



BMJ Open Association of Long COVID with mental health disorders: a retrospective cohort study using real-world data from the USA

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ABSTRACT

Objectives Mental health disorders (MHD) rank third for US adult hospitalisations. Given the substantial prevalence of 'Long COVID' in SARS-CoV-2 survivors, this study aims to assess its association with increased MHD risk using extensive real-world data.

Design A retrospective cohort study with propensity score matching was conducted. We used the International Classification of Diseases, 10th Revision codes to identify individuals with Long COVID status and COVID-19 histories. Multivariable stratified Cox proportional hazards regression analysis was conducted to determine the association of Long COVID status with MHD.

Setting Data were sourced from the TriNetX database, spanning records from 1 October 2021 to 16 April 2023.

Participants Two distinct cohorts were established: one comprising individuals diagnosed with Long COVID and another comprising individuals with no history of Long COVID or COVID-19. At the start of the study, none of the participants had a recorded MHD.

Primary and secondary outcome measures The main outcome of interest was a composite diagnosis of MHD. Secondary outcomes were individual mental health conditions.

Results The study included 43 060 control participants without Long COVID and 4306 Long COVID participants, demonstrating well-balanced distribution across all covariates. After adjusting for 4 demographic factors and 10 comorbidities, Long COVID was associated with MHD (adjusted HR, aHR 2.60; 95% CI 2.37 to 2.85). In subgroup analysis, Long COVID was associated with major depression disorder (aHR 3.36; 95% CI 2.82 to 4.00) and generalised anxiety disorder (aHR 3.44; 95% CI 2.99 to 3.96).

Conclusions In this retrospective large real-world cohort study, Long COVID was associated with an increased risk of incident MHD. The MHD impact is significant considering the vast number of patients with Long COVID. Enhanced MHD screening among COVID-19 survivors should be a priority.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, has profoundly impacted individual health and well-being globally.¹ While the effects of COVID-19 range from asymptomatic

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Included a large sample size of 4306 patients with Long COVID and 43 060 controls, with comprehensive measures to control for confounders and comorbidities.
- ⇒ Used a comprehensive propensity score matching approach to analyse the association between Long COVID and mental health disorder (MHD).
- ⇒ Employed a retrospective cohort design using US TriNetX data, with methodologies implemented to mitigate potential confounders and address timing-related issues.
- ⇒ Acknowledged potential misclassification in electronic health records due to misreporting or underreporting of MHD or Long COVID diagnosis codes.
- ⇒ Considered the possibility of undiagnosed mild or asymptomatic COVID-19 in untested controls, which may underestimate the strength of the Long COVID and MHD association.

or mild disease to multiorgan failure and death, a notable proportion of COVID-19 survivors with experience persistent symptoms. These are commonly referred to in the literature as postacute sequelae of COVID-19 or 'Long COVID'.² This condition represents a significant and ongoing public health crisis, as indicated by data suggesting that 10%–30% of non-hospitalised cases and 50%–70% of hospitalised cases report long-term effects.^{3 4} A recent meta-analysis found an increased incidence of anxiety, depression and appetite problems among post-COVID-19 infected children, compared with those without a previous infection.⁵

Mental health disorders (MHDs) such as depression and anxiety disorders are the third leading cause of hospitalisation in the USA.^{6 7} In 2020, nearly 21 million American adults (8.4% of the adult population) suffer from a major depressive disorder.⁸

Previous studies that have assessed the associations between COVID-19 and MHD

were limited to special populations such as children or US veterans.⁹ Studies so far have examined the impact of the pandemic on the incidence and prevalence of MHDs. However, the direct effect of COVID-19 among survivors is scarce and has not been delineated in diverse populations using large real-world data. Therefore, in this study, we used a large real-world data to estimate the effect of Long COVID using newly developed diagnosis codes on incident MHD. We hypothesise that since Long COVID presents with an array of symptoms that affect daily quality of life, including sleep disorders, chronic dyspnoea and myalgia/arthritis, it could have a negative impact on mental health outcomes.

METHODS

Data source

This analysis was conducted using a TriNetX database with data extracted from 1 October 2020 to 16 April 2023. TriNetX serves as a federated, multi-institutional health research network that compiles deidentified data derived from electronic health records (EHRs) across a broad spectrum of healthcare organisations (HCOs). These include academic medical centres, specialised physician practices and community hospitals, collectively encompassing over 250 million patients from more than 120 HCOs. This vast network enables longitudinal patient-level healthcare claims tracking, and delivers a wealth of data including, but not limited to, demographic attributes (age, race, gender, geographical location), medical histories and prescription details. TriNetX is compliant with the Health Insurance Portability and Accountability Act, the US federal law which protects the privacy and security of healthcare data, and any additional data privacy regulations applicable to the contributing HCO.¹⁰

Cohort derivation and assessment of exposure

Patients with Long COVID, aged 18 years and older, were identified from 1 October 2021 through 16 April 2023, using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes (online supplemental table 1). The Centers for Disease Control and Prevention officially characterises Long COVID as a post-COVID-19 condition manifesting in patients with a confirmed or probable history of SARS-CoV-2 infection. The corresponding ICD-10-CM code for this condition became effective on 1 October 2021.¹¹

We identified 9034 participants with Long COVID and 500 002 random participants without Long COVID, each with at least 1 month of follow-up after 1 October 2021. The index dates of Long COVID group were the diagnosis dates of Long COVID, and random pseudo index dates were assigned to the non-Long COVID group between 1 October 2021, and the maximum recorded dates for each participant, using data drawn from diagnosis records, lab test results and medication records. None of the participants had a history of MHD prior to the index dates, and those in the non-Long COVID group

had no record of Long COVID or COVID-19 diagnoses or testing positive for SARS-CoV-2. After all the exclusions (figure 1), we identified a total of 4306 eligible participants with Long COVID and 186 903 eligible participants without COVID-19 and without Long COVID. The nearest-neighbour propensity score matching methods were further used at a 1:10 matching ratio, with the 'without replacement' sampling method. This led to the final selection of 4306 participants with Long COVID and a corresponding control group of 43 060 participants for in-depth analysis (figure 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.¹²

Patient and public involvement

Patients and the public were not involved in the design or planning of this secondary data analysis.

Assessment of outcomes

The primary outcome was the composite of any MHD, defined using ICD-10 codes for mental health diagnosis or substance use disorders as done in previous studies (online supplemental table 1) that occurred after index dates during the follow-up period.^{13 14} As the secondary outcomes (major depression, anxiety and other mental health conditions), the association of Long COVID with these individual MHD groups was examined.

Assessment of potential covariates

To ensure a similar distribution of covariates at baseline and mitigate potential confounding effects, propensity score matching was conducted considering 4 demographic variables and 10 comorbidities. Demographic data on age (years), sex (male/female), race (white/black or African American/unknown/others) and US regional location (South/West/Midwest/Northeast/Unknown) were extracted directly from TriNetX patients' databases. For the identification of comorbidity covariates, we employed the Charlson Comorbidity Index and selected the 10 most prevalent comorbidities as matching variables.¹⁵ These included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatoid disease, mild liver disease, diabetes, renal disease and cancer (any malignancy).¹⁶ All these comorbidities were identified at baseline, defined at the 12 months preceding the index date, using their corresponding ICD-10-CM codes (online supplemental table 1).

Vaccination status was also taken into consideration, defined as any history of COVID-19 vaccination prior to the index date, determined by Current Procedural Terminology codes (online supplemental table 1).¹⁷

Statistical analysis

We summarised baseline participants characteristics across Long COVID and non-Long COVID groups, with mean (SD) values for continuous variables, and number and percentage for categorical variables, which were presented before matching and after 1:10 matching.

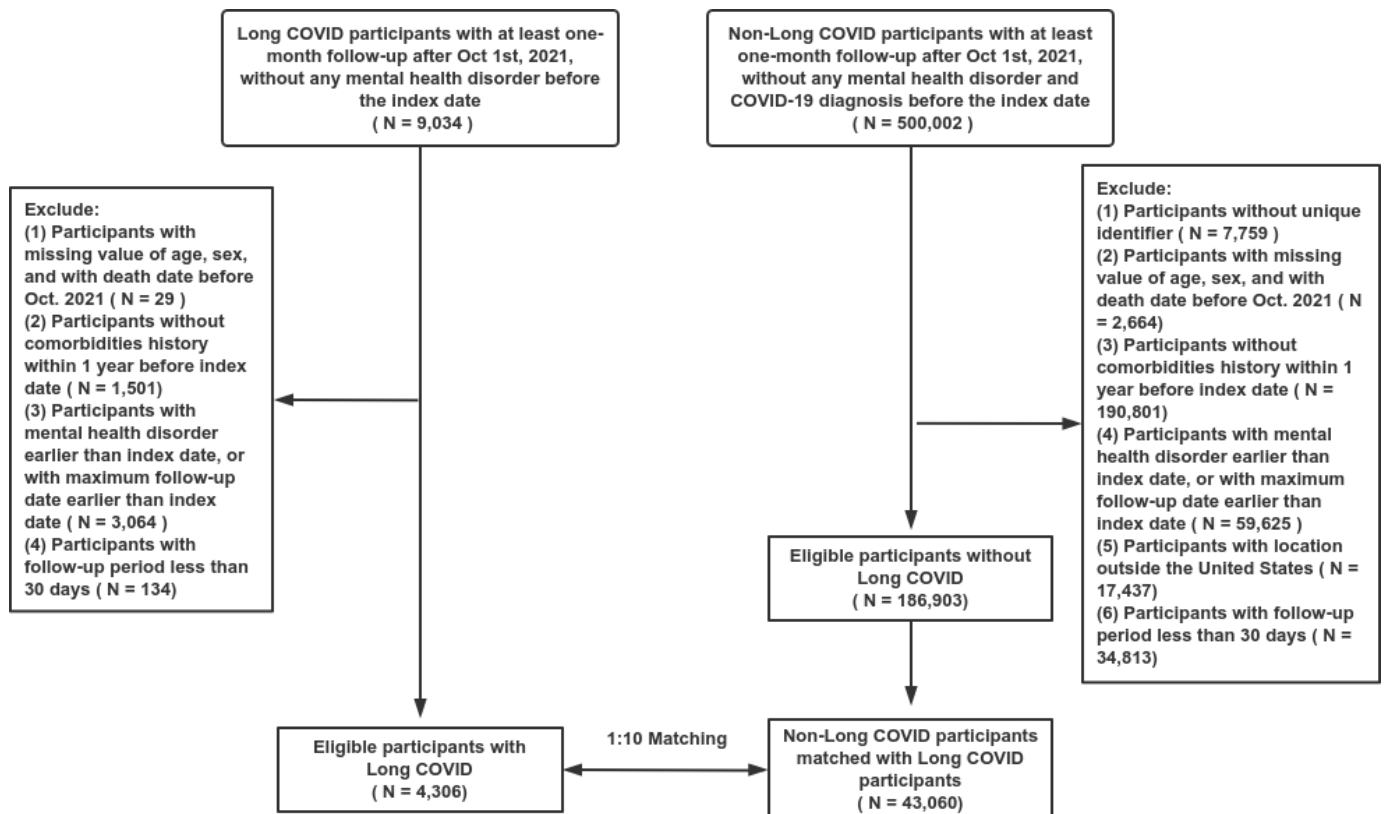


Figure 1 Long COVID and non-Long COVID participants inclusion from TriNetX datasets.

Standardised mean difference (SMD) was regarded as a measure to evaluate the matching results, and an SMD greater than 0.1 is a threshold recommended for declaring imbalance.¹⁸

We calculated the person-time of follow-up for each participant following the index date to the first occurrence of an outcome of interest (MHD), death date (if applicable) or the maximum follow-up date (the latest date recorded in diagnosis records, lab test results and medication records), whichever took place first. Long COVID status was deemed as the primary exposure. We conducted subgroup analyses by calculating the unadjusted incidence rates and corresponding 95% CI per 1000 person-years of (PY) follow-up for the two cohorts within each subgroup. Having confirmed no violations of the proportional hazards assumption (online supplemental figure 1), we initially applied a stratified Cox proportional hazards regression model adjusting for age and sex to calculate the HR and 95% CI. Subsequently, we implemented another stratified Cox proportional hazards regression model using a matching ID constructed from the propensity scores with the 4 demographic factors and 10 comorbidities, which provided an adjusted HR (aHR) and 95% CI. Secondary analyses were additionally performed using stratified Cox proportional hazards regression models, focusing specifically on different dimensions of MHD, including major depression, anxiety and other mental health conditions. In addition, we assessed the modification effects of baseline vaccination status, which was accomplished by examining

the significance of the interaction term between Long COVID status and vaccination within the confines of the stratified Cox proportional hazards regression model. Data were analysed in R software V.3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS Software V.9.4 (SAS Institute) using a two-tailed alpha level of 0.05.

RESULTS

The present analysis incorporated 43 060 non-Long COVID participants (mean (SD) age 54.43 (16.66) years; 58.3% female; 69.5% white) and 4306 Long COVID participants (mean (SD) age 54.62 (15.34) years; 58.2% female; 69.6% white). Prior to matching, imbalances in distribution were noted for patient regional location (SMD=0.265), baseline congestive heart failure status (SMD=0.131), baseline chronic pulmonary disease status (SMD=0.396) and baseline diabetes status (SMD=0.147). After the matching process, we observed balanced distributions across all covariates, with all SMDs falling below 0.1 (table 1).

The overall cumulative incidence rate of MHD was higher among those with Long COVID than those without Long COVID (figure 2). Similar results were observed when individual MHD diagnosis was examined as outcomes (figure 2). The overall unadjusted incidence rate of MHD was higher among participants with Long COVID (251.1 per 1000 PY) compared with those without Long COVID (99.5 per 1000-PY) (table 2). In the age-adjusted and

Table 1 Baseline characteristics before and after matching stratified with Long COVID status

Variables	Before matching			After 1:10 matching		
	Non-Long COVID n=186903	Long COVID n=4306	SMD	Non-Long COVID n=43060	Long COVID n=4306	SMD
Age (mean (SD))	55.22 (18.39)	54.62 (15.34)	0.036	54.43 (16.66)	54.62 (15.34)	0.012
Sex (male) (n (%))	77 742 (41.6)	1774 (41.2)	0.008	17 938 (41.7)	1774 (41.2)	0.009
Race (n (%))			0.084			0.013
Black or African American	24 815 (13.3)	511 (11.9)		5002 (11.6)	511 (11.9)	
Others	7888 (4.2)	137 (3.2)		1347 (3.1)	137 (3.2)	
Unknown	25 128 (13.4)	662 (15.4)		6786 (15.8)	662 (15.4)	
White	129 072 (69.1)	2996 (69.6)		29 925 (69.5)	2996 (69.6)	
Patient regional location (n (%))			0.265			0.017
Midwest	27 387 (14.7)	892 (20.7)		8955 (20.8)	892 (20.7)	
Northeast	64 765 (34.7)	1226 (28.5)		12 536 (29.1)	1226 (28.5)	
South	69 226 (37.0)	1362 (31.6)		13 409 (31.1)	1362 (31.6)	
Unknown	2215 (1.2)	26 (0.6)		240 (0.6)	26 (0.6)	
West	23 310 (12.5)	800 (18.6)		7920 (18.4)	800 (18.6)	
Baseline comorbidities (Yes)						
Myocardial infarction (n (%))	2045 (1.1)	102 (2.4)	0.098	837 (1.9)	102 (2.4)	0.029
Congestive heart failure (n (%))	5247 (2.8)	233 (5.4)	0.131	2033 (4.7)	233 (5.4)	0.031
Peripheral vascular disease (n (%))	4850 (2.6)	139 (3.2)	0.038	1157 (2.7)	139 (3.2)	0.032
Cerebrovascular disease (n (%))	4720 (2.5)	132 (3.1)	0.033	1142 (2.7)	132 (3.1)	0.025
Chronic pulmonary disease (n (%))	8965 (4.8)	727 (16.9)	0.396	7360 (17.1)	727 (16.9)	0.006
Rheumatoid disease (n (%))	2337 (1.3)	110 (2.6)	0.096	902 (2.1)	110 (2.6)	0.031
Mild liver disease (n (%))	3951 (2.1)	153 (3.6)	0.087	1324 (3.1)	153 (3.6)	0.027
Diabetes (n (%))	13 064 (7.0)	483 (11.2)	0.147	4635 (10.8)	483 (11.2)	0.014
Renal disease (n (%))	6538 (3.5)	235 (5.5)	0.095	2024 (4.7)	235 (5.5)	0.034
Cancer (any malignancy) (n (%))	9749 (5.2)	169 (3.9)	0.062	1523 (3.5)	169 (3.9)	0.020

An SMD greater than 0.1 is a threshold recommended for declaring imbalance.
SMD, standardised mean difference.

sex-adjusted stratified Cox model, Long COVID was associated with higher risk of incident MHD (aHR 2.53; 95% CI 2.32 to 2.75). Additional adjustment of the model with 4 demographic factors and 10 comorbidities did not dilute the association (aHR 2.60; 95% CI 2.37 to 2.85) (table 2).

In subgroup analyses, we observed a significant effect of Long COVID on major depression (aHR 3.36; 95% CI 2.82 to 4.00), generalised anxiety disorder (aHR 3.44; 95% CI 2.99 to 3.96), in the full adjusted stratified Cox regression models. Conversely, while the influence of Long COVID on other mental health conditions was statistically significant, the magnitude of the effect was smaller than the overall effects (aHR 1.31; 95% CI 1.08 to 1.60) (table 3). Baseline vaccination status did not modify the association between Long COVID and MHD (p value for interaction=0.96).

DISCUSSION

In the present analysis of real-world data using propensity score matching, survivors of COVID-19 with Long COVID

were more than twice as likely to develop mental health disorders. The impact was largest for major depressive disorders and generalised anxiety disorders. Our results are specifically applicable to the new incidence of MHD following a Long COVID diagnosis.

Compared with a previous retrospective cohort study conducted in the USA, our study demonstrated stronger effect estimates. Xie *et al* reported a moderately increased risk of depression (aHR 1.39; 95% CI 1.34 to 1.43) and anxiety disorders (aHR 1.35; 95% CI 1.30 to 1.39).⁹ The weakness of the prior study is the lack of generalisability due to the demographic composition of the cohort that were mostly older white men and the limited study time frame of nearly 30 days following acute COVID-19 illness, and yet there is a temporal dynamic nature of the epidemiology of mental health outcomes in the postacute phase of COVID-19. Moreover, our study extends these findings by concentrating not merely on COVID-19 infection, but specifically on the incidence of MHDs following a diagnosis of Long COVID.

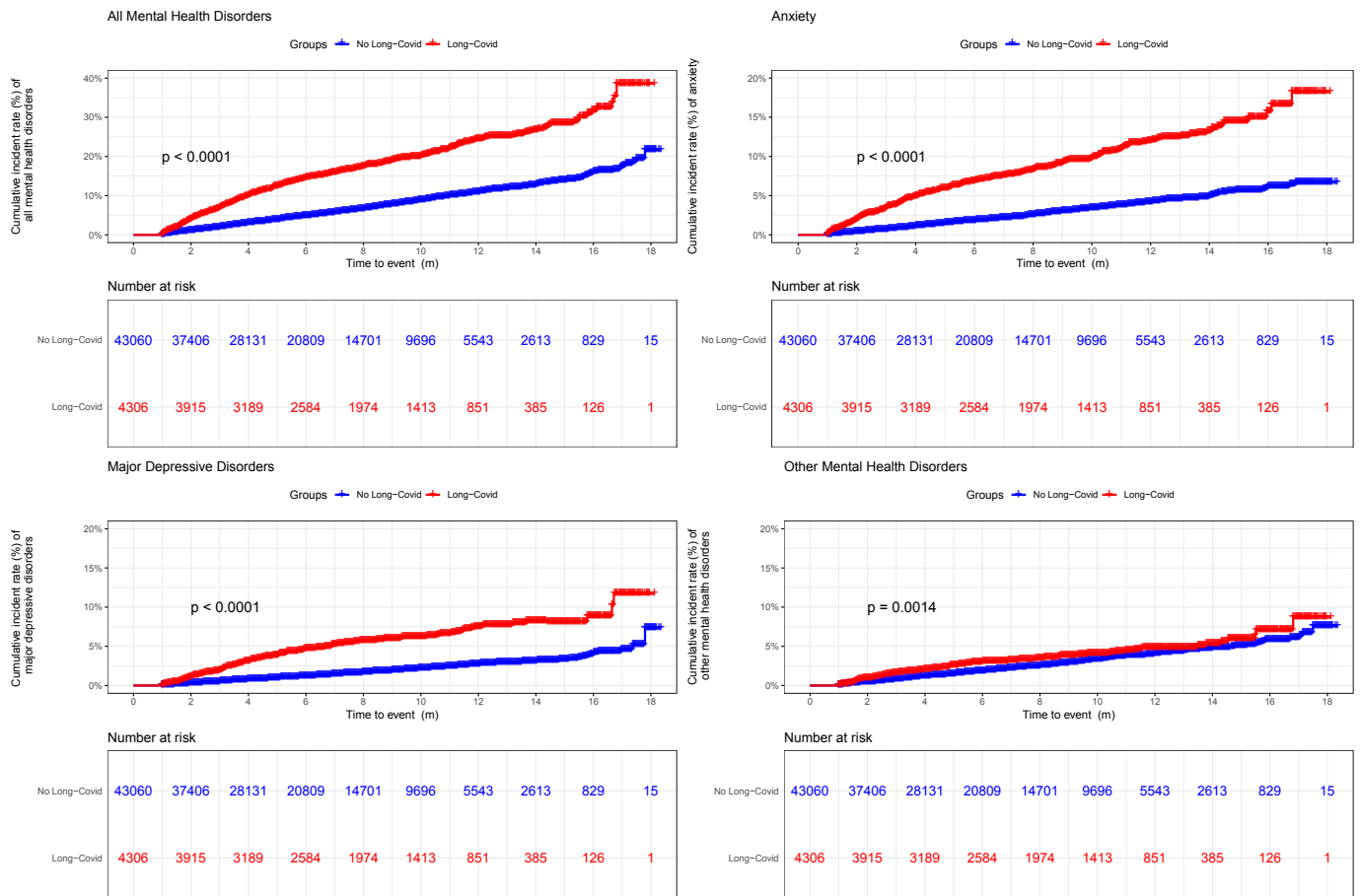


Figure 2 Cumulative incidence rates of total and categorised mental health disorders in patients with long COVID versus those without long COVID.

Our results are consistent with findings from studies conducted outside the USA. For instance, Murata *et al* observed an increased likelihood of mood, anxiety and psychotic disorders (OR 1.39; 95% CI 1.05 to 1.85) among 662 COVID-19 patients in Japan, observed from March 2020 to July 2021.¹⁹ Similarly, in Thailand, Phu *et al* reported that individuals experiencing Long COVID

symptoms were at a substantially higher risk of depression (OR 4.00) and anxiety (OR 6.93) in a study involving 939 hospitalised patients between January 2021 and May 2022.²⁰ The variation in increased risk may be attributable to differences in participant characteristics; for example, their cohorts were hospital based, whereas our study used general EHR data. Additionally, our approach involved survival analysis to account for time-to-event data and censoring, in contrast to these studies that employed logistic regression models for binary outcomes. In Europe, similar findings have been observed. A descriptive study in France reported a high incidence of cognitive impairment (61 out of 159 patients) among hospitalised COVID-19 patients, as well as a notable prevalence of depression (17 out of 94 patients) and anxiety (22 out of 94 patients) in individuals admitted to the ICU, with these observations made 4 months post-COVID-19.²¹ Additionally, a qualitative study conducted in Spain corroborates our findings. Samper-Pardo *et al* noted that patients with Long COVID reported diminished self-perceived well-being attributable to persistent symptoms. These patients expressed concerns such as anguish and anxiety about the future, fear of reinfection or relapse and apprehension regarding return to work. Notably, suicidal thoughts were also reported by several individuals in this cohort.²²

Table 2 Incidence rates and stratified Cox proportional hazard models HR (95% CI) for the association between Long COVID and mental health disorders

Variable	Non-Long COVID	Long COVID
Person-years, years	23586	2773
Mental health disorders cases, n	2347	695
Incidence rate, 95% CI per 1000 person-years*	99.5 (95.5 to 103.6)	251.1 (232.3 to 270.2)
Model 1	(Reference)	2.53 (2.32, 2.75)
Model 2	(Reference)	2.60 (2.37, 2.85)

Model 1: stratified by age categories (18–34, 35–44, 45–54, 55–64, 65+) and sex (men/women).

Model 2: stratified by fully propensity score matching ID.

*Unadjusted incidence rate per 1000-person-years.

**Table 3** Stratified Cox proportional hazard models HR (95% CI) for the association between Long COVID and four mental health disorders

	Non-Long COVID (n, %)	Long COVID (n, %)	HR (95% CI)*
Any mental health condition	2347 (100)	695 (100)	2.60 (2.37 to 2.85)
Major depression†	575 (24.5)	213 (30.6)	3.36 (2.82 to 4.00)
Anxiety‡	892 (38.0)	341 (49.1)	3.44 (2.99 to 3.96)
Other mental health condition§	880 (34.5)	141 (20.3)	1.31 (1.08 to 1.60)

*Stratified by full propensity score matching ID.
†Major depression (F32, F33).
‡Anxiety (F40–F48).
§Other mental health conditions (F10–F31, F34–F39, F49– F99).

We believe that our study represents a valuable contribution to the field and possesses the potential for global generalisability.

The pathophysiological of MHD among patients with Long COVID is not fully understood. However, there is emerging evidence of both direct and indirect effects of the virus on the brain and psychological outcomes respectively. Starting with the direct effect, the SARS-CoV-2 virus is neurotropic, indicating a direct invasion of the nervous system causing inflammation and gliosis.²³ These changes in the neuronal vascular coupling could lead to further breakdown in the blood–brain barrier, worsening the inflammatory cascade and the influx of inflammatory cells that cause injury to the neurons. Such a direct and neurotropic effect of the virus has been seen in human immunodeficiency virus (HIV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV).²⁴ Indirectly, the pandemic has been associated with psychological distress²⁵ due to increased isolation, increased rates of domestic violence,²⁶ disruption of social networks and unemployment,²⁷ all risk factors of MHD. However, much more research is needed to get a clear picture of how all of these variables may have contributed to MHD.

Moreover, patients with Long COVID often experience unique psychological distress. Fatigue is the leading symptom for Long COVID.²⁸ The persistent fatigue experienced in Long COVID can limit an individual's ability to engage in daily activities, leading to feelings of frustration, helplessness and even depression.²⁹ Additionally, cognitive impairments, commonly referred to as 'Brain Fog', are frequently observed. These impairments, which can include memory, concentration and decision-making difficulties, may significantly affect an individual's self-esteem and their capacity to work or study, potentially leading to anxiety and depressive symptoms.³⁰ Sleep disturbances were also commonly observed, with a reported prevalence of 34%–50% among patients with Long COVID.³¹ Issues with sleeping can further aggravate mental health problems, leading to a cycle of insomnia and increased psychological distress.³² Beyond physical symptoms, there is also a societal aspect to consider. Stigma and misunderstanding about Long COVID are prevalent, as evidenced by a qualitative study showing many participants encountering discrimination in healthcare settings.³² This lack of

understanding and the resultant stigma or dismissive attitudes can be particularly distressing for those suffering from Long COVID.³³ Finally, the unpredictable nature of Long COVID, including uncertainty about recovery, potential long-term impacts and possible effective treatments, can lead to significant anxiety and stress.³⁴

The findings of the current study have great public health and clinical implications. First, the stigma attached to MHD could hinder healthcare utilisation and thereby worsen the prognosing of the outcomes with a shift towards suicidality and homicidally. Next, given the disproportionality in lack of access to care in the marginalised communities including people of colour and the poor communities, and yet these are the same communities that were mostly affected by severe COVID-19, the burden of untreated mental health is likely to yield negative outcomes in such communities. For the healthcare providers, particularly primary healthcare providers, they should have a lower threshold to screen and treat MHDs in survivors of COVID-19. Furthermore, we anticipate an increase in the economic costs associated with MHD. In 2010, the global economic burden of mental disorders was estimated at US\$2.5 trillion.³⁵ Considering the extensive impact of the COVID-19 pandemic and the millions of survivors worldwide, it is reasonable to project a dramatic escalation in the costs attributed to MHD.

Study strengths and limitations

Strengths of our study include an analysis based on longitudinal data of a large sample of Long COVID individuals using most recently approved ICD-10 code and clean controls without any diagnosis of Long COVID or COVID-19 diagnoses or testing positive for SARS-CoV-2. To the best of our knowledge, this is the first large national-real-world analysis to examine the association between Long COVID and MHD using comprehensive propensity score matching approach. Nevertheless, our study has some limitations that should be addressed when interpreting the results. This is an observational study that used US TriNetX data, and therefore, causality cannot be inferred. We acknowledge that EHR databases can misclassify patients based on misreporting or underreporting of diagnoses codes or medications. Moreover, although we excluded any patients with Long COVID or

COVID-19 diagnoses or testing positive for SARS-CoV-2, some individuals in the control group might still have undetected mild or asymptomatic COVID-19 because they had not been tested. Such non-differential misclassification of the exposure may underestimate the strength of the association of COVID-19 with the onset of MHD. Lastly, we acknowledge the potential for information bias in the diagnosis of MHD for two key reasons: (1) There may be an underestimation of MHD prevalence due to limited access to healthcare services. This concern applies to both participants with Long COVID and those without, as constraints in healthcare access could lead to undiagnosed cases.³⁶ (2) Participants diagnosed with Long COVID are more likely to be identified with MHD. This is because they typically undergo more frequent follow-ups and screenings with healthcare professionals postdiagnosis, increasing the likelihood of MHD detection.³⁷

Conclusions

Using a large real-world, nationwide, propensity score matched cohort, we found that Long COVID was associated with an increased risk of new onset of MHD. The increase was independent of demographics, lifestyle factors and major chronic medical conditions. These findings reinforce the importance of integrating mental health screening and services in the treatment and management of Long COVID to prevent related chronic diseases, suicidal ideations, suicide attempts and deaths.

Contributors Designed research (project conception, development of overall research plan): YZ and DMB. Data extraction and study oversight: DMB. Analysed data: YZ, PS and DMB. Performed statistical analysis: YZ and DMB. Wrote the first draft of the manuscript: YZ, PS and DMB. Review and editing: YZ, VMC, PS and DMB. All authors have read and approved the final manuscript. YZ and DB is the guarantor and takes full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The protocol of this study was reviewed and received a determination of non-human subjects' research by the Penn State Institutional Review Board. The individual informed consent requirement was waived for this secondary analysis of deidentified data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are available from third-party partners 'TriNetX'.

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