxies for body mass index (BMI), lifetime smoking score, low-density lipoprotein cholesterol, systolic blood pressure, and type 2 diabetes (T2DM) liability, and apply these in Mendelian randomization (MR) analyses investigating their associations with risk of sepsis and severe COVID-19. Through leverage of randomly allocated genetic variants, this approach can better overcome the confounding that hinders causal inference in observational studies.

The methods and data sources relating to this work are described in detail elsewhere.[1] Briefly, genetic variants selected as instrumental variables were uncorrelated (r^2<0.001) single-nucleotide polymorphisms associated with the corresponding exposure trait at genome-wide significance (P<5×10^{-8}) in previously published genome-wide association study analyses.[1] Summary genetic association estimates for sepsis were obtained from the UK Biobank (10 154 cases and 452 764 controls) and HUNT Study (Trøndelag Health Study; 2301 cases and 67 121 controls).[1] We defined sepsis using a previously published list of explicit *International Classification of Diseases, Ninth Revision*, and *International Classification of Diseases, Tenth Revision*, codes derived by a panel of experts in critical care, infectious diseases, pediatrics, and sepsis epidemiology.[1] This was a binary variable based on the presence of 1 or more codes as a main or secondary diagnosis in the hospital inpatient admissions data or as a primary or secondary cause of death in the death registry data.[1] Sepsis cases were not restricted to those with presumed bacterial infection. Summary genetic association estimates for risk of severe COVID-19 with respiratory failure were obtained from a genome-wide association study performed in 1610 cases and 2205 controls (with no or mild COVID-19 symptoms) in Italy and Spain.[2] Genetic association estimates for hospitalization with COVID-19 were obtained from release 3 (June 2020) of the COVID-19 Host Genetics Initiative Genome-Wide Association Study, which considered 3199 cases and 897 488 controls from the general population.[3] The main MR analyses were performed using the inverse-variance weighted method, and sensitivity analyses were performed using the weighted median and the MR-Egger methods.[4] All summary data used in this work are publicly available, and they were obtained with relevant participant consent and ethical approval.

The MR analyses showed that higher genetically proxied BMI and lifetime smoking score were associated with increased risk of developing sepsis in both UK Biobank and the HUNT Study. Both higher genetically proxied BMI and

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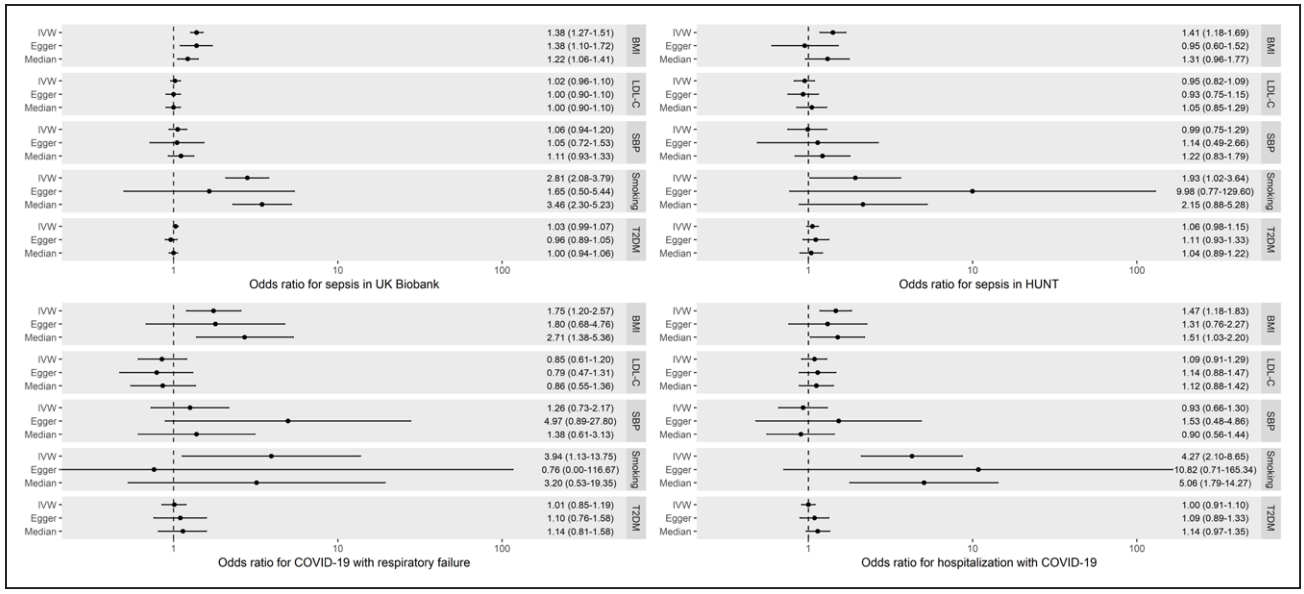

Figure. Results of Mendelian randomization (MR) analyses investigating the association of genetically proxied cardiometabolic traits with risk of sepsis and severe coronavirus disease 2019 (COVID-19).
Top left, sepsis, UK Biobank, 10 154 cases and 452 764 controls; **Top right**, sepsis, HUNT Study (Trøndelag Health Study), 2301 cases and 67 121 controls; **Bottom left**, COVID-19 with respiratory failure; 1610 cases and 2205 controls; bottom right: hospitalization with COVID-19, 3199 cases and 897 488 controls. Results are expressed per SD increase in genetically proxied levels of the exposure for continuous traits (BMI, LDL-C, SBP, and smoking), and per unit increase in log odds ratio for genetically proxied T2DM liability. The MR-Egger intercept *P* value was >0.05 for all analyses. BMI indicates body mass index; IVW, inverse-variance weighted Mendelian randomization; LDL-C, low-density lipoprotein cholesterol; median, weighted median MR; SBP, systolic blood pressure; smoking, lifetime smoking score; and T2DM, type 2 diabetes.

lifetime smoking score were also associated with increased risk of severe COVID-19 with respiratory failure and hospitalization with COVID-19 (Figure). Similar estimates were obtained in MR sensitivity analyses, although with wider 95% CIs (Figure). There was no strong evidence supporting an association of genetically proxied low-density lipoprotein cholesterol, systolic blood pressure, or T2DM liability with risk of sepsis or severe COVID-19.

Taken together, our findings support the hypothesis that elevated BMI and smoking increase susceptibility to sepsis and severe COVID-19. Many potential mechanisms may be underlying this causal relationship, especially immune dysregulation.[5] Furthermore, obesity and smoking status are both modifiable traits that may be targeted to reduce COVID-19–associated morbidity and mortality.

Our study has many strengths. We considered distinct data sources and performed MR methods that vary in their requisite assumptions about the inclusion of pleiotropic variants. Although the results were consistent, particular methods produced wider CIs than others, in keeping with known differences in their statistical power.[4] Furthermore, we considered COVID-19 cases that were severe enough to require hospitalization, and as such there was less risk of selection bias related to COVID-19 diagnosis, as all such patients would be expected to undergo testing.

Our study also has limitations. Our investigation was based on European ancestry participants. Initiatives to identify genetic factors related to risk of severe COVID-19 are ongoing,[3] and such work will also expand to other ethnic groups. It is important to appreciate that MR effect estimates should not be directly extrapolated to predict the effect of an intervention, but should rather be used as evidence to support a causal relationship. Although we explored the association of genetically proxied T2DM liability with risk of sepsis and severe COVID-19, we were not able to assess the effect of a clinical T2DM diagnosis directly, because for most individuals presence of these genetic variants does not necessarily result in a T2DM diagnosis. Thus, there may be a causal relationship between diabetes (or glycemic control) and severe COVID-19 that our study could not detect. Our analyses also had limited statistical power, as apparent from the CIs of the results. Given that the genetic variants used to proxy systolic blood pressure, low-density lipoprotein cholesterol, and T2DM explained 2.9%, 7.9%, and 16.3% of the variance in these traits, respectively,[1] our main MR analysis had 80% power to detect an odds ratio for hospitalization with COVID-19 of 1.29 for systolic blood pressure, 1.18 for low-density lipoprotein cholesterol, and 1.12 for T2DM liability.

In conclusion, we leveraged large-scale genetic summary data to investigate the effects of cardiometabolic traits on risk of sepsis and severe COVID-19. Our findings support causal effects of elevated BMI and smoking on susceptibility to sepsis and severe COVID-19.

ARTICLE INFORMATION

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Disclosures

Dr Moore has consulted for DNAelectronics (2015–2018), Dairy Crest (2017–2018), bioMerieux (2013–2020), Pfizer (2018–2020), and Umovis Laboratory (2020); received speaker fees from Profile Pharma (2018); received research grants from the National Institute for Health Research (2013–2020), CW+ Charity (2018–2019), and Leo Pharma (2016); and received educational grants from Eumedica (2016–2018). Dr Gill is employed part-time by Novo Nordisk. The other authors report no conflicts.

REFERENCES

1. Ponsford MJ, Gkatzionis A, Walker V, Grant A, Wootton RE, Moore LSP, Fatumo S, Mason A, Zuber V, Willer C, et al. Cardiometabolic traits, sepsis and severe covid-19 with respiratory failure: a Mendelian randomization investigation [published online June 20, 2020]. *medRxiv*. doi: 10.1101/2020.06.18.20134676. https://www.medrxiv.org/content/10.1101/2020.06.18.20134676v1.
2. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernández J, Prati D, Baselli G, Asselta R, et al. Genome-wide association study of severe Covid-19 with respiratory failure [published online June 17, 2020]. *N Engl J Med*. doi:10.1056/NEJMoa2020283
3. COVID-Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur J Hum Genet*. 2020;28:715–718. doi: 10.1038/s41431-020-0636-6
4. Slob EAW, Burgess S. A comparison of robust Mendelian randomization methods using summary data. *Genet Epidemiol*. 2020;44:313–329. doi: 10.1002/gepi.22295
5. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation*. 2020;142:4–6. doi: 10.1161/CIRCULATIONAHA.120.047659