

Original Research

Causal Associations between Posttraumatic Stress Disorder and COVID-19

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Abstract

Objective: We aimed to evaluate bidirectional genetic relationships between posttraumatic stress disorder (PTSD) and COVID-19. **Methods:** We investigated potential causal associations between PTSD and two COVID-19 conditions (COVID-19 hospitalization and SARS-CoV-2 infection) via Mendelian randomization (MR) analyses. Three genome-wide association study (GWAS) summary datasets were used in the study, including PTSD (N = 174,659), SARS-CoV-2 infection (N = 2,597,856), and COVID-19 hospitalization (N = 2,095,324). We performed a literature-based analysis to uncover molecular pathways connecting PTSD and COVID-19. **Results:** We found that PTSD exerts a causal effect on SARS-CoV-2 infection (odds ratio (OR): 1.10, 95% confidence interval (CI): 1.00–1.21, $p = 0.048$) and hospitalized COVID-19 (OR: 1.34, 95% CI: 1.07–1.67, $p = 0.001$). However, both SARS-CoV-2 infection and hospitalized COVID-19 were not associated with the risk of PTSD. Pathway analysis revealed that several immunity-related genes may link PTSD to COVID-19. **Conclusions:** Our study suggests that PTSD was associated with increased risks for COVID-19 susceptibility and severity. Early diagnosis and effective treatment of PTSD in individuals infected with the coronavirus may improve the management of the outcomes of COVID-19.

Keywords: posttraumatic stress disorder; COVID-19; Mendelian randomization

1. Introduction

To date, numerous risk factors of COVID-19 have been identified, including cardiovascular diseases, diabetes, obesity, and smoking [1–4]. The SARS-CoV-2 virus infiltrates the central nervous system, leading to neuropsychiatric manifestations [5]. The outcomes of COVID-19 are remarkably influenced by neuropsychiatric diseases and vice versa [6–11].

Posttraumatic stress disorder (PTSD) is a common mental disorder with a prevalence of 6–8% in the general population and even higher rates in special groups [12]. The risk for PTSD depends both on genetics and past trauma history. Pathophysiology of PTSD involves dysregulation of fear- and threat-related behavior and learning within the amygdala-hippocampus-medial prefrontal cortex circuit [12,13]. There is growing evidence indicating a higher occurrence of PTSD during the COVID-19 pandemic [14–16]. Notably, in COVID-19 survivors, total scores on the PTSD checklist for the diagnostic and statistical manual of mental disorders (DSM)-5 score were significantly higher compared with controls [17]. Overall scoping of the literature suggests that studies of PTSD as it relates to COVID-

19 were mostly performed in populations stressed by the spread of SARS-Cov-2 and related public health measures rather than in COVID-19 survivors affected by the virus itself.

The mendelian randomization (MR) design can be leveraged to detect causative associations between an exposure phenotype and an outcome by utilizing genetic variants as instrumental variables [18]. The MR technique is widely used to infer causality between an exposure and an outcome [19,20]. Previous MR studies have reported a myriad of causal risk factors for COVID-19, including obesity, higher basal metabolic rate, smoking, and others [2,21–23].

It's not known whether PTSD may promote the risk of COVID-19, or whether PTSD could be triggered by COVID-19 outcomes. We sought to assess the mutual causal relationships between PTSD and COVID-19 and explore molecular pathways underlying their connections.

2. Methods

2.1 GWAS Summary Datasets

In this study, the Genome-Wide Association Study (GWAS) data we used were obtained from two sources: the



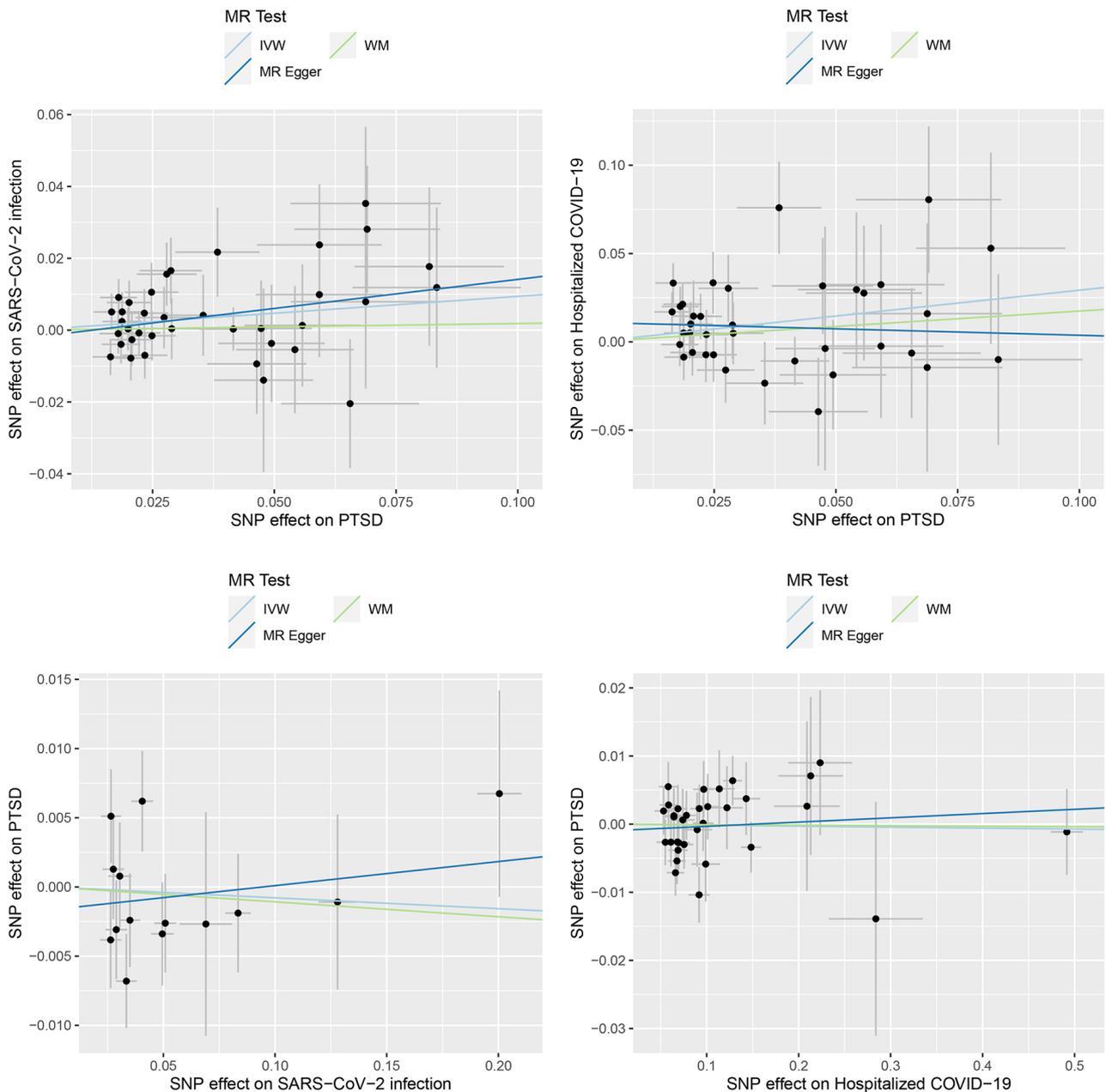


Fig. 1. Causal associations between PTSD and COVID-19. The upper panel shows the causal effects of PTSD on COVID-19 outcomes. Each point represents a specific SNP. The x-axis represents the SNPs' effect on the exposure factor (PTSD), and the y-axis represents the SNPs' effect on the disease outcomes (SARS-CoV-2 infection and hospitalized COVID-19, respectively). The lower panel displays the causal influences of COVID-19 outcomes on PTSD. The x-axis represents the SNPs' effect on the exposure factor (SARS-CoV-2 infection and hospitalized COVID-19, respectively), and the y-axis represents the SNPs' effect on the disease outcome (PTSD). The three lines represent the effect sizes (b) of the exposure on the disease calculated by three statistical methods: WM, IVW, and MR Egger. PTSD, posttraumatic stress disorder; SNP, single nucleotide polymorphism; WM, weighted median; IVW, inverse variance weighted; MR, Mendelian randomization.

Psychiatric Genomics Consortium (PGC) and the COVID-19 Host Genetic Initiative (HGI) [24]. The PTSD GWAS summary dataset consisted of 23,212 cases and 151,447 controls [25]. The PTSD data included a wide range of participant profiles, who were exposed to various types of

trauma, encompassing both civilian and military contexts, and in most cases, they also had a history of trauma exposure during childhood.

The COVID-19 datasets used in the study consisted of data on SARS-CoV-2 infections (COVID vs. popula-

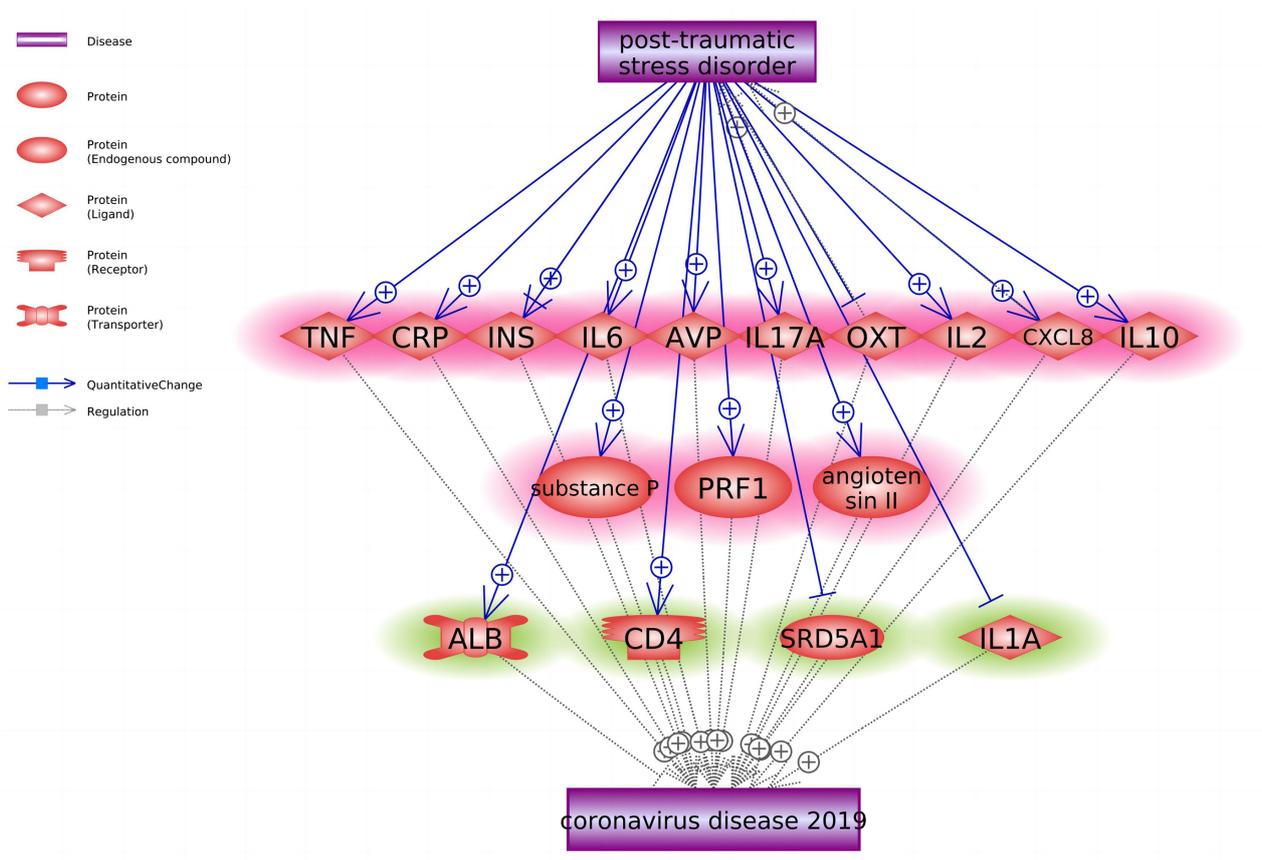


Fig. 2. Molecular pathways connecting PTSD and COVID-19. Promoting effects are shown in red, and inhibitory effects are shown in green. The line “+>” represents positive regulation; the line “-|” represents negative regulation. Quantitative genetic changes driven by PTSD exert more promoting (highlighted in red) than protective (highlighted in green) effects on COVID-19. AVP, arginine vasopressin; CRP, C-reactive protein; CXCL8, C-X-C motif chemokine ligand 8; IL, interleukin; INS, insulin; OXT, oxytocin; PRF1, perforin 1; TNF, tumor necrosis factor; ALB, albumin; CD4, cluster of differentiation 4; SRD5A1, steroid 5 alpha-reductase 1.

tion), which included 122,616 cases and 2,475,240 controls, as well as data on hospitalized COVID-19 (Hospitalized COVID vs. Population), which included 32,519 cases and 2,062,805 controls. The SARS-CoV-2 infection dataset provides insights into the general vulnerability to the virus. Because hospitalized COVID-19 was a severe outcome of the disease, we called it “severe COVID-19”.

2.2 MR Analysis

The MR analysis was achieved by the inverse variance weighting (IVW) model in the TwoSampleMR package (<https://github.com/MRCIEU/TwoSampleMR>) (version 0.5.6) [26]. The weighted median (WM) and MR-Egger models were employed as complementary measures to assess the sensitivity of the MR analysis. Potential horizontal pleiotropy was gauged by the intercept of the MR-Egger regression, and heterogeneity by both Cochran’s Q test ($p < 0.05$) and I^2 statistics ($I^2 > 0.25$).

First, we evaluated the causal effects of PTSD on the two COVID-19 phenotypes. The PTSD dataset was used as exposure and the three COVID-19 datasets were used as

outcomes. Then, we performed the reverse MR analyses by using the three COVID-19 datasets as exposures and the PTSD dataset as outcomes. For each MR analysis, we selected single nucleotide polymorphisms (SNPs) associated with the exposure trait ($p < 5 \times 10^{-8}$). Then, these SNPs were further pruned by a clumping r^2 value of 0.001 within a 10 Mb window. The resulting SNPs were used as instrumental variables (IVs) in the MR analysis. In the analyses of the causal effects of PTSD on COVID-19, the number of IVs was less than 10, and a p value threshold of 1×10^{-5} was used to select the IVs.

2.3 Knowledge-Based Analysis

To unravel molecular connections between PTSD and COVID-19, we leveraged the Pathway Studio environment to perform literature-based data mining [27]. The downstream targets and upstream regulators of PTSD and COVID-19 were obtained. Molecular pathways were then constructed between PTSD and COVID-19. More details were described previously [6]. In this study, we called the molecules/genes connecting PTSD and COVID-19 “mediating molecules/genes”.

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

Exposure	Outcome	Method	b (se)	OR [95% CI]	N_IV	Q_p	I ²	Egger_intercept	p_pleiotropy	p
PTSD	SARS-CoV-2 infection	IVW	0.094 (0.047)	1.10 [1.00–1.21]	37	0.695	–0.15	NA	NA	0.048
PTSD	SARS-CoV-2 infection	WM	0.018 (0.071)	1.02 [0.89–1.17]	37	NA	NA	NA	NA	0.796
PTSD	SARS-CoV-2 infection	MR Egger	0.162 (0.112)	1.18 [0.94–1.46]	37	0.673	–0.17	–0.002	0.507	0.156
PTSD	Hospitalized COVID-19	IVW	0.292 (0.112)	1.34 [1.07–1.67]	37	0.251	0.128	NA	NA	9.29 × 10 ^{–3}
PTSD	Hospitalized COVID-19	WM	0.174 (0.147)	1.19 [0.89–1.59]	37	NA	NA	NA	NA	0.237
PTSD	Hospitalized COVID-19	MR Egger	–0.073 (0.262)	0.93 [0.56–1.55]	37	0.307	0.069	0.011	0.134	0.783

WM, Weighted median; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio; b, effect size; N_IV, number of instrumental variables; se, standard error; Q_P, *p*-value of heterogeneity analysis; PTSD, posttraumatic stress disorder; MR, Mendelian randomization; NA, not applicable.

Table 2. Causal effects of COVID-19 outcomes on PTSD.

Exposure	Outcome	Method	b (se)	OR [95% CI]	N_IV	Q_p	I ²	Egger_intercept	p_pleiotropy	p
SARS-CoV-2 infection	PTSD	IVW	–0.008 (0.021)	0.99 [0.95–1.03]	14	0.359	0.085	NA	NA	0.702
SARS-CoV-2 infection	PTSD	WM	–0.011 (0.027)	0.99 [0.94–1.04]	14	NA	NA	NA	NA	0.686
SARS-CoV-2 infection	PTSD	MR Egger	0.017 (0.037)	1.02 [0.95–1.09]	14	0.339	0.031	–0.002	0.418	0.643
Hospitalized COVID-19	PTSD	IVW	–0.001 (0.007)	1.00 [0.98–1.01]	33	0.462	0.0029	NA	NA	0.836
Hospitalized COVID-19	PTSD	WM	–0.001 (0.011)	1.00 [0.98–1.02]	33	NA	NA	NA	NA	0.947
Hospitalized COVID-19	PTSD	MR Egger	0.006 (0.013)	1.01 [0.98–1.03]	33	0.436	–0.012	–0.001	0.495	0.639

WM, Weighted median; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio; b, effect size; se, standard error; Q_P, *p*-value of heterogeneity analysis; N_IV, number of instrumental variables; PTSD, posttraumatic stress disorder; NA, not applicable.

3. Results

3.1 MR Analysis

In the MR analyses of the causal effects of PTSD on COVID-19 outcomes, we obtained a total of 37 independent SNPs associated with PTSD at a significance level of $p < 1 \times 10^{-5}$, which were used IVs in the MR analyses. Our findings indicate that genetic predisposition to PTSD has a causal effect on SARS-CoV-2 infection (odds ratio (OR): 1.10, 95% confidence interval (CI): 1.00–1.21, $p = 0.048$) and hospitalized COVID-19 (OR: 1.34, 95% CI: 1.07–1.67, $p = 0.001$) (Table 1 and Fig. 1).

In the MR analyses of the causal effects of the COVID-19 outcomes on PTSD, we obtained IVs from the three COVID-19 datasets. The numbers of IVs were 14 for SARS-CoV-2 infection and 33 for hospitalized COVID-19. We found that neither SARS-CoV-2 infection (OR: 0.99, 95% CI: 0.95–1.03, $p = 0.702$) nor hospitalized COVID-19 (OR: 1.00, 95% CI: 0.98–1.01, $p = 0.836$) exerted a causal effect on PTSD (Table 2 and Fig. 1).

The results of the sensitivity analyses revealed consistent directions of causal effects among the various methods employed (Tables 1,2). The MR-Egger regression test did not provide evidence of directional pleiotropy (with an MR-Egger intercept < 0.01 and $p > 0.05$). Moreover, both the Cochran Q test and I^2 statistic did not indicate the presence of heterogeneity in the causal effects of PTSD on COVID-19.

3.2 Knowledge-Based Analysis

Mining of the molecular pathways discovered a total of 17 genes mediating the connections between PTSD and COVID-19 (Fig. 2). A set of 13 PTSD-related genes which quantitatively change in PTSD and also enhance COVID-19 includes angiotensin II, arginine vasopressin (AVP), C-reactive protein (CRP), C-X-C motif chemokine ligand 8 (CXCL8), interleukin (IL)10, IL17A, IL2, IL6, insulin (INS), oxytocin (OXT), perforin 1 (PRF1), substance P, and tumor necrosis factor (TNF). A total of 4 PTSD-driven genetic changes may suppress the risk of COVID-19, including albumin (ALB), cluster of differentiation 4 (CD4), steroid 5 alpha-reductase 1 (SRD5A1), and IL1A.

4. Discussion

Following the pandemic, there have been numerous reports of elevated levels of mental disorders [14]. Conversely, mental disorders and psychiatric conditions might contribute to a higher susceptibility to COVID-19 [28,29]. So far, evidence for associations between COVID-19 and psychiatric conditions was chiefly derived from correlational studies made in serial clinical observations. In this study, we conducted an MR analysis to explore the reciprocal relationship between PTSD and COVID-19. Our results indicated that individuals diagnosed with PTSD had a 10% greater likelihood of contracting SARS-CoV-2 and a 34%

higher risk of being hospitalized due to COVID-19. Our result is consistent with a previous study showing a higher risk for severe COVID-19 outcomes in individuals with PTSD [30].

Observational studies have documented a higher likelihood of PTSD associated with COVID-19, with the prevalence of PTSD being 15.45~21.94% among COVID-19-affected populations [14,16]. However, our results did not detect a causal effect of COVID-19 on PTSD. It is known that the COVID-19 pandemic served as a vital traumatic stressor [31]. Our analysis points out that post-pandemic PTSD may chiefly be caused by psychological reactions caused by COVID-19, rather than by COVID-19 itself, and that the high rate of psychological distress caused by COVID-19 [14] should be taken into account. It seems that COVID-19 and PTSD form a vicious circle, aggravating the risk for one another.

By using literature-based analysis, we explore potential mechanisms underlining the connection between PTSD and COVID-19. The severity of COVID-19 may be influenced by underlying genetics, and by prior environmental exposures, through the induced priming of microglia [32]. Previous studies of PTSD cohorts revealed increased circulatory levels of inflammatory cytokines, such as TNF- α and IL-6, when compared to the controls [33,34]. Additionally, in patients with PTSD, the levels of both activated nuclear factor- κ B, and the C-reactive protein were elevated [34–36]. In this light, it is not surprising that the genetic liability to PTSD was found to confer a causal effect on hospitalized COVID-19. In the context of PTSD-associated ongoing inflammation, it is likely that COVID-19 would further exacerbate both the inflammation and the immune response within the central nervous system (CNS), and therefore, the risks of a severe course of COVID-19 would increase. Accordingly, the reconstruction of molecular networks connecting PTSD with COVID-19 highlighted many well-known inflammation-related cytokines and chemokines (Fig. 2).

Another interesting molecule connecting PTSD with the severe course of COVID-19 is the perforin which is encoded by *PRF1*. This gene harbors highly prevalent, variant c.272C>T (p.A91V; rs35947132), which destabilizes the active form of perforin protein and leads to a significant decrease in natural killer (NK)-cell cytotoxicity. Variant rs35947132 is overrepresented in patients with hemophagocytic lymphohistiocytosis, a disease that resembles a cytokine storm phase of severe COVID-19, as well as in COVID-19 patients admitted to ICU [37]. When compared to controls, a reduction in the cytotoxicity of NK cells was repeatedly observed specifically in PTSD [38]. While the levels of perforin per NK cell in patients with PTSD were similar to that in controls, possible defects of perforin functionality were suggested [38].

Another interesting bridge between PTSD and COVID-19 is substance P and its receptor NK1 [39]. An

increase in levels of substance P in cerebrospinal fluid samples of PTSD patients led to the development of selective neurokinin-1 receptor (NK-1R) antagonists as anti-PTSD candidates capable of alleviating hyperarousal [40]. As NK1 antagonism may uncouple the perception of pain from the downstream cytokine storm, nociceptive blocker Aprepitant has also been suggested as a treatment for COVID-19 [41,42].

Individuals with PTSD exhibit a chronic stress response, leading to elevated levels of systemic inflammation. This is evidenced by an increase in the levels of soluble pro-inflammatory markers such as Vascular Cell Adhesion Molecule-1 (VCAM-1), TNF- α , IL-1 β , and IL-8 [43,44]. This chronic state of inflammation not only diminishes resistance to COVID-19 but may also predispose individuals to an exaggerated response to viral infections, potentially triggering a cytokine storm. Our analysis of molecular pathways further substantiates the connection between PTSD and COVID-19 through inflammation-promoting circuits.

Moreover, neuroimaging-based studies have revealed that alterations in inflammatory markers can impact both the structure and function of brain-related regions [45]. The reduced levels of anti-inflammatory hormones, such as corticosteroids, also influence the inflammatory response of neural cells [46]. Thus, pre-existing neuroinflammatory changes seen in individuals with PTSD lay the groundwork for their heightened vulnerability to COVID-19, exacerbating inflammation of the nervous system responding to viral infection.

On one hand, PTSD patients tend to engage in unhealthy lifestyles or behaviors, such as maintaining a poor diet, smoking, or lacking exercise, which may weaken their overall health status, thereby increasing their susceptibility to contracting symptomatic SARS-CoV-2. On the other hand, as previously discussed, the pre-existing state of chronic inflammation and altered pro-inflammatory hormone levels may further reduce the resistance of PTSD patients to infections, also increasing the risks. This stress, which overloads an entire body, may trigger a cytokine storm, leading to a worsening of COVID-19 condition, thereby, increasing the need for hospitalization. In the presence of neuroinflammation, the patient's condition exacerbates further, creating a vicious cycle.

Because ethnic differences play an important role in heredity, there may be genetic composition and genetic variation differences among different populations. This can lead to differences in disease susceptibility and treatment response in specific populations, indicating that ethnic differences can impact data analysis. Since our GWAS data only includes individuals of European descent, caution is necessary when generalizing our analysis results to the overall population. Further research is needed to determine the applicability in other populations.

Additionally, since genetic variations are inherent and directly related to an individual's genome, they are less in-

fluenced by confounding factors. Therefore, possible differences in age distributions did not affect our analysis results significantly. However, it is undeniable that age is an important factor in the severity and prognosis of COVID-19. Elderly populations with PTSD may face a higher risk of COVID-19. Therefore, in practical life, it is, indeed, important to pay more attention to elderly PTSD patients and take appropriate preventive and intervention measures.

5. Conclusions

Our study showed that PTSD is associated with an increased risk of COVID-19, primarily through the priming of neuroinflammatory cascades. Early diagnosis and treatment of PTSD in individuals infected with the coronavirus may improve the management of the outcomes of COVID-19.

Availability of Data and Materials

Data sharing is not applicable as no data were generated or analyzed.

Author Contributions

FZ conceived the project and supervised the study. FZ performed the research and analysed the data. HC provided help and advice on the research. AB and LF interpreted the data. YS collected and sorted references. LF, YS, and AB draft the manuscript. FZ, YS, and HC revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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