

DR. SUSANNA LARSSON (Orcid ID : 0000-0003-0118-0341)

Article type : Letter to the Editor

Genetic predisposition to allergic diseases is inversely associated with risk of COVID-19

To the Editor,

The host immune response is integral to determining susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severity of consequent coronavirus disease 2019 (COVID-19).¹ Allergic diseases such as allergic rhinitis (hay fever), atopic dermatitis (eczema) and asthma tend to cluster together in individuals, partly because of shared genetic factors that navigate the immune system.² However, it is not yet known whether genetic predisposition to allergic disease also relates to COVID-19 susceptibility. Understanding this relationship may provide mechanistic insight towards uncovering preventative and therapeutic strategies for COVID-19. To this end, we performed a Mendelian randomization analysis investigating how genetic predictors of allergic disease relate to COVID-19 susceptibility.

As genetic instruments for the primary analysis, we considered 136 uncorrelated ($r^2 < 0.02$) single nucleotide polymorphisms associated with a broad allergic disease phenotype (presence of at least one allergic disease, including allergic rhinitis, atopic dermatitis, and asthma) at $P < 3 \times 10^{-8}$ in a meta-analysis of 13 genome-wide association studies with a total of 180 129 cases and 180 709 controls (without the three allergic diseases), all of European descent.² Information on allergic disease was self-reported. The number of cases with each allergic disease are shown in Supplementary Table 1. The association estimates were adjusted for age, sex, and genetic principal components of ancestry.² In secondary analyses, we separately considered single nucleotide polymorphisms associated with each allergic disease (Supplementary Material).

Genetic association estimates for COVID-19 susceptibility were obtained from the COVID-19 Host Genetics Initiative genome-wide association meta-analyses (round 4, release October 20,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14728](https://doi.org/10.1111/ALL.14728)

This article is protected by copyright. All rights reserved

2020).³ To minimize population stratification bias, we restricted the analyses to individuals of European ancestry. The publicly available datasets comprising European-descent individuals included 14 134 cases with laboratory confirmed COVID-19 infection (RNA and/or serology-based) or physician confirmed COVID-19 vs. 1 284 876 population controls (everyone that is not a case) and 6406 cases of hospitalised laboratory-confirmed COVID-19 infection vs. 902 088 population controls. Of the 136 single nucleotide polymorphisms associated with any allergic disease, 130 were available in the COVID-19 outcome datasets. Details of the single nucleotide polymorphisms and their associations with COVID-19 are shown in Supplementary Table 2.

We conducted two-sample summary-level Mendelian randomization analyses using the random-effects inverse-variance weighted method (primary analysis) and several statistical sensitivity analysis methods that make different assumptions.⁴ Analyses were conducted in Stata/SE (version 14.2) and R (version 3.4.3) using summary-level data only. Ethical approval and participant consent had previously been obtained.

Genetic predisposition to any allergic disease was associated with reduced susceptibility to COVID-19 but not clearly with risk of being hospitalised with COVID-19 (Figure 1). Similar results were observed in statistical sensitivity analyses, although with wider confidence intervals that were likely attributable to lower statistical power (Figure 1). The associations of each single nucleotide polymorphism with allergic disease and COVID-19 susceptibility are displayed in Supplementary Figure 1. Secondary analyses based on genetic variants associated with different allergic diseases did not reveal associations with any particular allergic disease specifically, although the magnitude of the inverse association was most pronounced for allergic rhinitis albeit with broad confidence intervals (Supplementary Figure 2).

Our results provide evidence to support that the genetic factors underlying predisposition to allergic disease are protective against COVID-19. The pathophysiological process underlying COVID-19 involves an exaggerated host immune response.⁵ Previous work has highlighted genetic associations between obesity and smoking with both allergic disease and severe COVID-19,^{2, 6} supporting immune dysregulation as a common underlying mechanism. Further work is required to unravel the specific pathways linking susceptibility to allergic disease with risk of COVID-19, for the purpose of identifying opportunities for clinical intervention.

Susanna C. Larsson, PhD^{1,2}, Dipender Gill, BMBCh, PhD³⁻⁶

Affiliations: ¹Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ²Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; ³ Department of Epidemiology and Biostatistics, School of Public Health, St Mary's Hospital, Imperial College London, London, United Kingdom; ⁴Clinical Pharmacology and Therapeutics Section, Institute of Medical and Biomedical Education and Institute for Infection and Immunity, St George's, University of London, London, United Kingdom; ⁵Clinical Pharmacology Group, Pharmacy and Medicines Directorate, St George's University Hospitals NHS Foundation Trust, London, United Kingdom; ⁶Novo Nordisk Research Centre Oxford, Old Road Campus, Oxford, United Kingdom

Correspondence: Susanna C. Larsson, Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden. E-mail: susanna.larsson@ki.se

Acknowledgments: The authors thank the investigators of the COVID-19 Host Genetics Initiative for sharing summary-level data.

Conflict of interest: Dr. Gill is employed part-time by Novo Nordisk, outside the submitted work. Dr. Larsson has nothing to disclose.

Support statement: SCL acknowledges research support from the Swedish Heart-Lung Foundation (Hjärt-Lungfonden, 20190247), the Swedish Research Council (Vetenskapsrådet, 2019-00977), and the Swedish Research Council for Health, Working Life and Welfare (Forte, 2018-00123). DG is supported by the British Heart Foundation Research Centre of Excellence (RE/18/4/34215) at Imperial College London.

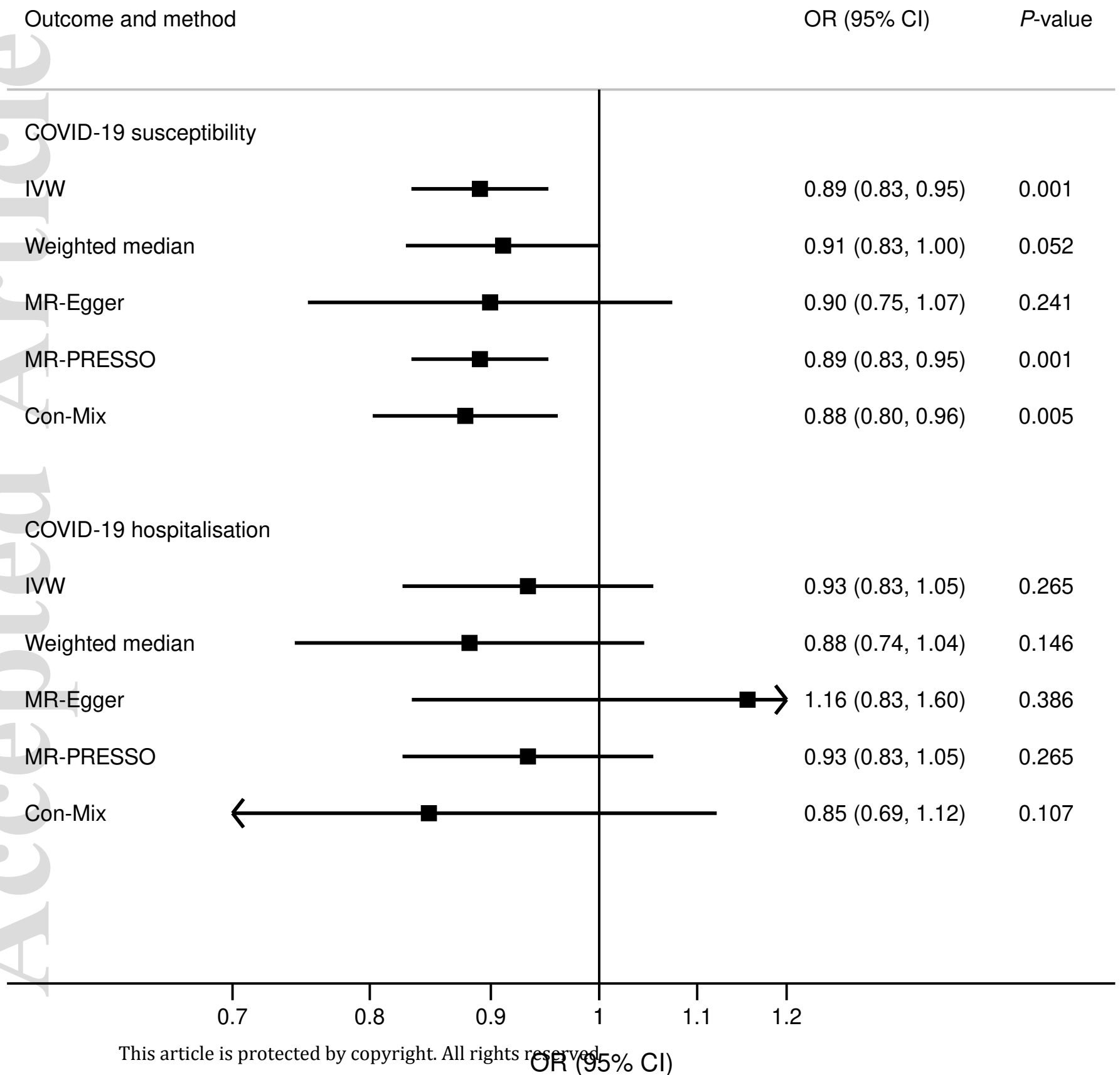
References

1. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020;369:718-724.
2. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet* 2017;49:1752-1757.

- Accepted Article
3. Covid-19 Host Genetics Initiative. 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;28:715-718.
 4. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res* 2019;4:186.
 5. McElvaney OJ, McEvoy NL, McElvaney OF, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. *Am J Respir Crit Care Med* 2020;202:812-821.
 6. Ponsford MJ, Gkatzionis A, Walker VM, et al. Cardiometabolic traits, sepsis, and severe COVID-19: a Mendelian randomization investigation. *Circulation* 2020;142:1791-1793.

FIGURE LEGEND

FIGURE 1. Associations of genetic predisposition to any allergic disease with COVID-19 with different Mendelian randomization statistical analysis methods with different assumptions. The I^2 value for heterogeneity between individual genetic variants was $\leq 27\%$. The P value for the intercept in the MR-Egger analyses was >0.16 in all analyses. No outlier SNP was detected in the MR-PRESSO analysis. CI: confidence interval; Con-Mix, contamination mixture; IVW, inverse-variance weighted; MR, Mendelian randomization; OR: odds ratio; PRESSO, Pleiotropy RESidual Sum and Outlier.



Supplementary Table 1. Number of cases with different allergic diseases

With only a single disease			With two allergic diseases			With all three diseases	Unclassifiable*
AR	AD	A	AR+AD	AR+AD	AD+A	AR+AD+A	
52 980	10 719	20 128	7667	20 523	2228	6418	59 466

Abbreviations: A, Asthma; AD, atopic dermatitis; AR, allergic rhinitis. *Missing information for at least one allergic disease and therefore could not be classified into one of the seven three-disease groups.

Supplementary Table 2. Details of the single nucleotide polymorphisms used as instruments for any allergic disease and corresponding summary statistics for COVID-19 susceptibility

rsID	GRCh37	Gene region	EA	OA	EAF	Allergic disease			COVID-19		
						Beta	SE	P	Beta	SE	P
rs7512552	1:150265704	C1orf54-[-MRPS21	C	T	0,52	0,031	0,005	1,40E-09	0,004	0,015	0,798
rs11204896	1:151796742	[RORC]	C	G	0,90	0,061	0,009	2,40E-12	0,030	0,026	0,242
rs12123821	1:152179152	RPTN-[-HRNR	T	C	0,05	0,105	0,012	6,80E-17	-0,012	0,038	0,746
rs61816761	1:152285861	[FLG]	A	G	0,01	0,202	0,021	7,40E-21	-0,071	0,054	0,184
rs2228145	1:154426970	[IL6R]	C	A	0,35	0,037	0,005	4,30E-13	-0,038	0,015	0,013
rs2070901	1:161185058	NDUFS2-[-FCER1G	T	G	0,26	0,038	0,006	1,30E-11	-0,060	0,018	0,001
rs2988277	1:167431352	[CD247]	C	T	0,66	0,039	0,005	4,00E-14	-0,015	0,015	0,310
rs1102705	1:172700868	FASLG-[-TNFSF18	G	A	0,11	0,056	0,009	3,10E-10	-0,041	0,041	0,320
rs4090390	1:173146921	TNFSF18-[-TNFSF4	A	C	0,22	0,047	0,006	1,30E-15	-0,038	0,019	0,042
rs697852	1:226914734	[ITPKB]	A	G	0,85	0,040	0,007	1,60E-09	0,020	0,020	0,326
rs10910095	1:2510755	TNFRSF14-[-FAM213B	G	A	0,84	0,041	0,007	2,70E-08	0,004	0,020	0,834
rs760805	1:25251923	[RUNX3]	T	A	0,58	0,037	0,005	6,40E-13	-0,013	0,015	0,358
rs76167968	1:35681738	SFPQ-[-ZMYM4	T	C	0,93	0,054	0,009	1,30E-08	-0,092	0,030	0,002
rs301806	1:8482078	[RERE]	T	C	0,54	0,047	0,005	1,80E-20	0,017	0,014	0,252
rs12470864	2:102926362	IL1RL2-[-IL18R1	A	G	0,35	0,055	0,005	4,20E-26	0,004	0,015	0,800
rs10865050	2:102941311	[IL18R1]	G	A	0,85	0,122	0,007	7,00E-61	-0,007	0,020	0,735
rs13403656	2:112269127	BCL2L11-[-ANAPC1	A	T	0,16	0,044	0,008	2,20E-08	-0,024	0,024	0,315
rs4848612	2:112388538	BCL2L11-[-ANAPC1	A	G	0,76	0,037	0,006	2,30E-10	-0,011	0,018	0,538
rs1143633	2:113590467	[IL1B]	C	T	0,70	0,033	0,005	1,70E-10	-0,006	0,016	0,700
rs74847330	2:143831599	KYNU-[-ARHGAP15	A	G	0,88	0,047	0,008	1,80E-09	-0,036	0,022	0,098
rs1064213	2:198950240	[PLCL1]	G	A	0,47	0,034	0,005	5,40E-12	-0,039	0,014	0,007
rs13384448	2:228707862	CCL20-[-DAW1	T	C	0,76	0,041	0,006	2,80E-12	0,016	0,020	0,411
rs1057258	2:234115629	[INPP5D]	C	T	0,80	0,044	0,007	1,40E-10	0,018	0,020	0,387
rs34290285	2:242698640	[D2HGDH]	G	A	0,73	0,079	0,006	4,00E-33	-0,002	0,016	0,902
rs4671601	2:64836267	[LOC339807]	C	T	0,83	0,038	0,006	8,80E-09	0,002	0,021	0,941
rs10174949	2:8442248	[LINC00299]	G	A	0,68	0,064	0,005	7,30E-31	0,009	0,016	0,564
rs13088318	3:101242751	FAM172BP-[-TRMT10C	A	G	0,62	0,031	0,005	8,60E-09	-0,027	0,015	0,080
rs75557865	3:121652141	[SLC15A2]	G	A	0,57	0,029	0,005	1,60E-08	-0,030	0,018	0,094
rs10663129	3:141321836	[RASA2]	AC T	A	0,33	0,041	0,005	1,10E-13	-0,011	0,022	0,624
rs519973	3:187633268	BCL6-[-LPP-AS2	A	G	0,35	0,033	0,005	4,50E-10	-0,005	0,018	0,787
rs2030030	3:187793833	BCL6-[-LPP-AS2	T	C	0,86	0,040	0,007	1,00E-08	0,020	0,019	0,302

Supplementary Material

rs60946162	3:188133336	[LPP]	T	C	0,42	0,040	0,005	8,60E-15	0,002	0,017	0,896
rs17607589	3:188402586	[LPP]	C	T	0,84	0,052	0,007	1,80E-14	0,002	0,020	0,936
rs80064395	3:196372546	FBXO45-[]-CEP19	C	T	0,94	0,068	0,009	1,60E-12	-0,010	0,027	0,714
rs6776757	3:33069091	[GLB1]	G	A	0,47	0,032	0,005	3,10E-10	0,021	0,014	0,142
rs61192126	3:72394852	LINC00870-[]-RYBP	T	C	0,69	0,036	0,006	8,90E-11	0,011	0,017	0,526
rs227275	4:103593898	[MANBA]	C	A	0,56	0,033	0,005	3,70E-11	-0,009	0,015	0,574
rs4145717	4:123316076	[ADAD1]	T	G	0,34	0,057	0,005	9,20E-27	-0,021	0,015	0,166
rs5743618	4:38798648	[TLR1]	C	A	0,70	0,095	0,006	3,30E-58	-0,012	0,018	0,505
rs10033073	4:4775401	STX18-[]-MSX1	G	A	0,35	0,039	0,006	1,20E-10	0,000	0,016	0,999
rs6869502	5:110166083	SLC25A46-[]-TSLP	T	A	0,18	0,076	0,007	6,40E-29	-0,059	0,020	0,004
rs1837253	5:110401872	SLC25A46-[]-TSLP	C	T	0,78	0,068	0,006	1,60E-31	0,003	0,017	0,845
rs6594499	5:110470137	WDR36-[]-CAMK4	C	A	0,48	0,072	0,005	4,60E-46	0,008	0,015	0,609
rs250308	5:118684297	[TNFAIP8]	T	C	0,37	0,031	0,005	4,00E-09	0,015	0,016	0,339
rs3749833	5:131799626	[C5orf56]	C	T	0,30	0,038	0,006	3,30E-11	-0,008	0,016	0,623
rs3091307	5:131989136	RAD50-[]-IL13	G	A	0,20	0,060	0,006	3,60E-21	0,008	0,019	0,689
rs848	5:131996500	[IL13]	A	C	0,24	0,066	0,006	1,50E-24	-0,025	0,018	0,159
rs740474	5:140925362	[DIAPH1]	C	T	0,42	0,033	0,005	5,60E-11	-0,019	0,015	0,205
rs10068717	5:141494934	[NDFIP1]	T	C	0,62	0,041	0,005	4,80E-15	0,005	0,015	0,733
rs16903574	5:14610309	[FAM105A]	G	C	0,08	0,069	0,010	1,40E-12	-0,009	0,029	0,757
rs2910162	5:159909345	MIR3142-[]-MIR146A	G	A	0,68	0,032	0,005	2,50E-09	-0,008	0,016	0,620
rs13153019	5:176782218	LMAN2-[]-RGS14	C	T	0,26	0,034	0,006	1,30E-08	0,025	0,017	0,144
rs7717955	5:35862841	[IL7R]	C	T	0,71	0,070	0,006	9,10E-36	-0,001	0,016	0,939
rs7714574	5:40492655	DAB2---[]-PTGER4	T	C	0,53	0,031	0,005	5,90E-10	-0,004	0,015	0,771
rs9372120	6:106667535	[ATG5]	G	T	0,18	0,041	0,006	4,20E-11	0,003	0,018	0,870
rs35469349	6:128294709	[PTPRK]	A	T	0,26	0,036	0,006	2,30E-10	-0,012	0,017	0,474
rs5029937	6:138195151	[TNFAIP3]	G	T	0,97	0,078	0,014	2,40E-08	0,028	0,040	0,491
rs9383820	6:157419508	[ARID1B]	C	T	0,76	0,036	0,006	1,20E-08	0,016	0,019	0,399
rs2854001	6:31323012	[HLA-B]	A	G	0,18	0,057	0,006	1,20E-19	-0,028	0,021	0,198
rs2507978	6:31351664	HLA-B-[]-MICA	G	A	0,41	0,034	0,005	1,20E-10	-0,006	0,015	0,701
rs28895016	6:31574525	NCR3-[]-AIF1	C	T	0,91	0,093	0,011	9,40E-16	0,026	0,030	0,373
rs34004019	6:32626403	HLA-DQA1-[]-HLA-DQB1	A	G	0,70	0,096	0,006	3,80E-52	-0,018	0,021	0,381
rs3097670	6:33046752	[HLA-DPA1]	G	C	0,88	0,062	0,009	7,70E-12	0,010	0,024	0,669
rs10947428	6:33647058	[ITPR3]	C	T	0,19	0,045	0,006	3,50E-13	-0,023	0,019	0,218
rs2134814	6:90987512	[BACH2]	C	G	0,65	0,045	0,005	1,70E-17	-0,018	0,015	0,230
rs10486391	7:20376018	[ITGB8]	A	G	0,53	0,030	0,005	6,80E-09	0,030	0,017	0,072
rs6461503	7:20560996	ITGB8-[]-ABCB5	T	C	0,53	0,038	0,005	1,70E-14	-0,008	0,015	0,596
rs6977955	7:28156887	[JAZF1]	T	C	0,21	0,045	0,006	7,10E-13	0,028	0,017	0,103
rs17664743	7:50253897	C7orf72-[]-IKZF1	A	G	0,20	0,041	0,006	6,20E-11	-0,009	0,018	0,596
rs4296977	7:77018542	[GSAP]	C	T	0,16	0,054	0,007	2,10E-13	0,029	0,021	0,174
rs6990534	8:128814091	[MYC]	A	G	0,36	0,041	0,005	6,40E-14	-0,014	0,016	0,366
rs7824394	8:81292599	MIR5708-[]-ZBTB10	A	C	0,37	0,049	0,005	3,50E-20	-0,014	0,019	0,465
rs10760123	9:123650534	PHF19-[]-TRAF1	T	G	0,38	0,031	0,005	5,20E-09	-0,016	0,015	0,295
rs12551834	9:131613191	C9orf114-[]-LRRRC8A	G	A	0,92	0,056	0,009	3,00E-09	-0,026	0,025	0,299

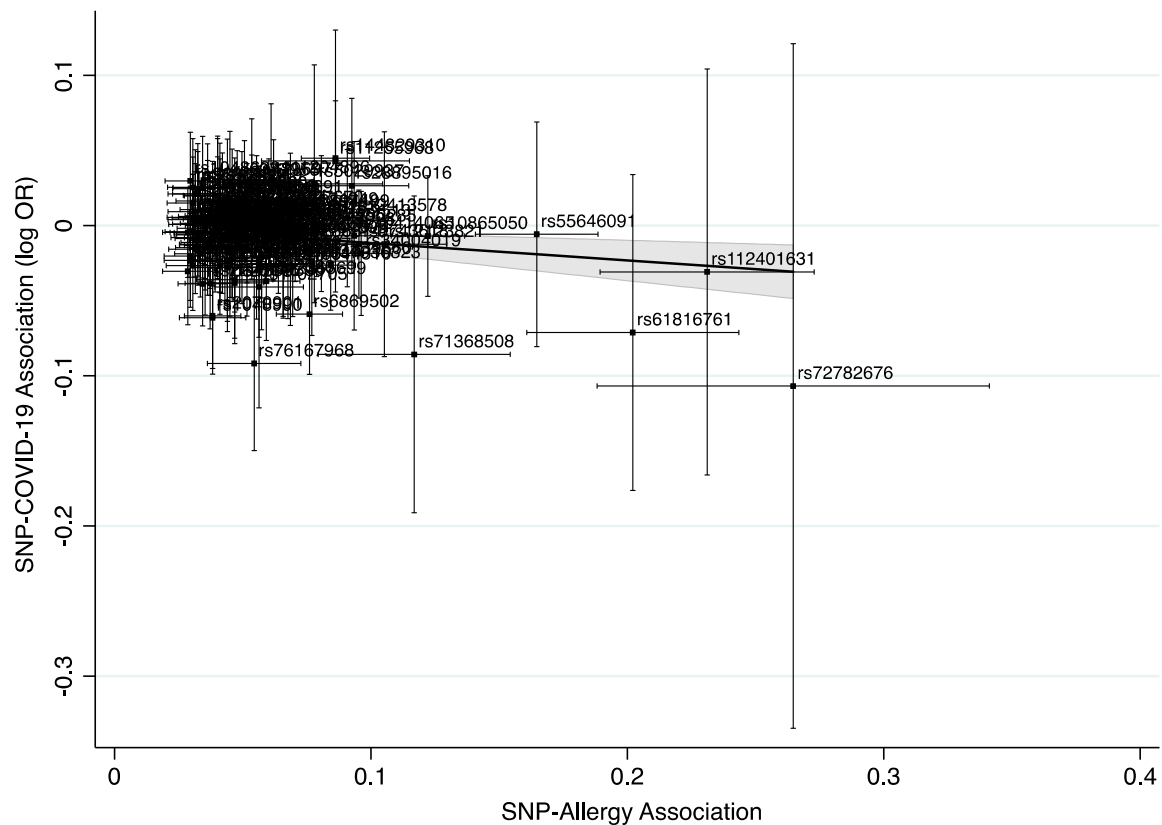
Supplementary Material

rs16922576	9:5064193	[JAK2]	C	T	0,32	0,035	0,006	3,20E-10	-0,002	0,017	0,916
rs343478	9:6051399	RANBP6-[]--IL33	G	A	0,52	0,032	0,005	2,60E-10	0,001	0,018	0,949
rs144829310	9:6208030	RANBP6-[]-IL33	T	G	0,16	0,086	0,007	1,20E-35	0,045	0,019	0,021
rs10883723	10:104225832	C10orf95-[]-ACTR1A	C	T	0,31	0,030	0,005	1,60E-08	-0,020	0,015	0,176
rs4747846	10:6074451	[IL2RA]	C	G	0,52	0,035	0,005	1,00E-11	-0,013	0,015	0,399
rs61839660	10:6094697	[IL2RA]	T	C	0,07	0,077	0,009	4,40E-19	-0,024	0,025	0,350
rs2893907	10:64382359	[ZNF365]	C	A	0,58	0,031	0,005	1,80E-09	0,025	0,017	0,126
rs11255753	10:8605553	GATA3--[]SFTA1P	T	G	0,26	0,040	0,006	2,00E-12	0,009	0,019	0,639
rs2025758	10:8841669	GATA3---[]---SFTA1P	T	C	0,58	0,040	0,005	4,70E-15	-0,005	0,015	0,747
rs11255968	10:8936162	GATA3---[]---SFTA1P	C	T	0,96	0,086	0,015	7,70E-09	0,043	0,044	0,333
rs72782676	10:9032555	GATA3---[]---SFTA1P	C	G	0,98	0,265	0,039	3,20E-11	-0,107	0,116	0,358
rs12413578	10:9049253	GATA3---[]---SFTA1P	C	T	0,90	0,091	0,008	1,30E-27	0,005	0,023	0,831
rs1444789	10:9064361	GATA3---[]---SFTA1P	C	T	0,20	0,064	0,006	1,50E-22	-0,007	0,020	0,732
rs7130753	11:111470567	LAYN-[]-SIK2	C	T	0,69	0,044	0,006	7,00E-15	-0,016	0,017	0,354
rs12365699	11:118743286	DDX6-[]-CXCR5	G	A	0,85	0,059	0,007	5,10E-18	-0,037	0,020	0,067
rs56129466	11:128158189	KIRREL3-AS3---[]-ETS1	A	G	0,79	0,046	0,006	1,90E-13	-0,001	0,017	0,953
rs479844	11:65551957	AP5B1-[]-OVOL1	G	A	0,57	0,037	0,005	1,60E-13	0,007	0,014	0,646
rs7936323	11:76293758	WNT11-[]-LRRC32	A	G	0,46	0,084	0,005	2,20E-63	-0,026	0,015	0,085
rs55646091	11:76299431	WNT11-[]-LRRC32	A	G	0,05	0,165	0,012	2,30E-40	-0,006	0,038	0,880
rs11236814	11:76343428	WNT11-[]-LRRC32	A	T	0,91	0,066	0,009	4,00E-14	-0,012	0,025	0,627
rs59593577	11:95425526	SESN3--[]-FAM76B	C	T	0,87	0,052	0,008	1,60E-11	-0,015	0,023	0,516
rs7137828	12:111932800	[ATXN2]	T	C	0,54	0,032	0,005	2,20E-10	0,025	0,015	0,109
rs6489785	12:121363724	SPPL3-[]-HNF1A-AS1	T	C	0,37	0,042	0,005	1,60E-15	-0,014	0,016	0,358
rs63406760	12:123742692	C12orf65-[]-CDK2AP1	T	TG	0,77	0,046	0,006	3,00E-13	-0,006	0,021	0,789
rs55726902	12:48196982	[HDAC7]	G	A	0,80	0,050	0,006	2,60E-16	0,001	0,017	0,943
rs11169225	12:50345671	[AQP2]	A	T	0,18	0,044	0,006	1,20E-11	-0,028	0,018	0,123
rs10876864	12:56401085	SUOX-[]-IKZF4	G	A	0,39	0,046	0,005	1,40E-19	-0,022	0,015	0,129
rs1059513	12:57489709	[STAT6]	T	C	0,89	0,081	0,008	1,00E-22	0,001	0,023	0,955
rs4943794	13:41173408	[FOXO1]	C	G	0,23	0,042	0,006	7,20E-12	0,012	0,019	0,534
rs9573092	13:73627275	PIBF1-[]-KLF5	A	G	0,70	0,030	0,005	2,70E-08	-0,023	0,016	0,146
rs9989163	14:103235012	RCOR1-[]-TRAF3	A	G	0,49	0,029	0,005	1,90E-08	-0,005	0,015	0,765
rs1048990	14:35761675	[PSMA6]	G	C	0,16	0,038	0,007	1,00E-08	-0,061	0,019	0,001
rs111914382	14:38097001	FOXA1-[]--TTC6	TG	T	0,27	0,035	0,006	8,10E-09	-0,015	0,023	0,522
rs2104047	14:68754417	[RAD51B]	T	C	0,36	0,041	0,005	1,60E-13	-0,027	0,016	0,105
rs9323612	14:75968608	JDP2-[]-BATF	A	G	0,70	0,031	0,005	8,60E-09	0,001	0,018	0,963
rs12440045	15:41782684	RTF1-[]-ITPKA	C	A	0,55	0,032	0,005	4,90E-10	0,005	0,017	0,765
rs10519067	15:61068347	[RORA]	G	A	0,86	0,054	0,007	9,30E-13	0,006	0,021	0,785
rs56375023	15:67448363	[SMAD3]	A	G	0,21	0,070	0,006	8,20E-32	-0,004	0,017	0,802
rs3540	15:91045408	[IQGAP1]	G	A	0,65	0,035	0,005	3,30E-11	0,006	0,016	0,711
rs11644510	16:11277358	CLEC16A-[]-RMI2	C	T	0,64	0,070	0,005	6,10E-38	-0,027	0,017	0,108
rs12596613	16:11491007	RMI2-[]--LITAF	C	G	0,67	0,031	0,005	6,10E-09	0,009	0,016	0,571
rs921650	17:38069076	[GSDMB]	A	G	0,48	0,057	0,005	5,70E-30	-0,020	0,014	0,161
rs11652139	17:38149033	[PSMD3]	A	G	0,59	0,050	0,005	7,50E-22	-0,001	0,026	0,959

Supplementary Material

rs112401631	17:38764524	CCR7-[]-SMARCE1	A	T	0,01	0,231	0,021	2,20E-26	-0,031	0,069	0,655
rs11464691	17:38770641	CCR7-[]-SMARCE1	TA	T	0,57	0,051	0,005	1,40E-21	0,017	0,020	0,393
rs7214661	17:43430696	MAP3K14-[]-ARHGAP27	G	A	0,32	0,031	0,005	1,20E-08	0,021	0,015	0,159
rs71368508	17:4521473	SMTNL2-[]-ALOX15	C	A	0,99	0,117	0,019	2,00E-09	-0,086	0,054	0,111
rs9889262	17:47398070	[ZNF652]	A	T	0,35	0,042	0,005	9,70E-16	0,006	0,016	0,712
rs4801001	18:52336175	DYNAP-[]--RAB27B	T	C	0,42	0,031	0,005	5,90E-09	0,005	0,015	0,708
rs4574025	18:60009814	[TNFRSF11A]	T	C	0,56	0,030	0,005	6,80E-09	-0,004	0,015	0,795
rs10414065	19:33721455	SLC7A10-[]-CEBPA	C	T	0,92	0,093	0,011	6,10E-18	-0,007	0,032	0,832
rs3787184	20:50157837	[NFATC2]	A	G	0,78	0,048	0,007	1,10E-12	0,011	0,020	0,595
rs2766678	20:52208356	[ZNF217]	G	A	0,21	0,055	0,006	5,00E-18	-0,008	0,028	0,777
rs6011033	20:62322699	[RTEL1]	G	A	0,78	0,046	0,006	3,50E-14	0,015	0,018	0,409
rs73205303	21:36467830	[RUNX1]	A	G	0,13	0,043	0,007	7,90E-10	-0,010	0,020	0,624
rs5758343	22:41816652	TEF-[]-TOB2	A	T	0,22	0,047	0,006	4,80E-14	-0,017	0,021	0,415

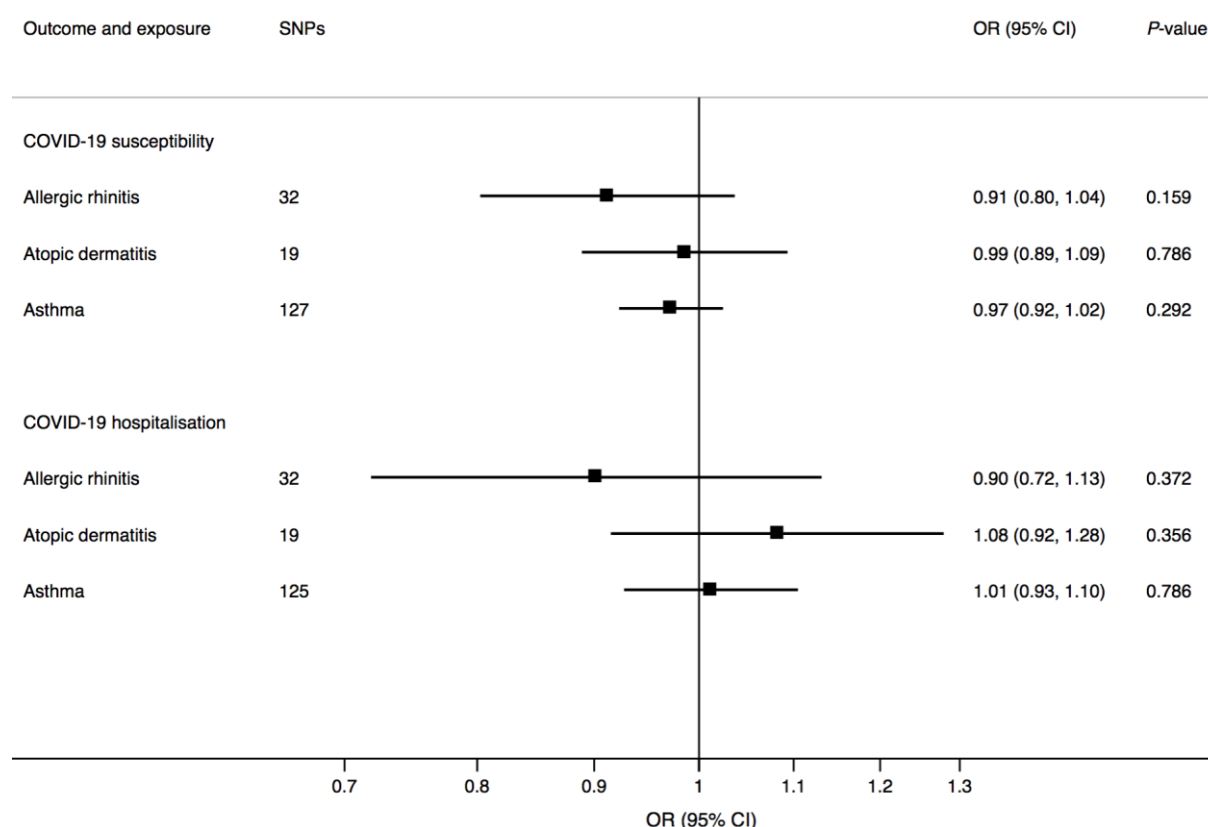
Abbreviations: EA, effect allele; EAF, effect allele frequency in European populations of the 1000 Genomes Project.; OA, other allele; SE, standard error.



Supplementary Figure 1. Scatter plot of the associations of the single nucleotide polymorphisms (SNPs) with any allergic disease and COVID-19 susceptibility. The solid line and grey area represent the inverse variance weighted estimate and its 95% confidence interval.

Genetic instruments for specific allergic diseases and associations with COVID-19

In secondary analyses, we constructed genetic instruments consisting of uncorrelated single nucleotide polymorphisms associated with each specific allergic disease at the genome-wide significance level ($P < 5 \times 10^{-8}$) in published large-scale studies, including: 1) a meta-analysis of 18 genome-wide association studies for allergic rhinitis (including 212 120 individuals [59 762 cases and 152 358 controls]);¹ 2) a meta-analysis of 22 genome-wide association studies for atopic dermatitis (including up to 103 066 individuals of European ancestry);² and 3) a genome-wide association analysis for asthma in the UK Biobank (including 393 859 individuals [64 538 asthma cases and 329 321 controls]).³ Results are shown in Supplementary Figure 2 below.



Supplementary Figure 2. Associations of genetic predisposition to specific allergic disease phenotypes with COVID-19 in Mendelian randomization analyses based on the random-effects inverse variance weighted method. OR: odds ratio; SNPs: single nucleotide polymorphisms.

References

1. Waage J, Standl M, Curtin JA, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. *Nat Genet.* 2018;50(8):1072-1080.
2. Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet.* 2015;47(12):1449-1456.
3. Han Y, Jia Q, Jahani PS, et al. Genome-wide analysis highlights contribution of immune system pathways to the genetic architecture of asthma. *Nat Commun.* 2020;11(1):1776.