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The Association Between Depression, Anxiety and COVID-19 Symptoms

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Abstract

Background: The variation of COVID-19 illness is not fully understood. There is a need for further identification of predictors for COVID-19-related health outcomes, which may improve the delivery of healthcare. The primary objective was to identify whether anxiety/depression symptoms are associated with the number of COVID-19 symptoms. The second objective was to examine differences in anxiety and depression symptoms between individuals with or without COVID-19 symptoms.

Methods: 782 Virginians ages 18 to 87 years, enrolled from March to May 2021 and were followed-up for six months. Vibrent Health online platform was used to collect data. PHQ-9, GAD-7, and CDC's COVID-19 tracing form, were used to assess depression, anxiety, and COVID-19 symptoms, respectively. An MMRM test was used to examine whether anxiety and depression symptoms were associated with the number of COVID-19 symptoms. Age, race, sex, medical diagnoses, and COVID-19 related economic/social hardships were included as covariates. Mann-Whitney U tests were used to assess differences in anxiety/depression at all study time points. We conducted analyses using SAS 9.4, *p*-values < .05 were considered significant.

Results: Depression/anxiety symptoms, COVID-19 related economic/social hardships, and medical diagnoses, were significantly associated with the number of COVID-19 symptoms ($p<.05$), whereas age, sex, and race were not ($p>.05$). Overall, PHQ9 and GAD7 scores were consistently and significantly higher for individuals with COVID-19 symptoms than those without COVID-19 symptoms ($p<.05$).

Conclusions: The severity of depression and anxiety symptoms is linked to symptoms of COVID-19 over time. Physical and mental health integrated healthcare approaches may be necessary. Further investigation into causative mechanisms is needed.

Introduction

Individuals with COVID-19 who have medical comorbidities[1-5], older age[1,4,5], or are from low socioeconomic status[1-4], are at increased risk of experiencing COVID-19 related adverse health effects. Poverty is a risk factor for developing hypertension, cardiovascular disease, obesity, and hypertension[1,2]. These medical conditions are also risk factors for contracting COVID-19[1,2,4,6,7]. Although there are predictors for COVID-19- related health outcomes, accurate prognostication is not possible[8]. The presentation of symptoms for acute COVID-19 or subsequent Long COVID varies from person to person[9], regardless of hospitalization status[10-12], SARS-CoV-2 variant type[11], or COVID-19 vaccination status[13].

Although some common symptoms for individuals with COVID-19 include fever, reduced general condition, dyspnea, and cough, COVID-19 shows significant variation. Individuals with COVID-19 could be asymptomatic, experience mild cold symptoms, develop Long COVID (defined as signs and symptoms for COVID-19, which persist more than four weeks from the onset of infection and result in an emerging health condition[14]), or have acute respiratory distress syndrome and death[8,15]. For example, among hospitalized patients, one study reported 14% of patients had atypical chest pain and 25% had symptoms of brain fog. Tissue abnormalities were noted in the lungs (60%), kidneys (29%), heart (26%), and liver (10%). Interestingly, younger age did not protect against Long-COVID[9].

There is a need for identification of other confounding predictors for COVID-19- related health outcomes to improve the coordination of necessary delivery of healthcare services. There is growing evidence that poor psychological health may be linked to biological processes and behaviors, which cause and exacerbate disease[16]. Previous findings suggest mental health and physical health are interconnected[16-19] by neural systems that jointly regulate somatic physiology and complex mental abilities[18]. People with mental illness are at higher risk for developing physical illness. For example, people with psychosis are more likely to smoke, have poor oral health, have cardiovascular risk factors, and increased risks of osteoporosis and sexual dysfunction. The increase in life expectancy in developed countries has not benefited people with psychosis, they are more likely to die 18 years earlier compared to the general population[17]. Conversely, individuals with chronic medical conditions such as diabetes, cardiovascular disease, and cancer, are at risk of developing mental illness. For example, individuals with diabetes are more likely to experience depression, anxiety, eating disorders, and cognitive impairments. When diabetes and eating disorder are comorbid, the mortality rate is seven times higher than the general population, and three times higher than individuals who have either diabetes or eating disorder alone[17].

We hypothesized the severity of anxiety and depression symptoms may be associated with COVID-19 symptoms. We also hypothesized that social and economic hardships related to the COVID-19 pandemic, age, race, sex, and having diagnosed medical conditions, could confound how COVID-19 illness is experienced. This longitudinal study aims to 1) identify whether anxiety and depression symptoms are associated with the number of COVID-19 symptoms experienced in a longitudinal model, and 2) examine differences in anxiety and depression symptoms between individuals with or without COVID-19 symptoms at baseline and follow-ups one through six. Findings may inform the best healthcare delivery practices for COVID-19 patients with anxiety and/or depression. Integrated healthcare approaches such as disease management programs, coordination between services, integrated care team, and integrated care management, have been proposed as means to reduce healthcare costs and improve health outcomes for multimorbidity[20]. An integrated healthcare approach addressing COVID-19 with comorbid mental illness may result in improved clinical effectiveness and may reduce the burden of COVID-19 short- and long-term healthcare costs.

Methods

COVIDsmart Study

The statewide COVIDsmart Study is a digital study designed to evaluate the economic, social, clinical, and behavioral impacts of COVID-19 on Virginians and their communities. This study is a partnership between the Eastern Virginia Medical School (EVMS) - Sentara Healthcare Analytics and Delivery Science Institute (HADSI), George Mason University (GMU), and Vibrent Health Inc[21].

Recruitment Strategies

A detailed methodology of COVIDsmart has been published previously[21]. Briefly, participants were recruited via online articles, employer e-newsletters, purchased email lists targeting racial/ethnic minorities, social media (e.g., Facebook, Instagram, and LinkedIn), television, and paper/digital flyers shared with multiple hospitals, churches, and other community organizations[21].

Data Collection

The COVIDsmart study used an online data collection platform designed by Vibrent Health Inc. This platform was compliant with the Health Insurance Portability and Accountability Act. It required an Internet connection but no other software was required[22]. A total of 782 residents of Virginia, ages 18 to 87 years, enrolled from March to May 2021 with six months follow-up of study participants. The COVIDsmart study collected clinical, social, economic, and behavioral data. This study included participants who completed demographic information and the mood modules containing the Patient Health Questionnaire-9 (PHQ9) and the Generalized Anxiety Disorder-7 (GAD7). The PHQ9[23] and GAD7[24] are valid and reliable instruments to measure symptoms of depression and anxiety, respectively. Demographic and medical history data were collected at baseline. PHQ9 and GAD7 scores, COVID-19 symptoms, and social/economic hardship variables were collected at baseline and monthly follow-ups one through six.

The survey question for COVID-19 symptoms was adapted from the 2020 Center for Disease Control and

Prevention (CDC)'s COVID-19 contact tracing form[25]. Symptoms listed included abdominal pain, chest pain, chills, cough (worse than usual), diarrhea, fatigue/general malaise, feeling feverish (not measured), fever (measured with a temperature ≥ 100.0 degrees F), headache, loss of appetite, loss of taste or smell, muscle/ joint aches or pains (worse than usual), nausea or vomiting, runny nose or extra mucus from the nose, scratchy or sore throat, shortness of breath or difficulty breathing/wheezing, or other symptoms.

Social and economic hardships were COVID-19 related negative experiences such as losing a job, inability to buy groceries, inability to visit family members at higher risk for infection, and other undesirable experiences caused by the pandemic. The survey questions to obtain the COVID-19 related economic and social hardships were created by an expert panel from GMU and EVMS, including an epidemiologist, a sociologist, a psychologist, a health services researcher, a cardiologist, and a pulmonologist. Survey questions were published by Bartholmae et al. 2022[21].

Research Ethics Approval

This COVIDsmart study received an expedited review and was approved by Eastern Virginia Medical School's Institutional Review Board (IRB), an independent regulatory body established to protect human research subjects (IRB# 20-07-EX-0138-OTHER).

Statistical Analysis

Descriptive statistics were used to analyze the demographics of COVIDsmart participants. To examine the relationship between anxiety symptom severity, depression symptom severity, and the number of COVID-19 symptoms, a Mixed Methods Repeated Measures (MMRM) test was used. MMRM is a robust statistical procedure widely known in the literature as the most efficient statistical analysis to address the bias from missing data[26-30]. In this model, the dependent variable was the number of symptoms reported, the independent variables were PHQ9 and GAD7 scores, and the covariate variables were age, race, sex, number of medical diagnoses, and the number of COVID-19 related social and economic hardships. These covariate variables were selected as low socioeconomic status[1-4], older age[1,4,5], being a racial/ethnic minority[1-4], being a male[5], and having medical comorbidities[1-5], are risk factors for COVID-19. The MMRM test was followed by a series of Mann-Whitney U tests to examine whether PHQ-9 and GAD-7 scores differed significantly between participants who reported one or more COVID-19 symptoms compared to participants who did not report any COVID-19 symptoms at baseline and follow-ups one through six. The number of social and economic hardships were included in the Mann Whitney U tests as they were a significant longitudinal covariate based on MMRM analysis. We conducted the analysis using SAS 9.4, and p values < .05 were considered significant.

Results

At baseline, the majority of participants were non-Hispanic White (89.3%) and female (78.14%). Mean values with respective standard deviations were as follows: age - 50 years (SD = 14.52), PHQ9 - 6.04 (SD = 5.67), GAD7 - 4.82 (SD = 5.08), and COVID-19 related hardships - 2.71 (SD = 1.81). The percent of participants remaining in the study from baseline were 66.37%, 53.66%, 44.54%, 37.22%, 35.28%, and 31.69% for follow-ups 1 through 6, respectively. Demographics for follow-ups 1 through 6 are in Tables 1 and 2.

Table 1: Descriptive Statistics for Categorical Variables for Each Study Time Point

Time Point	Categorical Variables	*n* (%)
Baseline	Sex	
	Female	522 (78.14%)
	Male	146 (21.86%)
	Race	
	White	593 (89.31%)
	Black	44 (6.63%)
	Other	23 (3.45%)
	Prefer not to say	4 (0.60%)
Follow-Up 1	Sex	
	Female	351 (79.23%)
	Male	92 (20.77%)
	Race	
	White	398 (90.25%)
	Black	23 (5.22%)
	Other	17 (3.86%)
	Prefer not to say	3 (0.68%)
Follow-Up 2	Sex	
	Female	281 (78.27%)
	Male	78 (21.73%)
	Race	
	White	318 (89.33%)
	Black	20 (5.62%)
	Other	15 (4.21%)
	Prefer not to say	3 (0.84%)
Follow-Up 3	Sex	
	Female	235 (78.86%)
	Male	63 (21.14%)
	Race	
	White	265 (89.83%)
	Black	16 (5.42%)
	Other	11 (3.73%)
	Prefer not to say	3 (1.02%)
Follow-Up 4	Sex	
	Female	194 (77.91%)
	Male	55 (22.09%)
	Race	
	White	224 (91.06%)

	Black	13 (5.28%)
	Other	7 (2.85%)
	Prefer not to say	2 (0.81%)
Follow-Up 5	Sex	
	Female	183 (77.54%)
	Male	53 (22.46%)
	Race	
	White	210 (90.13%)
	Black	13 (5.58%)
	Other	8 (3.44%)
	Prefer not to say	2 (0.86%)
Follow-Up 6	Sex	
	Female	164 (77.36%)
	Male	48 (22.64%)
	Race	
	White	190 (90.91%)
	Black	10 (4.78%)
	Other	7 (3.36%)
	Prefer not to say	2 (0.96%)

Longitudinal data collected on the study participants over the course of six months demonstrated that the number of COVID-19 symptoms was associated with increased levels of depression symptoms (F=22.70, p<.0001), anxiety symptoms (F= 4.04, p = 0.045), and COVID-19 related economic/social hardships (F= 26.21, p<.0001). Having a diagnosed medical condition significantly confounded this result (F= 19.47, p<.0001). Age (F=0.19, p = 0.663), sex (F=0.29, p = 0.590), and race (F=0.94, p=0.490) were not associated with the number of COVID-19 symptoms experienced.

Figures 1 through 7 display differences in PHQ-9, GAD-7, and COVID-19-related social and economic hardships among participants with COVID-19 symptoms versus participants without COVID-19 symptoms. At every time point (baseline and follow-ups 1 through 6), PHQ9 scores were consistently and significantly higher for participants experiencing COVID-19 symptoms compared to participants without COVID-19 symptoms (p<.05). When

Table 2: Descriptive Statistics for Continuous Variables for Each Study Time Point

Time Point	Continuous Variables	N	Min	Max	μ ± SD	Skewness	Kurtosis
Baseline	Age	667	18	87	50.61 (14.52)	0.008	-0.821
	PHQ9	669	0	26	6.04 (5.67)	1.184	0.882
	GAD7	664	0	21	4.82 (5.08)	1.242	0.913
	COVID-related hardships	670	0	11	2.71 (1.81)	1.037	1.145
Follow-Up 1	Age	442	20	87	50.82 (14.99)	0.047	-0.845
	PHQ9	445	0	23	4.85 (5.06)	1.421	2.01
	GAD7	444	0	21	4.23 (4.64)	1.377	1.412
	COVID-related hardships	445	0	8	1.35 (1.00)	3.013	13.006
Follow-Up 2	Age	358	20	87	51.89 (15.33)	-0.039	-0.903
	PHQ9	359	0	24	4.48 (4.91)	1.565	2.661
	GAD7	355	0	21	3.85 (4.47)	1.592	2.639
	COVID-related hardships	360	0	7	1.18 (0.75)	3.240	16.156
Follow-Up 3	Age	297	20	87	53.22 (15.03)	-0.194	-0.936
	PHQ9	298	0	26	4.24 (4.91)	1.694	3.462
	GAD7	296	0	21	3.68 (4.54)	1.790	3.299
	COVID-related hardships	298	0	6	1.11 (0.50)	4.842	35.142
Follow-Up 4	Age	248	20	83	54.83 (14.75)	-0.325	-0.837
	PHQ9	249	0	27	4.41 (5.16)	1.810	3.808
	GAD7	247	0	21	3.71 (4.46)	1.611	2.662
	COVID-related hardships	249	0	5	1.14 (0.62)	3.351	13.941
Follow-Up 5	Age	235	22	83	55.46 (14.69)	-0.331	-0.834
	PHQ9	236	0	26	4.22 (4.87)	1.800	3.949
	GAD7	236	0	21	3.71 (4.42)	1.720	3.154
	COVID-related hardships	236	0	4	1.05 (0.50)	2.171	10.389
Follow-Up 6	Age	212	22	83	64.89 (12.16)	-0.362	-0.864
	PHQ9	212	0	27	4.27 (5.11)	1.886	4.345
	GAD7	209	0	21	3.96 (5.06)	1.741	2.702
	COVID-related hardships	212	0	4	1.13 (0.51)	3.588	15.656

[a]At baseline, three participants reported having previously diagnosed anxiety and depression.

breaking down the PHQ-9 by question, scores remained higher for participants with COVID-19 symptoms compared to participants without COVID-19 symptoms across all PHQ-9 questions and across all study time points (Table 3). GAD7 scores were consistently higher for participants with COVID-19 symptoms than for participants without COVID-19 symptoms (Table 4). Differences in GAD7 between the two groups were significant at baseline, follow-ups one through four, and follow-up six ($p<.05$) but not for follow-up five ($p>.05$). Except for follow-up three, the COVID-19 related economic/social hardships were higher for participants with COVID-19 symptoms. However, statistical significance between the two groups was only achieved at baseline and follow up one ($p<.05$). Overall, the severity of PHQ-9 and GAD-7 was higher for participants with COVID-19 symptoms compared to participants without COVID-19 symptoms.

Table 3: PHQ-9 Severity Groups Comparison between Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms

	PHQ-9 (With COVID-19 Symptoms)			PHQ-9 (No COVID-19 Symptoms)		
	Severe	Moderately Severe	Moderate	Severe	Moderately Severe	Moderate
Baseline	8.72% (13/149)	14.76% (22/149)	16.78% (25/149)	2.30% (12/521)	4.80% (25/521)	8.45% (44/521)
FU1	6.82% (6/88)	10.23% (9/88)	17.05% (15/88)	1.40% (5/357)	2.24% (8/357)	7.5% (27/357)
FU2	5.88% (3/5)	9.80% (5/5)	5.88% (3/5)	0.65% (2/310)	2.26% (7/310)	8.71% (27/310)
FU3	2.63% (1/38)	7.89% (3/38)	21.05% (8/38)	1.5% (4/260)	1.5% (4/260)	7.69% (20/260)
FU4	2.70% (1/37)	2.70% (1/37)	10.81% (4/37)	2.35% (5/212)	3.30% (7/212)	5.66% (12/212)
FU5	3.7% (1/27%)	0% (0/0)	18.52% (5/27)	2.87% (6/209)	0.96% (2/209)	6.22% (13/209)
FU6	5.88% (2/34)	0% (0/0)	8.82% (3/34)	1.69% (3/178)	2.25% (4/178)	8.43% (15/178)

Table 4: GAD-7 Severity Groups: Comparison between Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms

	GAD-7 (With COVID-19 Symptoms)		GAD-7 (No COVID-19 Symptoms)	
	Severe	Moderate	Severe	Moderate
Baseline	19.46% (29/149)	14.09% (21/149)	3.45% (18/521)	8.83% (46/521)
FU1	7.95% (7/88)	20.45% (18/88)	3.98% (13/327)	6.44% (23/357)
FU2	7.84 % (4/51)	11.76% (6/51)	2.58% (8/310)	6.77% (21/310)
FU3	13.16% (5/38)	7.89% (3/38)	2.69% (7/260)	5.77% (15/260)
FU4	5.40% (2/37)	16.21% (6/37)	2.36% (5/212)	6.60% (14/212)
FU5	7.40% (2/27)	3.70% (1/27)	2.87% (6/209)	6.70% (14/209)
FU6	8.82% (3/34)	8.82% (3/34%)	5.62% (10/178)	5.62% (10/178)

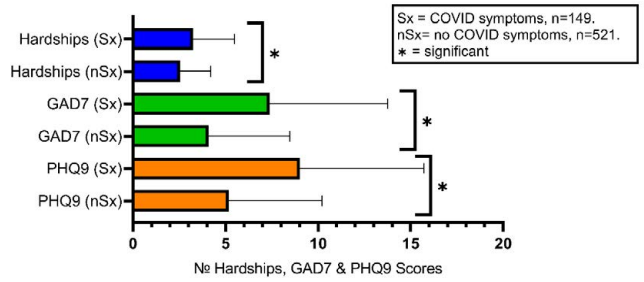

Figure 1. Baseline: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

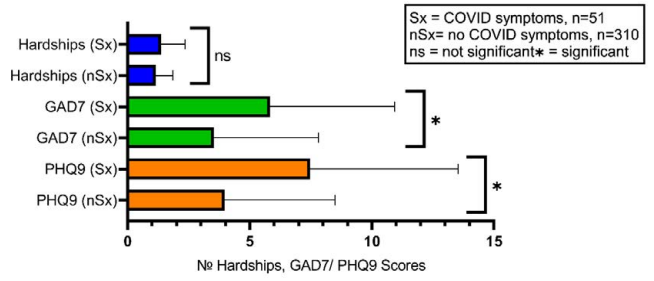

Figure 3. Follow-up #2: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

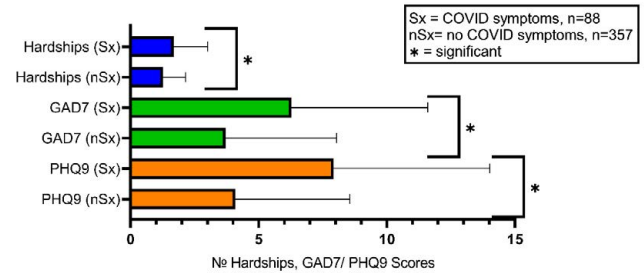

Figure 2. Follow-up #1: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

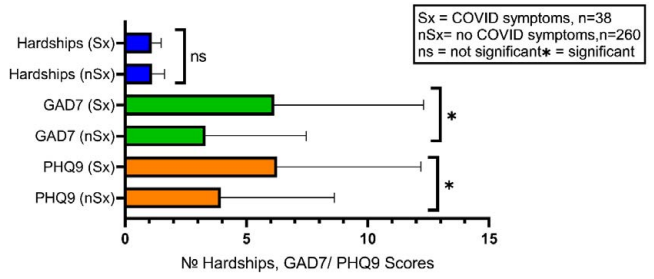

Figure 4. Follow-up #3: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

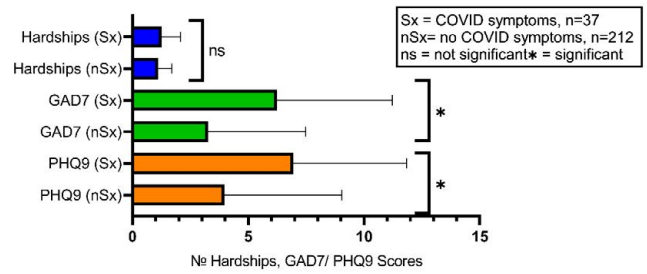

Figure 5. Follow-up #4: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

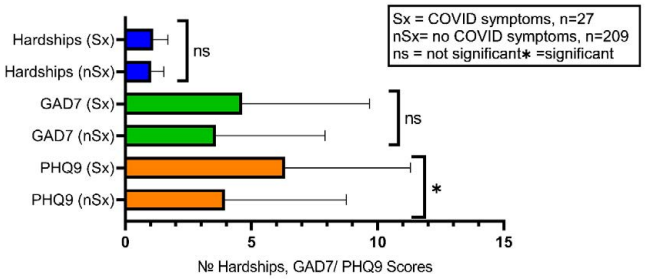

Figure 6. Follow-up #5: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

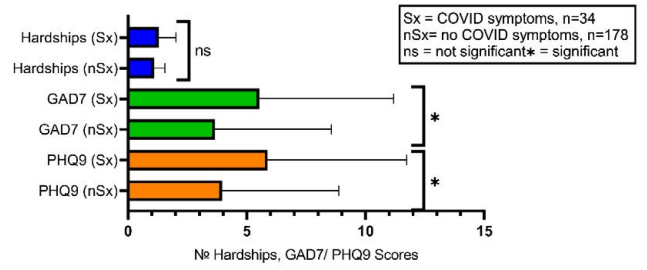

Figure 7. Follow-up #6: Comparison of GAD7, PHQ9, and COVID-19 Related Social and Economic Hardships among Participants with COVID-19 Symptoms vs Participants without COVID-19 Symptoms.

Discussion

There is significant variation in the manifestation of COVID-19 illness and subsequent Long COVID. Some individuals experience more COVID-19 symptoms with various levels of severity[8]. Although some factors such as low SES[7,9-13], age[5,7], and medical comorbidities[5,7] have been found to influence the occurrence of COVID-19, accurate prognostication is not possible regardless of COVID-19 vaccination status[8,11-12]. For example, it has been shown that during hospitalization, the most common symptoms were fever, dyspnea, myalgia, cough, and headache. Six months after hospitalization, the most common symptoms were fatigue, dyspnea, myalgia, cough, and headache[11]. Nevertheless, more than 100 symptoms affecting multiple systems have been reported[31]. For example, a systematic review suggests individuals with COVID-19 suffer from persistent symptoms: 7% to 42.9% posttraumatic stress disorder, 12% to 30% distress, 6.5% to 42% anxiety, 4.3% to 38.1% depression, 15% to 37.5% dementia/ memory loss, 5% to 21% obsessive compulsive disorder, 12% panic attacks, 39% psychiatric morbidity, 0.6% to 19.8% emotional symptoms, 39% to 72% low quality of life, and 1.7% dysphoria[31]. Other persistent symptoms reported include cardiovascular, pulmonary, respiratory, pain, fatigue, general infection, cognitive, sensory, dermatological, functional, and other symptoms[31].

There is a need to identify predictors for short- and long-term COVID-19-related health outcomes, which may inform necessary healthcare services to produce better health outcomes. The variation in COVID-19 and Long COVID symptoms may be partly explained by underlying psychological and/or psychiatric concerns. Preexisting mental illness has been found to be a risk factor for Long COVID development[14]. Using generalized estimating equation models adjusted for sociodemographic characteristics, health behaviors, and comorbidities, a study conducted by Wang et al, 2022, found that participants with two or more psychological conditions such as worry or perceived stress, had 50% increased risk for Long COVID symptoms[14]. These authors recommend further exploring the underlying biological mechanisms to better understand mental illness as a risk factor for Long COVID development[14]. Another study conducted by Hassan et al, 2021, suggests people with mental illness, in particular, people with schizophrenia/psychosis, bipolar disorder, and major depressive disorders, have higher risks of COVID-19 infection, hospitalization, and mortality[32]. Conversely, a study conducted by Mazza, Palladini, Poletti, and Benedetti, 2022, suggests a peripheral immune-inflammatory response occurs during and after COVID-19 infection, resulting in depression, anxiety, and cognitive impairments[33]. Given the significant connections between mental and physical illnesses, integrated healthcare approaches may be needed to improve clinical effectiveness and reduce healthcare costs associated with COVID-19 and mental illness comorbidity.

Our findings suggest a significant relationship between anxiety and depression symptoms and COVID-19 symptoms for participants remaining in the study from baseline (66.37%, 53.66%, 44.54%, 37.22%, 35.28%, and 31.69% for follow-ups 1 through 6, respectively). Medical diagnoses and social/economic hardships experienced during the pandemic significantly confound these longitudinal results. Age, sex, and race were not associated with the number of symptoms experienced. Overall, the number of symptoms significantly increase with higher PHQ-9 and GAD-7 scores at every study time point. More symptoms are likely to occur when there is a comorbid mental illness. All data in this study is self-reported, which is a significant limitation.

Nevertheless, the use of self-reported outcomes is becoming an integral part of health research studies to maximize the improvement of healthcare quality[34-36]. An important limitation for this study is the attrition rates over the six follow-ups, with only 31.69% of participants completing the entire study. In addition, the COVIDsmart population is composed of mainly White females. However, other large-scale online studies with no face-to-face interaction have had similar demographics[37-38]. Effective study recruitment strategies need to be identified for future online studies to capture a more diverse population.

In conclusion, our longitudinal study suggests that the presence of depression and/or anxiety is associated with increased short- and long-term symptoms of COVID-19. Integrated health approaches for COVID-19 and comorbid anxiety and/or depression may be necessary to improve overall health outcomes. Further investigation into the causative mechanisms is warranted.

Data Availability

Data cannot be shared as it was copyrighted by partners for the COVIDsmart study (Eastern Virginia Medical School - Sentara Healthcare Analytics and Delivery Science Institute (HADSI), George Mason University, and Vibrent Health Inc.

Conflict of Interest

Authors have no conflict of interest to report.

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