CAMBRIDGE
UNIVERSITY PRESS

Article

Self-Reported Symptoms of COVID-19, Including Symptoms Most Predictive of SARS-CoV-2 Infection, Are Heritable

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Abstract

Susceptibility to infection such as SARS-CoV-2 may be influenced by host genotype. TwinsUK volunteers ($n = 3261$) completing the C-19 COVID-19 symptom tracker app allowed classical twin studies of COVID-19 symptoms, including predicted COVID-19, a symptom-based algorithm to predict true infection, derived from app users tested for SARS-CoV-2. We found heritability of 49% (32−64%) for delirium; 34% (20−47%) for diarrhea; 31% (8−52%) for fatigue; 19% (0−38%) for anosmia; 46% (31−60%) for skipped meals and 31% (11−48%) for predicted COVID-19. Heritability estimates were not affected by cohabiting or by social deprivation. The results suggest the importance of host genetics in the risk of clinical manifestations of COVID-19 and provide grounds for planning genome-wide association studies to establish specific genes involved in viral infectivity and the host immune response.

Infectious diseases may demonstrate a heritable component — that is, the propensity to contract and develop active infection and the severity of the immune response — and is influenced not only by contact with the infectious agent but also by host genetic factors (Chapman & Hill, 2012). For instance, host genetic variants mediating the immune response, including the biosynthesis of host glycan structures, are associated with viral diversity (Fumagalli et al., 2010); immunogenetic factors are implicated in the risk and severity of influenza caused by H1N1 infection (Keynan et al., 2013). Little is known about host genetic factors influencing the infection of humans by coronaviruses in general, and almost nothing is known for SARS-CoV-2 in particular. Nevertheless, a recent genome-wide association study identified two genomic regions associated with respiratory failure caused by COVID-19 infection (Severe Covid-19 GWAS Group et al., 2020). A possible role of variation in *ACE2* and *TMPRSS2* genes in COVID-19 spread and severity is being explored (Delanghe et al., 2020; Lopera Maya et al., 2020; Strope et al., 2020).

We developed the C-19 COVID-19 symptom tracker app, which was launched on March 24, 2020, to collect real-time data during the SARS-CoV-2 pandemic (Drew et al., 2020). Once downloaded by a participant, the app asks about age, health risk

factors and location. It collects information about symptoms after an initial screening question to determine whether the participant feels well or not. Participants are invited to contribute further updates every few days regarding their symptoms, healthcare visits, COVID-19 testing and results and whether they were in quarantine.

The aim of the current study was to estimate the heritability of COVID-19 symptoms in app participants who are also twins registered with the TwinsUK study and identify phenotypes suitable for genome-wide association study that would shed light on the host genetic mechanisms of infection and symptom generation.

Materials and Methods

The app asks, on a daily basis, about how the participant feels and the presence or absence of common symptoms including cough, fever, chest pain, delirium and anosmia, and has been downloaded by >3 million people. Participants in the TwinsUK adult twin register (Verdi et al., 2019) who had reported current symptoms via the app were included in this study.

The stem question is: 'How do you feel now right now?' The possible answers include: 'I feel as healthy as normal' and 'I am not feeling quite right'. In case of answering 'I am not feeling quite right', another set of questions follows concerning COVID-19 related symptoms: fever, fatigue (mild or severe), delirium, persistent cough, shortness of breath (mild, severe, significant), anosmia (loss of smell and test), chest pain, abdominal pain, hoarse voice, diarrhea and loss of appetite (skipped meals). For the purpose of

Table 1. Demographics of the studied twins

Trait	Total sample	White British ancestry unpaired	White British ancestry full MZ pairs	White British ancestry full DZ pairs
Sample size	3261	1175	1348 (674 pairs)	576 (288 pairs)
Age (years)	53.7 ± 16.1	55.8 ± 15.9	51.4 ± 15.8	58.6 ± 14.4
Sex (males/females)	420/2841	175/1000	178/1170	44/532
BMI (kg/m²)	25.3 ± 5.1	25.5 ± 5.0	24.9 ± 4.9	25.7 ± 5.3
Distance between households (median [min; max]), km	–	–	17.5 [0; 712.2]	32.6 [0; 766.7]
IMD (median [min; max]), decile	7 [1; 10]	7 [1; 10]	7 [1; 10]	7 [1; 10]

Note: BMI, body mass index; IMD, index of multiple deprivation.

current study, individuals replying 'I feel as healthy as normal' have been assigned negative values (0) for all questions. For those reporting not feeling quite right, positive (1) or negative status was assigned based on the response to each question. Fatigue was considered positive if reported as severe and negative if reported as absent or mild. Shortness of breath was considered positive if reported as being severe or significant and negative if reported as absent or mild.

Casewise concordance between twin pairs and its standard error were estimated using the likelihood-based approach (Witte et al., 1999). Heritability of individual symptoms and 'predicted COVID-19' was estimated using biometric modeling for the liability threshold model (Falconer & Mackay, 1996). The liability-threshold model assumes an underlying continuous liability that follows a normal distribution. The model decomposes the variance of the liability into latent sources of variation: additive genetic (A), common environment (C) and unique environment variance (E). For each symptom, we fitted saturated model and models with the liability variance components: ACE, AE, CE and E. Models were compared using chi-squared statistic estimated as double the difference between log-likelihoods of the models, which under null follows the central chi-squared distribution with degrees of freedom equal to the difference between the number of estimated parameters for the models. The ACE model was compared with the saturated model; AE and CE models were compared with ACE and E model was compared with either AE or CE depending on which one provided the best fit. Narrow-sense heritability, the proportion of the variance in liability caused by additive genetic effects, was estimated from the most parsimonious model (with adjustment for age, sex and body mass index [BMI]) as determined by the Akaike information criterion (Akaike, 1974). Biometric modeling was performed using OpenMx package for R (Neale et al., 2016).

'Predicted COVID-19' status was determined by linear combination of self-reported age, sex and symptoms of anosmia, severe or significant persistent cough, fatigue and skipped meals. We have shown this model to be most predictive of SARS-CoV-2 positivity on a swab PCR test (Menni et al., 2020). We also examined real-time information obtained by SMS text from TwinsUK participants regarding their current cohabiting arrangement. To control for the influence of infection within households on estimates of C component, we repeated the heritability estimates excluding twins living together and those with cohabiting information missing. We also performed the estimates adjusting for the index of multiple deprivation.

Ethics committee approval was obtained for TwinsUK from St Thomas' Hospital Ethics Committee 2008 with further approval obtained to use health records for research.

Results

Adult same-sex twins (*n* = 3261) had provided data for analysis between March 25 and October 13, 2020 (Table 1). The sample included 3099 individuals of White British ancestry comprising 1175 unpaired twins, 674 total pairs of monozygotic (MZ) twins and 288 pairs of dizygotic (DZ) twins that have been used to calculate heritability estimates. There were differences in mean age between unpaired twins and paired twins of both zygosities and higher BMI compared to MZ twins. There were differences between MZ and DZ twins for age and BMI. Also, consistent with expectations, DZ twins lived further apart from each other compared to MZ twins. Prevalence of symptoms in TwinsUK was similar to the larger dataset of *n* = 3.45 million (Figure 1).

Table 2 shows prevalence of symptoms in the MZ and DZ twins and the casewise concordance and tetrachoric correlations. Based on the greater concordance and tetrachoric correlations in MZ twins compared to DZ twins, a heritable component is suggested for delirium, diarrhea, fatigue, anosmia, predicted COVID-19 and skipped meals. This was confirmed by biometric modeling, with the AE, model being the best fit for these traits and the following heritability estimates: delirium, 49% (95% CI [32, 64]); diarrhea, 34% (95% CI [20, 47]); fatigue, 31% (95% CI [8, 52]); anosmia, 19% (95% CI [0, 38]); predicted COVID-19, 31% (95% CI [11, 48]) and skipped meals, 46% (95% CI [31, 60]). For other traits, the CE was found to be the best-fitting model, suggesting a higher impact of environmental factors.

Heritability estimates, including only those twin pairs living apart and adjusting for intrapair distance (Supplementary Table S1) and adjusting for index of multiple deprivation (Supplementary Table S2), were largely similar.

Discussion

Here, we report that 31% of the variance of 'predicted COVID-19' phenotype is due to genetic factors. This value is in line with heritability estimates for other viral infections: the heritability of HIV acquisition is estimated to be 28−42% (Powell et al., 2020) and the heritability of hepatitis B viral load is 30−70% (Huang et al., 2011). We found that delirium, a symptom related to immune activation, has a high heritability (49%). The symptom of anosmia, previously reported by us to be an important predictive symptom of COVID-19, was also heritable at 19%. Anosmia is now considered a key and a rather specific symptom of COVID-19 at the early stage of the infection (Gengler et al., 2020; Passarelli et al., 2020). While the precise pathophysiology of anosmia associated with COVID-19 is not yet fully understood, it may be related to sino-nasal viral shedding, important as a key virus transmission mechanism (Gengler

Table 2. Prevalence, casewise concordance and tetrachoric correlation of the symptoms reported in TwinsUK

Trait	Complete MZ pairs, n = 1348			Complete DZ pairs, n = 576			p value comparing MZ vs DZ pairs		
	Prevalence, %	Casewise concordance	Tetrachoric correlation	Prevalence, %	Casewise concordance	Tetrachoric correlation	Prevalence	Casewise concordance	Tetrachoric correlation
Feeling unhealthy	54.8 ± 1.4	0.67 ± 0.02	0.41 ± 0.05	43.9 ± 2.1	0.61 ± 0.04	0.47 ± 0.08	**1.2e-5**	.1797	.2923
Abdominal pain	15.9 ± 1.0	0.27 ± 0.04	0.27 ± 0.08	13.0 ± 1.4	0.27 ± 0.07	0.38 ± 0.13	.1031	1.0000	.0814
Chest pain	16.5 ± 1.0	0.31 ± 0.04	0.33 ± 0.08	12.3 ± 1.4	0.25 ± 0.07	0.33 ± 0.13	**.0189**	.4575	1.0000
Delirium	9.1 ± 0.8	0.33 ± 0.05	0.53 ± 0.08	6.4 ± 1.0	0.11 ± 0.05	0.19 ± 0.21	**.0492**	**.0019**	**1.8e-8**
Diarrhea	18.0 ± 1.0	0.35 ± 0.04	0.38 ± 0.07	12.8 ± 1.4	0.19 ± 0.06	0.18 ± 0.14	**.0048**	**.0265**	**.0020**
Fatigue	6.5 ± 0.7	0.21 ± 0.06	0.39 ± 0.11	4.7 ± 0.9	0.07 ± 0.07	0.16 ± 0.26	.1267	.1289	**.0004**
Fever	9.3 ± 0.8	0.17 ± 0.05	0.23 ± 0.10	9.5 ± 1.2	0.25 ± 0.08	0.40 ± 0.14	.8902	.3964	**.0074**
Hoarse voice	13.3 ± 0.9	0.18 ± 0.04	0.12 ± 0.09	9.0 ± 1.2	0.27 ± 0.08	0.47 ± 0.14	**.0079**	.3143	**3.6e-8**
Loss of smell	9.2 ± 0.8	0.19 ± 0.05	0.27 ± 0.10	6.4 ± 1.0	0*	−0.89*	.0422	NA	**1.5e-127**
Persistent cough	16.1 ± 1.0	0.34 ± 0.04	0.40 ± 0.07	12.7 ± 1.4	0.33 ± 0.07	0.48 ± 0.12	.0563	.9013	.1600
Predicted COVID-19	8.8 ± 0.8	0.22 ± 0.05	0.34 ± 0.10	5.9 ± 1.0	0*	-0.89*	**.0311**	NA	**3.1e-139**
Shortness of breath	2.3 ± 0.4	0.19 ± 0.10	0.53 ± 0.15	1.7 ± 0.5	0.20 ± 0.17	0.69 ± 0.23	.4028	.9596	**0.0003**
Skipped meals	12.5 ± 0.9	0.36 ± 0.05	0.50 ± 0.07	11.1 ± 1.3	0.19 ± 0.07	0.25 ± 0.15	.3882	**.0481**	**3.2e-5**

Note: Only White British ancestry complete twin pairs are included. Values in bold type represent nominally statistically significant differences in estimated parameters.
*SE unidentifiable due to absence of concordant cases.
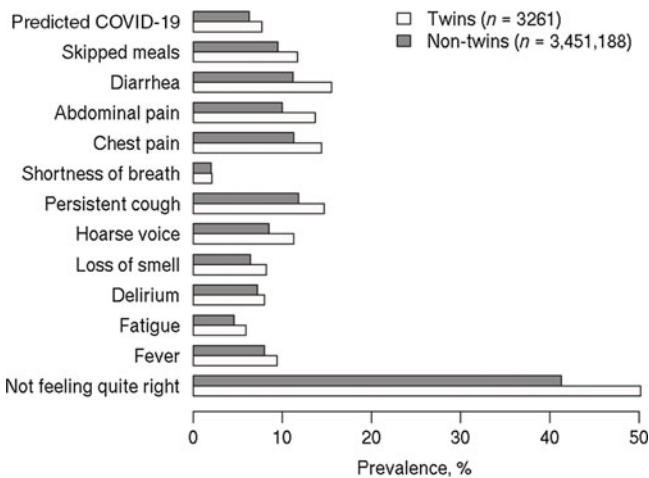
Fig. 1. Prevalence of symptoms and 'Predicted COVID-19' status reported by TwinsUK twins and non-twin population reported the symptoms using C-19 COVID-19 symptom tracker app.

et al., 2020). That heritable factors influence anosmia may help identify genetic variants responsible for susceptibility to infection. Symptomatic infection with SARS-CoV-2, rather than representing a purely stochastic event, is under host genetic influence to some extent and may reflect inter-individual variation to viral infection susceptibility and in the host immune response. Viral infections typically lead to T-cell activation with IL-1, IL-6 and TNF-α release causing flu-like symptoms such as fever. The genetic basis of this variability in response will provide important clues for therapeutics

and lead to the identification of groups at high risk of death, which is associated with a cytokine storm approximately 2 weeks after symptom onset (Vaninov, 2020).

Interestingly, for feeling unhealthy, abdominal pain, chest pain, hoarse voice, persistent cough and shortness of breath, we found the common environment to be more pronounced than the heritable component. Our sensitivity analysis including only twins living apart confirmed this (Supplementary Table S1). Another sensitivity analysis with adjustment for the possible social disparity was also in keeping with this observation (Supplementary Table S2). Importantly, the majority of these traits concern the airways, suggesting that they may have been exaggerated by the winter/early spring weather conditions inadvertently shared by most of the twins regardless of their living place.

Among unanticipated findings, we highlight a heritable component for skipped meals and diarrhea (Table 3) in keeping with evidence for active replication of SARS-CoV-2 in the digestive tract, even after clearance of the virus from the respiratory tract, and a high level of gastrointestinal symptoms in affected patients (Yang & Tu, 2020). This implies that host genetic factors control the manifestation of COVID-19 infection in the gut, perhaps by regulation of inflammation; an interplay with gut microbiota, which in turn is heritable, could also account for our findings (Zuo et al., 2020).

The study has a number of limitations. First, our data are likely to suffer from a healthy volunteer bias. Indeed, we report negative tetrachoric correlations for DZ twins for anosmia and predicted COVID-19 due to the few pairs concordant for rare symptoms. However, all methods currently available — testing healthcare workers, testing those admitted to hospital with symptoms, testing those with symptoms at home — have limitations that lead to inherent bias. Ours is among the best representations of the general population (Drew et al., 2020), albeit at the healthy end of the spectrum, and

Table 3. Biometric modeling for COVID-19 symptoms in TwinsUK

Trait	Model	Variance components			Model fit			Model comparison			
		A	C	E	es	−2LL	AIC	χ²	df	p	Base
Feeling unhealthy	Saturated	−	−	−	13	4078.39	−2093.61	−	−	−	
	ACE	0 [0, 0.33]	0.37 [0.07, 0.46]	0.63 [0.53, 0.73]	8	4087.18	−2098.82	8.79	7	.268	Saturated
	AE	0.39 [0.29, 0.49]	−	0.61 [0.51, 0.71]	7	4092.62	−2095.38	5.45	1	.020	ACE
	CE	**−**	**0.37 [0.27, 0.46]**	**0.63 [0.54, 0.73]**	**7**	**4087.18**	**−2100.82**	**0.00**	**1**	**1.000**	**ACE**
	E	−	−	1.00 [1.00, 1.00]	6	4139.26	−2050.74	52.09	1	5.3 E-13	CE
Abdominal pain	Saturated	−	−	−	13	2383.52	−3788.48	−	−	−	
	ACE	0 [0, 0]	0.25 [0, 0.37]	0.75 [0.62, 0.89]	8	2398.86	−3787.14	15.35	7	.032	Saturated
	AE	0.26 [0.11, 0.41]	−	0.74 [0.59, 0.89]	7	2400.29	−3787.71	1.43	1	.232	ACE
	CE	**−**	**0.25 [0.11, 0.38]**	**0.75 [0.62, 0.89]**	**7**	**2398.86**	**−3789.14**	**0.00**	**1**	**1.000**	**ACE**
	E	−	−	1.00 [1.00, 1.00]	6	2411.75	−3778.25	12.89	1	.000	CE
Chest pain	Saturated	−	−	−	13	2452.93	−3719.07	−	−	−	
	ACE	0.02 [0, 0.43]	0.27 [0, 0.42]	0.71 [0.56, 0.84]	8	2455.69	−3730.31	2.76	7	.906	Saturated
	AE	0.31 [0.16, 0.45]	−	0.69 [0.55, 0.84]	7	2456.59	−3731.41	0.90	1	.343	ACE
	CE	**−**	**0.29 [0.16, 0.42]**	**0.71 [0.58, 0.84]**	**7**	**2455.69**	**−3732.31**	**0.00**	**1**	**.946**	**ACE**
	E	−	−	1.00 [1.00, 1.00]	6	2473.51	−3716.49	17.81	1	2.4 E-05	CE
Delirium	Saturated	−	−	−	13	1652.11	−4519.89	−	−	−	
	ACE	0.49 [0, 0.64]	0 [0, 0]	0.51 [0.36, 0.68]	8	1657.51	−4528.49	5.39	7	.612	Saturated
	AE	**0.49 [0.32, 0.64]**	**−**	**0.51 [0.36, 0.68]**	**7**	**1657.51**	**−4530.49**	**0.00**	**1**	**1.000**	**ACE**
	CE	−	0.44 [0.28, 0.58]	0.56 [0.42, 0.59]	7	1659.88	−4528.12	2.37	1	.123	ACE
	E	−	−	1.00 [1.00, 1.00]	6	1686.77	−4503.23	29.26	1	6.3 E-08	CE
Diarrhea	Saturated	−	−	−	13	2578.44	−3593.56	−	−	−	
	ACE	0.34 [0, 0.47]	0 [0, 0]	0.66 [0.53, 0.8]	8	2584.64	−3601.36	6.20	7	.517	Saturated
	AE	**0.34 [0.2, 0.47]**	**−**	**0.66 [0.53, 0.8]**	**7**	**2584.64**	**−3603.36**	**0.00**	**1**	**1.000**	**ACE**
	CE	−	0.3 [0.18, 0.42]	0.70 [0.58, 0.82]	7	2586.38	−3601.62	1.74	1	.187	ACE
	E	−	−	1.00 [1.00, 1.00]	6	2607.39	−3582.61	22.75	1	1.8 E-06	AE
Fatigue	Saturated	−	−	−	13	1286.76	−4885.24	−	−	−	
	ACE	0.31 [0, 0.52]	0 [0, 0]	0.69 [0.48, 0.92]	8	1292.04	−4893.96	5.28	7	.626	Saturated
	AE	**0.31 [0.08, 0.52]**	**−**	**0.69 [0.48, 0.92]**	**7**	**1292.04**	**−4895.96**	**0.00**	**1**	**1.000**	**ACE**
	CE	−	0.28 [0.06, 0.47]	0.72 [0.53, 0.94]	7	1292.63	−4895.37	0.59	1	.442	ACE
	E	−	−	1.00 [1.00, 1.00]	6	1298.91	−4891.09	6.86	1	.009	AE
Fever	Saturated	−	−	−	13	1853.05	−4318.95	−	−	−	
	ACE	0 [0, 0]	0.21 [0, 0.38]	0.79 [0.62, 0.98]	8	1856.93	−4329.07	3.88	7	.793	Saturated
	AE	0.2 [0, 0.21]	−	0.8 [0.66, 0.99]	7	1858.20	−4329.80	1.27	1	.260	ACE
	CE	**−**	**0.21 [0.02, 0.38]**	**0.79 [0.62, 0.98]**	**7**	**1856.93**	**−4331.07**	**0.00**	**1**	**1.000**	**ACE**
	E	−	−	1.00 [1.00, 1.00]	6	1861.85	−4328.15	4.92	1	.027	CE
Hoarse voice	Saturated	−	−	−	13	2136.14	−4035.86	−	−	−	
	ACE	0 [0, 0]	0.16 [0, 0.32]	0.84 [0.68, 0.99]	8	2147.52	−4038.48	11.38	7	.123	Saturated
	AE	0.14 [0, 0.3]	−	0.86 [0.7, 1]	7	2149.26	−4038.74	1.75	1	.186	ACE
	CE	**−**	**0.16 [0.01, 0.32]**	**0.84 [0.68, 0.99]**	**7**	**2147.52**	**−4040.48**	**0.00**	**1**	**1.000**	**ACE**
	E	−	−	1.00 [1.00, 1.00]	6	2151.62	−4038.38	4.11	1	.043	CE
Loss of smell	Saturated	−	−	−	13	1671.91	−4500.09	−	−	−	
	ACE	0.19 [0, 0.38]	0 [0, 0]	0.81 [0.62, 1]	8	1677.71	−4508.29	5.81	7	.562	Saturated
	AE	**0.19 [0, 0.38]**	**−**	**0.81 [0.62, 1]**	**7**	**1677.71**	**−4510.29**	**0.00**	**1**	**1.000**	**ACE**
	CE	−	0.14 [0, 0.32]	0.86 [0.68, 1]	7	1678.90	−4509.10	1.19	1	.275	ACE
	E	−	−	1.00 [1.00, 1.00]	6	1680.85	−4509.15	3.14	1	.076	AE

(*Continued*)

Table 3. (Continued)

| Trait | Model | Variance components | | | Model fit | | | Model comparison | | | |
		A	C	E	es	−2LL	AIC	χ^2	df	p	Base
Persistent cough	Saturated	–	–	–	13	2464.03	−3707.97	–	–	–	
	ACE	0 [0, 0]	0.37 [0, 0.46]	0.63 [0.5, 0.72]	8	2468.42	−3717.58	4.38	7	.735	Saturated
	AE	0.39 [0.25, 0.52]	–	0.61 [0.48, 0.75]	7	2470.60	−3717.40	2.18	1	.139	ACE
	CE	**–**	**0.37 [0.24, 0.49]**	**0.63 [0.51, 0.76]**	**7**	**2468.42**	**−3719.58**	**0.00**	**1**	**1.000**	**ACE**
	E	–	–	1.00 [1.00, 1.00]	6	2497.30	−3692.70	28.88	1	7.7 E-08	CE
Predicted COVID-19	Saturated	–	–	–	11	1633.60	−4542.40	–	–	–	
	ACE	0.31 [0, 0.48]	0 [0, 0]	0.69 [0.52, 0.89]	6	1643.24	−4546.76	9.64	7	.210	Saturated
	AE	**0.31 [0.11, 0.48]**	**–**	**0.69 [0.52, 0.89]**	**5**	**1643.24**	**−4548.76**	**0.00**	**1**	**1.000**	**ACE**
	CE	–	0.26 [0.08, 0.43]	0.74 [0.57, 0.92]	5	1645.16	−4546.84	1.93	1	.165	ACE
	E	–	–	1.00 [1.00, 1.00]	4	1652.76	−4541.24	9.52	1	.002	AE
Shortness of breath	Saturated	–	–	–	13	594.89	−5577.11	–	–	–	
	ACE	0 [0, 0]	0.52 [0, 0.74]	0.48 [0.25, 0.78]	8	600.78	−5585.22	5.90	7	.552	Saturated
	AE	0.54 [0.21, 0.77]	–	0.46 [0.23, 0.79]	7	602.03	−5585.97	1.25	1	.264	ACE
	CE	**–**	**0.52 [0.22, 0.74]**	**0.48 [0.26, 0.78]**	**7**	**600.78**	**−5587.22**	**0.00**	**1**	**1.000**	**ACE**
	E	–	–	1.00 [1.00, 1.00]	6	611.70	−5578.30	10.92	1	.001	CE
Skipped meals	Saturated	–	–	v	13	2141.85	−4030.15	–	–	–	
	ACE	0.46 [0, 0.6]	0 [0, 0]	0.54 [0.4, 0.69]	8	2148.21	−4037.79	6.37	7	.498	Saturated
	AE	**0.46 [0.31, 0.6]**	**–**	**0.54 [0.4, 0.69]**	**7**	**2148.21**	**−4039.79**	**0.00**	**1**	**1.000**	**ACE**
	CE	–	0.39 [0.25, 0.52]	0.61 [0.48, 0.75]	7	2151.74	−4036.26	3.53	1	.060	ACE
	E	–	–	1.00 [1.00, 1.00]	6	2179.91	−4010.09	31.70	1	1.8 E-08	AE

Note: Biometric modeling was carried out using OpenMx package for R as detailed in the main text. Adjustments were done for age, sex and BMI for all traits except predicted COVID-19 for which no adjustment for age and sex was done. Bold type indicates the best-fit models according to AIC and χ^2 tests. 95% confidence intervals are shown in square brackets. es, number of estimated parameters in the model; −2LL, log-likelihood for the model multiplied by −2; AIC, Akaike Information Criteria; χ^2, test statistics for models comparison; df, degrees of freedom for χ^2; p value, corresponding p value; base, model against which the comparison was done.

it offers an important contribution to the accurate depiction of the totality of the epidemic. Another limitation is the lack of information about the exposure of the twins to SARS-CoV2. One can infer that COVID-19 cases are more likely to have been exposed to the virus than controls. This may be true for healthcare and social workers on the frontline of COVID-19 treatment and management. However, this does not necessarily apply to the general population, as a large proportion of people (40−45%) are reported to be asymptomatic (Oran & Topol, 2020), so cases cannot fully resemble exposure rates. Nevertheless, there is nothing to suggest that differential levels of virus exposure between MZ and DZ twins could have impacted heritability estimates. Another limitation is that many symptoms are nonspecific and are prevalent in spring in the Northern hemisphere when allergies and seasonal influenza are active, and are not indicative of infection status. In line with that, as a large proportion of twins logged their symptoms only once, we cannot assess the consistency of reporting for them. Among those who logged more than once, the following are prevalences of reporting the presence of symptoms more than once: feeling unhealthy, 71.4%; persistent cough, 64.4%; loss of smell, 62.7%; hoarse voice, 55.5%; shortness of breath, 51.8%; chest pain, 51.8%; delirium, 47.1%; skipped meals, 46.9%; fatigue, 42.1%; fever, 41.5%; abdominal pain, 37.8% and diarrhea, 36.8%. This may reflect both the course of the disease or changes in disease status perception in the responders, with the latter being a possible bias. We did have a sufficient sample size of people reporting symptoms and viral test results to indicate accurately which symptom pattern provides the greatest positive predictive value. The study could

have been biased by MZ twins cohabiting more than DZ twins, but real-time data collection allowed us to exclude cohabiting pairs. Also, adjusting for index of multiple deprivation, we controlled for the possible disparity between different regions of the country. Our twin sample is predominantly female for historical recruitment reasons and is not representative of non-European ancestries (Verdi et al., 2019). Finally, concerning predicted COVID-19, the predictive model is based on the results of RT-PCR tests, which themselves are not perfect; and the model itself is not 100% sensitive and specific. Nevertheless, RT-PCR test results are well correlated with chest CT-scan for the diagnosis of COVID-19 (Ai et al., 2020). Also, the model we used to predict COVID-19 has been validated in an independent dataset in the USA (Menni et al., 2020), suggesting that it has utility. Finally, there is a fair concordance between predicted COVID-19 and positive COVID-19 antibodies in the studied twins with Yule's coefficient of colligation of .52 (.46−.57) and Cohen's kappa of .36 (.29−.42).

Our study has several strengths. TwinsUK participants and their symptom reporting is representative of the UK population (Figure 1). Predicting infection with a validated combination of symptoms of virus-tested individuals offers a pragmatic solution to the challenges of widespread testing in the general population. One of the important contributions of our study is the real-time nature of the data collection and the very large sample drawn from the general population (Drew et al., 2020). While acknowledging the wide confidence intervals around the estimates of heritability, our study contributes to the understanding of COVID-19 within the general population.

The genetic influence on COVID-19 symptoms may reflect the genotype status of candidate genes such as *ACE2R*, which encodes the target for viral attachment (Hoffmann et al., 2020), and a number of other genes, including those identified in genome-wide association studies (Elhabyan et al., 2020). Another interesting possibility concerns the genetic factors underlying psychological and behavioral traits. Anxiety, depression, stress and disturbed sleep have been reported to be common psychological reactions to the COVID-19 pandemic (Rajkumar, 2020). Hereditable factors play a role in the variation of these traits (Smoller, 2016), and therefore may contribute to COVID-19 symptom reporting. Further genetic work is underway to determine whether twin genotype at *ACE2R* influences predicted positivity or symptoms and a global genetic study is underway (COVID-19 Host Genetics Initiative, 2020). Public health approaches to identify those at increased genetic risk of severe infection would be useful as a way of partially mitigating the economic effects of lockdown and social distancing policies.

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