

Table S1 Demographic characteristics of included Proteome GWASs used in the present MR analysis

GWAS	Sample size	Number of proteins	Measurement methods
YFS/FINRISK	8,293 Caucasians	41 cytokines	Bead-based immunoassays
IMPROVE	3,394 Caucasians	83 cardiovascular disease-related proteins	Modified antibodies conjugated to oligonucleotides
KORA F4/QMDiab	1,000 Caucasians	1,124 proteins	Slow off-rate modified aptamers (SOMAmers)
INTERVAL	3,301 Caucasians	2,994 proteins	SOMAmers
FHS	6,861 Caucasians	71 cardiovascular disease-related proteins	Modified enzyme-linked immunosorbent assay sandwich method
AGES	5,457 Caucasians	4,137 proteins	SOMAmers

Table S2 Demographic characteristics of included COVID-19 GWAS used in the present MR analysis (round 3)

GWAS	Sample information
Susceptibility	
C1	COVID (N=3,523) vs. lab/self-reported negative (N=36,634)
C2	COVID (N=6,696) vs. population (N=1,073,072)
D1	Predicted COVID from self-reported symptoms (N=1,865) vs. predicted or self-reported non-COVID (N=29,174)
Severity	
A2	Very severe respiratory confirmed COVID (N=536) vs. population (N=329,391)
B1	Hospitalized COVID (N=928) vs. not hospitalized COVID (N=2,028)
B2	Hospitalized COVID (N=3,199) vs. population (N=897,488)

Table S3 Genetic correlation between proteome and COVID-19 susceptibility and severity

Outcome	Biomarker	Method	N SNPs	OR	LCI	UCI	P value	
Susceptibility (C2)	Tissue factor	Wald ratio	1	0.667	0.484	0.850	1.47E-05	
	A disintegrin and metalloproteinase with thrombospondin motifs 6	Wald ratio	1	0.957	0.914	1.001	0.049	
	Agouti-signaling protein	Wald ratio	1	1.070	1.017	1.123	0.012	
	alpha-Fetoprotein	Wald ratio	1	0.797	0.642	0.952	0.004	
	Alpha-synuclein	Wald ratio	1	0.795	0.628	0.963	0.007	
	Binatriuretic peptides	Wald ratio	1	0.775	0.62	0.931	0.001	
	Cartilage acidic protein 1	Wald ratio	1	1.085	1.004	1.167	0.048	
	Cathepsin H	Wald ratio	1	1.043	1.008	1.078	0.02	
	C-C motif chemokine 25	Wald ratio	1	1.242	1.087	1.396	0.006	
	CD166 antigen	Wald ratio	1	0.851	0.718	0.983	0.017	
	Complement C1q subcomponent subunit C	Wald ratio	1	0.837	0.693	0.980	0.015	
	Complement factor H-related protein 1	Wald ratio	1	1.039	1.01	1.068	0.011	
	CXADR-like membrane protein	Wald ratio	1	1.165	1.041	1.288	0.015	
	Enoyl-CoA delta isomerase 2	Wald ratio	1	1.300	1.091	1.509	0.014	
	Fibroblast growth factor 19	Wald ratio	1	1.251	1.111	1.39	0.002	
	Galectin-4	Wald ratio	1	0.861	0.712	1.009	0.048	
	Golgi membrane protein 1	Wald ratio	1	1.161	1.068	1.254	0.002	
	Granulins	IVW	6	0.942	0.884	0.999	0.041	
	Inter-alpha-trypsin inhibitor heavy chain H1	IVW	2	0.934	0.868	1.000	0.042	
	Inter-alpha-trypsin inhibitor heavy chain H5	IVW	2	0.855	0.708	1.002	0.037	
	Interleukin-27	IVW	2	1.028	1.002	1.053	0.034	
	Interleukin-27 subunit alpha	IVW	2	1.056	1.004	1.108	0.041	
	Interleukin-7	Wald ratio	1	0.859	0.728	0.989	0.022	
	Kunitz-type protease inhibitor 1	Wald ratio	1	0.906	0.829	0.984	0.013	
	LanC like 1	Wald ratio	1	0.705	0.409	1.001	0.021	
	Low affinity immunoglobulin gamma Fc region receptor III-B	Wald ratio	1	0.919	0.853	0.985	0.012	
	Mitochondrial ubiquitin ligase activator of NFKB 1	Wald ratio	1	1.165	1.066	1.264	0.003	
	Multiple inositol polyphosphate phosphatase 1	Wald ratio	1	1.212	1.064	1.360	0.011	
	NAD(P)H dehydrogenase [quinone] 1	Wald ratio	1	0.873	0.760	0.986	0.019	
	NAD-dependent protein deacetylase sirtuin-2	IVW	3	0.936	0.878	0.993	0.023	
	Neurexin-3-beta	Wald ratio	1	1.168	1.028	1.308	0.030	
	N-terminal pro-BNP	Wald ratio	1	0.837	0.729	0.945	0.001	
	N-terminal prohormone of brain natriuretic peptide	IVW	2	0.876	0.747	1.005	0.045	
	OX-2 membrane glycoprotein	Wald ratio	1	1.248	1.114	1.382	0.001	
	Protein FAM163A	Wald ratio	1	1.085	1.012	1.158	0.029	
	Protein FAM3D	Wald ratio	1	1.082	1.033	1.131	0.002	
	Rho GTPase-activating protein 1	Wald ratio	1	1.277	1.087	1.466	0.011	
	Semaphorin-3G	Wald ratio	1	0.809	0.682	0.937	0.001	
	Xaa-Pro aminopeptidase 2	Wald ratio	1	1.264	1.082	1.446	0.012	
	Severity (B2)	C-C motif chemokine 4	Wald ratio	1	1.887	1.608	2.165	8.04E-06
		Tissue factor	Wald ratio	1	0.459	0.132	0.786	3.01E-06
		5-formyltetrahydrofolate cyclo-ligase	IVW	2	1.113	1.018	1.209	0.028
		Aspartyl/asparaginyl beta-hydroxylase	Wald ratio	1	1.470	1.218	1.721	0.003
Beta-1,4-galactosyltransferase 2		Wald ratio	1	1.190	1.040	1.340	0.023	
Beta-microseminoprotein		Wald ratio	1	1.096	1.012	1.179	0.033	
Binatriuretic peptides		Wald ratio	1	0.743	0.449	1.038	0.048	
Biotinidase		Wald ratio	1	1.100	1.026	1.175	0.012	
Carboxypeptidase B		Wald ratio	1	0.757	0.49	1.024	0.041	
Cathepsin H		Wald ratio	1	1.063	1.002	1.123	0.049	
Cation-dependent mannose-6-phosphate receptor		Wald ratio	1	1.320	1.075	1.565	0.026	
C-C motif chemokine 28		IVW	2	1.204	1.030	1.378	0.037	
Chondroitin sulfate N-acetylgalactosaminyltransferase 2		Wald ratio	1	1.462	1.142	1.782	0.020	
Collagen alpha-1(XV) chain		Wald ratio	1	0.807	0.599	1.016	0.044	
Complement component 1 Q subcomponent-binding protein, mitochondrial		Wald ratio	1	1.456	1.125	1.788	0.026	
CXADR-like membrane protein		Wald ratio	1	1.342	1.105	1.579	0.015	
Cytoskeleton-associated protein 2		Wald ratio	1	1.426	1.113	1.739	0.026	
Disintegrin and metalloproteinase domain-containing protein 19		Wald ratio	1	1.255	1.060	1.450	0.023	
Dual specificity protein phosphatase 4		Wald ratio	1	1.405	1.073	1.736	0.045	
Dynactin-associated protein		Wald ratio	1	0.671	0.319	1.023	0.026	
Dynein light chain 2, cytoplasmic		Wald ratio	1	1.513	1.122	1.905	0.038	
Endothelial monocyte-activating polypeptide 2		Wald ratio	1	0.824	0.634	1.014	0.046	
Ephrin type-B receptor 6		Wald ratio	1	1.358	1.094	1.621	0.023	
Ephrin-B1		Wald ratio	1	1.356	1.087	1.624	0.026	
Fibroblast growth factor 19		Wald ratio	1	1.301	1.042	1.559	0.046	
Fibroblast growth factor 7		Wald ratio	1	0.616	0.184	1.048	0.028	
Filamin-A		Wald ratio	1	0.701	0.388	1.014	0.026	
Golgi membrane protein 1		Wald ratio	1	1.191	1.019	1.364	0.046	
Heat shock protein beta-1		Wald ratio	1	1.209	1.042	1.376	0.026	
Heterogeneous nuclear ribonucleoproteins C1/C2		Wald ratio	1	1.456	1.125	1.788	0.026	
Interleukin-10 receptor subunit beta		Wald ratio	1	0.512	0.191	0.832	4.15E-05	
Interleukin-27 subunit alpha		IVW	2	1.129	1.032	1.226	0.014	
Interleukin-6 receptor subunit beta		Wald ratio	1	1.296	1.094	1.498	0.012	
Kallikrein-13		Wald ratio	1	0.855	0.721	0.99	0.022	
Kallikrein-14		IVW	2	1.134	1.011	1.256	0.046	
Kit ligand		Wald ratio	1	1.536	1.29	1.783	6E-04	
Leucine-rich repeats and immunoglobulin-like domains protein 3		Wald ratio	1	0.838	0.675	1.001	0.034	
Low affinity immunoglobulin gamma Fc region receptor III-B		Wald ratio	1	0.853	0.720	0.987	0.020	
Macrophage inflammatory protein-1β		IVW	2	1.144	1.046	1.241	0.007	
Mannosyl-oligosaccharide 1,2-alpha-mannosidase IB		Wald ratio	1	1.269	1.041	1.496	0.04	
Melanoma-derived growth regulatory protein		Wald ratio	1	0.921	0.86	0.982	0.009	
Methyltransferase-like protein 24		Wald ratio	1	0.676	0.319	1.033	0.031	
Mitochondrial ubiquitin ligase activator of NFKB 1		Wald ratio	1	1.314	1.131	1.497	0.003	
Multiple inositol polyphosphate phosphatase 1		Wald ratio	1	1.319	1.054	1.585	0.041	
NAD(P)H dehydrogenase [quinone] 1		Wald ratio	1	0.733	0.499	0.967	0.009	
Neuronal growth regulator 1		Wald ratio	1	0.684	0.305	1.063	0.049	
Neurotrimin		Wald ratio	1	0.829	0.702	0.955	0.004	
NKG2D ligand 3		Wald ratio	1	1.453	1.130	1.775	0.023	
Non-secretory ribonuclease		Wald ratio	1	0.776	0.539	1.013	0.036	
N-terminal pro-BNP	Wald ratio	1	0.78	0.586	0.974	0.012		
N-terminal prohormone of brain natriuretic peptide	IVW	2	0.705	0.457	0.952	0.006		
Osteoclast-associated immunoglobulin-like receptor	Wald ratio	1	0.511	0.106	0.916	0.001		
Out at first protein homolog	Wald ratio	1	0.861	0.735	0.987	0.019		
Peptidyl-prolyl cis-trans isomerase-like 1	IVW	2	1.219	1.027	1.410	0.043		
Poly(U)-specific endoribonuclease	Wald ratio	1	0.684	0.375	0.992	0.016		
Protein disulfide-isomerase A3	Wald ratio	1	1.494	1.129	1.859	0.031		
Protein eva-1 homolog C	IVW	2	1.212	1.075	1.349	0.006		
Protein FAM3D	Wald ratio	1	1.097	1.006	1.188	0.046		
Pyruvate kinase PKLR	Wald ratio	1	0.701	0.388	1.014	0.026		
Ras-related protein Rab-35	Wald ratio	1	1.237	1.050	1.425	0.026		
Sarcoplasmic/endoplasmic reticulum calcium ATPase 3	Wald ratio	1	0.651	0.405	0.897	6E-04		
Secreted frizzled-related protein 2	Wald ratio	1	1.400	1.103	1.696	0.026		
Semaphorin-4C	Wald ratio	1	1.495	1.200	1.790	0.008		
Serine/threonine-protein kinase 16	Wald ratio	1	1.456	1.125	1.788	0.026		
Sialic acid-binding Ig-like lectin 14	IVW	2	1.069	1.008	1.129	0.031		
Spondin-1	Wald ratio	1	1.231	1.082	1.381	0.006		
Testican-2	Wald ratio	1	1.314	1.046	1.582	0.046		
Testis-expressed sequence 29 protein	Weighted median	3	1.201	1.023	1.379	0.043		
Testis-expressed sequence 29 protein	IVW	3	1.196	1.041	1.350	0.024		
Trypsin-2	IVW	2	0.848	0.687	1.010	0.046		
Tumor necrosis factor receptor superfamily member 6	Wald ratio	1	1.279	1.124	1.434	0.002		
Xaa-Pro aminopeptidase 2	Wald ratio	1	1.542	1.21	1.874	0.011		
Zinc-alpha-2-glycoprotein	IVW	2	1.31	1.107	1.512	0.009		

Significant results after Bonferroni correction with $P < 1.98 \times 10^{-5}$ [$0.05/(1,263 \times 2)$]. Suggestive associations ($1.98 \times 10^{-5} < P < 0.05$). Susceptibility: COVID vs. population (C2); severity: hospitalized COVID vs. population (B2).