Cardiometabolic traits, sepsis and severe COVID-19: a Mendelian randomization investigation

Running title: Cardiometabolic traits, sepsis and severe COVID-19

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Conflict of Interest Disclosures
LSPM has consulted for DNAelectronics (2015-18), Dairy Crest (2017–2018), bioMerieux (2013-20), Pfizer (2018-2020), and Umovis Lab (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). DG is employed part-time by Novo Nordisk. All other authors have no conflicts of interest to declare.

Funding sources
MJP is a funded by the Welsh Clinical Academic Training programme and is a participant in the NIH Graduate Partnership Program. AG1 is funded by a Medical Research Council Methodology Research Panel grant (RG88311). VW is supported by the Medical Research Council Integrative Epidemiology Unit. The Medical Research Council and the University of Bristol support the Medical Research Council Integrative Epidemiology Unit [MC_UU_00011/1]. REW is supported by Wellcome Trust grant (204895/Z/16/Z). LSPM acknowledges the National Institute of Health Research Imperial Biomedical Research Centre and the National Institute of Health Research Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England. NMD and ES are supported by Norwegian Research Council Grants number 295989 and 312769, respectively. SB and AG2 are supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (204623/Z/16/Z). DG is supported by the British Heart Foundation Research Centre of Excellence (RE/18/4/34215) at Imperial College London. This work was supported by funding from the National Institute for Health Research (Cambridge Biomedical Research Centre at the Cambridge University Hospitals National Health Service Foundation Trust). The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health and Social Care. The funding sources did not have any role in designing the study, performing analysis or communicating findings. The genotyping in the Nord-Trøndelag Health Study was financed by the National Institutes of Health; University of Michigan; the Research Council of Norway; the Liaison Committee for Education, Research and Innovation in Central Norway; and the Joint Research Committee between St Olavs Hospital and the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology.

Acknowledgements
DG, SB and MJP designed the project. VW, ND, BOA, ES and TR provided the data. TR, VW, AG1, SF and DG analyzed the data. MJP, AG1, VW, AG2, SF, TR and DG drafted the manuscript. All authors interpreted the results and critically revised the manuscript for intellectual content. This research was conducted using the UK Biobank Resource under Application Number 743915825. Quality Control filtering of the UK Biobank data was conducted by R. Mitchell, G. Hemani, T. Dudding, L. Corbin, S. Harrison, L. Paternoster as described in the published protocol (doi: 10.5523/bris.1ovaau5sxunp2cv8rcy88688v). The MRC IEU UK Biobank GWAS pipeline was developed by B. Elsworth, R. Mitchell, C. Raistrick, L. Paternoster, G. Hemani, T. Gaunt (doi: 10.5523/bris.pnoat8cxo0u52p6ynfaekeigi). The views expressed are those of the authors and not necessarily those of the National Health Service, National Institute for Health Research, or

Department of Health and Social Care. The Nord-Trøndelag Health Study is a collaboration between the Nord-Trøndelag Health Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

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 due to 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 (LDL-C), systolic blood pressure (SBP) and type 2 diabetes mellitus (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 study.

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 ($p < 5x10^{-8}$) in previously published genome-wide association study (GWAS) analyses.[1] Summary genetic association estimates for sepsis were obtained from the UK Biobank (10,154 cases and 452,764 controls) and HUNT Study (2301 cases and 67,121 controls).[1] We defined sepsis using a previously published list of explicit ICD-9 and ICD-10 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 one 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 GWAS 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 GWAS, 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 obtained 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 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% confidence intervals (**Figure**). There was no strong evidence supporting an association of genetically proxied LDL-C, SBP 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. A number of potential mechanisms may be underlying this causal relationship, most notably 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 a number of strengths. We considered distinct data sources and performed MR methods that vary in their requisite assumptions regarding the inclusion of pleiotropic variants. While the results were consistent, particular methods produced wider confidence intervals 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, as 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. Finally, our analyses also had limited statistical power, as apparent from the confidence intervals of the results. Given that the genetic variants used to proxy SBP, LDL-C 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 SBP, 1.18 for LDL-C 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.

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. *medRxiv*. Preprint posted online June 20, 2020. doi: 10.1101/2020.06.18.20134676.
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. *N Engl J Med*. 2020. 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.
4. Slob EAW and Burgess S. A comparison of robust Mendelian randomization methods using summary data. *Genet Epidemiol*. 2020;44:313-329.
5. Sattar N, McInnes IB and McMurray JJV. Obesity Is a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms. *Circulation*. 2020;142:4-6.

Figure title

Figure. Results of Mendelian randomization analyses investigating the association of genetically proxied cardiometabolic traits with risk of sepsis in UK Biobank (top left; 10,154 cases and 452,764 controls) and the HUNT Study (top right; 2301 cases and 67,121 controls), and risk of severe COVID-19 with respiratory failure (bottom left; 1610 cases and 2205 controls) and hospitalization (bottom right; 3199 cases and 897,488 controls).

Figure legend

Results are expressed per standard deviation increase in genetically proxied levels of the exposure for continuous traits (BMI, LDL, 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: body mass index; IVW: inverse-variance weighted Mendelian randomization; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; Smoking: lifetime smoking score; T2DM: type 2 diabetes mellitus; Median: weighted median Mendelian randomization.