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Short communication

Severe COVID-19 increases the risk of schizophrenia

Ancha Baranova^{a,b,1}, Hongbao Cao^{a,1}, Fuquan Zhang^{c,d,*}^a School of Systems Biology, George Mason University, Manassas 20110, USA^b Research Centre for Medical Genetics, Moscow 115478, Russia^c Institute of Neuropsychiatry, The Affiliated Brain Hospital of Nanjing Medical University, 264 Guangzhou Road, Nanjing 210029, China^d Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing 210029, China

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ABSTRACT

The coronavirus SARS-CoV-2 invades the central nervous system, impacting the mental health of COVID-19 patients. We performed a two-sample Mendelian randomization analysis to assess the potential causal effects of COVID-19 on schizophrenia. Our analysis indicated that genetic liability to hospitalized COVID-19 was associated with an increased risk for schizophrenia (OR: 1.11, 95% CI: 1.02–1.20, $P = 0.013$). However, genetic liability to SARS-CoV-2 infection was not associated with the risk of schizophrenia (1.06, 0.83–1.37, $P = 0.643$). Severe COVID-19 was associated with an 11% increased risk for schizophrenia, suggesting that schizophrenia should be assessed as one of the post-COVID-19 sequelae.

1. Introduction

Since the inception of the SARS-CoV-2 infection pandemic, a significant subpopulation of individuals infected with SARS-CoV-2 suffers from a range of post-COVID symptoms or consequences, including various forms of “long-COVID”. In the course of COVID-19, neuropsychiatric manifestations are common. The coronavirus SARS-CoV-2 can invade the central nervous system, impacting the structure, metabolism, function, and activity of the brain (Dehghani et al., 2022). Therefore, the neurotropic properties of COVID-19 pose a remarkable threat to the mental health of affected individuals. On the other hand, preexisting brain pathology may make individuals more vulnerable to the invasion of the coronavirus, which may predispose infected individuals to severe outcomes.

The prevalence of newly established psychiatric diagnoses is rising along with pandemics (Cenat et al., 2021). Schizophrenia is a severe mental illness characterized by hallucinations, delusions, disorganized thinking, and cognitive deficits. In both schizophrenia and SARS-CoV-2 infection, a profound breakdown in neuron-glia homeostasis is notable (Savelieff et al., 2022). It has been reported that schizophrenia patients are at higher risk for COVID-19 mortality (Toubasi et al., 2021).

To date, evidence for associations between COVID-19 and schizophrenia has largely been derived from correlational studies or clinical observations. Exploring the causality between COVID-19 and

schizophrenia is hindered by confounding intermediating factors and possible reverse causation. We sought to test the potential causal effects of two COVID-19 outcomes, SARS-CoV-2 infection and COVID-19 hospitalization, on schizophrenia by using the Mendelian randomization (MR) framework.

2. Methods

2.1. GWAS summary datasets

In this study, we used publicly available summary results of previously completed GWAS. Two COVID-19 datasets were obtained from the COVID-19 HGI GWAS round 7 (Initiative, 2020), including one for SARS-CoV-2 infection (122,616 cases and 2,475,240 controls) and one for hospitalized COVID-19 (32,519 cases and 2,062,805 controls). The summary result of schizophrenia-related GWAS contained 53,386 schizophrenia cases and 77,258 controls, all of which were of European origin (Trubetskoy et al., 2022). In SARS-CoV-2 datasets, the data on infection reflect the overall susceptibility to the virus, whereas the hospitalized cases of COVID-19 represent the severity of the disease. In this study, all hospitalized COVID-19 cases were recognized as “severe COVID-19”.

* Corresponding author at: Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, 264 Guangzhou Road, Nanjing 210029, China.
 E-mail address: zhangfq@njmu.edu.cn (F. Zhang).

¹ These are co-first authors.

Table 1
Causal effects of COVID-19 outcomes on schizophrenia.

Exposure	Outcome	Method	b (se)	OR [95%CI]	N_IV	Egger_intercept	P_pleiotropy	P
SARS-CoV-2 infection	Schizophrenia	IVW	0.060 (0.128)	1.06 [0.83-1.37]	20	NA	NA	0.643
SARS-CoV-2 infection	Schizophrenia	WM	0.209 (0.111)	1.23 [0.99-1.53]	20	NA	NA	0.060
SARS-CoV-2 infection	Schizophrenia	MR Egger	-0.357 (0.512)	0.70 [0.26-1.91]	20	0.014	0.412	0.495
Hospitalized COVID-19	Schizophrenia	IVW	0.103 (0.041)	1.11 [1.02-1.20]	36	NA	NA	0.013
Hospitalized COVID-19	Schizophrenia	WM	0.089 (0.039)	1.09 [1.01-1.18]	36	NA	NA	0.022
Hospitalized COVID-19	Schizophrenia	MR Egger	0.036 (0.120)	1.04 [0.82-1.31]	36	0.005	0.560	0.765

IVW: inverse variance weighted; WM: Weighted median; OR: odds ratio; CI: confidence interval; b: effect size; se: standard error; N_IV: number of instrumental variables; Q_P: P-value of heterogeneity analysis.

2.2. MR analysis

The analyses were performed using three complementary methods implemented in TwoSampleMR (Hemani et al., 2018), including inverse variance weighted (IVW), weighted median, and MR-Egger. These methods differ in their assumptions about horizontal pleiotropy (Bowden et al., 2015). Here, the IVW model was used as the primary MR technique. The intercept from the MR-Egger regression was utilized to evaluate the average horizontal pleiotropy (Bowden et al., 2015). The IVs are not all valid when the MR Egger intercept significantly differs from zero. The significant associations between the COVID-19 outcomes and schizophrenia were determined by IVW-based $P < 0.025$ (0.05/2).

For each exposure phenotype, single-nucleotide polymorphisms (SNPs) with genome-wide significance ($P < 5 \times 10^{-8}$) were selected as IVs. These IVs were further pruned using a clumping r^2 cutoff of 0.01 within each 10 Mb window, using the 1000 Genomes Project Phase 3 (EUR) as the reference panel. For each MR analysis, we removed SNPs missing from the outcome dataset as well as palindromic SNPs with intermediate allele frequencies.

3. Results

3.1. MR analysis

In the MR analysis aiming to uncover the causal effects of the two COVID-19 outcomes, SARS-CoV-2 infection and hospitalized COVID-19, on schizophrenia, a total of 20 and 36 IVs were derived, respectively. We found that hospitalized COVID-19 (OR: 1.11, 95% CI: 1.02–1.20, $P = 0.013$) exerts a causal effect on schizophrenia (Table 1 and Fig. 1). However, SARS-CoV-2 infection does not have a causal effect on this psychiatric condition (1.06, 0.83–1.37, $P = 0.643$).

The sensitivity analyses revealed that the directions of causal effect estimates across the methods were largely the same (Table 1). Notably, in this MR analysis, tests of MR-Egger regression did not find evidence of directional pleiotropy (MR-Egger intercept < 0.02 , $P > 0.05$).

4. Discussion

Schizophrenia patients usually have considerable disability and poor quality of life. Previous studies have documented higher COVID-19-attributed mortality in schizophrenia patients (Toubasi et al., 2021). However, it is largely unknown whether the various COVID-19 outcomes play a causal role in the development of schizophrenia. Here, we show the causal effect of severe COVID-19 on schizophrenia. We utilized the MR framework to demonstrate that the association of COVID-19 with schizophrenia was severity dependent. While the viral infection may not increase the risk for schizophrenia, COVID-19 hospitalization was associated with an 11% increase in the risk of schizophrenia.

Our results are consistent with previously observed findings of an elevated rate of mental disorders during the pandemic (Cenat et al., 2021) and suggest that schizophrenia should be assessed as one of the possible post-COVID-19 sequelae. Our study points out that the protocols for post-acute COVID-19 care should include the diagnosis and management of this psychiatric condition.

The main strength of the study is that MR analysis is less affected by the causality pitfalls of confounding factors and reverse causation than traditionally designed observational studies. To trace the causative association between COVID-19 and schizophrenia, we utilized the largest available GWAS summary datasets. Moreover, all the participants in the GWAS datasets were of European ancestry, reducing the potential population heterogeneity.

Our study has several limitations. In particular, we assessed only genetic liability for both diseases with no regard to the effects of the environment, which are critical for both schizophrenia and COVID-19. Some confounding factors may influence the causal associations between schizophrenia and COVID-19, including smoking (Rao et al., 2021; Zhang and Baranova, 2021). We acknowledge that MR analyses may be biased due to pleiotropy, especially in nonhomogenous datasets. Therefore, we have tested the MR assumptions using various models.

5. Conclusions

In summary, our study supports that severe COVID-19 may increase the risk for schizophrenia. However, our results did not support a causal effect of SARS-CoV-2 infection on this psychiatric disease.

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Authors' contributions

FZ conceived the project and supervised the study. FZ analyzed the data. FZ, HC, and AB wrote the manuscript. All authors read and approved the final manuscript.

Declaration of Competing interest

The authors declare that they have no competing interests.

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