Genetic correlations between COVID-19 and a variety of traits and diseases

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The ongoing coronavirus disease (COVID-19) outbreak has posed an extraordinary threat to global public health. Patients with certain underlying medical conditions, such as obesity, hypertension, and diabetes are at increased risk for poor outcome in COVID-19.[1] Given the high genetic heritability of the aforementioned conditions, their shared genetic factors may play a crucial role in the severity of COVID-19. Indeed, a recent genome-wide association study (GWAS) of COVID-19 has reported two genomic loci associated with severe COVID-19, indicating a strong genetic influence on the severity of COVID-19.[2] Here, we analyzed GWAS results released by the COVID-19 Host Genetics Initiative,[3] the UK biobank, and the GWAS Catalog to explore the genetic overlap between COVID-19 and a broad spectrum of traits and diseases (Figure 1).

Summary statistics of selected COVID-19 GWAS (sample size >30,000 and percentage of Europeans >90%) were downloaded from COVID-19 Host Genetics Initiative, including A2_ALL (very severe respiratory confirmed COVID-19 against population), B2_ALL (hospitalized COVID-19 against population), B2_ALL_eur (hospitalized COVID-19 against population in Europeans), and C2_ALL_eur (COVID-19 against population in Europeans). GWAS summary statistics of selected diseases/traits were downloaded from the UK biobank and the GWAS Catalog.[4] Genetic correlation r_g between COVID-19 and interested diseases/traits were estimated by LD (linkage disequilibrium) score regression using GWAS summary statistics that overlap with HapMap3 SNPs as recommended. Pre-computed linkage disequilibrium scores for HapMap3 SNPs calculated based on European-ancestry individuals from the 1000 Genomes Project were used in the analysis (supplemental information).

We first investigated genetic correlations between COVID-19 and 1,555 diseases/traits from the analysis of UK biobank data by the Neale lab (http://www.nealelab.is/uk-biobank/) as described in Figure 1. Our results are consistent with the epidemiological observation that BMI is significantly associated with severe or hospitalized COVID-19 (A2_ALL, rg = 0.24, p = 3.35×10^{-6}; B2_ALL, rg = 0.39, p = 3.33×10^{-7}). COPD (chronic obstructive pulmonary disease), heart diseases, hypertension, diabetes, and smoking status exhibit substantial magnitude of genetic correlation with COVID-19, although statistical significance does not pass the strict threshold after adjustment for multiple testing (Table S1). Collectively, diseases of the

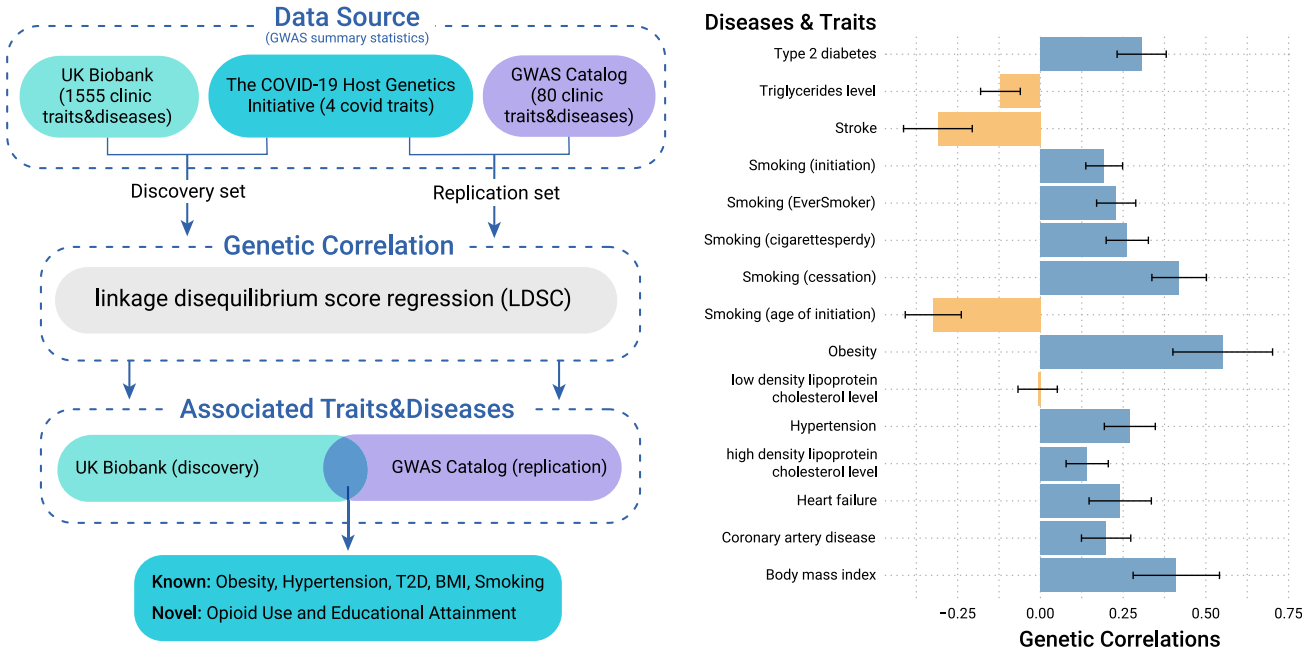

Figure 1. Flowchart of data preparation and analysis for COVID-19 and tested traits/diseases in this study More details of genetic correlation results are provided in https://roarchang.shinyapps.io/COV19_GC/.

circulatory system, diseases of the digestive system, and diseases of the musculoskeletal system and connective tissue are significantly associated with severe or hospitalized COVID-19 (Table S1). In agreement with this, a number of medication-taking traits linked to obesity, diabetes, hypertension, and digestion display modest correlation with COVID-19 (Table S1). Tramadol, an opioid pain medication, is significantly correlated with hospitalized COVID-19 (B2_ALL, rg = 0.65, p = 1.26×10^{-5}). Interestingly, our results indicated a significant negative correlation between severe or hospitalized COVID-19 and educational attainment-related traits, including college or university degree (A2_ALL, rg = −0.24, p = 8.51×10^{-7}; B2_ALL, rg = −0.32, p = 1.78×10^{-6}) and fluid intelligence score (A2_ALL, rg = −0.25, p = 2.40×10^{-5}; B2_ALL, rg = −0.26, p = 7.66×10^{-5}). Hospitalized COVID-19 (B2_ALL, rg = 0.73, p = 8.60×10^{-6}) is also significantly correlated with panic attacks.

We next estimated genetic correlations between COVID-19 and 80 diseases/traits from the GWAS Catalog[4] (Figure 1). Consistently, hypertension, type 2 diabetes, and obesity are significantly associated with severe or hospitalized COVID-19 (Table S1). Coronary artery disease, heart failure, and BMI are also modestly associated with severe COVID-19. Likewise, medication-taking traits related to obesity, diabetes, hypertension, and digestion are modestly associated with COVID-19, such as drugs for diabetes and antihypertensives (Table S1). Significant correlations are also found between hospitalized COVID-19 and drugs for peptic ulcer and gastro-esophageal reflux disease (B2_ALL, rg = 0.34, p = 3.01×10^{-5}; B2_ALL_eur, rg = 0.28, p = 0.0006), diuretic use and very severe respiratory confirmed COVID-19 (A2_ALL, rg = 0.25, p = 0.0002), opioids and severe or hospitalized COVID-19 (A2_ALL, rg = 0.30, p = 5.59×10^{-5}; B2_ALL, rg = 0.44, p = 4.78×10^{-7}; B2_ALL_eur, rg = 0.38, p = 0.0002). Consistent with the findings from the UK biobank data, a strong negative genetic correlation between educational attainment and severe or hospitalized COVID-19 (A2_ALL, rg = −0.33, p = 1.90×10^{-9}; B2_ALL, rg = −0.41, p = 1.82×10^{-8}; B2_ALL_eur, rg = −0.35, p = 2.07×10^{-6}) is observed. Further analyses of brain function and personality traits show that COVID-19 is significantly correlated with cognitive performance and verbal-numerical reasoning, but not memory performance, reaction time, or neuroticism (Table S1). In addition, very severe respiratory confirmed COVID-19 (A2_ALL, rg = −0.37, p = 0.0006) is significantly correlated with systemic lupus erythematosus.

Although the genetic correlation alone does not explain the causal mechanism that might link two diseases, it provides evidence of potential causal relationships among genetic diseases, and potentially lead to new disease interventions. Here, our genetic correlation results between COVID-19 and a variety of traits and diseases confirm medical conditions and risk factors reported from epidemiological studies, such as hypertension, type 2 diabetes, and obesity. However, as far as we are aware, the association between opioids and COVID-19 has not previously been reported using epidemiological data. As side effects associated with chronic opioid use at high doses may affect the immune system and increase the risk of pneumonia, there is an urgent need to evaluate the relationship between COVID-19 severity and opioid use by epidemiological studies.[5] Also, patients using chronic opioids may be considered a vulnerable group for careful monitoring. In addition, our results suggest that immune pathways involved in systemic lupus erythematosus may also play an important role in the severity of COVID-19. Finally, the observed negative correlation between COVID-19 severity and educational attainment reflects an indirect link mediated by environment or human behavior. For example, patients with different educational levels may differ in diet choices (BMI) or smoking status, and their occupations and/or living conditions may put them at higher risk of exposure to the virus. This study provides novel information on underlying conditions that might increase the risk of severe COVID-19 illness. Added epidemiological studies are warranted to further evaluate these findings.

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AUTHOR CONTRIBUTIONS

H.H. and X.C. designed the research and wrote the paper. X.C. and Y.L. performed the analysis. K.N., H.Q., and Y.L. collected the data and revised the paper. J.G., P.M.A.S., and H.H. supervised this study. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interest.

SUPPLEMENTAL INFORMATION

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Supplemental Information

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Supplementary Information:

Estimation of genetic correlation

We calculated the genome-wide genetic correlations (r_g) between COVID-19 and a variety of traits and diseases using LD score regression method [1], which is based on the relationship between LD score and χ^2-statistics: $E\left[x_j^2\right] \approx \frac{N_j h_g^2}{M} l_j + 1$, where $E\left[x_j^2\right]$ is the expected x^2-statistics between SNP j and the outcome, N_j is the sample size of study, M is the number of all variants, and l_j is the LD score of SNP j ($l_j = \sum_k (j,k)$, k is other variants within the LD region). The LD score regression equation is $E\left[\beta_j \gamma_j\right] \approx \frac{\sqrt{N_1 N_2} r_g}{M} l_j + \frac{N_s r}{\sqrt{N_1 N_2}}$, where β_j and γ_j denote the effect size of SNP j on the two tested traits, N_1 and N_2 are the sample sizes of two tested traits, N_s is the number of overlapping samples between two tested traits, r is the phenotypic correlation in overlapping samples and l_j is the aforementioned LD score. The LD score regression method has been implemented in the LDSC software (https://github.com/bulik/ldsc). Genetic correlation r_g between COVID-19 and interested diseases/traits were estimated by LDSC using GWAS summary statistics that overlap with HapMap3 SNPs as recommended [1]. Pre-computed linkage disequilibrium scores for HapMap3 SNPs calculated based on European-ancestry individuals from the 1000 Genomes Project were used in the analysis.

Table S1. Genetic correlations between COVID-19 and a variety of diseases and other medically relevant traits

Source	Disease/Trait	Reference	A2_ALL			B2_ALL			B2_ALL_eur			C2_ALL_eur		
			rg(se)	P	P-adj	rg(se)	P	P-adj	rg(se)	P	P-adj	rg(se)	P	P-adj
UK biobank	Diseases of the circulatory system	IX_CIRCULATORY	0.34 (0.08)	2.20E-05*	0.0342	0.38 (0.09)	4.33E-05	0.0673	0.32 (0.10)	0.0012	1	0.22 (0.11)	0.0422	1
	Diseases of the digestive system	XI_DIGESTIVE	0.25 (0.07)	0.0004	0.622	0.37 (0.08)	5.38E-06**	0.0083	0.38 (0.10)	8.40E-05	0.1306	0.08 (0.09)	0.3429	1
	Diseases of the musculoskeletal system and connective tissue	XIII_MUSCULOSKELET	0.33 (0.07)	1.38E-05*	0.0215	0.35 (0.09)	0.0001	0.1555	0.34 (0.10)	0.001	1	0.15 (0.10)	0.1371	1
	COPD, early/later onset	COPD_EARLYANDLATER	0.50 (0.15)	0.0011	1	0.55 (0.16)	0.0006	0.933	0.46 (0.17)	0.0081	1	0.33 (0.18)	0.0696	1
	COPD differential diagnosis	COPD_EXCL	0.16 (0.10)	0.1164	1	0.32 (0.11)	0.0041	1	0.31 (0.13)	0.0146	1	0.27 (0.14)	0.0434	1
	Major coronary heart disease event	I9_CHD	0.24 (0.09)	0.0088	1	0.26 (0.10)	0.0117	1	0.19 (0.11)	0.0786	1	0.07 (0.12)	0.5347	1
	Ischaemic heart disease, wide definition	I9_IHD	0.24 (0.08)	0.0014	1	0.30 (0.09)	0.0006	0.933	0.22 (0.09)	0.0155	1	0.14 (0.09)	0.1447	1
	Vascular/heart problems diagnosed by doctor: Heart attack	6150_1	0.33 (0.09)	0.0003	0.4665	0.35 (0.11)	0.002	1	0.30 (0.12)	0.0126	1	0.19 (0.12)	0.1119	1
	Vascular/heart problems diagnosed by doctor: Angina	6150_2	0.28 (0.09)	0.0017	1	0.36 (0.11)	0.0014	1	0.26 (0.11)	0.0169	1	0.23 (0.11)	0.0339	1
	Vascular/heart problems diagnosed by doctor: High blood pressure	6150_4	0.17 (0.05)	0.0011	1	0.22 (0.07)	0.0016	1	0.19 (0.07)	0.0065	1	0.21 (0.08)	0.0077	1

	Non-cancer illness code, self-reported: stroke	20002_1081	0.53 (0.22)	0.0158	1	0.50 (0.22)	0.0206	1	0.47 (0.23)	0.0452	1	0.32 (0.26)	0.2232	1
	Non-cancer illness code, self-reported: diabetes	20002_1220	0.28 (0.08)	0.0003	0.4665	0.36 (0.09)	7.96E-05	0.1237	0.38 (0.10)	0.0003	0.4665	0.24 (0.09)	0.0092	1
	Non-cancer illness code, self-reported: osteoarthritis	20002_1465	0.28 (0.10)	0.0042	1	0.27 (0.09)	0.0045	1	0.25 (0.10)	0.0164	1	0.02 (0.11)	0.8331	1
	Non-cancer illness code, self-reported: high cholesterol	20002_1473	0.19 (0.07)	0.0071	1	0.19 (0.08)	0.0172	1	0.19 (0.09)	0.0281	1	0.00 (0.08)	0.9863	1
	Smoking status: Never	20116_0	-0.06 (0.05)	0.2025	1	-0.22 (0.06)	0.0005	0.7775	-0.22 (0.07)	0.0024	1	-0.06 (0.07)	0.4181	1
	Smoking status: Current	20116_2	0.20 (0.06)	0.0014	1	0.35 (0.08)	1.97E-05*	0.0306	0.34 (0.09)	0.0002	0.311	0.13 (0.09)	0.146	1
	Body mass index (BMI)	21001_irnt	0.24 (0.05)	3.35E-06**	0.0052	0.39 (0.08)	3.33E-07***	0.0005	0.32 (0.08)	3.89E-05	0.0604	0.25 (0.07)	0.0008	1
	Age hay fever, rhinitis or eczema diagnosed	3761_irnt	0.27 (0.08)	0.0005	0.7775	0.27 (0.10)	0.0064	1	0.28 (0.10)	0.0058	1	0.29 (0.13)	0.0245	1
	Age asthma diagnosed	3786_irnt	0.15 (0.09)	0.1012	1	0.12 (0.10)	0.2563	1	0.07 (0.12)	0.5406	1	-0.03 (0.13)	0.8299	1
	Fluid intelligence score	20016_irnt	-0.25 (0.06)	2.40E-05*	0.0373	-0.26 (0.07)	7.66E-05*	0.1191	-0.25 (0.08)	0.001	1	-0.13 (0.08)	0.083	1
	Qualifications: College or University degree	6138_1	-0.24 (0.05)	8.51E-07**	0.0013	-0.32 (0.07)	1.78E-06**	0.0028	-0.28 (0.07)	9.62E-05	0.1496	-0.23 (0.07)	0.0016	1
	Mental health problems ever diagnosed by a professional: Panic attacks	20544_6	0.40 (0.12)	0.001	1	0.73 (0.16)	8.60E-06*	0.0134	0.64 (0.17)	0.0001	0.1555	0.38 (0.19)	0.0416	1
	Seen doctor (GP) for nerves, anxiety, tension or depression	2090	0.18 (0.06)	0.002	1	0.20 (0.07)	0.0022	1	0.18 (0.07)	0.0087	1	-0.03 (0.07)	0.6765	1
	Medication related adverse effects (Asthma/COPD)	PULM_MEDICATIO_COMORB	0.28 (0.10)	0.0059	1	0.32 (0.11)	0.0052	1	0.36 (0.12)	0.0022	1	0.15 (0.14)	0.2894	1
	Treatment/medication code: ramipril	20003_1140860806	0.31 (0.10)	0.0013	1	0.44 (0.12)	0.0004	0.622	0.34 (0.13)	0.0095	1	0.24 (0.13)	0.0565	1
	Treatment/medication code: simvastatin	20003_1140861958	0.26 (0.08)	0.001	1	0.26 (0.09)	0.0055	1	0.28 (0.10)	0.0046	1	0.07 (0.09)	0.432	1
	Treatment/medication code: tramadol	20003_1140864992	0.52 (0.13)	7.61E-05	0.1183	0.65 (0.15)	1.26E-05*	0.0196	0.63 (0.16)	5.30E-05	0.0824	0.49 (0.17)	0.0031	1
	Treatment/medication code: omeprazole	20003_1140865634	0.22 (0.09)	0.017	1	0.36 (0.10)	0.0004	0.622	0.30 (0.11)	0.0049	1	0.06 (0.13)	0.6624	1
	Treatment/medication code: aspirin	20003_1140868226	0.24 (0.09)	0.0067	1	0.32 (0.11)	0.0047	1	0.29 (0.12)	0.0162	1	0.17 (0.12)	0.1578	1
	Treatment/medication code: amitriptyline	20003_1140879616	0.38 (0.13)	0.0031	1	0.49 (0.16)	0.0016	1	0.44 (0.16)	0.0059	1	0.22 (0.16)	0.167	1
	Treatment/medication code: metformin	20003_1140884600	0.23 (0.08)	0.0045	1	0.31 (0.10)	0.0015	1	0.33 (0.11)	0.0016	1	0.20 (0.10)	0.0427	1
	Treatment/medication code: co-codamol	20003_1140923346	0.40 (0.11)	0.0002	0.311	0.49 (0.13)	0.0001	0.1555	0.32 (0.13)	0.0171	1	0.07 (0.15)	0.6292	1
	Treatment/medication code: paracetamol	20003_2038460150	0.26 (0.07)	0.0003	0.4665	0.35 (0.09)	0.0002	0.311	0.27 (0.10)	0.0038	1	-0.02 (0.10)	0.814	1
GWAS Catalog	ADHD	30478444	-0.23 (0.07)	0.0017	0.136	-0.26 (0.09)	0.0021	0.168	-0.23 (0.09)	0.0079	0.632	-0.05 (0.10)	0.5699	1
	Autism	30804558	-0.01 (0.09)	0.9165	1	0.08 (0.11)	0.4675	1	0.11 (0.11)	0.3164	1	0.08 (0.13)	0.546	1
	Depression	30718901	-0.15 (0.05)	0.0029	0.232	-0.16 (0.06)	0.0049	0.232	-0.13 (0.06)	0.0248	0.232	0.0219 (0.07)	0.7407	0.232
	Schizophrenia	25056061	-0.07 (0.05)	0.1711	1	-0.06 (0.06)	0.3	1	-0.08 (0.06)	0.1469	1	-0.04 (0.07)	0.6006	1
	Asthma	29785011	-0.16 (0.08)	0.037	1	-0.12 (0.09)	0.1763	1	-0.15 (0.10)	0.1386	1	-0.27 (0.12)	0.0263	1
	Allergy	29785011	-0.20 (0.07)	0.0067	0.536	-0.26 (0.09)	0.0046	0.368	-0.19 (0.10)	0.0511	1	-0.32 (0.12)	0.0078	0.624
	SLE	26502338	-0.37 (0.11)	0.0006*	0.048	-0.27 (0.13)	0.0489	1	-0.27 (0.15)	0.0736	1	-0.23 (0.17)	0.1758	1

Smoking (age of initiation)	30643251	-0.23 (0.07)	0.0008	0.064	-0.32 (0.08)	0.0001**	0.008	-0.24 (0.08)	0.0035	0.28	-0.15 (0.09)	0.0998	1
Smoking (initiation)	30643251	0.10 (0.05)	0.0274	1	0.19 (0.06)	0.0005*	0.04	0.18 (0.06)	0.0026	0.208	0.05 (0.07)	0.4577	1
Smoking (cessation)	30643251	0.27 (0.07)	0.0003*	0.024	0.42 (0.08)	3.60E-07***	2.88E-05	0.39 (0.09)	2.06E-05	0.0016	0.09 (0.11)	0.4288	1
Smoking (cigarettes per day)	30643251	0.16 (0.06)	0.0048	0.384	0.26 (0.06)	3.88E-05**	0.0031	0.17 (0.07)	0.0097	0.776	0.00 (0.08)	0.9573	1
Hypertension	30940143	0.21 (0.06)	0.0005*	0.04	0.27 (0.08)	0.0005*	0.04	0.18 (0.07)	0.0077	0.616	0.18 (0.08)	0.022	1
Coronary artery disease	28714975	0.22 (0.07)	0.001	0.08	0.20 (0.07)	0.0077	0.616	0.20 (0.08)	0.0113	0.904	0.11 (0.09)	0.207	1
Heart failure	31919418	0.20 (0.09)	0.0205	1	0.24 (0.09)	0.0103	0.824	0.22 (0.11)	0.0468	1	0.17 (0.12)	0.1823	1
Type 2 diabetes	25056061	0.22 (0.06)	0.0003*	0.024	0.31 (0.07)	3.75E-05**	0.003	0.29 (0.08)	0.0002	0.016	0.20 (0.08)	0.0107	0.856
Obesity	30677029	0.35 (0.13)	0.0082	0.656	0.55 (0.15)	0.0003*	0.024	0.55 (0.17)	0.0008	0.064	0.44 (0.17)	0.0092	0.736
BMI	23563607	0.26 (0.10)	0.0079	0.632	0.41 (0.13)	0.0016	0.128	0.29 (0.12)	0.0132	1	0.22 (0.15)	0.1477	1
Drugs for peptic ulcer and gastro-oesophageal reflux disease	31015401	0.23 (0.07)	0.0007	0.056	0.34 (0.08)	3.01E-05**	0.0024	0.28 (0.08)	0.0006	0.048	0.05 (0.10)	0.6493	1
Drugs for diabetes	31015401	0.17 (0.07)	0.0214	1	0.24 (0.08)	0.004	0.32	0.26 (0.09)	0.0042	0.336	0.19 (0.10)	0.0524	1
Antithrombotic agents	31015401	0.24 (0.09)	0.0085	0.68	0.28 (0.12)	0.0191	1	0.28 (0.12)	0.0266	1	0.29 (0.14)	0.0477	1
Vasodilators for cardiac diseases	31015401	0.33 (0.12)	0.0068	0.544	0.48 (0.16)	0.0021	0.168	0.43 (0.17)	0.0095	0.76	0.51 (0.21)	0.0151	1
Antihypertensives	31015401	0.30 (0.12)	0.0163	1	0.41 (0.14)	0.0049	0.392	0.40 (0.16)	0.0098	0.784	0.22 (0.17)	0.1972	1
Diuretic use	31015401	0.25 (0.07)	0.0002*	0.016	0.26 (0.08)	0.0018	0.144	0.29 (0.09)	0.0011	0.088	0.25 (0.11)	0.0196	1
Beta blocking agents	31015401	0.20 (0.07)	0.0078	0.624	0.22 (0.09)	0.0147	1	0.17 (0.09)	0.0762	1	0.09 (0.11)	0.3954	1
Agents acting on the renin-angiotensin system	31015401	0.19 (0.06)	0.001	0.08	0.21 (0.08)	0.0062	0.496	0.22 (0.08)	0.0068	0.544	0.19 (0.09)	0.0357	1
HMG CoA reductase inhibitors	31015401	0.22 (0.07)	0.0012	0.096	0.20 (0.08)	0.0121	0.968	0.22 (0.09)	0.0112	0.896	0.08 (0.09)	0.3783	1
Opioids	31015401	0.30 (0.07)	5.59E-05**	0.0045	0.44 (0.09)	4.78E-07***	3.82E-05	0.38 (0.10)	0.0002	0.016	0.26 (0.11)	0.0229	1
Subjective well-being	27089181	0.17 (0.09)	0.0682	1	0.09 (0.10)	0.3818	1	0.11 (0.11)	0.311	1	0.14 (0.14)	0.3173	1
Educational attainment (years of education)	27225129	-0.33 (0.06)	1.90E-09***	1.52E-07	-0.41 (0.07)	1.82E-08***	1.46E-06	-0.35 (0.07	2.07E-06	0.0002	-0.24 (0.08)	0.003	0.24
Neuroticism	27089181	0.00 (0.07)	0.9995	1	-0.01 (0.09)	0.9161	1	-0.04 (0.10)	0.6917	1	-0.07 (0.12)	0.5659	1
Cognitive performance	30038396	-0.22 (0.05)	3.95E-06	0.0003	-0.21 (0.06)	0.0001**	0.008	-0.20 (0.06)	0.0006	0.048	-0.22 (0.07)	0.0034	0.272
Memory performance	27046643	0.07 (0.10)	0.5018	1	0.07 (0.11)	0.5433	1	0.15 (0.11)	0.199	1	0.13 (0.12)	0.2675	1
Reaction time	27046643	0.08 (0.08)	0.3163	1	0.03 (0.08)	0.6847	1	-0.03 (0.09)	0.7716	1	-0.05 (0.11)	0.6457	1
Verbal-numerical reasoning	27046643	-0.33 (0.09)	0.0002*	0.016	-0.33 (0.10)	0.0007	0.056	-0.35 (0.11)	0.0018	0.144	-0.30 (0.13)	0.0164	1

Genetic correlation estimates, standard errors and p-values for COVID-19 and selected diseases/traits. The “Reference” column lists the phenotype code for the GWAS from UK biobank, and PMID (PubMed ID) for the GWAS from GWAS Catalog. The *P*-values are uncorrected *P*-values. Bonferroni correction was used for correction of multiple testing by the number of tests (1555 for the analysis of data from UK biobank, and 80 for the analysis of data

GWAS Catalog. For genetic correlations between COVID-19 and UK biobank traits, the significance level is $0.05/1555 = 3.22 \times 10^{-5}$. For genetic correlations between COVID-19 and GWAS catalog traits, the significance level is $0.05/80 = 6.25 \times 10^{-4}$.). *** adjusted *P*-value ≤ 0.001, ** adjusted *P*-value ≤ 0.01, * adjusted *P*-value ≤ 0.05. BMI = body mass index; SLE = systemic lupus erythematosus; rg = genetic correlation estimates; se = standard error, A2_ALL = very severe respiratory confirmed COVID-19 vs population, B2_ALL = hospitalized COVID-19 vs population, B2_ALL_eur = hospitalized COVID-19 vs population (European samples only), C2_ALL_eur = COVID-19 vs population (European samples only).

1. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C*, et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. **Nat Genet 2015**, 47(3)**:** 291-295.