**Title:** Prioritizing causal risk factors for severe COVID-19: an exhaustive Mendelian randomization study

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**Table S1. Notable Mendelian randomization studies of COVID-19.**

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| --- | --- | --- | --- | --- |
| **MR study** | **Exposure** | **Outcome** | **Outcome data sources** | **Findings** (positive associations) (no effects) (negative associations) |
| Wu et al. [1] | Coronary artery disease (CAD) | COVID-19 susceptibility | HGI released 2 (ANA5\_ALL\_inv\_var\_meta) | Genetically predicted CAD is causally associated with higher risk of COVID-19 susceptibility. |
| Zhang et al. [2] | Atrial fibrillation (AF) | COVID-19 susceptibility and severity | HGI released 3 (C1\_V2 and A2\_V2) | No causal effects of AF on COVID-19 susceptibility and severity. |
| Liu et al. [3] | Alzheimer’s disease (AD) | COVID-19 susceptibility and severity | NEJM, HGI release 3 (C1\_V2) | Genetically predicted AD is causally associated with higher risk of severe COVID-19, but no causal effects of AD on COVID-19 susceptibility. |
| Luykx & Lin [4] | Alzheimer’s disease (AD), major depressive disorder (MDD), bipolar disorder (BIP), schizophrenia (SCZ), and a combined anxiety of bipolar disorder and schizophrenia as cases vs. controls (BIP-SCZ). | COVID-19 susceptibility, hospitalization, and severity | HGI release 4 (C1, C2, D1, B1, B2, A1, and A2) | BIP-SCZ is causally associated with higher risk of COVID-19 susceptibility.  Genetic liability to BIP and SCZ slightly increase COVID-19 susceptibility and severity.  Genetic liability to AD slightly increases COVID-19 susceptibility. |
| Lorincz-Comi & Zhu [5] | Type 2 Diabetes (T2DM), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure | COVID-19 hospitalization | HGI released 3 (B1\_V2) | No causal effects of T2DM, BMI, SBP, DBP, and pulse pressure on COVID-19 hospitalization. |
| Leong et al. [6] | Type 1 diabetes (T1DM), type 2 diabetes (T2DM), hemoglobin A1c, fasting glucose (FG), fasting insulin (FI) adjusted for body mass index (BMI), BMI, waist-hip ratio (WHR) adjusted  for BMI, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP), creatinine-base estimated glomerular filtration rate (eGFR), chronic kidney disease, coronary artery disease (CAD), any stroke, and c-reactive protein (CRP). | COVID-19 susceptibility and hospitalization | HGI release 3 (C2\_V2 and B2\_V2) | Elevated BMI is causally associated with COVID-19 susceptibility and a higher risk of COVID-19 hospitalization.  No other cardiometabolic exposures (T1DM, T2DM, A1C, FG, FI adjusted for BMI, WHR adjusted for BMI, CRP, LDL-C, HDL-C, TG, SBP, DBP, creatinine-based eGFR, chronic kidney disease, CAD, and any stroke) tested were causally associated with a higher risk of severe COVID-19. |
| Ponsford et al. [7] | Body mass index (BMI), lifetime smoking score, low-density lipoprotein cholesterol, systolic blood pressure (SBP) and type 2 diabetes (T2DM). | COVID-19 severity and hospitalization | NEJM, HGI release 3 (B2\_V2) | Elevated BMI and smoking are causally associated with higher risk of severe COVID-19.  No causal effects of LDL-C, SBP, and T2DM on COVID-19 severity. |
| Zhang et al. [8] | Dyslipidemia, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG) and total cholesterol (TC). | COVID-19 severity and susceptibility | NEJM and HGI (between March 16 and June 5, 2020) | Dyslipidemia and higher level of blood TC is causally associated with higher risk of COVID-19 susceptibility.  No causal effects of TG, LDL-C, and HDL-C on COVID-19 susceptibility.  No causal effects of dyslipidemia, TC, TG, LDL-C, and HDL-C on COVID-19 severity. |
| Aung et al. [9] | Body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), fasting glucose (FG), serum glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). | COVID-19 susceptibility | UK Biobank (between March 16 and May 31, 2020) | Higher BMI and LDL-C cholesterol are causally associated with higher risk of COVID-19.  No causal relationships were identified between WC, SBP, FG, HbA1c, HDL-C, and TG and COVID-19. |
| Freuer et al. [10] | Body mass index (BMI), waist circumference (WC), and trunk fat ratio (TFR). | COVID-19 susceptibility and hospitalization | HGI release 3 (C2\_V2 and B2\_V2) | Elevated BMI is causally associated with higher risk of COVID-19 susceptibility and hospitalization.  There is suggestive evidence that WC and TFR increase risk of COVID-19 susceptibility and hospitalization. |
| Li [11] | Body mass index (BMI), lifetime smoking, alcohol consumption and physical activity | COVID-19 hospitalization and severity | HGI release 4 alpha (A2 and B2) | Genetically predicted BMI and lifetime smoking are causally associated with higher risk of COVID-19 hospitalization and severity.  Genetically predicted physical activity is causally associated with reduced risk of COVID-19 severity, but not with COVID-19 hospitalization.  No causal effects of alcohol consumption on COVID-19 hospitalization and severity. |
| Fan et al. [12] | Alcohol consumption | COVID-19 susceptibility | UK Biobank (between March 16 and July 27, 2020) | No causal effects of alcohol consumption on COVID-19 susceptibility. |
| Zhang et al. [13] | Physical activity | COVID-19 susceptibility | UK Biobank (between March 16 and June 29, 2020) | No causal effects of physical activity on COVID-19 susceptibility. |
| Butler-Laporte et al. [14] | 25-hydroxy-vitamin D (25OHD) level | COVID-19 susceptibility, hospitalization, and severity | HGI release 4 (C2, B2, and A2) | No causal effects of 25OHD levels by one standard deviation on the logarithmic scale on COVID-19 susceptibility, hospitalization, and severity. |
| Li et al. [15] | 25-hydroxy-vitamin D (25OHD) level | COVID-19 susceptibility | UK Biobank (between March 16 and June 29, 2020) | No causal effects of 25OHD levels on COVID-19 susceptibility. |
| Liu et al. [16] | 25-hydroxy-vitamin D (25OHD) concentration | COVID-19 susceptibility and severity | NEJM and HGI released 3 (C2\_V2, C1\_V2, and A2\_V2) | No causal effects of 25OHD concentration on COVID-19 susceptibility and severity. |
| Sun et al. [17] | 19 white blood cell traits | COVID-19 hospitalization | HGI release 3 (B2\_V2) | Lower white blood cell count, myeloid white blood cell count, and granulocyte count are causally associated with higher risk of COVID-19 hospitalization.  Higher eosinophil percentage of white blood cells is causally associated with higher risk of COVID-19 hospitalization. |
| Schooling et al. [18] | Nitric Oxide, platelet reactivity, and platelet count | COVID-19 susceptibility, hospitalization, and severity | HGI released 3 (C2\_V2, B2\_V2, and A2\_V2) | Nitric oxide is causally associated with reduced risk of severe COVID-19, but was not associated with COVID-19 susceptibility.  No causal effects of platelet reactivity, and platelet count on COVID-19 susceptibility and severe COVID-19. |
| Schooling et al. [19] | Tocilizumab, anakinra, statins, and dexamethasone use | COVID-19 susceptibility, hospitalization, and severity | HGI released 3 (C2\_V2, B2\_V2, and A2\_V2) | Using rs12916 (HMGCR) to proxy effects of statins use is causally associated with reduced risk of severe COVID-19.  No causal effects of tocilizumab, anakinra, and dexamethasone use on COVID-19 susceptibility and severe COVID-19. |
| Larsson et al. [20] | IL-6 receptor (IL6R) inhibition | COVID-19 susceptibility, hospitalization, and severity | NEJM, HGI release 3 (C2\_V2, B2\_V2, and B1\_V2) | Higher IL6R inhibition is causally associated with reduced risk of COVID-19 susceptibility, hospitalization, and severity. |
| Gaziano et al. [21] | 1,263 actionable proteins | Hospitalized COVID-19 | HGI release 4 (B2) | ACE2 and IL-10RB are causally associated with higher risk of COVID-19 hospitalization.  IFNAR2 is causally associated with reduced risk of COVID-19 hospitalization. |
| Zhou et al. [22] | 931 circulating protein levels from six large proteomic GWAS of European individuals. | COVID-19 susceptibility, hospitalization, and severity | HGI release 4 (C2, B2, and A2) | A standard deviation increase in 2'-5'-oligoadenylate synthetase 1 (OAS1) levels is causally associated with reduced risk of COVID-19 susceptibility, hospitalization, and severity.  Interleukin-10 receptor beta subunit (IL10RB) is causally associated with reduced risk of COVID-19 hospitalization and severity.  ABO is caussaly associated with increased risk of COVID-19 susceptibility, hospitalization, and severity. |
| Zhou et al. [23] | 12 coagulation factors including Factor VIII (FVIII), Factor XI (FXI), activated partial thromboplastin time (aPTT), Factor X (FX), endogenous thrombin potential (ETP), Factor VII (FVII), prothrombin time (PT), von Willebrand factor (VWF), ADAMTS13, D-dimer, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1). | COVID-19 severity | NEJM, HGI release 4 alpha (A2), and UK Biobank (between March 16 and October 7, 2020) | Genetic predisposition to the antigen levels of von Willebrand factor (VWF) and the activity levels of its cleaving protease ADAMTS13 are causally associated with higher risk of COVID-19 severity.  Lowered ADAMTS13 activity is causally associated with higher risk of severe COVID-19.  No significant causal association of tPA, PAI-1, D-dimer, FVII, PT, FVIII, FXI, aPTT, FX or ETP with COVID-19 severity was observed. |
| Liu et al. [24] | Gene expression | COVID-19 susceptibility, hospitalization, and severity | NEJM, HGI release 3 (C1\_V2, C2\_V2, B1\_V2, B2\_V2, and A2\_V2) | In blood, ILMN\_1765146 and ILMN\_1791057 tagging IFNAR2, that showed pleiotropic association with COVID-19 hospitalization. |
| Butler-Laporte et al. [25] | Angiotensin-converting enzyme 2 (ACE2) | COVID-19 susceptibility, hospitalization, and severity | HGI release 3 (C1\_V2, C2\_V2, B1\_V2, B2\_V2, A1\_V2, and A2\_V2) | No causal effects of ACE levels on COVID-19 susceptibility, hospitalization or severity. |
| Rao et al. [26] | 425 traits including diseases and proteins. | ACE2 lung expression | Genotype-Tissue Expression (GTEx) database | Type 1 diabetes, type 2 diabetes, and related traits including early start of insulin were each causally associated with increases in ACE2 expressions.  Inflammatory bowel disease, (estrogen receptor–positive) breast cancer, lung cancer, asthma, smoking, and elevated alanine aminotransferase were also causally associated with increases in ACE2 expressions. |
| Gill et al. [27] | body mass index (BMI), chronic obstructive pulmonary disease (COPD), lifetime smoking index, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP) and type 2 diabetes (T2DM). | Lung expression of ACE2 and TMPRSS2 | Gene-Tissue Expression (GTEx) project, the Lung eQTL Consortium, and the INTERVAL study | No causal effects of BMI, COPD, lifetime smoking index, LDL-C, SBP, and T2DM on lung expression of ACE2 and TMPRSS2. |

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