Cardiometabolic Risk Factors for COVID-19 Susceptibility and Severity: A Mendelian Randomization Analysis

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Word count: 2,722

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
ABSTRACT

Importance: Early epidemiological studies report associations of diverse cardiometabolic conditions especially body mass index (BMI), with COVID-19 susceptibility and severity, but causality has not been established. Identifying causal risk factors is critical to inform preventive strategies aimed at modifying disease risk.

Objective: We sought to evaluate the causal associations of cardiometabolic conditions with COVID-19 susceptibility and severity.

Design: Two-sample Mendelian Randomization (MR) Study.

Setting: Population-based cohorts that contributed to the genome-wide association study (GWAS) meta-analysis by the COVID-19 Host Genetics Initiative.

Participants: Patients hospitalized with COVID-19 diagnosed by RNA PCR, serologic testing, or clinician diagnosis. Population controls defined as anyone who was not a case in the cohorts.

Exposures: Selected genetic variants associated with 17 cardiometabolic diseases, including diabetes, coronary artery disease, stroke, chronic kidney disease, and BMI, at \( p<5\times10^{-8} \) from published largescale GWAS.

Main outcomes: We performed an inverse-variance weighted averages of variant-specific causal estimates for susceptibility, defined as people who tested positive for COVID-19 vs. population controls, and severity, defined as patients hospitalized with COVID-19 vs. population controls, and repeated the analysis for BMI using effect estimates from UKBB. To estimate direct and indirect causal effects of BMI through obesity-related cardiometabolic diseases, we performed pairwise multivariable MR. We used \( p<0.05/17 \) exposure/2 outcomes=0.0015 to declare statistical significance.
**Results:** Genetically increased BMI was causally associated with testing positive for COVID-19 [6,696 cases / 1,073,072 controls; \( p=6.7 \times 10^{-4} \), odds ratio and 95% confidence interval 1.08 (1.03, 1.13) per kg/m\(^2\)] and a higher risk of COVID-19 hospitalization [3,199 cases/897,488 controls; \( p=8.7 \times 10^{-4} \), 1.12 (1.04, 1.21) per kg/m\(^2\)]. In the multivariable MR, the direct effect of BMI was abolished upon conditioning on the effect on type 2 diabetes but persisted when conditioning on the effects on coronary artery disease, stroke, chronic kidney disease, and c-reactive protein. No other cardiometabolic exposures tested were associated with a higher risk of poorer COVID-19 outcomes.

**Conclusions and Relevance:** Genetic evidence supports BMI as a causal risk factor for COVID-19 susceptibility and severity. This relationship may be mediated via type 2 diabetes. Obesity may have amplified the disease burden of the COVID-19 pandemic either single-handedly or through its metabolic consequences.
KEY POINTS

**Question:** Is there a causal association between cardiometabolic conditions and COVID-19 susceptibility or severity?

**Findings:** Using two-sample Mendelian randomization of 17 cardiometabolic diseases and traits, only body mass index was found to be causally associated with testing positive for COVID-19 (6,696 cases/1,073,072 controls; \( p = 6.7 \times 10^{-4} \)) and a higher risk of COVID-19 (3,199 cases/897,488 controls; \( p = 8.7 \times 10^{-4} \)).

**Meaning:** Genetic evidence supports BMI as a causal risk factor for COVID-19 susceptibility and severity.
INTRODUCTION

There is high heterogeneity in both susceptibility and severity of SARS-CoV2 infection with clinical severity\textsuperscript{1,2} ranging from asymptomatic carriers to life-threatening respiratory failure and death\textsuperscript{3}. Epidemiological studies using both retrospective and prospective cohorts of different sizes and from multiple countries have reported evidence that underlying cardiometabolic conditions\textsuperscript{4-29} may be associated with an increased risk of severe COVID-19 illness (i.e., hospitalization, intubation, mechanical ventilation or death\textsuperscript{30}). Coronary artery disease\textsuperscript{4-6}, chronic kidney disease\textsuperscript{7-12}, obesity\textsuperscript{13-17} and type 2 diabetes\textsuperscript{8,18-21} have a strong and consistent evidence for association with COVID-19 severity\textsuperscript{30}. There is less compelling evidence for cerebrovascular disease\textsuperscript{4,22-28} (i.e., stroke) and hypertension\textsuperscript{4,6,27-29} leading to severe manifestations of COVID-19. Additional evidence suggests that these cardiometabolic traits may be associated with disease susceptibility\textsuperscript{31}; however without universal testing, this correlation is difficult to prove.

While early reports are crucial to inform clinical decision making and public health policy during a pandemic of a new pathogen, correlative observational data can be plagued by residual confounding. Thus, there remain inherent challenges in drawing causal inferences from these epidemiologic studies. Mendelian Randomization (MR) is an analytic approach that uses human genetic variation known to influence modifiable exposures to examine their causal effect on disease\textsuperscript{32}. MR is especially useful for disentangling causal pathways of phenotypically clustered risk factors that are difficult to randomize or prone to measurement error. By identifying causal relationships between cardiometabolic risk factors and COVID-19 susceptibility or severity, we may be able to mitigate their impact on disease risk and avoid spurious conclusions that lead to misinformation or incite unnecessary anxiety.
We hypothesize that only some cardiometabolic conditions have a causal relationship with COVID-19 illness or its disease course. Thus, we sought to evaluate the causal associations of 17 cardiometabolic exposures with COVID-19 susceptibility and severity using two-sample MR analyses. Causal effects were estimated from genome-wide association studies (GWAS) summary statistics of these cardiometabolic diseases and related traits and COVID-19-related outcomes from the COVID-19 host genetics initiative (https://www.covid19hg.org/)33.

METHODS

Candidate instrument selection for cardiometabolic diseases and traits

We extracted association summary statistics from published large-scale GWAS meta-analysis to generate sets of genetic instruments for 17 cardiometabolic diseases and traits, type 1 diabetes34, type 2 diabetes35, hemoglobin A1c36, fasting glucose adjusted for body mass index (BMI)36, fasting insulin adjusted for BMI36, BMI37, waist-hip ratio38, low-density lipoprotein cholesterol39, high-density lipoprotein cholesterol39, triglycerides39, systolic blood pressure40, diastolic blood pressure40, creatinine-based estimated glomerular filtration rate (eGFR)41, chronic kidney disease41 coronary artery disease42, any stroke43, and c-reactive protein44 (CRP), a non-specific biomarker of inflammation that can be elevated in people with high cardiometabolic risk. We used genetic variants associated with these exposures at genome-wide significance (p<5x10^-8) and excluded those that were not represented in the COVID-19 outcome GWAS datasets. Using the LD_clumping function, we pruned the list of candidate instruments for linkage disequilibrium (LD; R^2>0.01) and discarded variants that were within 1-Mb distance from other candidate instruments with a stronger association. Analyses were performed using the R package “twosampleMR” v.4.045,46.

COVID-19 susceptibility and severity from the COVID-19 Host Genetics GWAS meta-analysis
The COVID-19 Host Genetics Initiative is an international genetics collaboration that aims to uncover the genetic determinants of outcomes related to COVID-19 susceptibility and severity\(^3\). To accomplish this, investigators from around the world assembled individual-level clinical and genetic data and performed individual GWAS. Summary statistics were shared via a cloud-based computing platform, and centralized meta-analysis was performed. Single-variant association testing were adjusted for age, age\(^2\), sex, age*sex, genetic ancestry principal components and other study-specific covariates. An allele frequency filter of 0.0001 and an INFO filter of 0.6 was applied to each study prior to meta-analysis with inverse-variance weighting. Summary statistics from the third round of GWAS meta-analysis, shared publicly on July 2, 2020, were used to test the 17 sets of genetic instruments against COVID-19 outcomes assembled by the COVID-19 Host Genetics Initiative.

For our two primary analyses, we selected the COVID-19 outcomes with the largest number of cases. For Susceptibility: 1) COVID-19 by RNA PCR, serologic testing, or clinician diagnosis by chart review or ICD-coding (6,696) vs. population controls (N=1,073,072) and for Severity: 2) hospitalization of patients with COVID-19 by RNA PCR, serologic testing, or physician diagnosis (N=3,199) vs. population controls defined as any person who was not a case (i.e., people who tested negative, were never tested, or had an unknown testing status; N=897,488), As controls were not selected based on testing results, specific characteristics, or testing status, they were likely to be representative of the general population.

To determine whether statistically significant results from the primary analyses were consistent across different definitions for COVID-19 susceptibility, severity, and control groups, we performed secondary MR analyses of the four remaining available outcomes. For Susceptibility: 1) COVID-19 positive by RNA PCR, serologic testing, or clinician diagnosis (N=3,523) vs. COVID-19 negative by RNA PCR, serologic testing, or self-report (N=36,634); 2) predicted COVID-19 based on symptoms or COVID-19 positive by self-report (N=1,865) vs. no
predicted COVID-19 based on symptoms or no COVID-19 by self-report (N=29,174) using a model developed by Menni et al. 2020\textsuperscript{47}, and for Severity: 3) critical respiratory illness, defined by death, intubation, Continuous Positive Airway Pressure (CPAP), Bilevel Positive Airway Pressure (BiPAP), Continued external Negative Pressure (CNP), or very high flow positive end expiratory pressure oxygen in patients with COVID-19 by RNA PCR or serologic testing (N=536) vs. population controls (N=329,391) and 4) hospitalization (N=928) vs. no hospitalization within 21 days of testing positive for COVID-19 (N=2,028).

**Mendelian Randomization analysis of COVID-19 susceptibility and severity**

To estimate the causal association of each exposure with each outcome, we performed two-sample MR analyses using the random-effects inverse-variance weighted (IVW) method, whereby genetic variant-outcome coefficients were modeled as a function of genetic variant-exposure coefficients weighted by the inverse of the squared genetic variant-outcome standard errors\textsuperscript{48}. The use of random effects provides a concise estimation and considers potential heterogeneity among estimates from individual variants\textsuperscript{49}. We used $p<0.05 / 17$ exposures / 2 outcomes $= 0.0015$ to declare statistical significance with the understanding that this threshold may be conservative as exposures are clinically correlated. We reported causal effect estimates as odds ratios for the outcome per log-odds of binary exposures or unit change of continuous exposures. For BMI, we repeated the analysis using untransformed variables from UK Biobank (http://www.nealelab.is/uk-biobank) to report causal effect estimates per unit change of raw BMI.

**Accounting for pleiotropy**

An assumption of MR is that instruments do not influence the outcome independently of the risk factor of interest (i.e. non-mediated pleiotropy). We tested this assumption in a series of sensitivity analyses. We used the Weighted Median Estimator (WME)\textsuperscript{50} which requires $\geq 50\%$ of
the contribution to the causal estimate to be from valid instruments; if so, its causal estimate is stable. We then used the MR-Egger regression\textsuperscript{51} whereby a linear regression of variant-outcome on variant-exposure coefficients was performed without constraining the intercept to the origin. The slope of the regression line provides the corrected causal estimates even when none of the instruments are valid\textsuperscript{51}. Next, we used the mode-based estimate which is consistent when the largest number of similar single-variant MR estimates are derived from valid instruments even when the majority are invalid\textsuperscript{52}. If all MR models produce similar causal estimates despite making different assumptions on the validity of instruments, we would be more confident of the robustness of our results\textsuperscript{53}. In other sensitivity analysis, we applied MR pleiotropy residual sum and outlier (MR-PRESSO)\textsuperscript{54} and leave-one-out analysis to determine whether outliers may be biasing the overall causal estimate. To estimate direct and indirect causal effects of BMI via obesity-related cardiometabolic diseases, CAD, stroke, CKD, type 2 diabetes, and CRP, we performed pairwise multivariable MR wherein we conditioned upon the effects of these exposures with BMI to simultaneously estimate their independent causal effects.

RESULTS

Selection of genetic instruments for exposures

We obtained genetic instruments for the 17 exposures for MR analyses after excluding variants that were in LD ($r^2 > 0.01$) and in close proximity (1 Mb) to other candidate instruments with stronger $P$-values. Genetic instruments explained between 0.2 to 5.3% of the variance or liability of each exposure (Table 1). Contributing studies included in these exposure GWAS meta-analyses were predominantly of European ancestry.

Causal effect of each cardiometabolic exposure on COVID-19 susceptibility and severity

Of the 17 cardiometabolic exposures, only BMI was found to be causally associated with
COVID-19 susceptibility and severity even after accounting for multiple testing (Figure 1). Genetically increased BMI was associated with a higher risk of testing positive for COVID-19 \( (p=6.7 \times 10^{-4}) \) and a higher risk of COVID-19 hospitalization \( (p=8.7 \times 10^{-4}) \) compared to population controls using random effects IVW (Figure 1). For both outcomes, we identified no heterogeneity of effects \( (p=0.52; \ p=0.49,) \) or outlying genetic variants by the leave-one-out analysis or MR-PRESSO. To obtain interpretable effect estimates, we repeated the analysis using beta estimates of raw BMI from UK Biobank\textsuperscript{55} and found consistent results: odds ratio 1.08 per kg/m\(^2\) increase in BMI (95% CI 1.03, 1.13, \( p=1.3 \times 10^{-3} \) for testing positive with COVID-19; odds ratio 1.12 per kg/m\(^2\) increase in BMI (95% CI 1.04, 1.21, \( p=1.7 \times 10^{-3} \) for COVID-19 hospitalization. Point estimates from the MR-Egger, WME, and weighted MODE, were in the same direction as IVW (Figure 2 and Supplemental Figures 1-6). The MR-Egger intercept \( p \) was 0.49 and 0.24 for susceptibility and severity, respectively, indicating the absence of directional pleiotropy. The MR results of the remaining four COVID-19 susceptibility and severity outcomes had \( p>0.001 \) (Supplemental Table 1).

To determine whether the causal effect of BMI was mediated through obesity-related cardiometabolic diseases, we performed pairwise multivariable MR of BMI with each of the cardiometabolic diseases, type 2 diabetes, chronic kidney disease, coronary artery disease, any stroke, and CRP. The direct effects of BMI on the two COVID-19 outcomes were abolished upon conditioning on the genetic effects of type 2 diabetes \( (p>0.05) \). Adjusting for the genetic effects on the other diseases did not attenuate the direct effect of BMI \( (p<0.05, \text{Supplemental Table 2}) \)

While none of the other cardiometabolic exposures was found to increase COVID-19 susceptibility or severity, we found a borderline association between having a higher genetic predisposition to T1D with a lower risk of testing positive for COVID-19 and hospitalization vs. population controls, though the associations were not statistically significant after accounting for
multiple testing (Supplemental Table 3).

**DISCUSSION**

Cardiometabolic diseases have been identified to be risk factors for COVID-19 illness\(^{30}\). Since risk factors may be only correlated, and not causally related, with outcomes of interest, it is paramount to assess causality to inform preventive strategies. Using two-sample MR, we found that genetically increased BMI was the only risk factor for COVID-19 susceptibility and severity among the 17 cardiometabolic diseases and traits tested, whereby the odds of testing positive for COVID-19 was 8\% higher per kg/m\(^2\) increased in BMI and the odds of hospitalization with COVID-19 was 12\% higher per kg/m\(^2\) increase in BMI than the general population. Our MR findings support the multiple epidemiologic studies that have reported a strong and robust association between obesity and COVID-19 illness\(^{13-17}\). Adjusting for the genetic effect of type 2 diabetes obliterated the direct causal effect of BMI, suggesting that type 2 diabetes may be a mediator in the causal association of BMI and COVID-19 illness. By understanding causality, we can aim to modify causal exposures for the purpose of mitigating disease risk.

Apart from BMI, the other cardiometabolic exposures tested are unlikely to play a key causal role in contracting COVID-19 or worsening the illness. Observational correlations of cardiometabolic conditions with COVID-19 outcomes may be partly due to clinical clustering with obesity. It is noteworthy that correlational risk factors can still have clinical utility in identifying at-risk patients even if causality is refuted. However, if preventive efforts only target correlated, but not causal, risk factors, disease risk may not be reduced. We found a negative trend between a higher genetic predisposition for type 1 diabetes and a lower risk of hospitalization and testing positive for COVID-19. A negative association with COVID-19
outcomes could be observed if people with underlying medical conditions were more likely than
the general population to undergo testing for COVID-19 and receive a negative test result, made
concerted efforts at reducing their risk of viral exposure in response to public health messaging,
or were encouraged by health professionals to recuperate at home and not come to the hospital
when ill with mild viral symptoms. We could speculate that the autoimmune nature of type 1
diabetes provides protection compared to the general population. Additionally, it is noteworthy
that people with T1D, unlike T2D, do not generally have higher BMI than the general population.
More investigation is needed to further understand the cause of this negative association.

Our study had limitations. The variances explained in the exposures by genetic
instruments were modest, though well within the ranges that were typical for complex traits. The
use of weak genetic instruments could have limited our ability to detect subtle causal
associations and does not exclude the possibility of modest effects. It is also possible that, with
larger sample sizes, the association of other cardiometabolic exposures with COVID-19
outcomes may become significantly significant and confidence intervals would narrow around
ture estimates. Additionally, our analysis did not factor non-linear exposure-outcome
relationships. The causal estimates by MR-Egger were not as compelling suggesting that
horizontal pleiotropy or other confounding factors could have biased estimates. Yet, MR-Egger
is a less efficient estimator than the other methods\textsuperscript{50} and is generally considered as only one of
several sensitivity analyses used to evaluate the plausibility of findings. In our primary analyses
we chose to use controls that were broadly defined as not being a case. Without universal
testing, the control group, albeit representative of the general population, could have been
contaminated with people who had contracted COVID-19, particularly those with only mild or no
viral symptoms (asymptomatic), which would have biases estimates towards the null.
Nevertheless, our results were consistent when using controls that were narrowly defined as
people who tested negative for COVID-19.
Obesity contributes to higher levels of circulating proinflammatory adipokines and cytokines\textsuperscript{56-61} which may intensify virally induced inflammation,\textsuperscript{62-69} and could contribute to acute respiratory distress syndrome, the main cause of mortality from COVID-19\textsuperscript{70,71}. We did not include critical respiratory illness in the primary analysis because the sample size of cases was small. When larger samples become available, future MR analyses can be performed to clarify whether the causal relationship between BMI and COVID-19 illness extends to critical respiratory illness. While contributing studies to the Host Genetics Initiative did not provide information on self-reported race or ethnicity, most were presumably European and association analyses were adjusted for ancestry PCs. Well-powered studies in people of non-European ancestral origins are critically needed to as ethnic and racial minorities in the U.S. are disproportionately affected by the pandemic\textsuperscript{7,11,27,72-74}. We recognize that the primary social drivers of viral exposure and spread (i.e., crowding within households, wealth and education gaps, working in essential jobs that render social distancing challenging, language barriers, and poor access to healthcare) are likely correlated with, or are themselves, determinants of obesity\textsuperscript{75,76}. Future investigations are required to determine whether addressing these upstream social factors mitigates the impact of obesity on COVID-19 outcomes.

**CONCLUSION**

Our study provides genetic evidence that support or refute causality for a plethora of cardiometabolic conditions that can inform preventive strategies aimed at modifying risk of COVID-19 illness. Among the 17 cardiometabolic exposures tested, only BMI was found to be a causal risk factor for COVID-19 susceptibility and severity, which is consistent with multiple epidemiologic studies that have reported an association between obesity and COVID-19 illness. We conclude that obesity may have amplified the disease burden of the COVID-19 pandemic either single-handedly or through its metabolic consequences. To the extent that obesity is a modifiable risk factor with a strong environmental component, public health measures that aim
to diminish the societal obesity burden could be incorporated into an effective preventive strategy for COVID-19 outcomes. Similarly, preventive measures that increase the risk of obesity (e.g. limitation of access to open spaces for exercise) should be viewed with caution. Future research is required to understand the mechanisms through which obesity increases the risk of COVID-19 outcomes, and whether obesity-related conditions are along the causal pathway. Our study has shown how large-scale genotype-phenotype summary data rapidly assembled during a pandemic and made freely accessible to the research community can accelerate research with immediate and direct application to clinical practice and public health messaging.
CONFLICTS OF INTERESTS

None of the authors declare potential conflicts of interests relevant to this manuscript.

FUNDING AND ROLE OF SPONSOR

The project was partly supported by American Diabetes Association grant #7-20-COVID-003 and the American Diabetes Association Innovative and Clinical Translational Award 1-19-ICTS-068. JBC is supported by American Diabetes Association Postdoctoral Fellowship 1-19-PDF-028. AL is supported by Grant 2020096 from the Doris Duke Charitable Foundation. LB is partially supported by Apple Inc. JBM is supported by R01DK078616, U01DK078616 and R01HL151855. JCF is supported by NIDDK K24 DK110550. The funders played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DATA ACCESS AND RESPONSIBILITY

Drs. Aaron Leong and Josep M. Mercader had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

We thank all the genetics consortia and the COVID-19 Host Genetics Initiative for making summary statistics publicly accessible for this analysis. As supplemental information, we acknowledge the contribution of the studies in the COVID-19 Host Genetics Initiative listed at https://www.covid19hg.org/acknowledgements/ and list all MEGASTROKE authors. The MEGASTROKE project received funding from sources specified at http://www.megastroke.org/acknowledgments.html.
FIGURE LEGENDS

Figure 1. Forest plot causal effect estimates and 95% confidence interval for each exposure and the two main outcomes analyzed. Causal estimates are reported as odds ratios per unit of the exposure: hemoglobin A1c, A1C: %-unit; fasting glucose, FG: mg/dL; fasting insulin, FI: natural log; body mass index, BMI: inverse normally transformed residuals; waist-hip-ratio, WHR: inverse normally transformed residuals; c-reactive protein, CRP: rank-based inverse-normal transformed; low-density lipoprotein, LDL: standardized; high-density lipoprotein, HDL: standardized; triglycerides, TG: standardized; systolic and diastolic blood pressure: mmHg; eGFR ml min−1 per 1.73 m^2; type 1 diabetes, type 2 diabetes, coronary artery disease, chronic kidney disease, any stroke: log-odds.

Figure 2. Sensitivity analyses using other MR methods and results using UK Biobank effect estimates. Causal estimates were reported as odds ratios (OR) per unit increase in body mass index (BMI). Locke et al.: inverse normally transformed residuals; UK Biobank: kg/m^2
Table 1. Candidate genetic instruments of cardiometabolic diseases and traits.

| Exposure                     | PMID            | Sample size, N | Ancestry     | Candidate genetic instruments, N | Genetic instruments used in analysis, N | Estimated variance explained (%) |
|------------------------------|-----------------|----------------|--------------|----------------------------------|----------------------------------------|----------------------------------|
| Type 1 diabetes              | 25751624        | 6,808 cases/12,835 controls | European    | 75                               | 50                                     | 3.2                              |
| Type 2 diabetes              | 30297969        | 898,130 (9% cases) | European    | 243                              | 226                                    | 3.1                              |
| A1C                          | Chen J, BioRxiv 2020 | Up to 281,416 | 70% European | 216                              | 105                                    | 2.2                              |
| FG                           | Chen J, BioRxiv 2020 | Up to 281,416 | 70% European | 179                              | 91                                     | 1.6                              |
| FI adjusted for BMI          | Chen J, BioRxiv 2020 | Up to 281,416 | 70% European | 96                                | 61                                     | 1.0                              |
| BMI                          | 25673413        | Up to 339,224 | Mostly European | 75                               | 72                                     | 1.7                              |
| WHR adjusted for BMI         | 25673412        | Up to 224,459 | Mostly European | 53                                | 43                                     | 0.8                              |
| CRP                          | 31900758        | Up to 418,642 | European    | 439                              | 437                                    | 5.3                              |
| LDL                          | 24097068        | Up to 188,577 | European    | 65                                | 63                                     | 1.9                              |
| HDL                          | 24097068        | Up to 188,577 | European    | 54                                | 53                                     | 1.8                              |
| Triglycerides                | 24097068        | Up to 188,577 | European    | 39                                | 38                                     | 1.3                              |
| Systolic blood pressure      | 30224653        | >1,000,000    | European    | 185                              | 181                                    | 1.5                              |
| Diastolic blood pressure     | 30224653        | >1,000,000    | European    | 190                              | 183                                    | 1.5                              |
| Creatinine-based eGFR        | 31152163        | >1,000,000    | Mostly European | 547                              | 280                                    | 3.3                              |
| Chronic kidney disease       | 31152163        | 64,164 cases/561,055 controls | Mostly European | 23                               | 21                                     | 0.6                              |
| CAD                          | 28714975        | 10,801 cases/137,914 controls | Mostly European | 50                               | 50                                     | 0.9                              |
| Any stroke                   | 29531354        | 67,162 cases and 454,450 controls | Mostly European and East Asian | 23                               | 16                                     | 0.22                             |

Where available, we used European-specific effect estimates in the MR analysis. Sample sizes were the maximum number indicated in the published manuscript. Estimated variance explained by genetic instruments was a sum of estimated variance explained by each variant calculated from reported \( P \)-values, sample sizes, and proportion of cases and controls using the TwoSampleMR R functions `get_r_from_lor()` and `get_r_from_pn()`.
REFERENCES

1. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. The New England journal of medicine. 2020;382(10):970-971.
2. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA. 2020.
3. Fan S, He P, Guan J, Song W, Zhi H, Wang L. No association between interleukin-18 levels and risk of cardiovascular disease: A Mendelian randomization study. Hereditas. 2020;157(1):12.
4. Chen R, Liang W, Jiang M, et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. Chest. 2020;158(1):97-105.
5. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020.
6. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95.
7. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):458-464.
8. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020.
9. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation. N Engl J Med. 2020;382(25):2475-2477.
10. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. JAMA. 2020.
11. Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69(18):545-550.
12. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209-218.
13. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis. 2020.
14. Hur K, Price CPE, Gray EL, et al. Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19. Otolaryngol Head Neck Surg. 2020;163(1):170-178.
15. Simonnet A, Chetboun M, Poissy J, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020;28(7):1195-1199.
16. Kalligeros M, Shehadeh F, Mylona EK, et al. Association of Obesity with Disease Severity Among Patients with Coronavirus Disease 2019. Obesity (Silver Spring). 2020;28(7):1200-1204.
17. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.
18. Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab.* 2020;31(6):1068-1077 e1063.

19. Bode B, Garrett V, Messler J, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. *J Diabetes Sci Technol.* 2020;14(4):813-821.

20. Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes care.* 2020;43(7):1399-1407.

21. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest.* 2020;43(6):867-869.

22. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis.* 2020;29(8):104949.

23. Wang K, Zhang Z, Yu M, Tao Y, Xie M. 15-day mortality and associated risk factors for hospitalized patients with COVID-19 in Wuhan, China: an ambispective observational cohort study. *Intensive Care Med.* 2020;46(7):1472-1474.

24. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol.*

25. Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. *Eur J Intern Med.* 2020;76:97-99.

26. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. *J Infect.* 2020;80(6):639-645.

27. Killerby ME, Link-Gelles R, Haight SC, et al. Characteristics Associated with Hospitalization Among Patients with COVID-19 - Metropolitan Atlanta, Georgia, March-April 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(25):790-794.

28. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature.* 2020.

29. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.* 2020;55(5).

30. Centers for Disease Control and Prevention (CDC). Evidence used to update the list of underlying medical conditions that increase a person’s risk of severe illness from COVID-19. [https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html). Accessed 7/20/2020.

31. Jordan RE, Adab P. Who is most likely to be infected with SARS-CoV-2? *The Lancet Infectious Diseases.*

32. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol.* 2015;181(4):251-260.

33. Initiative C-HG. 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(6):715-718.

34. Onengut-Gumuscu S, Chen WM, Burren O, et al. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. *Nat Genet.* 2015;47(4):381-386.

35. Mahajan A, Talieu D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet.* 2018;50(11):1505-1513.

36. Chen J. The Trans-Ancestral Genomic Architecture of Glycaemic Traits. *bioRxiv.* 2020.

37. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature.* 2015;518(7538):197-206.
38. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature. 2015;518(7538):187-196.
39. Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45(11):1274-1283.
40. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet. 2018;50(10):1412-1425.
41. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nat Genet. 2019;51(6):957-972.
42. Nelson CP, Goel A, Butterworth AS, et al. Association analyses based on false discovery rate implicate new loci for coronary artery disease. Nat Genet. 2017;49(9):1385-1391.
43. Malik R, Chauhan G, Traylor M, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet. 2018;50(4):524-537.
44. Han X, Ong JS, An J, Hewitt AW, Gharaikhani P, MacGregor S. Using Mendelian randomization to evaluate the causal relationship between serum C-reactive protein levels and age-related macular degeneration. Eur J Epidemiol. 2020;35(2):139-146.
45. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018;7.
46. Walker VM, Davies NM, Hemani G, et al. Using the MR-Base platform to investigate risk factors and drug targets for thousands of phenotypes. Wellcome Open Res. 2019;4:113.
47. Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020.
48. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG, Consortium E-I. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol. 2015;30(7):543-552.
49. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. Stat Med. 2017;36(11):1783-1802.
50. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol. 2016;40(4):304-314.
51. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512-525.
52. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol. 2017;46(6):1985-1998.
53. Hwang LD, Lawlor DA, Freathy RM, Evans DM, Warrington NM. Using a two-sample Mendelian randomization design to investigate a possible causal effect of maternal lipid concentrations on offspring birth weight. Int J Epidemiol. 2019;48(5):1457-1467.
54. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nature genetics. 2018;50(5):693-698.
55. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203-209.
56. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6(10):772-783.
57. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol. 2009;6(6):399-409.
58. Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. *Atherosclerosis*. 2005;183(2):308-315.
59. Gil A, Maria Aguilera C, Gil-Campos M, Canete R. Altered signalling and gene expression associated with the immune system and the inflammatory response in obesity. *Br J Nutr*. 2007;98 Suppl 1:S121-126.
60. Romeo GR, Lee J, Shoelson SE. Metabolic syndrome, insulin resistance, and roles of inflammation–mechanisms and therapeutic targets. *Arterioscler Thromb Vasc Biol*. 2012;32(8):1771-1776.
61. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol*. 2011;11(2):98-107.
62. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *The Journal of clinical investigation*. 2020;130(5):2620-2629.
63. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI Insight*. 2020;5(10).
64. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020.
65. Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. *Acta Diabetol*. 2020;57(6):759-764.
66. Korakas E, Ikonomidis I, Kousathana F, et al. Obesity and COVID-19: Immune and metabolic derangement as a possible link to adverse clinical outcomes. *American journal of physiology Endocrinology and metabolism*. 2020.
67. Michalakis K, Ilias I. SARS-CoV-2 infection and obesity: Common inflammatory and metabolic aspects. *Diabetes Metab Syndr*. 2020;14(4):469-471.
68. Ryan PM, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation and Cytokine Amplification in COVID-19. *Obesity (Silver Spring)*. 2020.
69. Mauvais-Jarvis F. Aging, Male Sex, Obesity, and Metabolic Inflammation Create the Perfect Storm for COVID-19. *Diabetes*. 2020.
70. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
71. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *New England Journal of Medicine*. 2017;377(6):562-572.
72. Yancy CW. COVID-19 and African Americans. *JAMA*. 2020.
73. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759-765.
74. Millett GA, Jones AT, Benkeser D, et al. Assessing Differential Impacts of COVID-19 on Black Communities. *Ann Epidemiol*. 2020.
75. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. *N Engl J Med*. 2007;357(4):370-379.
76. Lakerveld J, Mackenbach J. The Upstream Determinants of Adult Obesity. *Obes Facts*. 2017;10(3):216-222.
| Exposure                              | COVID-19 Susceptibility: COVID positive vs. population controls | COVID-19 Severity: Hospitalization vs. population controls |
|--------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|
|                                      | OR (95% CI)                                                   | P-value                                                   | OR (95% CI)                                                   | P-value                                                   |
| Type 1 Diabetes                      | 0.97 (0.95 to 0.99)                                           | 7.5 x 10^-5                                              | 0.96 (0.93 to 1.00)                                           | 0.03                                                      |
| Type 2 Diabetes                      | 1.02 (0.96 to 1.08)                                           | 0.49                                                     | 1.04 (0.95 to 1.13)                                           | 0.37                                                      |
| Hemoglobin A1c                        | 0.97 (0.87 to 1.08)                                           | 0.59                                                     | 0.88 (0.82 to 1.16)                                           | 0.79                                                      |
| Fasting Glucose – BMI Adjusted        | 0.94 (0.83 to 1.08)                                           | 0.38                                                     | 0.96 (0.77 to 1.20)                                           | 0.73                                                      |
| Fasting Insulin – BMI Adjusted        | 0.94 (0.75 to 1.18)                                           | 0.59                                                     | 1.00 (0.73 to 1.39)                                           | 0.98                                                      |
| Body Mass Index                       | 1.41 (1.16 to 1.71)                                           | 6.7 x 10^-4                                              | 1.66 (1.23 to 2.25)                                           | 8.7 x 10^-4                                               |
| C-reactive Protein                    | 1.00 (0.90 to 1.10)                                           | 0.95                                                     | 1.01 (0.87 to 1.16)                                           | 0.90                                                      |
| Waist-hip Ratio                       | 1.01 (0.70 to 1.45)                                           | 0.97                                                     | 0.95 (0.53 to 1.68)                                           | 0.85                                                      |
| Low Density Lipoprotein              | 1.04 (0.92 to 1.18)                                           | 0.52                                                     | 1.08 (0.90 to 1.29)                                           | 0.42                                                      |
| High Density Lipoprotein             | 0.87 (0.75 to 1.02)                                           | 0.08                                                     | 0.80 (0.64 to 1.00)                                           | 0.05                                                      |
| Triglycerides                         | 1.04 (0.96 to 1.13)                                           | 0.31                                                     | 1.04 (0.93 to 1.16)                                           | 0.51                                                      |
| Systolic Blood Pressure               | 1.01 (0.99 to 1.03)                                           | 0.31                                                     | 1.02 (0.99 to 1.04)                                           | 0.20                                                      |
| Diastolic Blood Pressure              | 0.99 (0.96 to 1.02)                                           | 0.40                                                     | 0.98 (0.93 to 1.02)                                           | 0.31                                                      |
| Creatinine-based eGFR                 | 1.51 (0.58 to 3.94)                                           | 0.40                                                     | 0.32 (0.07 to 1.47)                                           | 0.14                                                      |
| Chronic Kidney Disease                | 1.01 (0.86 to 1.18)                                           | 0.94                                                     | 1.06 (0.84 to 1.35)                                           | 0.62                                                      |
| Coronary Artery Disease               | 1.02 (0.92 to 1.12)                                           | 0.74                                                     | 1.06 (0.89 to 1.25)                                           | 0.52                                                      |
| Any Stroke                            | 1.14 (0.93 to 1.41)                                           | 0.20                                                     | 1.19 (0.86 to 1.63)                                           | 0.29                                                      |
### COVID-19 Susceptibility:
**COVID positive vs. population controls**

| Method               | Locke et al. Body Mass Index | UK Biobank Body Mass Index |
|----------------------|-----------------------------|---------------------------|
|                      | OR (95% CI)                 | OR (95% CI)               |
| Inverse Variance Weighted | 1.41 (1.16 to 1.71) 6.7 x 10^{-4} | 1.08 (1.03 to 1.13) 1.3 x 10^{-3} |
| MR Egger             | 1.08 (0.66 to 1.75) 0.77    | 1.00 (0.91 to 1.11) 0.95  |
| Weighted Median      | 1.11 (0.82 to 1.51) 0.51    | 1.02 (0.95 to 1.10) 0.59  |
| Weighted Mode        | 1.12 (0.76 to 1.65) 0.58    | 1.04 (0.96 to 1.12) 0.38  |

### COVID-19 Severity:
**Hospitalization vs. population controls**

| Method               | Locke et al. Body Mass Index | UK Biobank Body Mass Index |
|----------------------|-----------------------------|---------------------------|
|                      | OR (95% CI)                 | OR (95% CI)               |
| Inverse Variance Weighted | 1.66 (1.23 to 2.25) 8.7 x 10^{-4} | 1.12 (1.04 to 1.21) 1.7 x 10^{-3} |
| MR Egger             | 1.31 (0.62 to 2.74) 0.48    | 1.03 (0.88 to 1.21) 0.69  |
| Weighted Median      | 1.93 (1.16 to 3.22) 0.01    | 1.16 (1.02 to 1.30) 0.02  |
| Weighted Mode        | 1.80 (0.98 to 3.33) 0.06    | 1.15 (1.01 to 1.31) 0.05  |