Contents lists available at ScienceDirect

European Journal of Internal Medicine

Letter to the Editor

COVID-19 infection survivors and the risk of depression and anxiety symptoms: A nationwide study of adults in the United States

Dear Editors,

Recently, media reports and scientific publications have started highlighting the long-term sequalae of COVID-19 infections. A wide variety of persistent symptoms such as respiratory distress, cough and fever, loss of smell and taste, muscle and joint pain, fatigue and weakness have been reported in COVID-19 infection survivors [1,2]. Among the most common long-term complications reported are neuropsychiatric symptoms such as confusion and memory problems, difficulty concentrating, headaches, depression and anxiety [1–5]. One of the largest multinational studies to date, a retrospective assessment of health records of 236,379 COVID-19 survivors found the incidence of neuropsychiatric conditions 6 months post-infection to be 33.62% (with 12.84% receiving their first such diagnosis) [5]. Another systematic review with data available until March 2021 found that among COVID-19 infection survivors, almost a third were diagnosed with generalized anxiety disorders and nearly a fifth with depression [4]. In contrast, a systematic review of data till June 2021 reported that the prevalence of depression and anxiety among COVID-19 infected individuals could range from 0% to 30% across studies (despite the finding that depression and anxiety were the most commonly reported psychiatric problems) [3]. Several other studies highlighted the burden of depression and anxiety symptoms in COVID-19 survivors. However, most of the studies that have examined the neuropsychiatric sequelae of COVID-19 have been conducted with unique samples (e.g., data from healthcare facilities, individuals recruited when seeking treatment for COVID-19 or in follow-up care due to COVID-19 complications, patients of older age and higher comorbidity burden, military veterans, and COVID-19 patients mostly outside of the United States) [3–6]. Such samples have the potential for selection biases, limited generalizability, and may not help assess the true burden of psychological distress in COVID-19 survivors, especially when compared to those who were not infected. We conducted a population-based national assessment of the burden of psychological distress among COVID-19 infection survivors in the United States (U.S.)

A multi-component online questionnaire was deployed via Amazon mTurk and community networks throughout the U.S. using emails and social media sites in May 2021 after approval from the Institutional Review Board. After reading an informed consent form, individuals who were 18 years of age or older and resided in the U.S. could participate in the study. The first section of the survey asked participants about history of COVID-19 infection with response options 'yes' vs. 'no' for infection history. To assess psychological distress in the study population, the valid and reliable Patient Health Questionnaire-4 (PHQ-4) tool was used to assess clinical levels of depression (PHQ-2), anxiety (GAD-2), and moderate to severe psychological distress symptoms (i.e., symptoms of both depression and anxiety) [7]. Cronbach alphas for scales were computed from the final sample of respondents in this study, and the internal consistency reliability was found to be acceptable for PHQ-2 (alpha=0.69), GAD-2 (alpha=0.72), and PHQ-4 (alpha=0.81). The final section of the study questionnaire asked participants about their sociodemographic information.

A total of 3,633 participants responded to the questionnaire and were predominantly White (61%), males (61%), married (63%), working full time (79%), urban dwellers (57%), and with a bachelor's degree or higher (65%) (Table 1). Almost a quarter of the participants reported a history of COVID-19 infection (23%) and more than a third had symptoms of depression (47%), anxiety (40%), or both depression and anxiety (38%). Those who had symptoms of depression were statistically significantly more likely to be Hispanics (58%), White (52%), aged 18–25 years (50%), married (50%) or divorced/separated (46%), living in rural areas (56%), earning $30,001-$60,000 annually (53%), and had a history of COVID-19 infection (64%). Symptoms of anxiety were significantly more likely to be reported by Whites (46%), Hispanics (45%), aged 18–25 years (43%), married (42%), living in rural areas (49%), earning $30,001-$60,000 per year (45%), and those had a history of COVID-19 infection (63%). Similarly, psychological distress (i.e., symptoms of both depression and anxiety) were more likely to be reported by Whites, Hispanics, younger (18–25-year-old), married, earning $30,001-$60,000 per year, living in rural areas, or those with a history of COVID-19 infection (60%) (Table 1).

Logistic regression analyses were conducted to assess the probability of depression and anxiety symptoms in those with a history of COVID-19 infections (those without a history of COVID-19 infection were treated

Table 1
Sociodemographic characteristics of study participants and those with psychological distress.

Variable	Total N (%)	Depression Symptoms N (%)	Anxiety Symptoms N (%)	Psychological Distress N (%)
All Participants	3633 (100)	1728(47)	1458(40)	1400(38)
Sex				
Male	2232 (61)	1086(49)	918(41)	886(40)
Female	1401 (39)	642(46)	540(39)	514(37)
Race/Ethnicity				
White	2211 (61)	1140(52)*	1009(46)*	995(45)*
African-Americans	568 (16)	243(43)	196(35)	182(32)
Asian	251(7)	86(34)	77(31)	67(27)
Multiracial	272(8)	111(41)	51(19)	43(16)
Other race	331(9)	148(45)	125(38)	113(34)
Hispanic	1573 (43)	899(58)	699(45)	676(43)
Age Group				
18-25 years	542 (15)	273(50)*	234(43)*	229(42)*
26-35 years	1818 (50)	864(48)	718(40)	687(38)
36-45 years	769 (21)	374(49)	313(41)	296(39)
46-59 years	352 (10)	165(47)	149(42)	141(40)
≥ 60 years	152(4)	52(34)	44(29)	47(31)
Marital Status				
Single/ never married	932 (26)	402(43)*	352(38)*	337(36)*
Married	2270 (63)	1134(50)	954(42)	922(41)
Engaged/ living with a partner	220(6)	98(45)	78(36)	75(34)
Divorced/ separated	165(5)	75(46)	57(35)	51(31)
Other (e.g. widowed)	46(1)	19(41)	17(37)	15(33)
Education				
High school or less	321(9)	121(38)*	113(35)*	109(34)*
Some college experience	934 (26)	378(41)	314(34)	286(31)
Bachelor's degree	1837 (50)	966(53)	800(44)	773(42)
≥Master's degree	541 (15)	263(49)	231(43)	232(43)
Current Employment Status				
Full-time	2864 (79)	1389(49)*	1200(42)*	1172(41)
Part-time	563 (16)	268(48)	194(35)	176(31)
Not employed	206(6)	71(35)	64(31)	52(25)
Annual Household Income				
0-$30,000	404 (11)	172(43)*	174(43)*	169(42)
$30,001-$60,000	1643 (45)	876(53)	744(45)	703(43)
$60,001-$99,999	1265 (35)	572(45)	443(35)	432(34)
≥$100,000	321(9)	108(34)	97(30)	96(30)
Area of Residence				
Rural	784 (22)	440(56)*	388(49)*	362(46)*
Urban		1011(49)	837(41)	809(39)

Table 1 (*continued*)

Variable	Total N (%)	Depression Symptoms N (%)	Anxiety Symptoms N (%)	Psychological Distress N (%)
	2051 (57)			
Suburban	798 (21)	277(35)	233(29)	229(29)
History of COVID-19 infection				
Yes	836 (23)	530(64)*	530(63)*	501(60)*
No	2797 (77)	1198(43)	928(33)	899(32)

* Indicates *p*<0.05. N(%) Indicates frequencies and percentages.

as the reference category) (Table 2). In unadjusted analyses, COVID-19 infection survivors were significantly more likely to have moderate or severe psychological distress (OR= 3.16; 95%Ci=2.70–3.71) and more specifically, symptoms of either depression (OR=2.31; 95% Ci=1.97–2.72) or anxiety (OR=3.49, 95% Ci=2.97–4.10). In the final regression model, we adjusted for eight sociodemographic characteristics (from Table 1) and found that those who had survived a COVID-19 infection were about two and a half times (AOR=2.58) more likely to have moderate to severe psychological distress, almost three times more likely to report anxiety symptoms (AOR=2.93), and almost twice as likely to report symptoms of depression (AOR=1.83), compared to those who did not have a COVID-19 infection.

In this national assessment of U.S. adults, we found that compared to those without a history of COVID-19 infection, those who had been infected with COVID-19 were more likely to report anxiety, depression, or symptoms of both. Anxiety was the most significant difference of mental health sequalae reported among COVID-19 infection survivors. While these findings confirm the evidence from clinical studies, the pathways for development of psychological distress in COVID-19 infection survivors remain a subject of ongoing investigation [3,4,6]. Clinicians and scholars have speculated on the etiology of psychological distress in COVID-19 infection survivors and a variety of mechanisms have been proposed, including, but not limited to neurobiological changes due to the pathophysiology of the disease, psychological impact of infection, and socioeconomic factors [6,8,9]. For example, COVID-19 infections might have mental health consequences since both the highly contagious coronaviruses SARS (Severe Acute Respiratory Syndrome coronavirus) and MERS (Middle East Respiratory Syndrome) had been found to increase post-illness anxiety and depressed mood [2]. Recent studies also suggest that structural brain abnormalities could be seen in

Table 2
Regression analyses to predict psychological distress based on COVID-19 infection history.

Outcome	Not Infected Reference	COVID-19 Infection Survivors	
		Model 1 OR (95%CI)	Model 2 AOR (95%CI)
Depression	1	2.31(1.97–2.72)*	1.83(1.54–2.16)*
Anxiety	1	3.49(2.97–4.10)*	2.93(2.47–3.46)*
Moderate to Severe Psychological Distress	1	3.16(2.70–3.71)*	2.58(2.18–3.05)*

* Indicates *p*<0.05. OR= odds ratios, AOR=adjusted odds ratios, 95%CI= confidence intervals. The binary outcomes were depression, anxiety, and moderate to severe psychological distress (yes vs. no). The predictor variable was COVID-19 infection (yes. vs. no). Not infected served as the comparison group (Ref, OR=1). Model 1 illustrates unadjusted regression analysis to predict psychological outcomes. Model 2 shows multiple regression analysis after adjusting for all the sociodemographic characteristics (*n* = 8) from Table 1.

more than a quarter of all COVID-19 patients [3]. Systemic inflammation and biomarker abnormalities related to infection severity have also been linked with neuropsychiatric problems in COVID-19 infection survivors. Additional factors have also been proposed that could cause psychological distress among COVID-19 infection survivors such as fear of infecting family members, cost of care and not knowing outcome of illness, home confinement and quarantining, economic hardships and job loss due to disease, and other health complications occurring with COVID-19 infections that can deteriorate mental health [6,9,10].

Given the findings from this study and existing evidence, the etiology and causal pathways of psychological distress in COVID-19 infection survivors appear to be complex and multifactorial. For example, many groups in the U.S. who were more likely to have depression and anxiety before the pandemic were also more likely to have COVID-19 infections and higher rates of depression and anxiety during the pandemic. Also, a very large and rigorous recent study proposes a bidirectional relationship between COVID-19 infections and mental illnesses [7–9]. Based on these reports and findings from our study, it can be assumed that there could be three broader etiological factors for high rates of psychological distress in COVID-19 infection survivors- neurobiological and pathophysiologic changes related to infection, psychosocial stressors associated with getting infected, and pre-existing mental illness and sociodemographic factors making individuals more vulnerable to COVID-19 infections and subsequent post-infection sequelae such as depression and anxiety [8–10]. If so, our findings have major implications for clinical practice (e.g., comprehensive clinical evaluation and psychiatric consultation for all COVID-19 patients, and appropriate pharmacotherapy or psychotherapy for COVID-19 infection survivors). Further research is warranted in community-based samples to assess longitudinal trends of psychological distress in individuals with and without prior psychological distress to understand the phenotypes of survivors, duration of psychological distress, and other long-term consequences among COVID-19 infection survivors [7–10].

The results of this national assessment are subject to potential limitations. First, this was a cross-sectional and observational study with all traditional limitations of a survey design (e.g., self-reported information, socially desirable responses, recall bias, etc.) which could limit the validity of the findings. Second, the exact history and timing of COVID-19 infections was not ascertained and the type of clinical or psychiatric care received (if any) by those who had the infection was not assessed. Third, while this study involved a large national sample of adult Americans, it is limited to predominantly younger individuals with high education and familiarity with online surveys which could limit the external validity of the findings. Despite these limitations, this is one of the largest population-based studies from the U.S. to have a high representation of racial and ethnic minorities and those who had COVID-19 infections. The sample resembles the U.S. adult population in several ways (e.g., majority of the participants were White, employed full-time, and lived in urban or suburban areas). Finally, the assessment of depression and anxiety symptoms within the past 2 weeks was done by a clinical screening measure indicating current depression and anxiety in the study population to compare these mental health measures between COVID-19 infection survivors versus those who did not have an infection history.

Declaration of Competing Interests

The authors have no conflicts of interests to declare.

References

[1] Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 2021;4(5):e2111417–8.
[2] Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, David AS. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020;7(7):611–27.
[3] Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19–a systematic review. Brain Behav Immun 2021;97:328–48.
[4] Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, Chinchilli VM. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. JAMA Netw Open 2021;4(10):e2128568–9.
[5] Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021;8(5):416–27.
[6] Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594(7862):259–64.
[7] Khubchandani J, Sharma S, Webb FJ, Wiblishauser MJ, Bowman SL. Post-lockdown depression and anxiety in the USA during the COVID-19 pandemic. J Public Health 2021;43(2):246–53.
[8] Stein, M.B., (2021). COVID-19: psychiatric illness. Available at: https://www.uptodate.com/contents/covid-19-psychiatric-illness.
[9] Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021;8(2):130–40.
[10] Kyzar EJ, Purpura LJ, Shah J, Cantos A, Nordvig AS, Yin MT. Anxiety, depression, insomnia, and trauma-related symptoms following COVID-19 infection at long-term follow-up. Brain Behav Immun-Health 2021;16:100315.

Jagdish Khubchandani[a,*], James H. Price[b], Sushil Sharma[c], Michael J. Wiblishauser[d], Fern J. Webb[e]

[a] *Public Health New Mexico State University, Las Cruces, NM 88003, USA*
[b] *Public Health University of Toledo, Toledo, OH 43606, USA*
[c] *Texas A&M University, Texarkana, TX 75503, USA*
[d] *University of Houston-Victoria, Victoria, TX 77901, USA*
[e] *University of Florida College of Medicine, Jacksonville, FL 32209, USA*

[*] Corresponding author.
E-mail address: jagdish@nmsu.edu (J. Khubchandani).