Matters arising

A first update on mapping the human genetic architecture of COVID-19

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COVID-19 Host Genetics Initiative*✉

The COVID-19 pandemic continues to pose a major public health threat, especially in countries with low vaccination rates. To better understand the biological underpinnings of SARS-CoV-2 infection and COVID-19 severity, we formed the COVID-19 Host Genetics Initiative[1]. Here we present a genome-wide association study meta-analysis of up to 125,584 cases and over 2.5 million control individuals across 60 studies from 25 countries, adding 11 genome-wide significant loci compared with those previously identified[2]. Genes at new loci, including *SFTPD*, *MUC5B* and *ACE2*, reveal compelling insights regarding disease susceptibility and severity.

Here we present meta-analyses bringing together 60 studies from 25 countries (Fig. 1 and Supplementary Table 1) for three COVID-19-related phenotypes: (1) individuals critically ill with COVID-19 on the basis of requiring respiratory support in hospital or who died as a consequence of the disease (9,376 cases, of which 3,197 are new in this data release, and 1,776,645 control individuals); (2) individuals with moderate or severe COVID-19 defined as those hospitalized due to symptoms associated with the infection (25,027 cases, 11,386 new and 2,836,272 control individuals); and (3) all cases with reported SARS-CoV-2 infection regardless of symptoms (125,584 cases, 76,022 new and 2,575,347 control individuals). Most studies have reported results before the roll out of the COVID-19 vaccination campaign. An overview of the study design is provided in Supplementary Fig. 1. We found a total of 23 genome-wide significant loci ($P < 5 \times 10^{-8}$) of which 20 loci remain significant after correction for multiple testing ($P < 1.67 \times 10^{-8}$) to account for the number of phenotypes examined (Fig. 2, Supplementary Fig. 2 and Supplementary Table 2). We compared the effects of these loci between the previous[2] and current analysis and found that only one locus did not replicate (rs72711165). All of the other loci showed the expected increase in statistical significance (Supplementary Fig. 3).

Across the genome-wide significant loci, we observed clear patterns of association with the different phenotypes under study. We therefore developed a two-class Bayesian model for classifying loci based on the patterns of association across the two better-powered phenotypes (COVID-19 hospitalization and SARS-CoV-2 reported infection). Intuitively, loci that are associated with susceptibility will also be associated with severity as, to develop COVID-19, SARS-CoV-2 infection needs to first occur. By contrast, those genetic effects that solely modify the course of illness should be associated with severity of illness and not show any association with reported infection except through preferential ascertainment of hospitalized cases in a cohort (Supplementary Methods). We identified 16 loci that are substantially more likely (>99% posterior probability) to affect the risk of COVID-19 hospitalization and 7 loci that clearly influence susceptibility to SARS-CoV-2 infection (Supplementary Table 3 and Supplementary Fig. 4).

We observed that several loci had a significant heterogeneous effect across studies (6 out of 23 loci with a *P* value for heterogeneity of $<2.2 \times 10^{-3}$; Supplementary Table 2). Owing to an increased diversity in our study population (Supplementary Fig. 5), we were able to examine whether such heterogeneity was due to effect differences across continental ancestry groups. Only one locus (*FOXP4*) showed a significantly different effect across ancestries (*P* value heterogeneity of $<7 \times 10^{-5}$; Supplementary Table 4 and Supplementary Fig. 6), although even at this locus all of the ancestry groups showed a positive effect estimate. This confirms that factors related to between-study heterogeneity (such as variable definition of COVID-19 severity owing to different thresholds for testing, hospitalization and patient recruitment) rather than differences across ancestries are a more likely explanation for the observed heterogeneity in the effect sizes across studies.

For the 23 genome-wide significant loci, we examined candidate causal genes and performed a phenome-wide association study to better understand their potential biological mechanisms (Supplementary Tables 2, 5 and 6 and Supplementary Fig. 7). Several of these loci with previous and direct connections to lung disease and SARS-CoV-2 infection mechanisms are highlighted here.

Several loci involved in COVID-19 severity implicate lung surfactant biology. A missense variant rs721917:A>G (p.Met31Thr) in *SFTPD* (10q22.3) confers risk for hospitalization (odds ratio (OR) = 1.06, 95% confidence interval (CI) = 1.04–1.08, $P = 1.7 \times 10^{-8}$) and has been previously associated with increased risk of chronic obstructive pulmonary disease[3] (OR = 1.08, $P = 2.0 \times 10^{-8}$) and decreased lung function[4] (FEV1/FVC; $\beta = -0.019$; $P = 2.0 \times 10^{-15}$). *SFTPD* encodes surfactant protein D (SP-D), which participates in innate immune response, protecting the lungs against inhaled microorganisms. The recombinant fragment of SP-D binds to the S1 spike protein of SARS-CoV-2 and potentially inhibits binding to ACE2 receptor and SARS-CoV-2 infection[5]. Another missense variant rs117169628:G>A (p.Pro256Leu) in *SLC22A31* (16q24.3) also confers risk of hospitalization (OR = 1.09, 95% CI = 1.06–1.13, $P = 2.6 \times 10^{-8}$). *SLC22A31* belongs to the family of solute carrier proteins that facilitate transport across membranes[6] and is co-regulated with other surfactant proteins[7].

We found that the variant rs35705950:G>T located in the promoter of *MUC5B* (11p15.5) is protective against hospitalization (OR = 0.83, 95% CI = 0.86–0.93, $P = 6.5 \times 10^{-9}$). This well-studied promoter variant increases the expression of *MUC5B* in lung in GTEx ($P = 6.7 \times 10^{-16}$) and is the strongest known variant associated with an increased risk of

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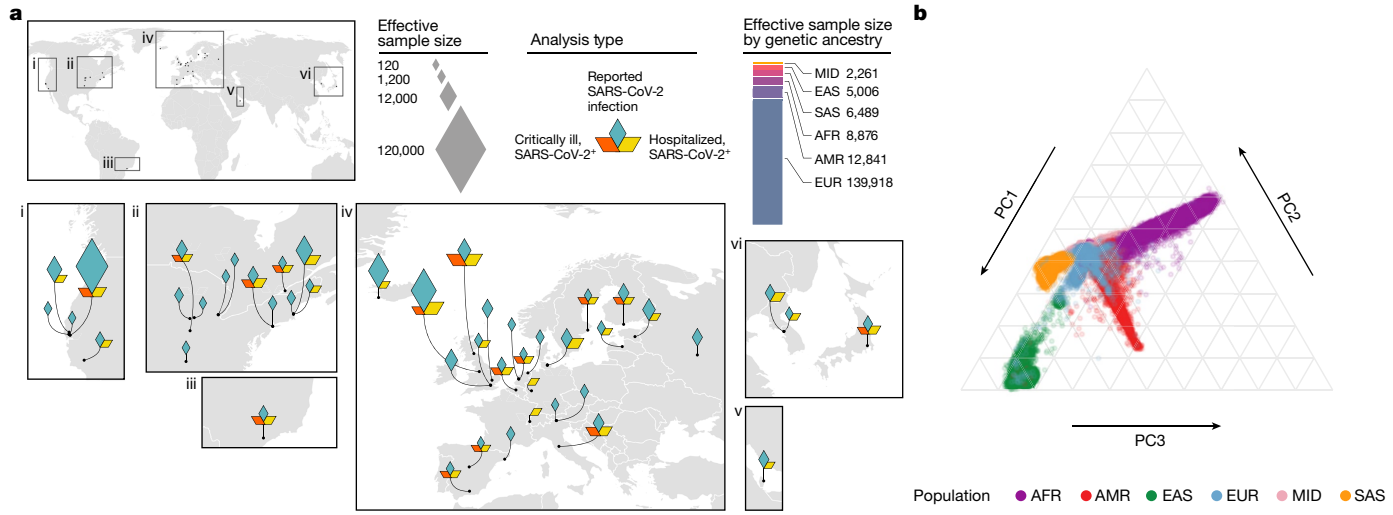

Fig. 1 | Overview of contributing studies in Host Genetics Initiative data freeze 6. a, Geographical overview of the contributing studies to the COVID-19 Host Genetics Initiative and composition by major continental ancestry groups. Ancestry groups are defined as Middle Eastern (MID), south Asian (SAS), east Asian (EAS), African (AFR), admixed American (AMR) and European (EUR). **b**, Principal components analysis highlighting the population structure and the sample ancestry of the individuals participating in the COVID-19 Host Genetics Initiative. This figure is reproduced from the original publication by the COVID-19 Host Genetics Initiative[2] with modifications reflecting the updated analysis from data freeze 6.

developing idiopathic pulmonary fibrosis (IPF)[8,9], but also improves survival in patients with IPF carrying this mutation[10].

Finally, we found that rs190509934:T>C, which is located 69 bp upstream of *ACE2* (Xp22.2), is associated with decreased susceptibility risk (OR = 0.69, 95% CI = 0.63–0.75, $P = 3.6 \times 10^{-18}$). ACE2 is the SARS-CoV-2 receptor and functionally interacts with SLC6A19 and SLC6A20[11], one of which also showed a significant association with susceptibility (rs73062389:G>A at *SLC6A20*; OR = 1.18, 95% CI = 1.16–1.20, $P = 2.5 \times 10^{-74}$). Notably, rs190509934 is ten times more common in south Asian populations (minor allele frequency (MAF) = 0.027) than in European populations (MAF = 0.0024), demonstrating the importance of diversity for variant discovery. Recent results have shown that the

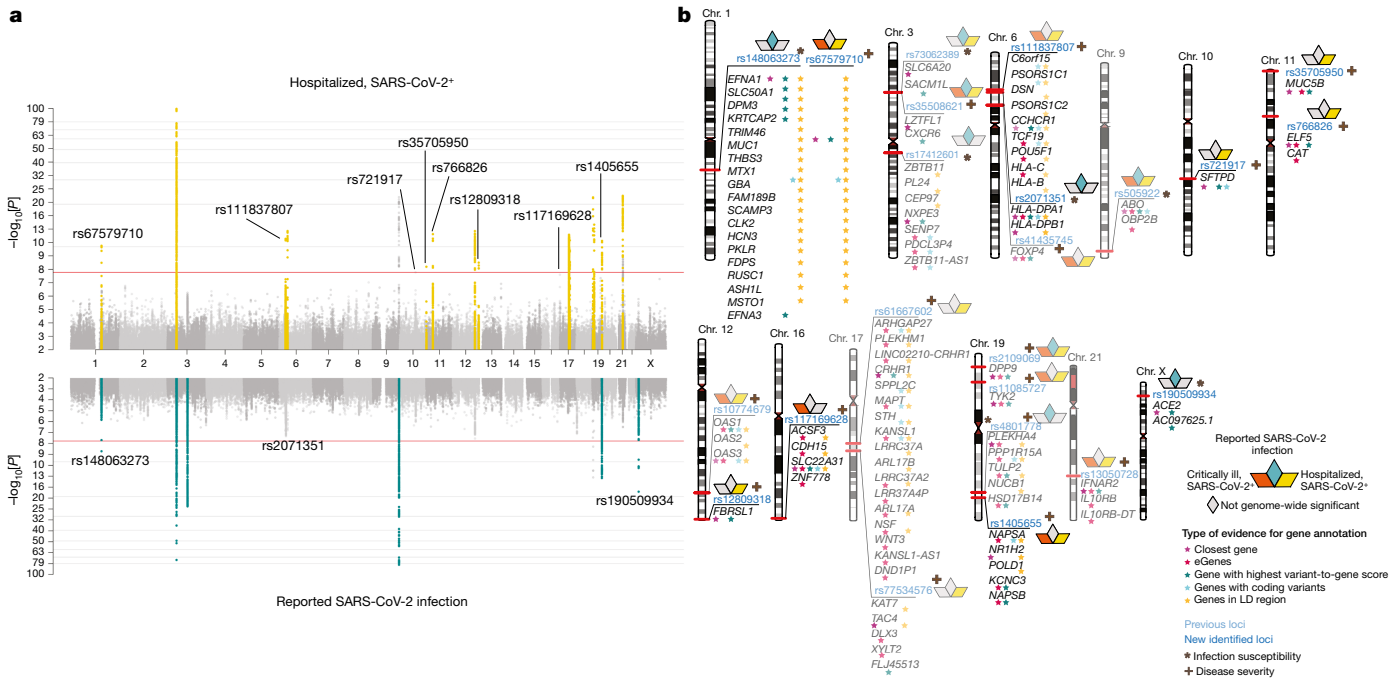

Fig. 2 | Genome-wide association results for COVID-19. a, The results of the genome-wide association study of hospitalized COVID-19 ($n = 25{,}027$ cases and $n = 2{,}836{,}272$ control individuals) (top), and the results of reported SARS-CoV-2 infection ($n = 125{,}584$ cases and $n = 2{,}575{,}347$ control individuals) (bottom). Loci highlighted in yellow (top) represent regions associated with the severity of COVID-19 manifestation. Loci highlighted in green (bottom) are regions associated with SARS-CoV-2-reported infection. Lead variants for the loci identified in this data release are annotated with their respective rs ID. Horizontal lines denote genome-wide significant thresholds. **b**, The results of gene prioritization using different evidence measures of gene annotation. Genes in regions of linkage disequilibrium (LD), genes with coding variants and eGenes (fine-mapped *cis*-eQTL variant PIP > 0.1 in GTEx Lung) are annotated if in linkage disequilibrium with a COVID-19 lead variant ($r^2 > 0.6$). V2G denotes the highest gene prioritized by OpenTargetGenetics' V2G score. The asterisk (*) indicates SARS-CoV-2 reported infection and the plus symbol (+) indicates COVID-19 severity. The transparent loci were reported in the previous freeze (data release 5), and loci in bright blue were identified in the current freeze (data release 6). This figure is reproduced from the original publication by the COVID-19 Host Genetics Initiative[2] with modifications reflecting the updated analysis from data freeze 6.

rs190509934:T>C variant lowers *ACE2* expression, which in turn confers protection against SARS-CoV-2 infection[12].

We applied Mendelian randomization to infer potential causal relationships between COVID-19-related phenotypes and their genetically correlated traits (Supplementary Methods; Supplementary Tables 7–9 and Supplementary Fig. 8). A causal association was observed between genetic liability to type 2 diabetes and SARS-CoV-2 reported infection (OR = 1.02, 95% CI = 1.01–1.03, $P = 1.6 \times 10^{-3}$), and COVID-19 hospitalization (OR = 1.06, 95% CI = 1.03–1.1, $P = 1.4 \times 10^{-4}$). Multivariable Mendelian randomization was used to estimate the direct effect of liability to type 2 diabetes on COVID-19-related phenotypes that was not mediated through body mass index. This analysis indicated that the observed causal association of liability to type 2 diabetes on COVID-19 phenotypes is mediated by body mass index (Supplementary Table 10).

We have substantially expanded the genetic analysis of SARS-CoV-2 infection and COVID-19 severity by doubling the case size, identifying 11 loci. We developed an approach to systematically assign the 23 discovered loci to either disease susceptibility (7 loci) or disease severity (16 loci). Although distinguishing between the two phenotypes is challenging because progression to a severe form of the disease requires susceptibility to infection in the first place, it is now evident that the genetic mechanisms involved in these two aspects of the disease can be differentiated. Among the new loci associated with disease susceptibility, *ACE2* represents an expected, albeit interesting, finding. *MUC5B*, *SFTPD* and *SLC22A31* are the three most interesting new loci associated with COVID-19 severity. Their relationship with lung function and lung diseases is consistent with loci previously associated with disease severity. The surfactant proteins secreted by alveolar cells, representing an emerging biological mechanism, maintain healthy lung function and facilitate the clearance of pathogens[13]. The protective effect of the *MUC5B* variant is unexpected given the otherwise risk-increasing, concordant effect between IPF and COVID-19 observed for other variants[9]. Nonetheless, this result aligns with the *MUC5B* promoter variant association that shows a twofold higher survival rate among patients with IPF[10]. In mice, *Muc5b* seems to be essential for effective mucociliary clearance and for controlling infection[14], which suggests that therapies to control mucin secretion may be beneficial in patients with COVID-19.

Expanding genomic research to include participants from around the world enabled us to test whether the effect of COVID-19-related genetic variants was markedly different across ancestry groups. We did not detect obvious heterogeneity between ancestry groups, and we attribute the observed heterogeneity in the effect of COVID-19-related genetic variants to the diverse inclusion criteria across studies in terms of COVID-19 severity. However, we also note that ascertainment differences across studies might mask true underlying differences in effect sizes between ancestry groups.

The biological insights gained by this expansion of the COVID-19 Host Genetic Initiative showed that increasing sample size and diversity remain a fruitful activity to better understand the human genetic architecture of COVID-19.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-022-04826-7.

Data availability

Summary statistics generated by COVID-19 Host Genetics Initiative are available online (https://www.covid19hg.org/results/r6/). The analyses described here use the freeze 6 data. The COVID-19 Host Genetics Initiative continues to regularly release new data freezes. Summary statistics for samples from individuals of non-European ancestry are not currently available owing to the small individual sample sizes of these groups, but the results for 23 loci lead variants are reported in Supplementary Table 3. Individual-level data can be requested directly from the authors of the contributing studies, listed in Supplementary Table 1. We used publicly available data from GTEx (https://gtexportal.org/home/), the Neale laboratory (http://www.nealelab.is/uk-biobank/), the Finucane laboratory (https://www.finucanelab.org), the FinnGen Freeze 4 cohort (https://www.finngen.fi/en/access_results) and eQTL catalogue release 3 (http://www.ebi.ac.uk/eqtl/).

Code availability

The code for summary statistics lift-over, the projection PCA pipeline including precomputed loadings and meta-analyses are available on GitHub (https://github.com/covid19-hg/), and the code for the Mendelian randomization and genetic correlation pipeline is available at GitHub (https://github.com/marcoralab/MRcovid). Codes for implementing the multivariable Mendelian randomization analysis and subtype analyses are available at GitHub (https://github.com/marcoralab/multivariate_MR and https://github.com/mjpirinen/covid19-hgi_subtypes).

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Competing interests A full list of competing interests is supplied as Supplementary Table 11.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-022-04826-7.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No code was used to collect data in the study.
Data analysis	Each individual study that contributed genetic-phenotype association summary statistics to the consortium carried out their association analyses independently of the consortium (study-specific information outlined in Supplementary Table 1). However, the consortium did release phenotyping and analysis guidelines as a recommendation (https://www.covid19hg.org/). For quality control of genotype data we recommended using the Ricopili pipeline (PMID: 31393554). For genotype phasing and imputation we recommended the TopMed Imputation Server (PMID: 27571263) or Michigan Imputation Server (PMID: 27571263). For genome-wide association study (GWAS), we recommended SAIGE (PMID: 30104761), but some studies used PLINK (PMID: 17701901). Each study then submitted their GWAS summary statistics to the consortium for meta-analysis. LD score regression v 1.0.1 [PMID: 25642630] was used for heritability and partitioned heritability analyses. Variants for Mendelian randomization instruments were selected using PLINK version 1.90b6.18 (PMID: 17701901). Exposure and outcome datasets were harmonized, and MR statistical analysis conducted using R version 4.0.3. with the R-package TwoSampleMR version 0.5.5 (PMID: 29846171) (which included Fixed-effects IVW analysis (PMID: 24114802), weighted median estimator (WME) (PMID: 27061298), weighted mode based estimator (WMBE) and MR Egger regression (PMID: 26050253)) and additionally MR-PRESSO version 1.0 (PMID: 29686387). Code availability statement: The code for summary statistics liftover, projection PCA pipeline including precomputed loadings and metaanalysis are available at https://github.com/covid19-hg/ , the code for Mendelian randomization and genetic correlation pipeline at https://github.com/marcoralab/MRcovid , and code for Probabilistic assignment of variants into susceptibility vs. severity effects is at https://github.com/mjpirinen/covid19-hgi_subtypes

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Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Summary statistics generated by COVID-19 HGI are available at https://www.covid19hg.org/results/r6/ . The analyses described here utilize the freeze 6 data. COVID-19 HGI continues to regularly release new data freezes. Summary statistics for non-European ancestry samples are not currently available due to the small individual sample sizes of these groups, but results for 23 loci lead variants are reported in Supplementary Table 4. Individual level data can be requested directly from contributing studies, listed in Supplementary Table 1. We used publicly available data from GTEx (https://gtexportal.org/home/), the Neale lab (http://www.nealelab.is/uk-biobank/), Finucane lab (https://www.finucanelab.org), FinnGen Freeze 4 cohort (https://www.finngen.fi/en/access_results), and eQTL catalogue release 3 (http://www.ebi.ac.uk/eqtl/).

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The consortium meta-analysed genome-wide association study (GWAS) summary statistics from any individual study that had included a minimum of 50 cases and 50 controls in their analysis. The cutoff was aimed at reducing noise for the meta-analysis, but also to be inclusive of studies that had not yet accumulated large numbers of COVID-19 patient data. No statistical calculation for adequate sample size was performed, but the results identifying multiple genomic regions at genome-wide significance threshold indicates adequate power for genetic discovery.
Data exclusions	Individual level phenotype and genotype data exclusions were performed by each individual study, following the consortium analysis plan recommendations (www.covid19hg.org). Possible reasons for sample exclusion included removing genetic ancestry outliers within a study (using principal components analysis), poor quality of genetic data or lack of phenotypic data for a sample. The consortium manually examined GWAS summary statistics data submitted by each study (for each submitted analysis separately), including sample size used for analysis, allele frequency check against Gnomad reference panel, and distribution of test statistics. After meta-analysis, the results were checked for heterogeneity variant effects between contributing studies in SupplementaryTable 2
Replication	No replication was performed. The consortium meta-analysed GWAS summary statistics, bringing together as many studies as possible to achieve the largest possible sample size and statistical power for association. this meant that the consortium included most large studies of COVID-19 host genetics that have been performed to date, so it was not possible to perform replication analyses in external cohorts. Therefore we performed manual checks on each study contributing summary statistics before entering them into the meta-analysis. In addition, after meta-analysis, we performed a check for heterogeneity between variant association estimates across studies contributing data. This allowed us to better understand whether the variant effects differed much between individual studies.
Randomization	No randomization was performed because there was no allocation of samples to experimental groups
Blinding	Blinding was not relevant to the study. The case status and severity of symptoms was evaluated for each sample by investigators from each study respectively. The consortium recommended using covariates to control for confounding: age + age2 + sex + age*sex + 20 principal components (obtained using genetic data) + study specific covariates (if any). The consortium meta-analysed summary statistics from these case/control studies, not individual level data. Details of which variables each study used and how the calculated PCs for their analysis are available in Supplementary Table 1.

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Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Summary statistics from 60 independent studies were included in consortium meta-analyses. Mean age of cases across studies was 53.36 years. The effective sample size for genetic ancestry populations for Sars-CoV2 reported infection was: n=6147 Middle Eastern; n=23391 South Asian; 13152 East Asian; 39571 African; 39817 Ad-mixed American; 440696 European. Population characteristics regarding age, sex and exact case and control sample numbers for each contributing study are given in Supplementary Table 1.
Recruitment	The consortium pre-defined phenotype criteria for cases and controls, but the specific recruitment was carried out independently by each contributing study. COVID-19 disease status (critical illness, hospitalization status) was assessed following the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (PMID: 32358325). The critically ill COVID-19 group included patients who were hospitalized due to symptoms associated with laboratory-confirmed SARSCoV-2 infection and who required respiratory support or whose cause of death was associated with COVID-19. The hospitalized COVID-19 group included patients who were hospitalized due to symptoms associated with laboratoryconfirmed SARS-CoV-2 infection. The reported infection cases group included individuals with laboratory-confirmed SARSCoV-2 infection or electronic health record, ICD coding or clinically confirmed COVID-19, or self-reported COVID-19 (e.g. by questionnaire), with or without symptoms of any severity. Genetic ancestry-matched controls for the three case definitions were sourced from population-based cohorts, including individuals whose exposure status to SARS-CoV-2 was either unknown or infection- negative for questionnaire/electronic health record based cohorts.
Ethics oversight	Ethical statements for each contributing study are given in Supplementary Table 1.

Note that full information on the approval of the study protocol must also be provided in the manuscript.