

CLINICAL AND POPULATION STUDIES



COVID-19 Is a Coronary Artery Disease Risk Equivalent and Exhibits a Genetic Interaction With ABO Blood Type

James R. Hilser¹, Neal J. Spencer¹, Kimia Afshari, Frank D. Gilliland¹, Howard Hu¹, Arjun Deb¹, Aldons J. Lusis¹, W.H. Wilson Tang¹, Jaana A. Hartiala¹, Stanley L. Hazen¹,* Hooman Allayee¹*

BACKGROUND: COVID-19 is associated with acute risk of major adverse cardiac events (MACE), including myocardial infarction, stroke, and mortality (all-cause). However, the duration and underlying determinants of heightened risk of cardiovascular disease and MACE post-COVID-19 are not known.

METHODS: Data from the UK Biobank was used to identify COVID-19 cases (n=10 005) who were positive for polymerase chain reaction (PCR⁺)-based tests for SARS-CoV-2 infection (n=8062) or received hospital-based *International Classification of Diseases version-10 (ICD-10)* codes for COVID-19 (n=1943) between February 1, 2020 and December 31, 2020. Population controls (n=217 730) and propensity score-matched controls (n=38 860) were also drawn from the UK Biobank during the same period. Proportional hazard models were used to evaluate COVID-19 for association with long-term (>1000 days) risk of MACE and as a coronary artery disease risk equivalent. Additional analyses examined whether COVID-19 interacted with genetic determinants to affect the risk of MACE and its components.

RESULTS: The risk of MACE was elevated in COVID-19 cases at all levels of severity (HR, 2.09 [95% CI, 1.94–2.25]; $P<0.0005$) and to a greater extent in cases hospitalized for COVID-19 (HR, 3.85 [95% CI, 3.51–4.24]; $P<0.0005$). Hospitalization for COVID-19 represented a coronary artery disease risk equivalent since incident MACE risk among cases without history of cardiovascular disease was even higher than that observed in patients with cardiovascular disease without COVID-19 (HR, 1.21 [95% CI, 1.08–1.37]; $P<0.005$). A significant genetic interaction was observed between the *ABO* locus and hospitalization for COVID-19 ($P_{\text{interaction}}=0.01$), with risk of thrombotic events being increased in subjects with non-O blood types (HR, 1.65 [95% CI, 1.29–2.09]; $P=4.8\times10^{-5}$) to a greater extent than subjects with blood type O (HR, 0.96 [95% CI, 0.66–1.39]; $P=0.82$).

CONCLUSIONS: Hospitalization for COVID-19 represents a coronary artery disease risk equivalent, with post-acute myocardial infarction and stroke risk particularly heightened in non-O blood types. These results may have important clinical implications and represent, to our knowledge, one of the first examples of a gene-pathogen exposure interaction for thrombotic events.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: COVID-19 ■ genetics ■ major adverse cardiac events ■ myocardial infarction ■ SARS-CoV-2 ■ stroke ■ thrombosis

Over the course of 4 years, the global pandemic caused by the SARS-CoV-2 virus has led to nearly 800 million confirmed infections and over seven million deaths.¹ One intriguing aspect of COVID-19,

the severe respiratory illness associated with SARS-CoV-2 infection, is the markedly increased rate of cardiovascular disease (CVD) complications and postacute risk of thrombotic events observed in patients, such as

Correspondence to: Hooman Allayee, PhD, Department of Population and Public Health Sciences, Keck School of Medicine of USC, 2250 Alcazar St, CSC202, Los Angeles, CA 90033. Email hallayee@usc.edu

*S.L. Hazen and H. Allayee contributed equally.

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Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CVD	cardiovascular disease
ICD-10	International Classification of Diseases version-10
MACE	major adverse cardiac event
MI	myocardial infarction
PAD	peripheral artery disease

myocardial infarction (MI) and stroke. For example, rates of major adverse cardiac events (MACE=MI, stroke, or all-cause mortality) in COVID-19 patients are increased immediately after and during the first 30 days after infection as well as up to 2 years after infection.^{2–14} However, it is not known how long the heightened risk of MACE persists in COVID-19 patients, or what factors modulate this risk. Furthermore, whether certain subgroups of COVID-19 patients are at greater increased risk of adverse CVD events is not entirely clear, and whether or not any of these subgroups rise to the level of a coronary artery disease (CAD) risk equivalent has not been explored. In this regard, CAD risk equivalence has historically been used as a benchmark for escalation of global CVD prevention efforts, including lowering lipid goals and initiation of antiplatelet therapies.^{15–24} As a consequence of these and other unanswered questions, regulatory bodies across the world have yet to adapt preventive CVD guidelines for patients with prior COVID-19 infection. Thus, determining the duration of increased CVD risk in COVID-19 patients and whether COVID-19 represents a CAD risk equivalent could have important clinical implications for patient care.

Given the variability in CVD outcomes exhibited by patients, it is also reasonable to assume that increased risk of MACE associated with post-COVID-19 infection can be attributed, at least in part, to genetic predisposition. For example, large-scale genetic analyses have identified over 20 loci that are associated with susceptibility to SARS-CoV-2 infection and COVID-19 severity,²⁵ including regions on chromosome *3p21* and the *ABO* locus on chromosome *9q34*. Interestingly, *ABO*, which defines A, B, AB, and O blood types, was previously identified as a genetic susceptibility factor for plaque rupture and MI in the presence of CAD^{26,27} and one of the first loci to be identified for SARS-CoV-2 infection.^{28–32} Thus, it is plausible that COVID-19 may increase the risk of MACE through interactions with shared genetic determinants, such as *ABO*. However, a link between incident MACE risks among post-COVID-19 subjects and genetic variants associated with COVID-19-related traits or CVD has not been reported.

In the present study, we leveraged data from the UK Biobank to investigate the long-term risk of MACE

Highlights

- Risk of incident major adverse cardiac event was increased during different time periods out to nearly 3 years among COVID-19 patients, particularly among those requiring hospitalization.
- Hospitalized COVID-19 represented a coronary artery disease risk equivalent since risk of major adverse cardiac event among COVID-19 cases without history of cardiovascular disease was higher than that observed in patients with cardiovascular disease without COVID-19.
- Use of antiplatelet agents among primary care subjects without known cardiovascular disease attenuated risk of myocardial infarction or stroke due to hospitalization for COVID-19.
- Increased risk of thrombotic events (myocardial infarction or stroke) among hospitalized COVID-19 cases resulted from a genetic interaction with the *ABO* locus and was more pronounced in subjects with non-O blood types.

among COVID-19 patients and whether COVID-19 rises to the level of a CAD risk equivalent. We also tested whether the association of COVID-19 with risk of MACE exhibited genetic interactions with known susceptibility variants that were specific to either risk of CVD outcomes or COVID-19 traits.

MATERIALS AND METHODS

Data Availability

Individual-level data used in the present study are available upon application to the UK Biobank (<https://www.ukbiobank.ac.uk/>). All other relevant data are either provided in the article or available upon request from the authors.

Study Population

Between 2006 and 2010, the UK Biobank recruited a total of 503 325 participants who were 40 to 69 years of age and registered with a general practitioner of the UK National Health Service.³³ At enrollment, extensive data on demographics, medication use, and disease-related outcomes were obtained through questionnaires and health records. Baseline blood samples were also collected for measurement of serum biomarkers that are either established disease risk factors or routinely measured as part of clinical evaluations. All UK Biobank participants provided informed consent. The study protocol was approved by the North West Multicenter Research Ethics Committee and performed according to the Declaration of Helsinki principles. The present study was approved by the Institutional Review Board of the USC Keck School of Medicine.

Definition of COVID-19 Cases and Controls

Subsequent to the emergence of SARS-CoV-2 in early 2020, the UK Biobank released results of polymerase chain

reaction (PCR)-based tests for SARS-CoV-2 infection (data-field 40100) among its participants and data on hospital-based *International Classification of Diseases version-10 (ICD-10)* codes related to COVID-19 (U07.1 or U07.2). Based on the information provided for the period between February 1, 2020 and December 31, 2020, a total of 11 115 COVID-19 cases were identified (Figure 1). Of these individuals, 2868 cases had been assigned a U07.1 or U07.2 *ICD-10* code and were therefore hospitalized for COVID-19, whereas the remaining 8247 cases only received a positive PCR test for SARS-CoV-2 infection. As a comparison group, we defined population controls as subjects who were already part of the UK Biobank hospital in patient data system but had never received a positive PCR test for SARS-CoV-2 or were assigned a COVID-19 *ICD-10* code between February 1, 2020 and December 31, 2020. Population controls were first assigned a random number using the rand function with uniform distribution in SAS (v9.4, SAS Institute Inc, Cary, NC). Controls were then ranked based on their random number and reiteratively matched 20× to each of the 11 115 cases. This strategy resulted in 222 300 controls being assigned, at a ratio of 20:1, a start date that corresponded to the same date that each matched case received a positive PCR test for SARS-CoV-2 or was assigned an *ICD-10* code for COVID-19 hospitalization (Figure 1). After exclusion of individuals who experienced an MI, stroke, or who died within 30 days of entry into the analysis, complete demographic and clinical data were available in 8062 cases with only a positive PCR test for SARS-CoV-2 infection, 1943 cases who were hospitalized for COVID-19, and 217 730 randomly assigned population controls (Figure 1; Table 1; Table S2). We also used propensity score matching as another analytical method to minimize the potential confounding effects of predisposing risk factors among hospitalized COVID-19 cases. Propensity scores were generated for hospitalized COVID-19 cases and population controls based on age, sex, education, self-reported ethnicity, diabetes, asthma, smoking, obesity, CVD status, lipid-lowering medication use, and antihypertension medication using the Twang package in R³⁴ (v4.3.0, R Core Team, Vienna, Austria). Controls were then matched to cases at a ratio of 20:1 based on the proximity of their propensity scores using a K-nearest neighbor algorithm, as implemented in the Matching package in R³⁵ (v4.3.0, R Core Team, Vienna, Austria). This strategy yielded a data set of 1943 hospitalized COVID-19 cases and a subset of 38 860 propensity score-matched controls.

Clinical and Demographic Definitions

CAD was defined as positive for *ICD-10* codes I24 and I25 and MI was defined based on *ICD-10* codes I21, I22, I23, I25.2, as well as doctor-diagnosed and self-reported MI, as described previously.²⁷ Similarly, stroke was defined based on *ICD-10* codes I63 and I64, as well as doctor-diagnosed and self-reported stroke. CVD was defined as the composite of CAD, MI, or stroke. Peripheral artery disease (PAD) was defined based on *ICD-10* codes I730, I731, I738, and I739. Obesity was defined as a BMI ≥30 and diabetes was defined based on *ICD-10* codes E10, E11, E12, E13, and E14.³⁶ Asthma was defined using previously reported criteria³⁷ based on *ICD-10* codes J45 and J46, as well as doctor-diagnosed or self-reported asthma. Education was categorized based on data provided by the UK Biobank: (1) college/university/nursing/teaching;

(2) national vocational qualification/higher national diploma/higher national certificate; (3) A level; (4) O level/certificate of secondary education; or (5) none of the above/not available. Self-reported ethnicity was assessed using Data Field 21000. Smoking status was defined as reporting never or ever smoking using data field 20116. Use of lipid-lowering medications, antihypertension medications, or antiplatelet agents (aspirin or clopidogrel) at the time of enrollment in the UK Biobank was based on self-reported data using Data Fields 6153, 6177, 10004, 6154, or 20003 (1141168318 and 1141168322 for clopidogrel) and classified as never or ever. The numbers of all COVID-19 cases and population controls for whom these data were available are summarized in Table S2.

Time-to-Event Data

Incident MACE (MI, stroke, or death) were based on the number of days from the date of receiving a positive PCR test for SARS-CoV-2 infection or an initial *ICD-10* code assignment for COVID-19 between February 1, 2020 and December 31, 2020 up to the assignment of an *ICD-10* code for MI, stroke, or all-cause mortality until October 31, 2022 (up to ≈1000 days of follow-up). The causes of death for all COVID-19 cases and population controls based on *ICD-10* code data are shown in Table S3. A subanalysis with cardiovascular mortality was also performed where death could be attributed to an *ICD-10* code for Diseases of the Circulatory System (Chapter IX). Control subjects who were assigned an *ICD-10* code for COVID-19 or had a positive PCR test for SARS-CoV-2 infection after December 31, 2020 were censored at that date in the time-to-event analyses.

Statistical Analyses

Differences in demographic and clinical characteristics at the time of enrollment into the UK Biobank between cases and controls were evaluated using χ^2 tests for categorical variables and 2-sample *t*-tests for continuous traits, respectively. Time-to-event analyses were performed with Cox proportional hazards models to test whether COVID-19 was associated with risk of incident thrombosis (MI or stroke), all-cause mortality, or the composite MACE trait with all 3 outcomes (MI, stroke, or all-cause mortality) over 1003 days of follow-up from the date of entry into the analysis. Age at the time of COVID-19 diagnosis, sex, self-reported ethnicity, education, diabetes, asthma, smoking status, lipid-lowering medication use, and antihypertension medication use were included as covariates. Sensitivity analyses were also performed in subjects stratified by CVD status, age, sex, obesity, diabetes, and smoking. Conditional Cox proportional hazards models were used for time-to-event analyses with hospitalized cases and propensity score-matched population controls, with inclusion of age at the time of COVID-19 diagnosis, sex, self-reported ethnicity, education, diabetes, asthma, smoking status, lipid-lowering medication use, and antihypertension medication as covariates.

Genetic and Gene-Pathogen Interaction Analyses

Details on genotyping arrays, quality control metrics, and imputation methods used by the UK Biobank have been described previously.³³ Briefly, ABO blood types were provided by the UK

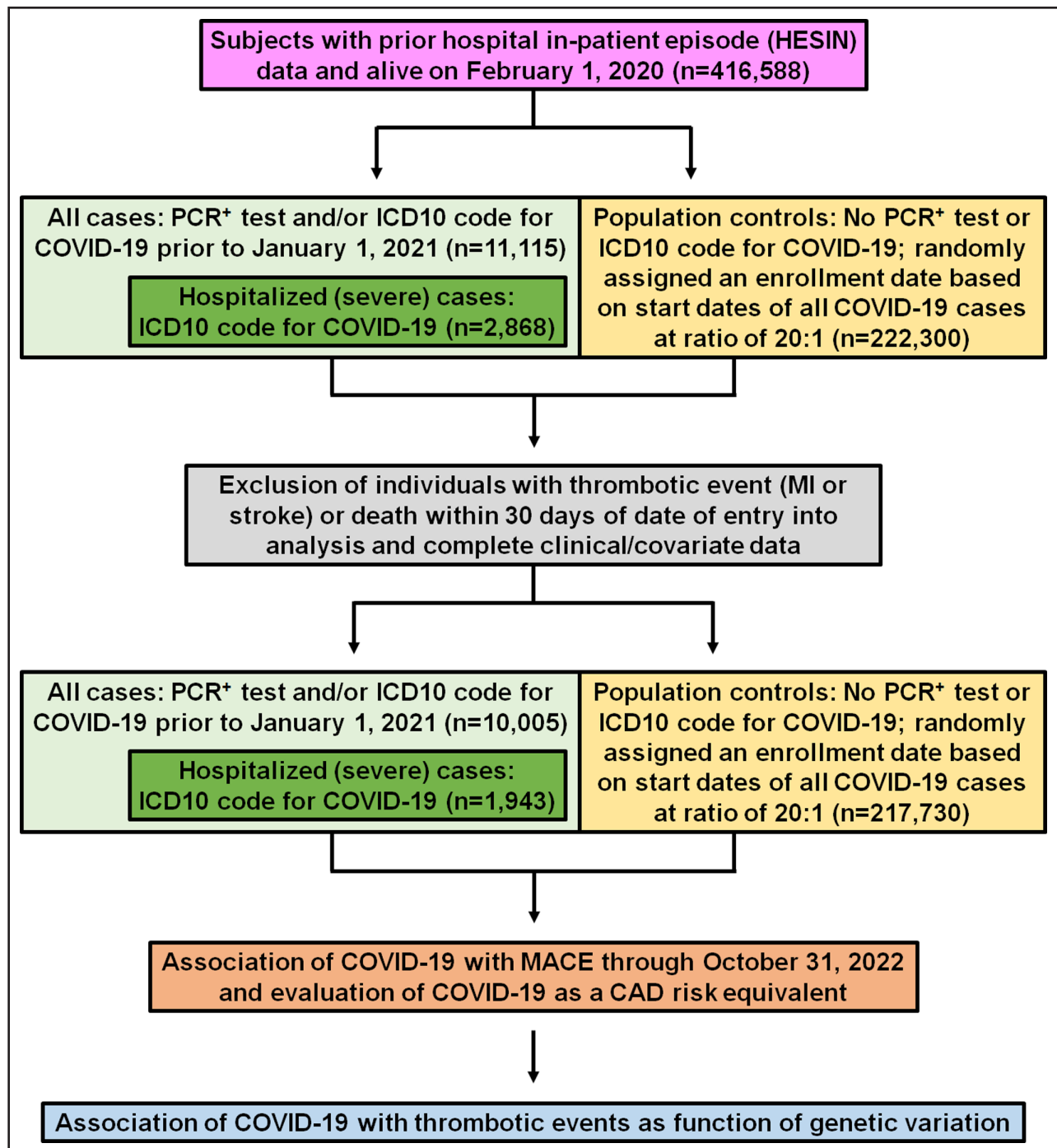


Figure 1. Overview of clinical and genetic analyses.

A study was designed with 416 588 UK Biobank subjects who had hospital in-patient data and were alive on February 1, 2020 (pink box). COVID-19 cases at all levels of severity were defined as subjects who had either a positive polymerase chain reaction (PCR) test for SARS-CoV-2 infection or received a hospital-based *International Classification of Diseases version-10 (ICD-10)* code for COVID-19 through October 31, 2022 (light green box). Severe cases were defined as the subset of subjects who were hospitalized for COVID-19 (dark green inset box). Population controls were defined as subjects alive on February 1, 2020 and who did not have a positive PCR test for SARS-CoV-2 infection or who had ever been assigned a hospital-based *ICD-10* code for COVID-19 through December 31, 2020 (yellow box). Controls were then randomly assigned an enrollment date based on the start dates of all COVID-19 case and matched to cases at a ratio of 20:1. After exclusion of subjects with thrombotic events or death within 30 days of the date of entry into analysis (gray box), 10 005 COVID-19 cases and 217 730 population controls (green and yellow boxes) were used to evaluate association of COVID-19 with major adverse cardiac events (MACE), defined as myocardial infarction (MI), stroke, or all-cause mortality, up until October 31, 2022 (orange box). Gene-pathogen exposure interactions on the risk of thrombotic events were performed with previously identified genetic variants (blue box).

Table 1. Clinical Characteristics of Hospitalized COVID-19 Cases and Population Controls

Trait	Cases (n=1943)	All controls (n=217 730)	P value*	Propensity score-matched controls (n=38 860)	P value†
Age at start of follow-up	70.4 (8.1)	68.4 (8.1)	<0.001	70.6 (8.0)	0.32
Men/Women	1069/874	96 403/121 327	<0.001	21 730/17 130	0.44
Ethnicity			<0.001		1.00
White	1750 (90.1)	205 378 (94.3)		35 068 (90.2)	
Asian	65 (3.4)	4222 (1.9)		1331 (3.4)	
Black	75 (3.9)	3541 (1.6)		1390 (3.6)	
Chinese	8 (0.4)	706 (0.3)		160 (0.4)	
Mixed	11 (0.6)	1246 (0.6)		234 (0.6)	
Other	24 (1.2)	1920 (0.9)		481 (1.2)	
Unknown	10 (0.5)	717 (0.3)		196 (0.5)	
Education			<0.001		0.59
College/University/Nursing/Teaching (A)	694 (35.7)	102 402 (47.0)		13 471 (34.7)	
NVQ/HND/HNC (vocational qualification; B)	242 (12.5)	27 947 (12.8)		4705 (12.1)	
A level (high school; C)	79 (4.1)	11 793 (5.4)		1610 (4.1)	
O level/CSE (less than high school; D)	300 (15.4)	36 854 (16.9)		5816 (15.0)	
None of the above/not available (E)	628 (32.3)	38 734 (17.8)		13 258 (34.1)	
Ever smoker	1069 (55.0)	96 301 (44.2)	<0.001	21 685 (55.8)	0.50
History of MI stroke, or CAD (CVD)	392 (20.2)	25 236 (11.6)	<0.001	8321 (21.4)	0.19
Diabetes	498 (25.6)	20 433 (9.4)	<0.001	10 660 (27.4)	0.08
Asthma	427 (22.0)	32 197 (14.8)	<0.001	8707 (22.4)	0.65
Lipid-lowering medication use	579 (29.8)	41 698 (19.2)	<0.001	12 289 (31.6)	0.09
Antihypertension medication use	633 (32.6)	47 863 (22.0)	<0.001	13 252 (34.1)	0.17

Data are shown as mean (SD) for age and numbers (%) for categorical traits. *P* values for comparisons between cases and controls were derived from a 2-sample *t* test for age and χ^2 tests for categorical traits. Matching of controls was done using propensity scores generated using all variables shown in the Table. CAD indicates coronary artery disease; CSE, certificate of secondary education; CVD, cardiovascular disease; HNC, higher national certificate; HND, higher national diploma; MI, myocardial infarction; and NVQ, national vocational qualification.

*For comparisons between cases and all controls.
†For comparisons between cases and propensity score-matched controls.

Biobank using Data Field 23165 and were defined based on genotypes of 2 variants at the *ABO* locus (rs8176746 and rs8176719), as described previously.³⁸ Genotypes of the lead variants at the loci with the strongest effect sizes for SARS-CoV-2 infection only (rs73062389) or hospitalized COVID-19 (rs11385942) on chromosome 3p21,²⁵ and for CAD (rs4977574) on chromosome 9p21^{39–42} were extracted from the imputed data for ~90 million single nucleotide polymorphisms (SNPs) that were available in the UK Biobank³³ for the same subset of subjects used in the clinical analyses. Logistic regression models were used to test the association of ABO-derived blood types (A, B, or AB versus O), rs73062389, rs11385942 with hospitalized COVID-19 cases versus SARS-CoV-2[−] controls; hospitalized COVID-19 cases versus SARS-CoV-2⁺ subjects; and SARS-CoV-2⁺ cases versus SARS-CoV-2[−] controls, with adjustment for age at the time of COVID-19 diagnosis, sex, ethnicity, based on the first 10 principal components, as provided by the UK Biobank in Data Field 22009, and genotyping array. Cox proportional hazards models were used to assess whether ABO blood type (non-O [AA, AO, BB, BO, or AB] versus O) or genotypes at rs73062389, rs11385942, or rs4977574 were associated with incident MI or stroke, with adjustment for age at the time of *ICD-10* code assignment, sex, first 10 principal components, genotyping array, education, diabetes, asthma, smoking, lipid medication use, and antihypertension medication

use. To determine whether the association of COVID-19 with risk of MI or stroke differed as a function of ABO blood type or genotype, an interaction term was included in the model, with adjustment for the same covariates. Due to the relatively low frequency of the minor alleles of rs73062389 and rs11385942 (~10% for each) and since previous studies had demonstrated that increased risk of hospitalized COVID-19 was similar in subjects with 1 or 2 copies of the risk allele (A) at rs11385942,²⁸ dominant models were used for genetic analyses with these 2 variants. Analyses with rs4977574 assumed an additive genetic model. All clinical and statistical genetics analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Definition and Clinical Characteristics of COVID-19 Cases and Controls

An overview of the analytical strategy used to identify COVID-19 cases and controls in the UK Biobank is presented in Figure 1. We first validated our definitions of COVID-19 cases using the strongest known genetic determinants of SARS-CoV-2 infection (rs73062389) and hospitalization for COVID-19 (rs11385942)

on chromosome *3p21*.^{25,28} Both rs73062389 and rs11385942 yielded associations specifically with SARS-CoV-2 infection and severe COVID-19, respectively (Table S1) that were directionally consistent with previous reported effect sizes.²⁵ Compared with controls, COVID-19 cases at all levels of severity were more likely to be male, exhibit differences in demographic and clinical characteristics, and have more CVD-associated comorbidities (Table S2). These differences were even more pronounced when population controls were compared with hospitalized COVID-19 cases (Table 1). In addition, the most common causes of death among COVID-19 cases and population controls were due to diseases of the circulatory system, including CVD, followed by diseases of the respiratory system and neoplasms (Table S3).

Association of COVID-19 With Increased Risk of MACE

Consistent with prior studies, COVID-19 at all levels of severity was associated with significantly higher risk of MI, stroke, or all-cause mortality over 1003 days of follow-up (HR, 2.09 [95% CI, 1.94–2.25]; $P < 0.0005$; Figure S1; Table S4). Association of COVID-19 with MACE was even more pronounced among cases requiring hospitalization (HR, 3.85 [95% CI, 3.51–4.24]; $P < 0.0005$; Figure 2A; Table 2). To account for unmeasured confounders, we also used a set of controls matched to hospitalized cases based on propensity scores (Table 1). As shown in Table 2 and Figure 2B, hospitalization for COVID-19 was similarly associated with increased risk of MACE in comparison to propensity score-matched controls (HR, 3.65 [95% CI, 3.30–4.05]; $P < 0.0005$).

We next performed a series of sensitivity analyses to evaluate the consistency of the associations with COVID-19. Notably, risk of MACE in cases at all levels of severity and particularly in those requiring hospitalization was consistently elevated during the first, second, or third year after COVID-19 diagnosis (Table S5). The effect sizes for association of COVID-19 at all levels of severity with risk of MACE and its components were also comparable between groups, except in men and younger subjects (Tables S6 through S8). Among hospitalized cases and all population controls, similar differential risk of MACE and its components was also observed in men, younger subjects, and individuals with preexisting obesity or diabetes (Tables S9 through S11). Moreover, hospitalization for COVID-19 was associated with increased risk of mortality attributable to CVD (Table S12). Collectively, these observations demonstrate that risk of MACE among COVID-19 patients was elevated out to nearly 3 years after SARS-CoV-2 infection regardless of the presence or absence of co-associated CVD risk factors.

Hospitalization for COVID-19 Is a CAD (CVD) Risk Equivalent

We next evaluated whether COVID-19 represented a CAD risk equivalent. Among participants who remained COVID-19 negative throughout the follow-up period, the risk of MACE was increased in subjects with diabetes (HR, 1.88 [95% CI, 1.73–2.04]; $P < 0.0005$), peripheral artery disease (PAD; HR, 5.08 [95% CI, 4.62–5.59]; $P < 0.0005$), or CVD (HR, 5.63 [95% CI, 5.36–5.92]; $P < 0.0005$; Figure 3; Table 3). However, risk of MACE among hospitalized COVID-19 cases without a history of CVD was also increased (HR, 7.04 [95% CI, 6.25–7.92];

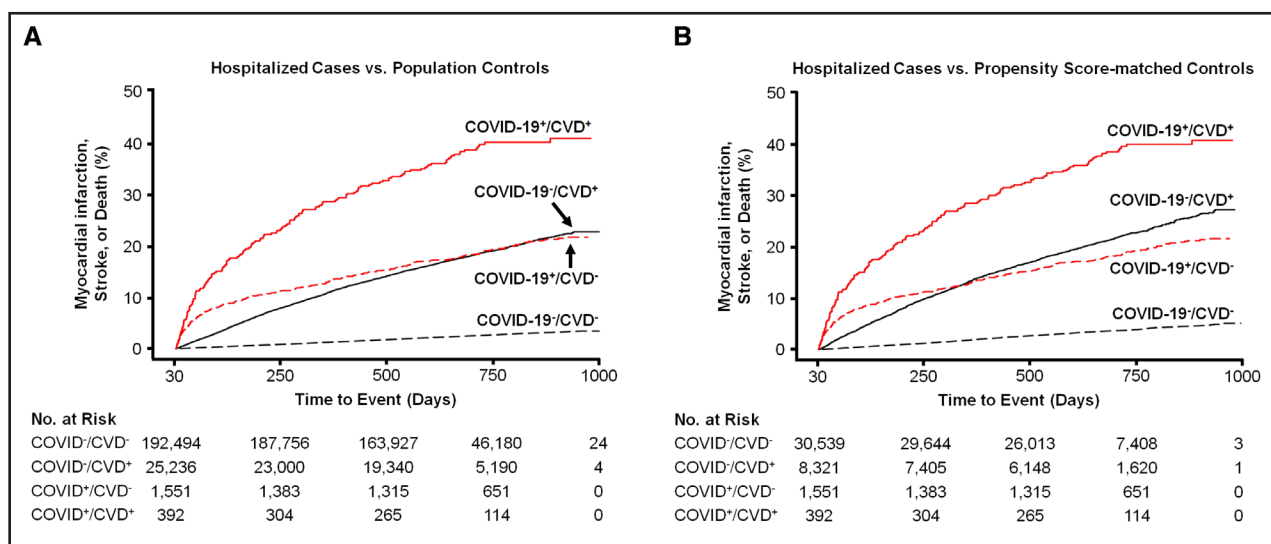


Figure 2. Hospitalization for COVID-19 is associated with an increased risk of major adverse cardiac event (MACE).

A, Among hospitalized cases and all population controls, COVID-19 increased cumulative incidence of MACE (MI, stroke, or all-cause mortality) in both subjects with and without cardiovascular disease (CVD). **B**, COVID-19 similarly increased cumulative incidence of MACE when comparing hospitalized cases to propensity score-matched population controls.

Table 2. Association of Hospitalization for COVID-19 With Increased Risk of MACE

Outcome	Outcome among hospitalized cases (yes/no)	Outcome among all population controls (yes/no)	Outcome among propensity score-matched matched controls (yes/no)	HR (95% CI)*	HR (95% CI)†
Thrombotic events					
All subjects	102/1841 (5.3%)	5466/212 264 (2.5%)	1813/37 047 (4.7%)	1.37 (1.13–1.67)§	1.24 (1.01–1.53)‡
Without CVD	38/1513 (2.5%)	1836/190 658 (1.0%)	428/30 111 (1.4%)	1.85 (1.34–2.55)‖	1.76 (1.23–2.50)§
With CVD	64/328 (16.3%)	3630/21 606 (14.4%)	1385/6936 (16.6%)	1.08 (0.85–1.39)	1.08 (0.82–1.43)
All-cause mortality					
All subjects	395/1548 (20.3%)	4297/213 433 (2.0%)	1278/37 582 (3.3%)	7.09 (6.38–7.87)‖	6.99 (6.19–7.90)‖
Without CVD	284/1267 (18.3%)	3055/189 439 (1.6%)	726/29 813 (2.4%)	8.30 (7.33–9.39)‖	9.22 (7.85–10.8)‖
With CVD	111/281 (28.3%)	1242/23 994 (4.9%)	552/7769 (6.6%)	4.87 (4.00–5.93)‖	5.64 (4.31–7.38)‖
MACE					
All subjects	463/1480 (23.8%)	9183/208 547 (4.2%)	2870/35 990 (7.4%)	3.85 (3.51–4.24)‖	3.65 (3.30–4.05)‖
Without CVD	307/1244 (19.8%)	4672/187 822 (2.4%)	1092/29 447 (3.6%)	5.93 (5.28–6.67)‖	6.37 (5.52–7.34)‖
With CVD	156/236 (39.8%)	4511/20 725 (17.9%)	1778/6543 (21.4%)	2.08 (1.78–2.45)‖	2.18 (1.80–2.66)‖

Data are shown as HRs and 95% CIs for association of hospitalized COVID-19 with risk of thrombotic events (MI or stroke), all-cause mortality, and MACE (MI, stroke, or all-cause mortality). HR indicates hazard ratio; MACE, major adverse cardiac event; and MI, myocardial infarction.

*HRs and 95% CIs from analyses with all population controls were derived from Cox proportional hazards models adjusted for age, sex, ethnicity, education, diabetes, asthma, smoking, lipid-lowering medication use, and antihypertension medication use.

†HRs and 95% CIs from analyses with propensity score-matched controls were derived from conditional Cox proportional hazards models with adjustment for age, sex, ethnicity, education, diabetes, asthma, smoking, lipid-lowering medication use, and antihypertension medication use.

‡ $P<0.05$; § $P<0.005$; ‖ $P<0.0005$.

$P<0.0005$) compared with COVID-19-negative controls without any of the selected CAD equivalents (Figure 3; Table 3). More specifically, hospitalized COVID-19 cases without a history of CVD had an $\approx 20\%$ increased risk of MACE compared with COVID-19-negative subjects with CVD (HR, 1.21 [95% CI, 1.08–1.37]; $P<0.005$).

Given the observation that COVID-19 represented a CAD equivalent, we next explored whether thrombotic risk could be modulated by the use of antiplatelet agents. Thrombotic risk remained elevated among primary prevention patients without known CVD who

were hospitalized for COVID-19 and not on antiplatelet agents at the time of enrollment in the UK Biobank (HR, 1.98 [95% CI, 1.39–2.82]; $P<0.0005$; Table S13). By comparison, risk of MI or stroke was not significantly increased among primary prevention COVID-19 patients who reported taking antiplatelet agents (Table S13). Taken together, these results demonstrate that, in the context of our UK Biobank data set, hospitalization for COVID-19 increased the risk of MACE among primary prevention subjects to the same degree as in COVID-19 negative subjects with preexisting CAD equivalent risk

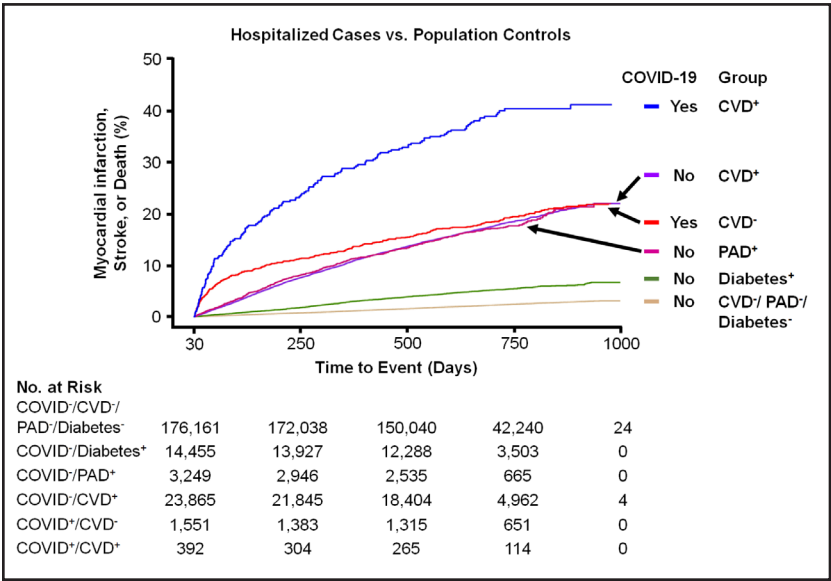


Figure 3. COVID-19 Represents a CAD (CVD) Risk Equivalent. Cumulative incidence of MACE in hospitalized COVID-19 cases without CVD (red line) was equivalent to that observed in all population controls with CVD (purple line) or PAD (pink line), and even greater than in population controls with diabetes (green line). Incidence of MACE was highest among hospitalized COVID-19 cases with CVD (blue line).

Table 3. Hospitalization for COVID-19 is a CAD (CVD) Risk Equivalent

Hospitalized COVID-19	CAD risk equivalent group	MACE (yes/no) (%)	HR (95% CI)
No	Without CVD	3817/172334 (2.2%)	1
No	With Diabetes	756/13984 (5.1%)	1.88 (1.73–2.04)*
No	With PAD	545/2704 (16.8%)	5.08 (4.62–5.59)*
No	With CVD	4511/20725 (17.9%)	5.63 (5.36–5.92)*
Yes	Without CVD	307/1244 (19.8%)	7.04 (6.25–7.92)*
Yes	With CVD	156/236 (39.8%)	12.2 (10.3–14.3)*

Data are shown as HRs and 95% CIs for association of hospitalized COVID-19 and indicated CAD equivalent group with risk of MACE (MI, stroke, or all-cause mortality). HRs and 95% CIs were derived from Cox proportional hazards models adjusted for age, sex, ethnicity, education, asthma, smoking, lipid-lowering medication use, and antihypertension medication use. Reference group is population control subjects who did not have CVD) and who remained SARS-CoV-2 and COVID-19 negative over the entire follow-up period. CAD indicates cardiovascular disease; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction; and PAD, peripheral artery disease.

* $P < 0.0005$.

factors. Furthermore, our data suggest that thrombotic risk can potentially be mitigated by the use of antiplatelet agents.

Hospitalization for COVID-19 Increases Risk of Thrombotic Events through Genetic Interaction with ABO Blood Type

We next used a candidate gene approach to test whether the increased risk of thrombosis post-COVID-19 could be affected through interactions with genetic susceptibility factors. Based on its identification as a specific

susceptibility locus for MI and stroke^{26,27,43} and SARS-CoV-2 infection (but not with hospitalized COVID-19),^{25,28} we focused our initial analyses on the *ABO* locus. In our UK Biobank data set, non-O blood types increased the likelihood of testing positive for SARS-CoV-2 infection (OR, 1.16 [95% CI, 1.11–1.22]; $P = 2.3 \times 10^{-10}$) but did not increase risk of being hospitalized for COVID-19 (Table S1). These results are consistent with prior studies demonstrating that non-O blood types are specifically associated with increased susceptibility to being infected with SARS-CoV-2 but not necessarily with risk of developing its severe postinfection respiratory complications.⁴⁴ We next tested the hypothesis that incident risk of MI and stroke among hospitalized COVID-19 patients could exhibit a gene-pathogen interaction with ABO blood types. Consistent with this notion, a significant genetic interaction was observed between COVID-19 and *ABO* ($P_{\text{interaction}} = 0.011$) where hospitalization for COVID-19 increased the risk of MI and stroke to a greater extent in subjects with non-O blood types (HR, 1.65 [95% CI, 1.29–2.09]; $P = 4.8 \times 10^{-5}$) than individuals with blood type O (HR, 0.96 [95% CI, 0.66–1.39]; $P = 0.82$; Figure 4; Table 4).

To explore whether the gene-pathogen interaction between COVID-19 and *ABO* was indirectly due to the association of non-O blood types with COVID-19 traits, we also tested the same genetic determinants of SARS-CoV-2 infection susceptibility (rs73062389) and severe COVID-19 (rs11385942) used to verify our definition of COVID-19 cases (Table S1). However, there was no evidence that hospitalization for COVID-19 increased the risk of MI and stroke through gene-pathogen interactions with rs73062389 ($P_{\text{interaction}} = 0.81$) or rs11385942 ($P_{\text{interaction}} = 0.71$; Table S14). Finally, we applied the same

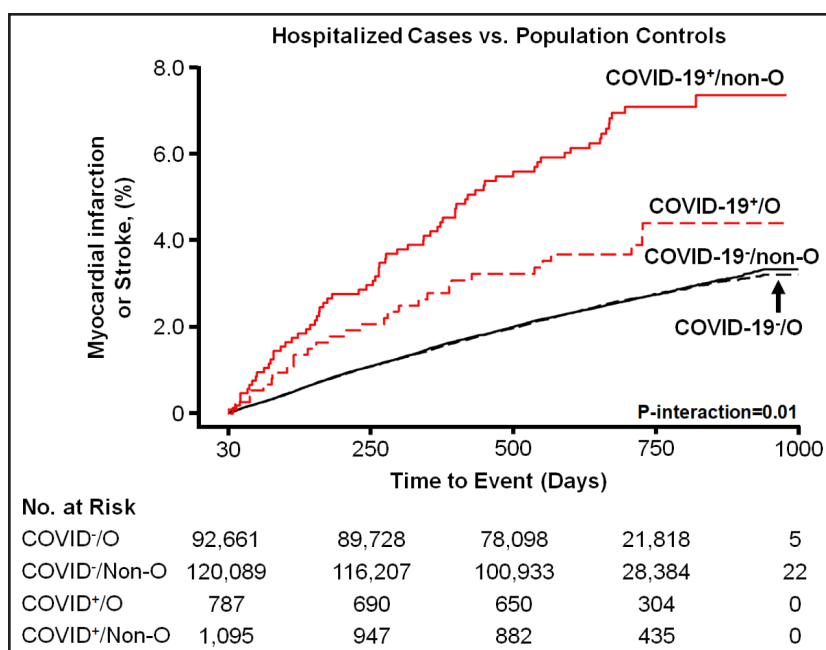


Figure 4. Hospitalization for COVID-19 increases risk of thrombotic events through a genetic interaction with ABO blood group.

COVID-19 increased cumulative incidence of myocardial infarction and stroke to a greater extent among hospitalized cases with non-O blood types than blood type O, leading to a significant gene-pathogen exposure interaction ($P_{\text{interaction}} = 0.01$). No differences in rate of thrombotic events was observed as a function of ABO blood type among all population controls.

Table 4. Hospitalization for COVID-19 Increases Risk of Thrombotic Events Through Genetic Interaction with ABO Blood Type

Outcome	ABO blood type	Outcome among hospitalized cases (yes/no)	Outcome among all population controls (yes/no)	HR (95% CI)	P value	P _{interaction} *
Thrombotic events	O	29/758 (3.7%)	2329/90 332 (2.5%)	0.96 (0.66–1.39)	0.82	0.01
	Non-O	69/1026 (6.3%)	3023/117 066 (2.5%)	1.65 (1.29–2.09)	4.8×10 ^{−5}	
All-cause mortality	O	152/635 (19.3%)	1786/90 875 (1.9%)	6.74 (5.69–7.97)	1.5×10 ^{−109}	0.56
	Non-O	229/866 (20.9%)	2409/117 680 (2.0%)	7.25 (6.31–8.32)	3.1×10 ^{−173}	
MACE	O	173/614 (22.0%)	3880/88 781 (4.2%)	3.51 (3.01–4.10)	5.8×10 ^{−58}	0.11
	Non-O	275/820 (25.1%)	5101/114 988 (4.3%)	4.07 (3.60–4.60)	2.7×10 ^{−111}	

Data are shown as HR and 95% CIs for association of hospitalization for COVID-19 with risk of thrombotic events (MI or stroke), all-cause mortality, and MACE (MI, stroke, or all-cause mortality) stratified by ABO blood group. HRs and 95% CIs were derived from Cox proportional hazards models adjusted for age, sex, first 10 principal components, genotyping array, education, diabetes, asthma, smoking, lipid-lowering medication use, and antihypertension medication use. HR indicates hazard ratio; MACE, major adverse cardiac event; and MI, myocardial infarction.

*P_{interaction} were obtained from models that included an interaction term between COVID-19 status and ABO blood type (non-O [A, B, or AB] vs O).

approach to assess whether an increased risk of thrombosis among hospitalized COVID-19 patients could result from interactions with genetic susceptibility factors for atherosclerotic CAD. Of the ≈300 known CAD loci,^{41,42} we tested the lead SNP at chromosome *9p21* (rs4977574) since it is one of the most strongly associated loci for CAD itself but not associated specifically with MI or stroke in patients with CAD.^{26,45,46} Similar to rs73062389 and rs11385942, there was no evidence ($P_{\text{interaction}}=0.96$) that thrombosis risk among hospitalized COVID-19 cases differed as a function of genotype at the chromosome *9p21* locus (Table S14). Collectively, these observations suggest that increased thrombosis risk among hospitalized COVID-19 patients differs as a function of ABO blood type but not through interactions with genetic determinants of COVID-19 severity, SARS-CoV-2 infection susceptibility, or atherosclerotic CAD.

DISCUSSION

In the present study, we leveraged the UK Biobank resource to demonstrate that patients all levels COVID-19 severity (from simply being PCR⁺ for SARS-CoV-2 to those requiring hospitalization) are at significantly increased long-term risk of MACE. These associations were observed among subjects stratified by 1-year intervals after developing COVID-19 or the presence of CVD, diabetes, obesity, and other comorbidities. Furthermore, the magnitude of the effect sizes for MACE and its components were consistently more pronounced among COVID-19 cases requiring hospitalization and comparable to those reported in 2 of the largest published studies for the same outcomes out to 2 years.^{6,14} Notably, effect sizes for increased risk of MACE as a result of hospitalization for COVID-19 were similar in analyses using propensity score–matched controls. Taken together, our data indicate that the elevated risk of MACE in COVID-19 patients shows no apparent signs of attenuation up to nearly 3 years after SARS-CoV-2 infection and suggest that COVID-19 continues to pose a significant public health burden with lingering adverse cardiovascular risk.

A major finding from our analyses was that the risk of MACE among the subset of hospitalized COVID-19 cases without known CVD (ie, primary prevention patients) was comparable to (or even slightly higher than) the risk in patients with CVD, PAD, or diabetes but without COVID-19. These observations argue that primary prevention subjects who developed severe COVID-19 carry the same risk as a CAD (CVD) risk equivalent for as long as follow-up data are available. Clinical guidelines across the world (United States, EU, Australia, Asia) use CAD risk equivalence as a metric to escalate CVD risk reduction as part of primary prevention efforts, including both lowering of LDL cholesterol goals and initiation of antiplatelet agents.^{15–23} For example, subjects with any form of CVD or CAD risk equivalent (eg, diabetes, PAD) are routinely treated with heightened preventive treatment goals comparable to those used for subjects with preexisting CVD (as if the subject just experienced an MI). Thus, our findings raise the question of whether hospitalized COVID-19 infection should also be given consideration as a CAD risk equivalent, which would invoke a discussion of altering preventive cardiovascular practice in patients previously hospitalized with COVID-19. In this regard, retrospective observational studies have suggested that antiplatelet therapy reduces the risk of mortality.^{47,48} However, randomized controls trials with antiplatelet therapy among COVID-19 patients individually did not demonstrate therapeutic benefits,^{49–53} although a meta-analysis of data from these same trials did provide evidence for reduced risk of thrombotic events.⁵⁴ It is important to note that the antiplatelet therapy in these clinical trials was administered during the acute phase of COVID-19 infection in a hospital setting and for relatively short durations (follow-up of 90 days or less) compared with the observational studies in which historical use of aspirin and other agents were considered. Thus, whether antiplatelet therapy provides cardiovascular benefit in subjects who developed severe COVID-19 will need to be evaluated more thoroughly in larger numbers of subjects and with prospective study designs of longer duration.

Systemic or localized infections increase the risk of thrombosis ≈ 2 - to 20-fold and are independent risk factors for thromboembolic diseases, such as deep vein thrombosis, pulmonary embolism, MI, and stroke.^{55–60} Since the emergence of SARS-CoV-2, these clinical associations have extended to COVID-19 as well,⁶¹ including the results presented herein. However, our analyses also revealed that increased thrombosis risk due to COVID-19 differed as a function of ABO blood type, which represents, at least to our knowledge, one of the first examples of a gene-pathogen exposure interaction for CVD-related outcomes. Specifically, hospitalization for COVID-19 increased the risk of MI or stroke by ≈ 2 -fold among patients with non-O blood types but not in patients with blood type O. Given that non-O blood types comprise $\approx 60\%$ of the global population, our results would indicate that a substantial fraction of individuals in the world who developed COVID-19 are at increased risk for thrombosis. Consistent with our data, a retrospective observational analysis also reported an increased risk of MACE in a small number of COVID-19 patients with blood type A versus O.⁶² However, this study only reported outcomes over the first 30 days following SARS-CoV-2 infection, was underpowered to detect associations with other non-O blood types, and did not test for other genetic interactions.

Our results also raise important questions with respect to the biological mechanism(s) through which COVID-19 interacts with host genetic factors. For example, incident thrombotic events in COVID-19 patients with non-O blood types may have been increased because of known associations between *ABO* and COVID-19 traits and MI or stroke in the presence of CAD. In our UK Biobank dataset, *ABO* was specifically associated with increased susceptibility to infection by SARS-CoV-2 but not development of hospitalized COVID-19 itself. While our findings are consistent with those from large-scale genetic analyses,²⁵ association of *ABO* with COVID-19 severity has not been uniformly observed in all studies.^{63,64} With respect to the 2 variants identified for COVID-19 at the chromosome *3p21* locus, one increases susceptibility to SARS-CoV-2 infection (rs73062389) whereas the other increases risk of becoming hospitalized from COVID-19 (rs11385942).⁶⁵ Interestingly, both variants are part of a 50 kb haplotype that was introgressed into the human genome from Neanderthals.⁶⁶ However, rs73062389 and rs11385942 are not in linkage disequilibrium with each other ($r^2=0.0$)⁶⁷ and thus reflect independent association signals for COVID-19-related traits. This concept is further supported by functional studies implicating *SLC6A20* and *CXCR6* as 2 candidate causal genes at *3p21* that could mediate SARS-CoV-2 infection and development of severe COVID-19, respectively.⁶⁸ However, we did not obtain evidence for the risk of thrombotic events differing as

a result of genetic interactions between COVID-19 and the 2 variants at the chromosome *3p21* locus or with the lead variant (rs4977574) at one of the strongest genetic determinants of atherosclerotic CAD on *9p21*.^{26,45} Taken together, these observations suggest that interactions between COVID-19 and increased risk of MI and stroke may be specific to genetic factors that influence risk of plaque rupture and thrombus formation (*ABO*) but not those that directly increase risk of hospitalization for COVID-19 (*3p21*), susceptibility to SARS-CoV-2 infection (*3p21*), or that promote atherosclerosis (*9p21*). It should also be noted that *ABO* is one of the most pleiotropic loci in the genome and exhibits associations with numerous cardiometabolic traits,⁶⁹ including coagulation biomarkers.⁷⁰ Thus, increased thrombotic risk as a result of genetic interaction between *ABO* and COVID-19 could be due to synergistic effects of non-O blood types and SARS-CoV-2 infection at the level of the vessel wall that potentially destabilizes vulnerable plaques and renders the endothelium more prone to thrombus formation.

While our results point to interesting clinical and genetic associations with COVID-19, we also note certain limitations of our study. First, defining cases and appropriate controls using data from the UK Biobank requires special consideration, given how the original SARS-CoV-2 strain and its virulence have evolved over time, improvements in patient care since the beginning of the pandemic, and development of vaccines in early 2021. For these reasons, and due to the unavailability of complete data on vaccination dates or the SARS-CoV-2 strain that UK Biobank subjects were infected with, we only used cases who developed COVID-19 before the availability of COVID-19 vaccines. Second, it is also possible that severe COVID-19 patients may have required hospitalization because of underlying undiagnosed CVD, which we were not able to ascertain given the nature of the UK Biobank as a population-based cohort. Third, information on medication use in the UK Biobank was not specific to the beginning of the pandemic in 2020 or the date of being infected with SARS-CoV-2. Furthermore, the number of subjects on antiplatelet agents may have also limited our power to evaluate the effects of these medications on thrombosis risk, particularly among primary prevention subjects. Despite these limitations, the consistency of the results obtained within the framework of our study design, coupled with extensive prior published evidence that COVID-19 and *ABO* are each associated with CVD outcomes, suggests that the clinical and genetic relationships we observed with MACE outcomes represent true associations. However, additional studies in larger and non-European ancestry populations will be needed to determine whether risk of MACE among COVID-19 patients remains elevated beyond 3 years and to replicate interactions with host genetic factors.

In summary, our findings demonstrate that development of COVID-19 requiring hospitalization confers a CAD risk equivalent to the subject, with a heightened risk of thrombosis particularly evident among cases with non-O blood types. These observations suggest that more aggressive cardiovascular risk reduction efforts may be warranted as part of primary prevention in patients hospitalized for COVID-19 and provide new avenues for understanding the biological mechanisms underlying CVD-related adverse outcomes of severe SARS-CoV-2 infection.

ARTICLE INFORMATION

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Affiliations

Department of Population and Public Health Sciences (J.R.H., N.J.S., K.A., F.D.G., H.H., J.A.H., H.A.) and Department of Biochemistry and Molecular Medicine (J.R.H., N.J.S., K.A., H.A.), Keck School of Medicine, University of Southern California, Los Angeles. Department of Medicine (A.D., A.J.L.), Department of Microbiology, Immunology, and Molecular Genetics (A.J.L.), and Department of Human Genetics (A.J.L.), David Geffen School of Medicine of UCLA, CA. Department of Cardiovascular and Metabolic Sciences, Lerner Research Institute (W.H.W.T., S.L.H.), Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute (W.H.W.T., S.L.H.), and Center for Microbiome and Human Health (W.H.W.T., S.L.H.), Cleveland Clinic, OH.

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Disclosures

Dr Hazen reports being named as co-inventors on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics and therapeutics. Dr Hazen also reports having received royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from Cleveland Heart Laboratory, a fully owned subsidiary of Quest Diagnostics, and Procter & Gamble. Dr Hazen is a paid consultant for Zehna Therapeutics and Procter & Gamble and has received research funds from Zehna Therapeutics, Procter & Gamble, Pfizer, and Roche Diagnostics. All other authors have no competing financial interests or personal relationships to declare related to the work reported in this article.

Supplemental Material

Figure S1
Tables S1–S14
Major Resources Table

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