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Original article

Worsening physical functioning in patients with neuroinflammatory disease during the COVID-19 pandemic

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ABSTRACT

Objective: To quantify changes in psychological wellbeing and physical function as reported by people with neurological inflammatory disease (PwNID) during the COVID-19 pandemic.

Methods: 1134 PwNID and 868 control participants were recruited through five major academic medical centers in the Northeast/Mid-Atlantic U.S. beginning in April 2020. Participants completed serial surveys throughout the COVID-19 pandemic that aimed to quantify mood symptoms and physical function, analyzed cross-sectionally with a smaller cohort analyzed longitudinally.

Results: Throughout the pandemic, depression scores were not significantly different between PwNID and controls, although a higher proportion of PwNID reported clinically significant depression at study entry. Depression scores did not worsen over time for either group. Loneliness was the strongest predictor of worse depression, along with older age, male gender in both PwNID and controls, as well as lack of disease modifying therapy use, and disease duration in PwNID only. In contrast, physical disability worsened significantly over time for both PwNID and controls. Age, DMT status and comorbid health conditions emerged as significant predictors of physical function.

Conclusions: Depressive symptoms remained consistent for both PwNID and controls throughout the COVID-19 pandemic, but physical function worsened significantly over time for both groups. This is particularly impactful for PwNID, who have higher baseline levels of physical disability, and underscores the importance of reinstituting services and interventions that facilitate exercise and reconditioning for this population.

1. Introduction

The declaration of the COVID-19 pandemic by the World Health Organization (WHO) on March 11th, 2020, initiated global changes in lifestyle and activities. These restrictions have negatively impacted mental and physical health (Dubey et al., 2020), financial security and social connection (Smith and Lim, 2020). Just months into the pandemic, reports began to surface illustrating that both healthy individuals and those with pre-existing health problems were experiencing moderate to severe psychological symptoms (Haji Akhoundi and

Sahraian, 2020; Wang et al., 2020).

People with underlying neurological inflammatory diseases (PwNID) such as multiple sclerosis (MS) have a higher baseline prevalence of neuropsychiatric disease and are at particular risk for experiencing negative physical, mental, and social impacts from the COVID-19 pandemic (Motolese et al., 2020; Chiaravalloti et al., 2021). Comorbid cognitive dysfunction is observed in up to 70% of MS patients (Oreja-Guevara et al., 2019), and anxiety/depression affect more than half (Butler et al., 2016; Feinstein et al., 2014). This population also relies heavily on existing medical infrastructure including attending doctor visits and physical therapy sessions, utilizing rehabilitation and health facilities for the exercise necessary to maintain their current condition (Kobelt et al., 2017). Given that higher levels of physical activity improve physical function in MS (Rooney et al., 2021; Cederberg et al., 2018), the pandemic-imposed restrictions on in-person activities raise concerns that PwNID may experience accelerated deterioration in their physical condition during the pandemic.

Upon recognition of the COVID-19 threat, five large academic medical centers in the Mid-Atlantic and Northeastern United States began recruiting persons with PwNID and healthy controls to prospectively report on how the pandemic was influencing their daily lives. Participants completed regular surveys every 2–4 weeks, reporting on domains such as loneliness, depression and physical function (Levin et al., 2021). We hypothesized that PwNID would experience worsened depression and physical function as the COVID-19 pandemic persisted and used these survey data to evaluate this question.

2. Methods

2.1. Subject selection

Potential subjects were identified through association with MS/neuroimmunology departments at Yale University, Columbia University Irving Medical Center (CUIMC) (this center additionally enrolled several patients from University of Toronto and MS Center of Northeastern New York), University of Pittsburgh MS Center (UPMC), University of Pennsylvania Comprehensive MS Center, the Jacobs MS Center at the University of Buffalo with additional help from the National Multiple Sclerosis Society in disseminating the study information (Supplementary Table 1). We recruited adults 18 years and older with a diagnosis of multiple sclerosis or another inflammatory neurological disease, including clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), neuromyelitis optica spectrum disorders (NMOSD), anti-MOG syndrome (MOG), autoimmune encephalitis (AIE), neurosarcoidosis, and CNS vasculitis. Participants completed standardized online surveys every 2–4 weeks using the Research Electronic Data Capture (REDCap) platform. Participants were recruited on a rolling basis, beginning April 2020 and continuing throughout the pandemic. Controls were identified through registries and local advertising at each institution. We excluded non-English speakers given some of the questionnaires had no validated non-English versions. Of the 1810 PwNID and 896 controls, 1134 PwNID and 834 controls who filled out depression and physical function PROMIS surveys were included in analysis. All participants gave informed consent for participation. The institutional review board at all institutions approved the study protocols.

2.2. Web based surveys

Given the rolling basis of enrollment, participants began completing surveys at various time points beginning after the declaration of the COVID-19 pandemic on March 11th, 2020 (Supplemental Table 2). Data collection is ongoing. The current analysis included data from first survey deployment in April 2020 through December 31st, 2020. Surveys incorporated the following information:

Neurological history and changes in neurological care: For PwNID, we ascertained diagnosis, disease duration, current, and past disease modifying therapies (DMT) as well as any treatment changes that were made due to the pandemic and new COVID-related measures that had occurred (handwashing, masking, social distancing, COVID testing, hospitalization).

Psychosocial Outcomes: Symptoms of depression were assessed via the National Institute of Health Patient-Reported Outcomes Measurement Information System (PROMIS) Depression version 1.0 scale, which has been validated in MS (Amtmann et al., 2018; Pilkonis et al., 2014) and can be used to measure changes in depression severity over time, with higher scores indicating more severe depression. We quantified subjective loneliness using the UCLA Loneliness Scale, a 20-item survey previously used in MS (Leavitt et al., 2020; Russell, 1996). The Modified Social Support Survey was administered to quantify perceived social support (Bambara et al., 2014).

Physical Function and Neurological Outcomes: Physical function was assessed using one general and two disease-specific self-reported outcomes. The National Institute of Health Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function version 1.2 was utilized for general physical function, in which higher scores represent better physical function.

2.3. Data analysis

Statistical tests were performed using R-Studio statistics software (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2018). For time-based comparisons, the pandemic was separated into three periods. The first period (P1) represented the first COVID-19 surge and included surveys submitted March 1st, 2020 – May 31st 2020. The second period (P2) represented the summer trough in cases and included surveys submitted June 1st 2020 – September 30th 2020, and the third period (P3) represented the second COVID-19 surge and included surveys submitted October 1st 2020 – December 31st 2020. These time periods were chosen as they were approximately even in length and meaningfully represented different stages of the pandemic facing the study population in 2020. Only patients who filled out depression and physical function PROMIS surveys were included in analysis. These data were analyzed cross-sectionally, using ANOVA with Tukey's post-hoc testing to compare the three time periods. Linear regression models for PROMIS depression and physical function scores were created using stepwise model selection and Akaike Information Criteria (StepAIC function for R) to generate models with the minimal set of optimal features. A subset of patients who submitted longitudinal depression and physical function questionnaires were analyzed separately with repeated measures ANOVA.

2.4. Data availability

The data that support the findings of this study are available from the corresponding author, EL, upon reasonable request.

2.5. Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all patients (or guardians of patients) participating in the study.

3. Results

3.1. Baseline characteristics of subjects

Participants were recruited from a collaborative network of MS centers in the Northeast/Middle Atlantic regions (Supplementary Table 1). Importantly, the study sites were geographically congruent and experienced similar ebbs and flows of COVID-19 cases during the pandemic. Three centers began recruiting during the initial phase (P1)

of the pandemic, while other centers began recruiting later. Given this heterogeneity in recruitment timelines, we opted to perform cross-sectional data analyses to evaluate depression and physical function in relation to the pandemic's duration. A subset of patients who contributed longitudinal data were used for a confirmatory analysis with repeated measures ANOVA.

The study population included 1810 (67%) PwNID and 896 (33%) control participants who completed at least one set of surveys during the study period. Only patients who completed the PROMIS depression and physical function surveys were included in analysis, including 1134 PwNID (55.9%) and 896 controls (44.1%) (Table 1). MS was the most common inflammatory neurologic disease (1721 cases, 95.2%), and the age and sex ratio of the study participants was in line with the reported demographics of people living with MS. There were no statistically significant differences in gender ($p = 0.9$), age ($p = 0.2$), or race ($p = 0.9$) between cases and controls (Table 1). More surveys were returned during Periods 1 and 3 compared to P2 (Table 1).

Over 95% of both PwNID and controls reported adhering to national guidelines for social/physical distancing and increasing their hand-washing frequency throughout the course of the pandemic as well as wearing masks in public places and when in contact with anyone who was feeling unwell. The proportion of participant-reported positive COVID tests decreased over time in cases and controls, coincident with increased numbers of tests performed as the pandemic progressed, with 9/28 (32%) tested cases being positive in P1 and 6/14 (42%) tested cases being positive during P2. In P3, 9/134 (7%) tested cases were positive for COVID-19. Control subjects had similar rates of positive tests, with 6/16 (38%) cases positive in P1 and 5/137 (4%) in P3. As this survey study aimed to capture the experience of people with mild to absent COVID-19 symptoms, hospitalizations were low in the surveyed population, occurring in <2% of cases and controls. A change in employment was reported by 16% of cases in P1, while 37% of controls reported employment change during this period. By P3, 16% of cases and 19% of controls reported employment change.

3.2. Change in depression throughout the pandemic

To examine changes in psychological outcomes during the pandemic, we compared PROMIS depression scores over Periods 1, 2 and 3. Depression scores were slightly higher in PwNID than controls, which was most apparent during P1 ($p = 0.008$) (Fig 1A). A higher proportion of PwNID also exhibited clinically significant depression (PROMIS scores >60) at study entry, although there was no difference in the proportion of clinically significant depression between PwNID and controls during P3 (Fig 1B). Depression scores generally remained stable over time. While average scores for PwNID in P3 were slightly lower than in P1 (mean 51.2 vs 52.6, $p = 0.014$), this was unlikely to represent a clinically significant change (Amtmann et al., 2018). Control subjects similarly exhibited stable depression scores over time (mean 51.2 vs 51.0 in P1 and P3, $p = 0.72$). Notably, the proportion of PwNID with clinically significant depression declined over time (20.3% of patients in P1 vs. 14.4% in P3), while the proportion of control subjects with clinically significant depression remained fairly stable over time (11.3% v. 14.3% in P1 and P3). There was participant dropout over time, but individuals who were clinically depressed at baseline continued to fill out surveys at similar rates compared to those who were not clinically depressed at baseline (24% of depressed individuals and 32% of non-depressed completed longitudinal surveys; $p = 0.2$).

To determine the contribution of clinical and demographic factors to depression scores, we simplified linear regression models while preserving model performance by utilizing stepwise model selection and Akaike Information Criteria. The best performing model for depression severity (R^2 0.29, p-value < 0.001) included loneliness, disease status (PwNID vs control), DMT status, age, and gender as significant predictors, with loneliness score carrying the largest weight (Table 3). Male sex, older age, and no current use of immunomodulatory therapy were

Table 1

Overall demographics of all centers including total and period-specific patient demographics.

		PwNID	Controls	p-value
Total participants, n (%)		1134 (55.9)	868 (44.1)	
	P1	423	404	
	P2	88	38	
	P3	623	426	
MS diagnosis, n (%)		1076 (94.9)	–	–
	P1	402/423 (95)		
	P2	85/88 (97)		
	P3	589/623 (95)		
Female gender, n (%)		879 (77.5)	593 (68.3)	p-value = 0.9
	P1	333/423 (79)	326/404 (80)	
	P2	68/88 (77)	28/38 (74)	
	P3	478/623 (77)	342/426 (80)	
Age, mean (sd), total and cross-sectionally		50.4 (12.8)	46.2 (15.0)	p-value = 0.2
	P1	48.1 (12.5)	41.6 (9.6)	
	P2	47.2 (13.2)	50.6 (16.9)	
	P3	52.1 (12.5)	43.0 (11.4)	
Race, Caucasian (%) total and cross-sectionally		1022 (90.1)	823 (94.8)	p-value = 0.9
	P1	380/423 (89)	386/404 (96)	
	P2	71/88 (81)	33/38 (87)	
	P3	571/623 (92)	404/426 (95)	
Disease duration, years (sd), total and cross-sectionally		12.8 (10.3)	–	
	P1	11.8 (9.5)		
	P2	9.2 (8.2)		
	P3	13.9 (10.4)		
CCI, total and cross-sectionally, mean (sd)		1.04 (1.3)	0.96 (1.5)	p-value = 0.002
	P1	1.0 (1.2)	0.8 (1.3)	
	P2	1.1 (1.4)	1.6 (1.9)	
	P3	1.0 (1.4)	1.1 (1.4)	
Loneliness Composite Index, mean (sd), total and cross-sectionally		40 (11.7)	39.3 (10.1)	p-value = 0.1
	P1	40.3 (11.5)	38.8 (9.5)	
	P2	40.2 (10.5)	42.6 (10.9)	
	P3	39.7 (11.6)	38.7 (9.7)	
PROMIS Depression T-score mean (sd), total and cross-sectionally		51.8 (8.5)	50.9 (7.8)	p-value = 0.002
	P1	52.6 (8.1)	51.2 (7.3)	
	P2	53.1 (8.2)	50.6 (8.0)	
	P3	51.2 (8.4)	51.0 (7.5)	
PROMIS Physical Function T-score mean (sd), total and cross-sectionally		45.3 (10.9)	55.7 (9.3)	p-value < 0.001
	P1	47.0 (10.8)	58.8 (7.9)	
	P2	48.0 (10.9)	52.9 (10.0)	
	P3	45.1 (10.9)	56.8 (9.1)	

Periods are defined as first peak (period 1, P1), trough (P2), and second peak (P3) of the pandemic. PwNID, patients with inflammatory neurologic disease; CCI, Charlson Comorbidity Index.

Table 2

ANOVA analysis of PROMIS depression and physical function T-scores over the three periods of the pandemic in 2020 and post-hoc analysis. Post-hoc analysis via Tukey HSD indicates which pair of means was significantly different.

ANOVA, PROMIS Depression T Scores and Pandemic Periods	p-value	Post-hoc analyses
PwNID	0.008	P1 vs P3, p-value 0.017
Controls	0.87	N/A
ANOVA, PROMIS Physical Function T Scores and Pandemic Periods	**p-value**	**Post-hoc analyses**
PwNID	0.006	P1 vs P3, p-value=0.018
Controls	< 0.001	P1 vs P2, p-value <0.001; P1 vs P3, p-value=0.012; P2 vs P3, p-value=0.02

significant risk factors in the model. We generated similar optimal models when including only PwNID or only longitudinal participants (Supplementary Table 3). Interestingly, no regression models found duration of the pandemic or self-reported physical function to be a significant predictor of depression scores, both of which have been previously reported to have close association with depressive symptoms (Ettman et al., 2020; Jones and Amtmann, 2015). For the subset of

participants (21%) who completed questionnaires at two time points (week 1 and week 24), there was no significant change in depression symptoms over time.

3.3. Change in physical function throughout the pandemic

To examine changes in physical function during the pandemic, we compared physical function scores (as measured by PROMIS) between Periods 1, 2 and 3. As expected, PwNID reported worse physical functioning than control subjects at all time points (Fig 2A). Physical function worsened over time for PwNID, with significantly worse physical functioning in P3 compared to P1 (mean score of 45.1 +/- 10.8 in P1 vs 47.0 +/- 10.9 in P3, $p = 0.01$). Interestingly, control subjects also reported significantly worsening physical function over time (mean score of 58.8 +/- 7.9 in P1 vs 56.8 +/- 9.1 in P3, $p = 0.005$). The proportion of individuals with clinically significant physical disability (PROMIS scores of ≤ 40) (Amtmann et al., 2018) was higher in PwNID compared to controls throughout the pandemic, and this proportion rose over time: 25.3% versus 35.5% of PwNID had clinically significant physical disability in P1 and P3, respectively (Fig 2B).

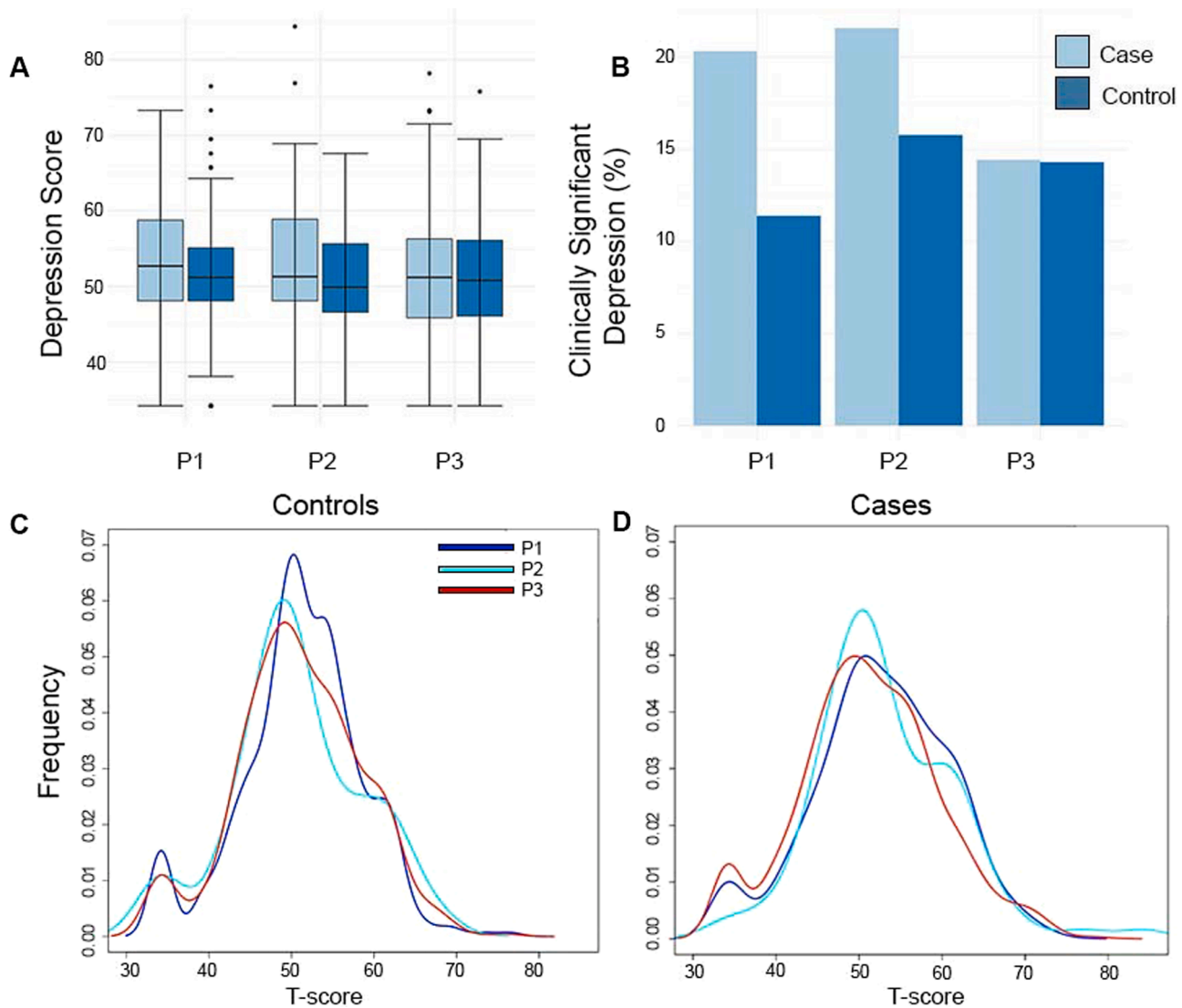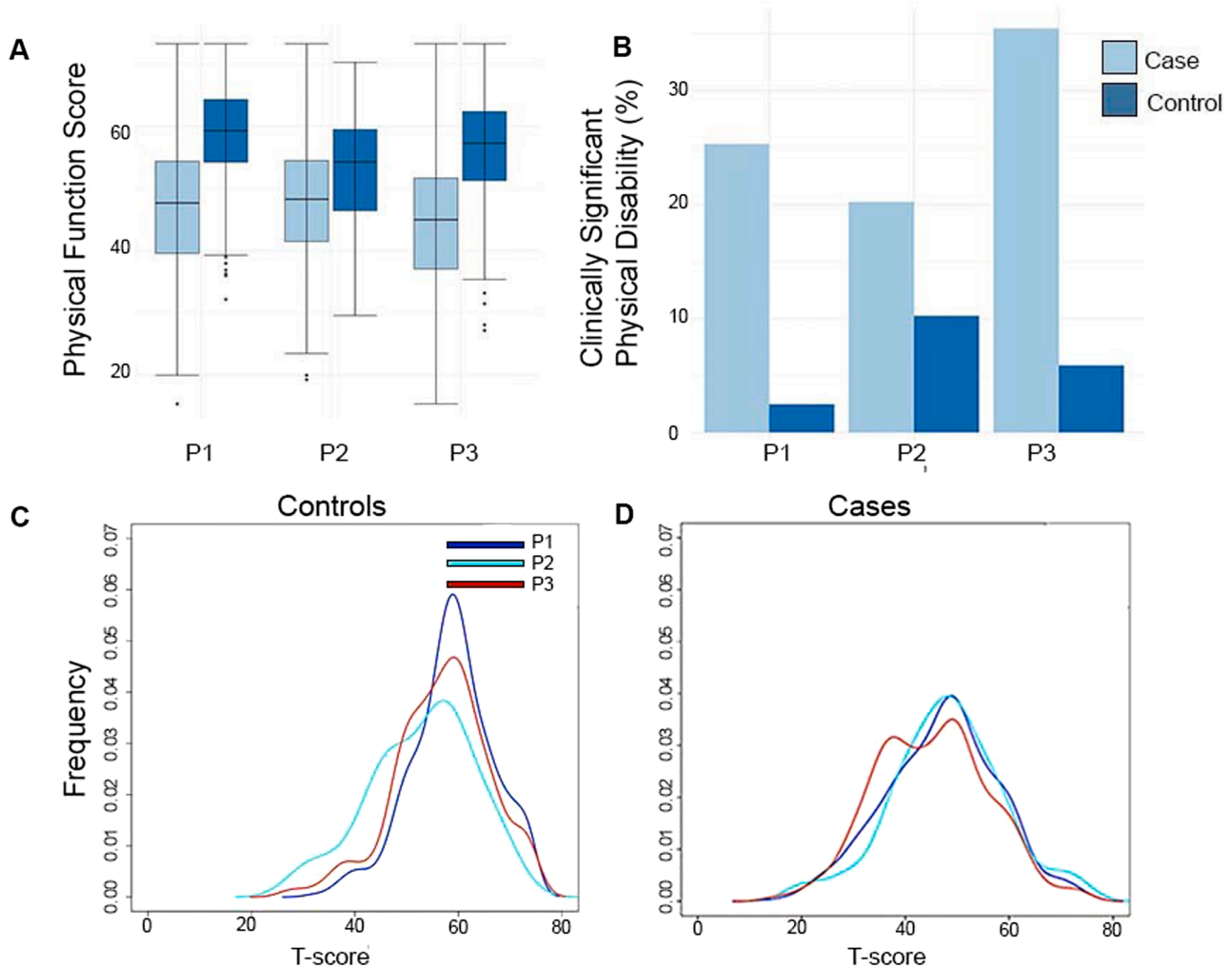The optimal linear regression model for physical function (R^2 0.39,

Fig. 1. PROMIS Depression T-Scores in PwNID and controls during the three periods of the pandemic in 2020: first-wave (P1), trough (P2), and second-wave (P3) pandemic. Higher scores represent increasing depression. (A) Boxplot shows median/interquartile range. B) Proportion of patients with clinically significant depression, defined as PROMIS score of ≥ 60. Distribution of depression scores of controls (C) and PwNID (D) over time.

Table 3

Linear regression models of outcomes.

Dependent Factor	Population	Variables	Coefficients	p-value	Adjusted R-squared
PROMIS Depression	*PwNID and controls*	Older age	−4.3	< 0.001	0.2902
		Male gender	−2.1		
		No neuroinflammatory disease	−6.0		
		Lack of DMT use	5.3		
		Higher loneliness composite index score	12.9		
PROMIS Physical Function	*PwNID and controls*	Older age	−6.3	< 0.001	0.3585
		No neuroinflammatory disease	18.8		
		Higher CCI	−6.2		

Disease status indicates PwNID vs. controls. DMT status, disease modifying therapy; PwNID, person with neurologic inflammatory disease; CCI, Charlson Comorbidity Index.

Fig. 2. PROMIS Physical function scores in PwNID and controls during the three periods of the pandemic in 2020: first-wave (P1), trough (P2), and second-wave (P3) pandemic. Lower scores represent higher physical disability. (A) Boxplot represents median/interquartile range. B) Proportion of patients with clinically significant physical disability, defined as PROMIS scores of ≤40. Distributions of physical function scores for controls (C) and PwNID (D) over time.

p-value <0.001) included age, DMT status, and CCI (Table 3). Older individuals, those with a neuroinflammatory disease, and those with higher CCI scores were at higher risk. Likewise, we generated similar optimal models including only PwNID and only longitudinal participants (Supplementary Table 3). The duration of the pandemic was not a significant predictor of physical function outcomes in the regression models. Similar to depression, the subset of participants who completed questionnaires at two time points (week 1 and week 24) showed no significant change in self-reported physical function over time.

4. Discussion

As of this writing, the COVID-19 pandemic has been ongoing for more than a year. While we have more insight into the risk for COVID-19 and prevention strategies, we lack information on how the pandemic has impacted PwNID both mentally and physically, and how healthcare professionals can best support their patients towards health and recovery. This is the first large, multicenter cohort study to examine pandemic-related changes in mood and physical function among patients with neuroinflammatory disease across a large geographically

contiguous region in North America. As PwNID have a higher incidence of physical disability and comorbid mood conditions at baseline, (Oreja-Guevara et al., 2019; Butler et al., 2016; Feinstein et al., 2014) we initially hypothesized that the COVID-19 pandemic would disproportionately impact this population.

While PwNID had slightly higher depression scores than control subjects at baseline, we found that overall depression scores did not worsen during the pandemic. Indeed, average depression scores decreased slightly over time for PwNID, and the proportion of individuals with clinically significant depression was lower in the second wave (P3) than the first wave (P1) of the pandemic. The rapid shifts in behavior necessitated by the pandemic might have contributed to the higher proportion of PwNID (20.3%) than controls (11.3%) reporting clinically significant depression in the early pandemic, consistent with previous findings that PwNID are at increased risk for mental health disorders and suicide (Feinstein et al., 2014; Kalb et al., 2019; Boeschoten et al., 2017). Interestingly, the proportions of participants with clinically significant depression did not differ between PwNID and controls during the second wave. The lower proportion of PwNID who reported clinically significant depression in P3 suggests the resilience of PwNID with respect to depression and seems to support anecdotal clinical experience. The variables supporting resilience are not entirely clear and warrant further studies. It is conceivable that the emergence of COVID vaccinations in late 2020 and anticipation of the coming end of the pandemic contributed to the modest improvement in depression that was observed. Mood did not appear to significantly impact study retention, as there was no difference in the proportion of subjects who continued to fill out surveys when comparing those with and without clinically significant depression. Loneliness was the strongest predictor of depression identified in our dataset in both PwNID and controls. As the current study surveyed loneliness at only one timepoint, we were unable to evaluate whether loneliness itself changed during the pandemic. Prior analysis of a subset of this patient cohort found that PwNID perceived less social support than the general population (Levin et al., 2021). Importantly, perceived social isolation (i.e., feeling of loneliness) has wide ranging consequences for both physical and mental health (Bzdok and Dunbar, 2020). Although we did not find that the pandemic measurably worsened depression, clinicians should remain vigilant with regular screening and referral for appropriate mental health resources given the high risk of depression among PwNID.

We observed that physical function worsened over time in the pandemic. This was particularly evident for PwNID, with 35% of respondents noting clinically significant disability by P3. The cause is likely multifactorial. During the pandemic, many PwNID were no longer able to access resources such as community centers, gyms, public transportation, home care and rehabilitative services (Block et al., 2021; Lebrasseur et al., 2021), and there may have been interruptions with access to infusion therapies for the 54.6% of patients who reported current infusion DMT therapy (Supplemental Table 4). These restrictions would likely have a greater adverse effect on those with pre-existing physical limitations. Additionally, disrupted use of DMT therapy may have adversely impacted function. Unmeasured lifestyle factors impacting physical function, such as weight and substance use, may also have changed during the pandemic. Many PwNID viewed themselves as at higher risk for COVID-19, either due to their disease or to their immunomodulatory medication and, accordingly, adopted more stringent isolation practices (Zhang et al., 2021). Previous work demonstrated that ambulatory MS patients with high levels of physical activity maintained better physical function regardless of baseline disease severity (Rooney et al., 2021). With the pandemic prompting many PwNID to adopt a "house-bound" status, regular physical exercise likely declined. The effects of the pandemic on lifestyle changes were not restricted to PwNID. Indeed, measurable worsening in physical function was observed across control participants during the mid- and late-pandemic. Age, disease status, and comorbidity burden were the strongest predictors of physical function scores (Learmonth et al., 2013;

Ford et al., 2001; Chou et al., 2020). Our study supports the vulnerability of PwNID to physical deterioration during the pandemic and underscores the need to help patients think creatively about physical activity and suggest COVID-safe ways to maintain a healthy activity level. It will also be important for healthcare professionals to advocate at the individual, local and national levels for prioritized re-institution of rehabilitation and social work services for PwNID.

This survey based study was intended to capture the broad experience of PwNID during the pandemic (in contrast to physician-reported COVID-19 registries, which are enriched for moderate to severe COVID-19 cases). However, there is a limitation of sampling bias. As we recruited a convenience sample to capture the consequences of the pandemic in real time, this cohort does not adequately capture the experience of racial minorities. The online survey format and use of English-language surveys would also have limited participation from those with less technological knowledge/access and from non-English speakers. Therefore, we expect that socioeconomically disadvantaged populations are under-represented in the current data, and dedicated work incorporating these people is needed to accurately represent the magnitude of the pandemic's psychosocial and physical impact This is particularly important, as many health-related as well as socioeconomic consequences of the pandemic have weighed disproportionately on minorities (Rogers et al., 2020; Smith et al., 2020). Additionally, this study utilized rolling enrollment, which was uneven over the course of the pandemic. There were fewer new enrollments in P2 compared to P1 and P3 and some of the patients who enrolled during P1 were no longer regularly completing surveys by P3, limiting the availability of longitudinal data.

Our collaborative multicenter study represents a snapshot of how PwNID experienced the COVID-19 pandemic. This characterization will aid clinicians in understanding and treating PwNID during this and other public health emergencies. As the COVID-19 pandemic evolves, more work will be needed to investigate temporal trends of both mental health and physical function over time, evaluating vicissitudes that may emerge coincident with vaccination and other unexpected events in this at-risk patient population.

CRediT authorship contribution statement

Elle Levit: Conceptualization, Investigation, Methodology, Formal analysis, Writing – original draft. **Inessa Cohen:** Data curation. **Megan Dahl:** Writing – review & editing. **Keith Edwards:** Writing – review & editing. **Bianca Weinstock-Guttman:** Data curation, Formal analysis. **Toshinari Ishikawa:** Data curation, Formal analysis. **Katelyn Kavak:** Writing – review & editing. **Victoria Leavitt:** Writing – review & editing. **Katie Nelson:** Writing – review & editing. **Kaho Onomichi:** Writing – review & editing. **Amit Bar-Or:** Writing – review & editing. **Christopher Perrone:** Writing – review & editing. **Claire Riley:** Writing – review & editing. **Shruthi Venkatesh:** Writing – review & editing. **Philip L. De Jager:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Zongqi Xia:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Erin E. Longbrake:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103482.

References

Dubey, S., Biswas, P., Ghosh, R., et al., 2020. Psychosocial impact of COVID-19. Diabetes Metab. Syndr. 14, 779–788.

Smith, B.J., Lim, M.H., 2020. How the COVID-19 pandemic is focusing attention on loneliness and social isolation. Public Health Res. Pract. 30.

Haji Akhoundi, F., Sahraian, M.A., 2020. Naser Moghadasi A. Neuropsychiatric and cognitive effects of the COVID-19 outbreak on multiple sclerosis patients. Mult. Scler. Relat. Disord. 41, 102164.

Wang, C., Pan, R., Wan, X., et al., 2020. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int. J. Environ. Res. Public Health 17.

Motolese, F., Rossi, M., Albergo, G., et al., 2020. The Psychological Impact of COVID-19 Pandemic on People With Multiple Sclerosis. Front. Neurol. 11, 580507.

Chiaravalloti, N.D., Amato, M.P., Brichetto, G., et al., 2021. The emotional impact of the COVID-19 pandemic on individuals with progressive multiple sclerosis. J. Neurol. 268, 1598–1607.

Oreja-Guevara, C., Ayuso Blanco, T., Brieva Ruiz, L., Hernández Pérez, M., Meca-Lallana, V., Ramió-Torrentà, L, 2019. Cognitive Dysfunctions and Assessments in Multiple Sclerosis. Front. Neurol. 10, 581.

Butler, E., Matcham, F., Chalder, T., 2016. A systematic review of anxiety amongst people with Multiple Sclerosis. Mult. Scler. Relat. Disord. 10, 145–168.

Feinstein, A., Magalhaes, S., Richard, J.F., Audet, B., Moore, C., 2014. The link between multiple sclerosis and depression. Nat. Rev. Neurol. 10, 507–517.

Kobelt, G., Thompson, A., Berg, J., et al., 2017. New insights into the burden and costs of multiple sclerosis in Europe. Mult. Scler. 23, 1123–1136.

Rooney, S., Riemenschneider, M., Dalgas, U., et al., 2021. Physical activity is associated with neuromuscular and physical function in patients with multiple sclerosis independent of disease severity. Disabil. Rehabil. 43, 632–639.

Cederberg, K.L., Motl, R.W., McAuley, E., 2018. Physical Activity, Sedentary Behavior, and Physical Function in Older Adults With Multiple Sclerosis. J. Aging Phys. Act 26, 177–182.

Levin, S.N., Venkatesh, S., Nelson, K.E., et al., 2021. Manifestations and impact of the COVID-19 pandemic in neuroinflammatory diseases. Ann. Clin. Transl. Neurol. 8, 918–928.

Pilkonis, P.A., Yu, L., Dodds, N.E., Johnston, K.L., Maihoefer, C.C., Lawrence, S.M., 2014. Validation of the depression item bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a three-month observational study. J. Psychiatr. Res. 56, 112–119.

Amtmann, D., Bamer, A.M., Kim, J., Chung, H., Salem, R, 2018. People with multiple sclerosis report significantly worse symptoms and health related quality of life than the US general population as measured by PROMIS and NeuroQoL outcome measures. Disabil. Health J. 11, 99–107.

Leavitt, V.M., Riley, C.S., De Jager, P.L., eSupport, Bloom S., 2020. Feasibility trial of telehealth support group participation to reduce loneliness in multiple sclerosis. Mult. Scler. 26, 1797–1800.

Russell, D.W., 1996. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J. Pers. Assess. 66, 20–40.

Bambara, J.K., Turner, A.P., Williams, R.M., Haselkorn, J.K., 2014. Social support and depressive symptoms among caregivers of veterans with multiple sclerosis. Rehabil. Psychol. 59, 230–235.

Ettman, C.K., Abdalla, S.M., Cohen, G.H., Sampson, L., Vivier, P.M., Galea, S., 2020. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. JAMA Netw. Open 3, e2019686.

Jones, S.M., Amtmann, D., 2015. The relationship of age, function, and psychological distress in multiple sclerosis. Psychol. Health Med. 20, 629–634.

Kalb, R., Feinstein, A., Rohrig, A., Sankary, L., Willis, A., 2019. Depression and Suicidality in Multiple Sclerosis: red Flags, Management Strategies, and Ethical Considerations. Curr. Neurol. Neurosci. Rep. 19, 77.

Boeschoten, R.E., Braamse, A.M.J., Beekman, A.T.F., et al., 2017. Prevalence of depression and anxiety in Multiple Sclerosis: a systematic review and meta-analysis. J. Neurol. Sci. 372, 331–341.

Bzdok, D., Dunbar, R.I.M., 2020. The Neurobiology of Social Distance. Trends Cogn. Sci. 24, 717–733.

Block, V.J., Bove, R., Gelfand, J.M., Cree, B.A.C., 2021. Effects of COVID-19 "Sheltering in Place" on Activity in People With Multiple Sclerosis. Neurol. Clin. Pract. 11, e216–e218.

Lebrasseur, A., Fortin-Bédard, N., Lettre, J., et al., 2021. Impact of COVID-19 on people with physical disabilities: a rapid review. Disabil. Health J. 14, 101014.

Zhang, Y., Staker, E., Cutter, G., Krieger, S., Miller, A.E., 2021. Perceptions of risk and adherence to care in MS patients during the COVID-19 pandemic: a cross-sectional study. Mult. Scler. Relat. Disord. 50, 102856.

Learmonth, Y.C., Motl, R.W., Sandroff, B.M., Pula, J.H., Cadavid, D., 2013. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. BMC Neurol. 13, 37.

Ford, H.L., Gerry, E., Johnson, M.H., Tennant, A, 2001. Health status and quality of life of people with multiple sclerosis. Disabil. Rehabil. 23, 516–521.

Chou, I.J., Kuo, C.F., Tanasescu, R., et al., 2020. Comorbidity in multiple sclerosis: its temporal relationships with disease onset and dose effect on mortality. Eur. J. Neurol. 27, 105–112.

Rogers, J.P., Chesney, E., Oliver, D., et al., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 7, 611–627.

Smith, K., Bhui, K., Cipriani, A., 2020. COVID-19, mental health and ethnic minorities. Evid. Based Ment. Health 23, 89–90.