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Supplemental Information

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

Xiao Chang, Yun Li, Kenny Nguyen, Huiqi Qu, Yichuan Liu, Joseph Glessner, Patrick M.A. Sleiman, and Hakon Hakonarson

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.