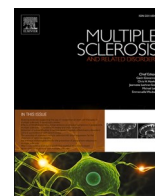




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Original article

Sociodemographic and clinical factors associated with depression, anxiety, and general mental health in people with multiple sclerosis during the COVID-19 pandemic

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ABSTRACT

Background People with multiple sclerosis (PwMS) may be at increased risk for psychological distress during COVID-19. We study the self-reported mental health of U.S. PwMS during COVID-19, prior to vaccine rollout.

Methods A cross-sectional survey was distributed online to PwMS through iConquerMS (12/18/2020–02/10/2021). Depressive and anxiety symptom burdens and general mental health status were measured via the Patient-Health Questionnaire-9, Generalized Anxiety Disorder-7, and PROMIS Global Mental Health scales. Linear regression models assessed associations between mental health variables and age, sex, disability status, comorbidities, and social determinants of health.

Results Of 610 U.S. PwMS (mean age 56 years, standard deviation 11, range 20–85; female, 81%; relapsing remitting disease, 62%; previous depression diagnosis, 40%), the prevalences of moderate-to-severe depressive and anxiety symptom burden were 27.4% and 14.7%, respectively; 55.1% endorsed fair/poor general mental health. PwMS who tested positive for COVID-19 ($n = 47$, 7.7%) reported higher depressive and anxiety symptom burdens ($p < 0.05$). Increased disability status score and social determinants of health were each associated with more depressive symptoms and worse general mental health. Younger age was associated with increased depressive and anxiety symptom burdens and worse general mental health. Female sex was associated with greater anxiety symptoms.

Conclusion There are specific associations for worse mental health among PwMS during COVID-19 that reflect a combination of clinical, demographic, and social determinants of health. Multidisciplinary care teams and vigilance are important to address the ongoing mental health impacts of COVID-19 in PwMS.

1. Introduction

The coronavirus disease-2019 (COVID-19) pandemic and its ensuing social, economic, and healthcare challenges have impacted the mental health of individuals worldwide. Social distancing orders, high unemployment rates, and fears of the novel virus affected the everyday lives of U.S. residents. As of April 2020, the prevalence of depression increased three-fold since 2017–2018 in the U.S. (Ettman et al., 2020). In February 2021, 41.5% of U.S. adults reported symptoms of depression or anxiety within the previous seven days (Vahratian et al., 2021). In addition, from August 2020–February 2021, the unmet need for mental healthcare services increased from 9.2 to 11.7% (Vahratian et al., 2021). This rise in mental illness has spotlighted the negative psychological effects

of the pandemic on the general population and vulnerable groups, including those with chronic diseases and pre-existing mental illness (Neelam et al., 2021; Wu et al., 2021).

Multiple sclerosis (MS) is a chronic inflammatory, neurodegenerative disorder that affects more than 810,000 individuals in the U.S. (Briggs and Hill, 2020). People with MS (PwMS) are often treated with immunosuppressive disease-modifying agents, which were thought to increase the risk of acquiring COVID-19 and may be associated with a worse prognosis. Additionally, there is a high prevalence of depression and anxiety among PwMS, compared to the general population (Boeschoten et al., 2017). These factors may place PwMS at greater risk for the psychological impacts of the COVID-19 pandemic. In April–May 2020, during the lockdown in Italy, PwMS had a significantly greater

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depressive symptom burden compared to healthy controls (Costabile et al., 2020). Similarly, PwMS in the United Kingdom experienced a greater burden of clinically significant depression and anxiety compared to controls (Garjani et al., 2021). Surveillance of the psychological well-being of PwMS living across the U.S. has not been well studied and remains important given the U.S. has the greatest number of COVID-19 cases and deaths to date, globally (CDC 2021).

In this cross-sectional study of a convenience cohort of PwMS in the U.S., prior to widespread COVID-19 vaccine rollout, we aim to characterize the mental health status of PwMS in the U.S. and assess socio-demographic and clinical associations for depressive and anxiety symptom burdens and general mental health status.

2. Methods

2.1. Ethics approval

The study received approval from the Massachusetts General Brigham Institutional Review Board and an independent ethics board for the Accelerated Cure Project (ACP), a non-governmental organization focused on patient-centered MS research, based in Massachusetts. All respondents electronically signed a consent form prior to completing the survey.

2.2. Survey development and distribution

A survey instrument was created and implemented via a cross-sectional design using the web-based platform iConquerMS (<https://www.acceleratedcure.org/iconquerms>), a patient-powered research network with participants in all 50 states of the U.S., U.S. territories, and other countries. Adults registered on the platform and > 20 years of age were eligible for participation. Recruitment for this survey occurred via an email from the iConquerMS website and advertisement on social media. Enrollment occurred in English from December 18, 2020 to February 10, 2021.

The survey, entitled, "COVID-19 and MS - Recent Experiences," aimed to assess personal experiences with COVID-19 among PwMS. iConquerMS users are part of a longitudinal cohort study, with demographic, socioeconomic, and clinical data available, in addition to topic-specific questions. Users with and without MS worldwide were eligible to respond, although most users have MS and reside within the U.S. No reference to mental health was made in the survey title or invitation.

2.3. Respondent measurements

Mood assessments: Depressive and anxiety symptom burdens were assessed via the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder 7-item scale (GAD-7) respectively. Both were self-administered and have been previously validated as screening tools in PwMS (Williams et al., 2020; Terrill et al., 2015).

The PHQ-9 queries major depressive symptoms within the last two weeks, using scores from 0 (not at all) to 3 (nearly every day). Total scores range from 0 to 27 points and are used to stratify depressive symptom burden: 0–4, minimal; 5–9, mild; 10–14, moderate; 15–19, moderately severe; and > = 20, severe (Kroenke et al., 2001). A score of 10 or more points was used to dichotomize the depressive symptom burden into moderate to severe versus minimal to mild.

The GAD-7 assesses the presence of seven core anxiety symptoms and symptom severity. Subjects are asked, within the last two weeks, how often they have experienced these symptoms from 0 (not at all) to 3 (nearly every day). Scores range from 0 to 21, with cut off points of 5, 10, and 15 corresponding with mild, moderate and severe levels of anxiety symptom burden (Spitzer et al., 2006). A score of 10 or more points was used to dichotomize the anxiety symptom burden into moderate to severe versus minimal to mild.

General mental health status: The Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 is a 10-item health assessment tool (Cella et al., 2007). We used the four items assessing global mental health (GMH), which query participants on quality of life, mental health, satisfaction with social activities, and emotional problems (Hays et al., 2009), to assess participants' general mental health statuses. Each item was rated on a 5-point scale ranging from 1 (poor) to 5 (excellent), with the exception of the emotional problems item which was rated on a 5-point scale ranging from 1 (always) to 5 (never) (Hays et al., 2009). Responses from all four items were summed to give a composite score ranging from 4 to 20, where higher scores signify better mental health status. A score of 14 or greater was used to signify good or better mental health status, with scores less than 14 signifying fair or poor mental health (Health-Related Quality of Life and Well-Being Data Details | Healthy People, 2020, 2021).

Social determinants of health count: A social determinants of health (SDH) count was adapted from Safford et al. (2021). Variables in the count include Black race, low education (high school or less), low income (< 30,000 USD/year), residing in a zip code with high poverty (> 25% residents living below U.S. Federal poverty line), residence in a state with the least public health infrastructure (based on America's Health Ranking data), social isolation (interacted with one or no family members/friends in the past month, including virtually), and lack of health insurance. Income data were not collected in the current survey and supplemented with previous survey data by iConquerMS of the same participants, occurring within the last three years. The summation of variables was used, with a higher count representing a greater burden of SDH (Safford et al., 2021). The range of the SDH count was 0 to 4 and a cut off of 1 was used to dichotomize this variable.

Disability assessment: Functional status was measured with the Patient-Determined Disease Steps (PDDS), a patient-reported outcome of disability validated in MS (Learnmonth et al., 2013). The scale ranges from 0 to 8, corresponding with "normal" to "bedridden," respectively. PDDS was used as a continuous variable.

Comorbidity index: A comorbidity index was calculated based on the Charlson-Deyo Comorbidity Index (Deyo et al., 1992). These comorbidities were found to be significantly associated with increased odds of mortality due to COVID-19 (Rosenthal et al., 2020). In our comorbidity index, the following self-reported comorbidities were included: cancer, diabetes, kidney disease, heart disease, liver disease, and lung disease. The variable was dichotomized as the presence of 1 or more comorbidity/comorbidities versus none.

COVID-19 positivity: Respondents were considered COVID-19 positive if they self-reported at least one positive laboratory test result. The remaining respondents (including those who tested negative and those who were never tested) were categorized as COVID-19 negative/not tested.

COVID-19 impact on diet, exercise, and personal finances: Respondents were asked what type of impact COVID-19 had on their (a) diet or access to food, (b) ability to exercise, and (c) personal financial situations. Answer choices ranged from 1 (significant positive impact) to 7 (significant negative impact), with an answer of 4 corresponding to "neutral." The three variables were dichotomized, with a score of >= 5 signifying some negative impact of COVID-19 on the variable of interest, and scores of <= 4 signifying no negative impact.

2.4. Statistical analysis

Respondents who self-reported that they did not have MS, lived outside the U.S. and/or who failed to answer > 20% of the key variables of interest were excluded from this analysis. Missing data were otherwise assumed to be missing completely at random.

Descriptive statistics were calculated for demographic and clinical variables. Wilcoxon rank-sum tests were used to evaluate the association of mental health between subgroups of interest including: respondents with a positive COVID-19 laboratory test versus those without and

respondents who reported a negative impact on diet, exercise, and/or personal finances due to COVID-19 versus those without a negative impact. Spearman correlation was used to assess the relationship between continuous variables.

Linear regression models were used to determine the possible associations of variables of interest with the outcomes of (1) depressive symptom burden, (2) anxiety symptom burden, and (3) general mental health status. Based on previous literature, the following variables were determined *a priori* as potentially associated: age, sex, Patient-Determined Disease Step (PDDS), comorbidity index, and SDH count. To determine variables independently associated with the mood symptom burden of interest, we controlled for depressive symptom burden in the anxiety symptoms model and anxiety symptom burden in the depressive symptoms model.

Sensitivity analyses were conducted by dichotomizing depressive and anxiety symptom burden into moderate to severe versus minimal to mild to assess clinical relevance. General mental health status was dichotomized into poor/fair versus good/better. We used multivariable logistic regression models with the aforementioned covariates. Relative risks were calculated using an odds ratio (OR) with corresponding 95% confidence intervals (CI). A two-tailed *p*-value of less than 0.05 was considered statistically significant for all statistical tests. Analyses were performed using the statistical program R (Vienna, Austria).

3. Results

Of 1662 active iConquerMS users, 789 responded, of whom 773 respondents reported a diagnosis of MS. Analysis was limited to PwMS residing in the U.S., given the limited number of respondents from other countries and the variable evolution of the pandemic globally. Therefore, 610 PwMS in the U.S. were analyzed for this study.

The mean (standard deviation) age of the respondents was 56.2 (11.4) years. Four hundred and ninety-one (80.5%) respondents were female and 214 (35.1%) had progressive MS. Demographic and clinical characteristics are presented in Table 1.

3.1. COVID-19 prevalence, severity, and symptoms

Of the 610 analyzed respondents, 47 (7.7%) reported testing positive for COVID-19. Forty-three of the 47 (91.5%) respondents testing positive for COVID-19 experienced symptoms. Tiredness, muscle aches/pain, headache, malaise, and cough were the most reported symptoms, experienced by greater than 30 of the 43 symptomatic respondents (Supplemental Table 1). There were 28 (59.6%) who were not treated for their COVID-19 infection, while 12 (25.5%) were treated but not hospitalized. Seven respondents were hospitalized for their COVID-19 infection, of whom six required breathing assistance while two required admission to an intensive care unit (ICU).

Twenty-three (48.9%) respondents reported new or worsening neurological symptoms around the same time as their COVID-19 infection. Twenty reported that their neurological symptoms were at the same time or after their COVID-19 symptoms, while three reported that the neurological symptoms preceded their COVID-19 symptoms.

3.2. Mental health characteristics

The prevalences of depressive and anxiety symptom burdens are depicted in Table 2. Of the 610 respondents, 584 completed the PHQ-9 questionnaire and 160 (27.4%) endorsed moderate to severe depressive symptom burden. Two hundred and forty-six (40.3%) of all 610 respondents self-reported a diagnosis of depression. More respondents endorsing moderate to severe depressive symptoms also endorsed a history of depression (115/230 (50.0%) versus 45/353 (12.7%), *p* < 0.001). Most respondents who reported a history of depression were being treated (89.0%), and 42.3% reported that depression limits their activities.

Table 1
Respondent characteristics.

Characteristic	(n = 610)
Age, median (interquartile range; IQR) in years	58.0 (15.0)
Female sex ^a , n (%)	491 (80.5)
Region of U.S. ^b , n (%)	
Northeast	146 (24.5)
Midwest	128 (21.5)
South	186 (31.3)
West	133 (22.4)
SDH Count ≥ 1, n (%)	173 (28.4)
Black race	18 (3.0)
Uninsured	7 (1.1)
Low education (high school graduate or less)	23 (3.8)
Income (<\$30,000 USD/year)	63 (10.3)
Social isolation	3 (0.5)
Residing in state with the least public health infrastructure	71 (11.6)
Residing in zip code with >25% below federal poverty line	29 (4.8)
Employment status ^c , n (%)	
Employed outside home	141 (23.2)
Employed at home	88 (14.5)
Unemployed	47 (7.7)
Student	5 (0.8)
Disabled	225 (37.1)
Retired	101 (16.6)
Disease duration, median (IQR) in years	14.9 (13.5)
Disease course, n (%)	
Relapsing remitting MS	378 (62.0)
Secondary progressive MS	142 (23.3)
Primary progressive MS	72 (11.8)
Clinically isolated/unknown	18 (3.0)
Patient Determined Disease Steps, median (IQR)	3 (4)
Current DMT use, n (%)	431 (70.7)
Alemtuzumab	8 (1.9)
Cladribine	7 (1.6)
Fumarates	61 (14.2)
Glatiramer acetate	44 (10.2)
Interferon beta	34 (7.9)
Natalizumab	43 (10.0)
Ocrelizumab	140 (32.5)
Ofatumumab	3 (0.7)
Rituximab	21 (4.9)
Sphingosine 1-phosphate receptor modulators	38 (8.8)
Teriflunomide	29 (6.7)
Comorbidities, ≥ 1, n (%)	107 (17.5)
Cancer	22 (3.6)
Diabetes	35 (5.7)
Kidney disease	10 (1.6)
Heart disease	27 (4.4)
Liver disease	10 (1.6)
Lung disease	24 (3.9)

^a One respondent preferred not to answer.

^b Regions as defined by the U.S. Census Bureau; two respondents from Puerto Rico and 15 who did not respond.

^c Three respondents preferred not to answer.

Table 2
Prevalence of depressive and anxiety symptom burden and general mental health status.

	n (%)
Depressive symptom burden (score)	
Minimal (0–4)	241/584 (41.3)
Mild (5–9)	183/584 (31.3)
Moderate (10–14)	104/584 (17.8)
Moderately severe (15–19)	40/584 (6.8)
Severe (20–27)	16/584 (2.7)
Anxiety symptom burden (score)	
None (0–4)	363/598 (60.7)
Minimal (5–9)	147/598 (24.6)
Mild (10–14)	52/598 (8.7)
Moderate (15–21)	36/598 (6.0)
General mental health status (score)	
Fair or poor mental health (4–13)	336/610 (55.1)
Good or better mental health (14–20)	274/610 (44.9)

Of 598 respondents to the GAD-7 questionnaire, 88 (14.7%) reported moderate to severe anxiety symptom burden. Depressive and anxiety symptom burdens were highly correlated (Spearman rho 0.70, $p < 0.001$).

All 610 participants completed the PROMIS Global Mental Health subscale (range 4–20). Three hundred and thirty-six (55.1%) endorsed fair or poor mental health status, while 274 (44.9%) endorsed good or better mental health. Scores on this measure were negatively correlated with both depressive symptoms (Spearman rho -0.71 , $p < 0.001$) and anxiety symptoms (Spearman rho -0.65 , $p < 0.001$).

Respondents who reported testing positive for COVID-19 endorsed higher depressive and anxiety symptom burdens. The median PHQ-9 score of the COVID-19 positive respondents (7.0) was significantly higher than that of the remaining respondents (5.0, $p = 0.046$). Similarly, the median GAD-7 score of the COVID-19 positive respondents (5.0) was significantly higher than that of the remaining respondents (3.0, $p = 0.009$). The median PROMIS Global Mental Health score of COVID-19 positive respondents (13.0) did not differ from that of COVID-19 negative respondents (13.0, $p = 0.86$).

Due to the COVID-19 pandemic, 242 (39.7%) experienced a negative impact on the ability to exercise, 125 (20.5%) on diet or access to food, and 126 (20.7%) on their personal financial situation. Respondents who reported a negative impact in each of these categories generally endorsed greater depressive and anxiety symptom burdens and worse general mental health (Table 3).

3.3. Regression outcomes

The outcomes of the multivariable linear regressions for depressive and anxiety symptoms and general mental health status are displayed in Table 4. Increased functional disability, greater than or equal to one SDH count, and moderate to severe anxiety symptom burden were each associated with greater depressive symptoms. Older age was associated with a decrease in depressive symptoms. When analyzing the outcome of moderate to severe depressive symptom burden, greater than or equal to one SDH count (OR 1.82, 95%CI 1.15–2.89) and moderate to severe anxiety (OR 15.40, 95%CI 8.73–28.40) were significantly associated.

In the multivariable linear regression of anxiety symptoms, female sex and moderate to severe depressive symptom burden was associated with increased anxiety symptoms, while older age was associated with decreased anxiety symptoms (Table 4). In the sensitivity analysis, older age was associated with a decreased odds (OR 0.95, 95%CI 0.92–0.98) and moderate to severe depressive symptom burden was associated with increased odds (OR 16.32, 95%CI 9.18–30.45) of moderate to severe anxiety symptom burden.

In the multivariable linear regression model for general mental health status, younger age, increased functional disability, and ≥ 1 SDH count were all associated with worse general mental health status. In the sensitivity analysis, where mental health status was dichotomized into fair/poor mental health versus good/better mental health, older age was associated with increased odds of good/better mental health (OR 1.03, 95%CI 1.02–1.05), while increased functional disability (OR 0.82, 95%CI 0.75–0.89), SDH count ≥ 1 (OR 0.60, 95%CI 0.41–0.88), and comorbidity index ≥ 1 (OR 0.60, 95%CI 0.38–0.96) were all associated with decreased odds of good/better mental health.

Table 3
Differences in mental health variables by COVID-19 impact on ability to exercise, diet/access to food, and personal finances in PwMS.

	Ability to Exercise			Diet/Access to Food			Personal Finances		
	No negative impact	Negative impact	<i>p</i> value	No negative impact	Negative impact	<i>p</i> value	No negative impact	Negative impact	<i>p</i> value
Depression score, median	5	6	<0.01	5	10	<0.01	5	8	<0.01
Anxiety score, median	3	4	.06	2	6	<0.01	2	6	<0.01
General mental health status, median	13	13	.03	14	11	<0.01	13	11	<0.01

4. Discussion

Among a geographically diverse convenience sample of PwMS in the U.S. during the COVID-19 pandemic, prior to widespread vaccine roll out, 27% endorsed moderate to severe depressive symptoms, 15% endorsed moderate to severe anxiety symptoms, and 55% endorsed fair or poor mental health. PwMS who reported testing positive for COVID-19 reported a greater burden of depressive and anxiety symptoms compared to those who did not. The subsets of PwMS who reported a negative impact on their ability to exercise, their diet or access to food, and/or their personal finances due to COVID-19 also reported higher burdens of depressive and anxiety symptoms and worse general mental health status.

The COVID-19 pandemic has resulted in nearly 600,000 deaths in the U.S. to date (NVSS - Provisional Death Counts for COVID-19 - Executive Summary, 2021). In our cohort, the cumulative incidence of COVID-19 was 7.7%, similar to the overall U.S. population in February 2021 (CDC, 2021). Nearly 15% of COVID-19 positive respondents were hospitalized, and 4% were admitted to intensive care units. Of the PwMS who tested positive for COVID-19, 91% reported at least one symptom, with the most frequently reported symptoms including tiredness, muscle aches or pain, headache, cough, and fever. These are similar to symptoms commonly reported by COVID-19 positive individuals in other cohorts of PwMS and in the general population. Additionally, fatigue and pain are prevalent in PwMS, which overlap with the symptom profile of COVID-19 (Wood et al., 2013; Wang et al., 2021).

PwMS are vulnerable to the effects of the COVID-19 pandemic on mood symptoms, in part due to the high prevalence of pre-existing depression and anxiety. Prior to the pandemic, in a meta-analysis of studies using the PHQ-9 assessment method, 24% of PwMS experienced moderate to severe depressive symptoms, while the pooled prevalence of clinically significant anxiety symptoms among PwMS, using the Hospital Anxiety and Depression Scale, was 34% (Boeschoten et al., 2017). The findings in our cohort imply a slightly higher rate of moderate to severe depressive symptoms (27% versus 24%) and a lower rate of moderate to severe anxiety symptoms (15% versus 34%) in December 2020–February 2021, compared to that pre-pandemic assessment. Among PwMS in Italy, there was little change in symptoms of depression or anxiety during the pandemic (Capuano et al., 2021), while a study of PwMS in Iran found higher prevalences of both anxiety and depression during the pandemic (Ramezani et al., 2021).

Compared to PwMS in the United Kingdom in May–July 2020, the prevalence of moderate to severe depressive and anxiety symptoms in this U.S. cohort is marginally lower (27% versus 33% with moderate to severe depression and 15% versus 20% with moderate to severe anxiety) (Garjani et al., 2021). This may be due to differences in the baseline characteristics of the cohorts, differences in the study time frame, the societal and political response to the pandemic, and/or the announcement of the first COVID-19 vaccines in the U.S. Notably, another study found a decrease in affective symptoms among PwMS in December 2020, compared to July–November 2020 (Fitzgerald et al., 2021). Some research suggests that PwMS on immunosuppressive therapies may be at higher risk for health-related anxiety during the pandemic and that PwMS experience decreased social support due to social distancing measures, which could have long-term implications for mental health

Table 4
Linear regression statistics.

	Depressive symptoms			Anxiety symptoms			General mental health status		
	Effect estimate	Standard error	p value	Effect estimate	Standard error	p value	Effect estimate	Standard error	p value
Age	-0.04	0.02	.03	-0.08	0.02	<0.01	0.06	0.01	<0.01
Female sex	0.48	0.48	.32	0.89	0.40	.03	-0.36	0.35	.30
PDDS	0.22	0.09	.02	-0.05	0.08	.52	-0.39	0.07	<0.01
SDH count >=1	1.20	0.43	.01	0.34	0.37	.36	-0.79	0.31	.01
Comorbidities > = 1	0.86	0.52	.10	0.28	0.44	.53	-0.72	0.37	.05
Moderate to severe anxiety symptom burden	7.98	0.55	<0.01	-	-	-	-	-	-
Moderate to severe depressive symptom burden	-	-	-	5.86	0.37	<0.01	-	-	-

(Akhoundi et al., 2020). Continued surveillance is needed as it is unclear how the mental health of PwMS will change throughout and after the pandemic. Longitudinal monitoring of PwMS through mobile health anxiety/depression scales and therapeutic interventions including physical activity and psychiatric medications when appropriate could be beneficial (Akhoundi et al., 2020). As an example of negative longitudinal mental health outcomes during a previous disease outbreak, the Severe Acute Respiratory Syndrome outbreak in 2003 resulted in increased suicide rates that remained elevated in the year following that pandemic (Cheung et al., 2008).

While previous studies earlier in the pandemic found no differences in the mental health of PwMS who were COVID-19 positive versus not infected (Garjani et al., 2021), we found evidence of significant adverse mental health issues among PwMS who self-reported testing positive for COVID-19. In previous coronavirus outbreaks, high rates of depression and anxiety symptomatology have been found during the acute illness and post-illness stage among the general population (Rogers et al., 2020). Similarly, among COVID-19 survivors in the general population, >30% report depressive and anxiety symptoms (Mazza et al., 2020). These high rates of mental health impact may be due to the immune response to the virus with a reported association between self-reported depression and increased immune response in convalescent COVID-19 patients (Yuan et al., 2020). However, we were unable to characterize the timing of COVID-19 infection and the onset of self-reported mental health outcomes in this cross-sectional study. Other explanations of increased rates of poor mental health may include the psychological stress associated with infection from a novel virus with limited outcomes information, necessary quarantine, and/or worse overall health status.

In the multivariable models, younger age was associated with increased depressive and anxiety symptom burdens and worse general mental health, while the presence of at least one SDH and greater functional disability were associated with increased depressive symptom burden and worse general mental health. The association of worse mental health with younger age during the COVID-19 pandemic is consistent with previous studies in the general population (Panchal and Kamal, 2021; Czeisler et al., 2020). It is hypothesized that this may be due to the higher prevalence of mental illness prior to the pandemic among young adults and/or consequences of COVID-19 such as unemployment, the closure of post-secondary educational institutions, and increased social isolation. Our results are in line with other research finding that younger PwMS have been more adversely affected by the COVID-19 pandemic (Morris-Bankole and Ho, 2021; Talaat et al., 2020).

Endorsing one or more SDH was associated with worse mental health and greater depressive symptoms during the pandemic. The SDH count combines micro- and macro-level socioeconomic disparities; many variables in this index have been shown to be associated with higher rates of depression and/or anxiety in the general population including low income status (Sareen et al., 2011), Black race (Dunlop et al., 2003), and individuals who are socially isolated (Blazer, 2020). Furthermore, Black communities have been disproportionately impacted by the COVID-19 pandemic (Millett et al., 2020).

Our study also suggests that increased functional disability was associated with worse general mental health. People with disabilities are particularly impacted by the COVID-19 pandemic due to factors such as decreased access to healthcare (Lebrasseur et al., 2021) and high rates of depression and anxiety in individuals with disabilities have been seen during the pandemic (Necho et al., 2020). Among PwMS, greater functional disability is an independent risk factor for severe COVID-19 outcomes (Louapre et al., 2020). Increased functional disability has been found to be associated with depression (but not anxiety) in PwMS during the pandemic in other research, specifically showing a moderating role of physical exercise; i.e., physical activity may play a role in pandemic depression, regardless of functional disability status (Carotenuto et al., 2021). PwMS with increased functional disability are a sub-group at risk for poor mental health and may benefit from targeted mental health support.

The current findings should be interpreted considering the following limitations. The anonymity of the survey prevents verification of reported data. This impacts the certainty of disease specific findings, such as COVID-19 laboratory test results, and other personal factors such as personal income and self-reported disease characteristics. Our study is also subject to sampling bias. This unpaid, web-based survey, administered in English only, does not fully reach certain populations including lower-income populations who cannot afford to volunteer their time, those with limited access to the Internet, and non-English speakers. Our study did not report on the outcomes of PwMS in comparison to a control group of healthy subjects, which could have contributed to the specificity of our findings to people with MS. Of note, a study exploring anxiety, stress, and depression in PwMS compared to their caretakers and healthy controls in Egypt found that PwMS had higher rates of anxiety, stress, and depression during the pandemic (Talaat et al., 2020). A study comparing PwMS to the general population in Italy similarly reported a higher burden of depressive symptoms in PwMS during the pandemic (Motolese et al., 2020).

The iConquerMS cohort has a high proportion of women and non-Hispanic/Latinx White populations. Therefore, even though our respondents represent a geographically diverse sample in the U.S., they may not fully reflect all PwMS in the U.S. In the case that our data do not include the poorest segments of the population with MS, it is likely that the mental health burden is even higher than reported here. Finally, our results are not able to conclude that COVID-19 is a cause of worse mental health among PwMS or the etiology of this association. Since we did not survey this cohort for depressive and anxiety symptoms prior to COVID-19, we are only able to report cross-sectional findings of the respondents' self-assessments. Moreover, the mental health measures were self-reported by participants; although patient-reported outcomes are a relative strength in some circumstances, comparison to a clinician-administered depression measure would be most useful in contextualizing the depressive symptom findings reported as clinical disorders. Additionally, the GAD-7, used in this study, is a measure of generalized anxiety, while previous research on anxiety in PwMS during the pandemic suggests that PwMS may be more affected by situational

anxiety (Motolese et al., 2020).

The present study also has several strengths. First, our sample includes respondents from 48 of the 50 U.S. states, the District of Columbia, and Puerto Rico. The anonymous nature allowed the collection of comprehensive clinical and demographic characteristics across a range of ages, MS disease stages, and socioeconomic backgrounds. We used the SDH index, which has not been widely used in the MS literature to date but offers a composite variable that addresses factors important to MS, the outcomes of interest (mental health), and COVID-19. The SDH index has utility for future research on the social determinants of health in MS. We include a sufficiently high sample size with complete data to consider associations of interest. We also identify a combination of sociodemographic, MS-focused, clinical, and socioeconomic variables that may impact mental health - a construct that reflects mental health better than any one angle of analysis. Given the voluntary basis of the study, patient-driven nature of the platform, and the lack of advertisement of the study as focused on mental health, the uptake and expectations of the participants were not pre-supposed. Finally, our data can provide information on preparedness for future public health crises, with an emphasis on who may be suffering with the highest degree of symptoms based on disease, demographic, and socioeconomic factors in PwMS.

5. Conclusion

In a geographically diverse cohort of PwMS in the U.S., our findings shed light on the mental health burden in this population during a critical time point in the COVID-19 pandemic. We find a relatively high burden of depressive symptoms and lower burden of anxiety symptoms. Risk factors for increased mood symptom burden and/or poor mental health include younger age, female sex, social determinants of health, and functional disability. At-risk patient subgroups are identified and may benefit from multidisciplinary care teams and longitudinal mental health surveillance.

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Data sharing statement

De-identified data will be made available to investigators upon reasonable request and subject to ethics board approvals.

CRedit authorship contribution statement

Lauren Uhr: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Dylan R. Rice:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Farah J. Mateen:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors report no relevant conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in

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