Interplay between the genetics of personality traits, severe psychiatric disorders and COVID-19 host genetics in the susceptibility to SARS-CoV-2 infection

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Background
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, with its impact on our way of life, is affecting our experiences and mental health. Notably, individuals with mental disorders have been reported to have a higher risk of contracting SARS-CoV-2. Personality traits could represent an important determinant of preventative health behaviour and, therefore, the risk of contracting the virus.

Aims
We examined overlapping genetic underpinnings between major psychiatric disorders, personality traits and susceptibility to SARS-CoV-2 infection.

Method
Linkage disequilibrium score regression was used to explore the genetic correlations of coronavirus disease 2019 (COVID-19) susceptibility with psychiatric disorders and personality traits based on data from the largest available respective genome-wide association studies (GWAS). In two cohorts (the PsyCourse (n = 1346) and the HeiDE (n = 3266) study), polygenic risk scores were used to analyse if a genetic association between psychiatric disorders, personality traits and COVID-19 susceptibility exists in individual-level data.

Results
We observed no significant genetic correlations of COVID-19 susceptibility with psychiatric disorders. For personality traits, there was a significant genetic correlation for COVID-19 susceptibility with extraversion (P = 1.47 × 10−5; genetic correlation = 0.284). Yet, this was not reflected in individual-level data from the PsyCourse and HeiDE studies.

Conclusions
We identified no significant correlation between genetic risk factors for severe psychiatric disorders and genetic risk for COVID-19 susceptibility. Among the personality traits, extraversion showed evidence for a positive genetic association with COVID-19 susceptibility, in one but not in another setting. Overall, these findings highlight a complex contribution of genetic and non-genetic components in the interaction between COVID-19 susceptibility and personality traits or mental disorders.

Keywords
COVID-19; extraversion; severe mental disorders; personality traits; genetics.

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Personality traits (i.e. relative stable patterns of feelings, thoughts and behaviour) might influence disease risk by mediating health-related behaviours such as the adherence to health regulations and recommendations (for example social distancing or mask wearing). In line with this, studies support an inverse relationship between extraversion and likelihood of engaging in social distancing behaviour at the beginning of the pandemic.1,8

The genetic underpinnings of psychiatric traits are known to not only show a large overlap among each other but also with other diseases such as metabolic disorders.6,8 An increased overall load of infections in individuals with psychiatric disorders has also been reported and may, in part, be because of shared genetic liability,10 although only few large-scale studies have tried to answer this question to date. In addition to many other factors ranging from gender to pre-existing medical conditions and socioeconomic factors,11,12
both common and rare genetic variants have been identified that may predispose individuals to an infection with SARS-CoV-2 or a severe course of COVID-19.13–15

A recent GWAS by the COVID-19 Host Genetics Initiative,16 identified 13 loci of genome-wide significance for susceptibility to COVID-19, comparing participants with a self- or physician-reported COVID-19 diagnosis with the general population. Four of these loci seem to be specific to COVID-19 susceptibility rather than disease severity. The identified loci include variants in genes implicated in the innate immune response to viruses but also genomic loci harbouring many genes of yet-undetermined function in the context of COVID-19.

**Aims**

In light of these findings, we asked whether genetic underpinnings are shared between COVID-19 susceptibility, major psychiatric disorders and personality traits. We approached this question using both results from the largest GWAS in the respective fields and individual-level data from two observational studies of psychiatric disorders (PsyCourse) and personality traits (PsyCourse and HeiDE).

**Method**

We performed linkage disequilibrium score regression (LDSC)17 to calculate genetic correlations18 between susceptibility to COVID-19 and psychiatric disorders as well as personality traits. We used summary statistics for COVID-19 susceptibility derived from a GWAS performed by the COVID-19 Host Genetics Initiative16 (self- or physician-reported COVID-19 diagnosis \(n = 87\,870\) versus general population \(n = 2\,210\,804\); analysis 'C2' for European ancestry without 23andMe, Inc, release 6, downloaded from https://www.covid19hg.org/results/r6/, accessed 30 July 2021).

For psychiatric disorders, summary data from the following GWAS were used: schizophrenia (SCZ; 33 640 cases; 43 456 controls),19 bipolar disorder (BPD; 41 917 cases; 37 549 controls),20 depression (as a broader phenotype closely related to major depressive disorder (MDD), 246 363 cases; 561 190 controls)21 and Big 5 personality traits \(n = 3266\), age \(\text{mean} = 52.78, \text{s.d.} = 7.06, 52.38\% \text{female}\). Briefly, HeiDE ('Heidelberger Langzeitstudie zu Risikofaktoren und Diagnose chronischer Erkrankungen') is a population-based study carried out in the German city of Heidelberg and surrounding area with an initial aim of characterising associations of personality and somatic disease. Data analysed in this study were collected during

![Fig. 1 Study design for polygenic risk scores (PRS) analyses.](https://doi.org/10.1192/bjo.2021.1030)
No genetic correlation was found between COVID-19 susceptibility and severe psychiatric disorders or personality traits. Among these, we shed light on a potential role for shared genetic variation both when assessing summary statistics of large GWAS by LDSC and when looking at PRS in individual-level data, in line with emerging data in the field.16,32,33

With regard to personality traits, the picture is more heterogeneous with a significant signal for a positive genetic correlation between extraversion and COVID-19 susceptibility by LDSC, which needs to be explored further once larger data-sets become available. However, it has to be assumed that the genetic make-up is only one contributor in a very complex network of factors connecting extraversion to COVID-19 susceptibility.

**Interpretation of our findings and comparison with findings from other studies**

The positive correlation identified between COVID-19 susceptibility and extraversion highlighted by the LDSC approach appears to be in line with the literature. Numerous studies performed both before and during the SARS-CoV-2 pandemic have demonstrated the effect of personality determinants on health behaviour and outcomes (such as5,34,35). For example, it was shown that narcissistic tendencies coincide with decreased perceived susceptibility to infection with SARS-CoV-236 whereas, at least for neuroticism, no genetic overlap was found.37 Intuitively, less extroverted individuals may find social distancing during the pandemic easier than extroverted individuals and may, therefore, be more compliant with social distancing rules and at an overall decreased risk of COVID-19.5,6

There is even evidence of a bidirectionality of this phenomenon – the general risk for infectious diseases in a given region may, in part, influence personality traits at population level such that lower mean levels of extraversion are reported in regions with higher prevalence of COVID-19 susceptibility.43

**Results**

No genetic correlation was found between COVID-19 susceptibility and MDD, BPD, or SCZ risk (Table 1). When analysing the genetic correlation between personality traits22 and COVID-19 susceptibility, a significant positive correlation ($P = 0.177$, beta = 0.142) was found. No statistically significant correlation was present with any other Big-5 personality trait (Table 2).

To corroborate these findings with a second, independent line of evidence using individual-level data from two independent cohorts, we turned to an assessment of PRS. In the PsyCourse study, PRS for extraversion was specifically designed to evaluate the interaction between personality traits and somatic disorders. Here, however, we also did not detect a significant association for PRS for COVID-19 susceptibility and extraversion (model comparison $P = 0.758$, AIC 5149.51 (model with PRS) and AIC 5147.60 (model without PRS)).

**Discussion**

**Main findings**

It is likely that many interdependencies exist between COVID-19 susceptibility and major psychiatric disorders or personality traits. Among these, we shed light on a potential role for shared common genetic risk factors. For major psychiatric disorders, we did not identify a significant genetic overlap that can be ascribed to common genetic variation both when assessing summary statistics of large GWAS by LDSC and when looking at PRS in individual-level data, in line with emerging data in the field.16,32,33

With regard to personality traits, the picture is more heterogeneous with a significant signal for a positive genetic correlation between extraversion and COVID-19 susceptibility by LDSC, which needs to be explored further once larger data-sets become available. However, it has to be assumed that the genetic make-up is only one contributor in a very complex network of factors connecting extraversion to COVID-19 susceptibility.

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**Table 1** Results from linkage disequilibrium score regression between coronavirus disease 2019 susceptibility and severe psychiatric disorders

<table>
<thead>
<tr>
<th>Trait</th>
<th>MDD</th>
<th>Bipolar disorder²⁰</th>
<th>Schizophrenia³⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic correlation</td>
<td>0.072</td>
<td>0.004</td>
<td>−0.037</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.044</td>
<td>0.045</td>
<td>0.044</td>
</tr>
<tr>
<td>$P$</td>
<td>0.100</td>
<td>0.930</td>
<td>0.398</td>
</tr>
</tbody>
</table>

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**Table 2** Results from linkage disequilibrium score regression between coronavirus disease 2019 (COVID-19) susceptibility and Big 5 personality traits³⁹

<table>
<thead>
<tr>
<th>Trait</th>
<th>Agreeableness</th>
<th>Conscientiousness</th>
<th>Extraversion</th>
<th>Neuroticism</th>
<th>Openness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic correlation</td>
<td>0.177</td>
<td>0.056</td>
<td>0.284</td>
<td>−0.105</td>
<td>0.095</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.093</td>
<td>0.079</td>
<td>0.066</td>
<td>0.071</td>
<td>0.067</td>
</tr>
<tr>
<td>$P$</td>
<td>0.057</td>
<td>0.478</td>
<td>1.47 × 10⁻⁵</td>
<td>0.142</td>
<td>0.153</td>
</tr>
</tbody>
</table>

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a. The $P$ for genetic correlation between extraversion and COVID-19 susceptibility was statistically significant.
of infectious diseases. Of possible reason for this could be that in regions where ever-present infectious diseases present a comparably large threat to health and well-being, less extraversion is present at population level either because people have adapted their behaviour or because of potential selective pressure. Yet, it is likely that many interdependencies exist between COVID-19 susceptibility and personality traits or major psychiatric disorders and we investigated only shared common genetic risk factors.

Limitations
Although all included GWAS are the currently largest in the respective fields, sample sizes may still not be large enough to confidently detect genetic correlations in settings with many natural confounders such as levels of exposure to the virus or socioeconomic differences, to name only a few. Also, different instruments were used to evaluate personality traits in PysCourse and HeIDE and the study populations (individuals with severe psychiatric disorders and controls versus the general population) were different, possibly contributing to the observed heterogeneity.

Although LDSC represents a powerful tool to assess genetic correlations, other methods to quantify polygenic overlap irrespective of genetic correlations also exist (for example 38) and could be used to explore potential shared genetic underpinnings in even greater depth but are beyond the scope of this study. An additional limitation lies in the fact that no direct risk assessment was possible for the individuals with individual-level data on major psychiatric disorders and personality traits since no COVID-19 phenotypes were available. Finally, we are unable to fully exclude sample overlap especially for the controls used in the included GWAS. However, LDSC results should be robust to this overlap. 18

Implications
Hypothetically, it is possible that – for example – only a small subset of common genetic risk factors in a given pathway relevant to major psychiatric disorders or personality traits is associated with COVID-19 susceptibility. Although we cannot fully exclude all such effects, our data suggest that non-genetic factors play important roles in the interplay between personality traits and COVID-19. A direct genetic overlap is unlikely to contribute to the increased, but yet-unexplained COVID-19 risk seen in individuals with a psychiatric diagnosis prior to SARS-CoV-2 infection 1 but a shared genetic risk could still be mediated by intermediate phenotypes such as, for example, lower socioeconomic status or educational attainment in those with severe psychiatric disorders. As a consequence, an even greater focus should be placed on psycho-social interventions, ensuring the best treatment for individuals with severe psychiatric disorders as well as targeted measures of prevention and psychoeducation for individuals with personality characteristics that pose an increased pandemic-related risk for health and well-being.

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Data availability
The data that support the findings in this study are available from the corresponding author, E.C.S., upon reasonable request. The relevant summary statistics from the GWAS used in the analyses are available from the authors of the primary studies.16–19,115 Interested researchers
Acknowledgements

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Author contributions


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Declaration of interest

M.S. is a member of the advisory board of Janssen. B.T.B. reports the following conflicts of interest with regard to this manuscript: Advisory Board – Lundbeck, Janssen-Clariant, Consultant – National Health and Medical Research Council, Australia; Grant/Research Support – AstaRhezzena, Fay Fuller Foundation, Janssen. M.R. is a member of the advisory board of Janssen. C.H.C. is a member of the advisory board of Janssen. O.A.A. has received speaker’s honorarium from Lundbeck and Synovion, and is a consultant to Healthylinx. All other authors do not report conflicts of interest with regard to this manuscript.

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