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The Impact of COVID-19 on Fatigue in Multiple Sclerosis

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Running head: COVID-19, Fatigue, and MS

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Practice Points

- People with multiple sclerosis reported worse physical, mental, and emotional fatigue during the COVID-19 quarantine.
- Physical and emotional fatigue remained significantly worse than levels from before quarantine even after the lifting of quarantine restrictions.
- It is critical that health care providers inquire about all types of fatigue in multiple sclerosis.

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Abstract

Background: Although the COVID-19 quarantine required everyone to make lifestyle changes, it may have had especially profound implications for individuals who experience multiple sclerosis (MS)-related fatigue. Individuals with MS who suffer from fatigue are already predisposed to inactivity and social isolation and are at risk of worsening symptoms. The objective of this study was to examine the impact of the COVID-19 national quarantine and related restrictions on the mental, emotional, and physical fatigue in persons with MS in the United States.

Methods: We conducted a survey open to all adults (>18 years) with MS within the United States. The survey gathered demographic information and asked how the COVID-19 pandemic impacted their physical, mental, and emotional fatigue.

Results: The survey was completed by 600 individuals, 478 with relapsing MS and 122 with progressive MS. There was a significant 2-way interaction for time by fatigue type; both physical and emotional fatigue significantly increased during the pandemic ($P < .01$) and remained significantly higher after the pandemic than prior to the pandemic ($P < .01$). Mental fatigue increased significantly during the pandemic ($P < .01$) and although it remained higher, on average, after the pandemic, it was not significantly different than prepandemic.

Conclusions: Individuals with MS experienced increases in physical, mental, and emotional fatigue over the course of the COVID-19 quarantine. Even after the lifting of quarantine restrictions, these levels have not returned to baseline. To adequately address fatigue, it is critical that health care professionals inquire about all types of fatigue in persons with MS. *Int J MS Care*. 2024; XX:XXX-XXX.

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Introduction

Fatigue is one of the most common and debilitating symptoms of multiple sclerosis (MS);¹ it is present in 64% to 81% of people with MS.² Fatigue is commonly reported across disease subtypes and at all stages of the disease. It may arise both from central nervous system damage (primary fatigue) or as a result of accumulation of disease burden (secondary fatigue).³ Regardless of cause, fatigue contributes to a downward spiral of inactivity and social isolation⁴ and is the primary reason for job loss in persons with MS.⁵

To limit the spread of COVID-19, a national emergency was declared in the United States on March 13, 2020, prompting a national quarantine. Although the quarantine forced all residents to make lifestyle changes, it may have had especially profound implications for individuals who experience MS-related fatigue. People with MS who suffer from fatigue are at risk for symptom worsening and are predisposed to inactivity and social isolation. Thus, it is possible that prolonged isolation due to the pandemic may have further diminished physical activity and exacerbated symptoms of MS-related fatigue among people with MS. Indeed, in Turkey, people with MS reported greater fatigue, anxiety, and depression during quarantine than adults without MS;⁶ however, a critical limitation of this study was the cross-sectional assessment of fatigue, anxiety, and depression during the pandemic that did not directly assess the impact of COVID-19 on these symptoms. Whether the pandemic affected self-reported fatigue in people with MS is unclear.

In Italy, when compared to the 12 months prior, the 3-month lockdown resulted in perceived worsening of fatigue and overall disability in 32.4% of individuals with progressive MS, worsening depressive symptoms in 30.4%, and a shift to a more sedentary lifestyle, with 47.1% completely stopping exercise.⁷ Although this study describes COVID-19–related changes in fatigue in people with progressive MS, the study fails to report data on the severity and type of fatigue before or after lockdown. Despite these findings from recent European studies, the impact of the COVID-19 quarantine and the subsequent lifting of quarantine restrictions on

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fatigue in people with MS in the United States has not been examined. Thus, the objective of this study was to examine the impact of the COVID-19 national quarantine and its related restrictions on the mental, emotional, and physical fatigue experienced by people with MS in the United States.

Methods

We conducted a nationwide survey using REDCap (Vanderbilt University), a secure, HIPAA-compliant, browser-based database and survey platform. Part of a larger cross-sectional study evaluating fatigue in people with MS, the survey was distributed through the National Multiple Sclerosis Society monthly newsletter and was available from November 1, 2021 through January 30, 2022. The Impact of COVID-19 survey was open to all adults (>18 years) with MS within the United States and took about 20 minutes to complete. All study procedures were approved by the Wayne State University Institutional Review Board.

The survey gathered demographic information and asked questions regarding fatigue severity, fatigue impact on daily activities, other MS symptoms, and how the COVID-19 pandemic impacted physical, mental, and emotional fatigue. Physical fatigue was defined as a lack of energy, weakness, or feeling “drained”; mental fatigue was defined as a lack of energy to think, brain fog, or feeling mentally tired; emotional fatigue was defined as feeling emotionally overwhelmed, burned out, or defeated.⁸ Each type of fatigue was rated using a scale ranging from 0 (no fatigue) to 10 (extreme fatigue). The survey asked for ratings of fatigue in 3 periods: (1) Prior to March 2020; (2) March 2020 through May 2021; and (3) June 2021 to the present (ie, the day the survey was submitted), representing before the quarantine, during the quarantine, and the period after the easing of quarantine restrictions. Demographic information included age, sex, race, living situation, and employment status. Additionally, we collected information about current disease-modifying therapy, fatigue medication use, ambulatory status, assistive device use, and comorbidities. Disease severity was characterized with the self-reported Patient

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Determined Disease Steps (PDDS). The PDDS is a valid and reliable measure of disease disability in MS.⁹

Analytical Approach

Descriptive data were examined for all variables. Participants who identified as having primary progressive MS or secondary progressive MS were pooled for analysis into a single progressive MS group. This is consistent with the most recent revisions of the MS phenotype descriptions, which consider primary and secondary progressive MS to fall under the umbrella of “progressive MS.”¹⁰ To determine if fatigue levels and fatigue types were significantly different among the 3 time periods, a 2-way analysis of variance (ANOVA) was applied. We explored differences in fatigue across disease subtypes using ANOVA. Tukey post-hoc comparisons were used to examine significant interaction effects.

Results

Sample Demographics

Six hundred individuals living in the United States completed the survey, 478 with relapsing-remitting MS (RRMS) and 122 with progressive MS. Respondents had an average age of 50.9 ±12.5 years. The sample was largely female (82.8%), White (88.1%), living alone (83%), working full- or part-time (53.3%), ambulatory (96%) with relatively low disability (PDDS ≤3) (71%), and taking disease-modifying therapies (83.3%). In this sample, only 31.3% reported current use of medications to manage fatigue (**Table 1**).

Impact of COVID-19 on Fatigue

When asked to rate their physical, mental, and emotional fatigue levels, individuals reported greater fatigue (0-10 scale) during lockdown than before lockdown, and although the level of physical, mental, and emotional fatigue declined following the lifting of quarantine restrictions, fatigue levels did not return to previous levels. Physical fatigue was 0.6 points higher, mental fatigue 1.0 point higher, and emotional fatigue 0.8 points higher (**Table S1**) than before the

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pandemic. There was a significant 2-way interaction of time by fatigue type; physical fatigue significantly increased during the pandemic ($P < .01$) and it remained significantly higher after the pandemic than before it ($P < .01$). Emotional fatigue also significantly increased during the pandemic ($P < .01$) and it remained significantly higher after the pandemic than before it ($P < .01$). Mental fatigue increased significantly during the pandemic ($P < .01$) and although it remained higher, on average after the pandemic, it was not significantly different after the pandemic than before it. Before the pandemic, physical fatigue was significantly greater than emotional ($P < .01$) and mental fatigue ($P < .01$), which did not differ from each other. During the pandemic, there was no difference between severity of physical and emotional fatigue, and both were significantly greater than mental fatigue. After the pandemic, physical fatigue was again significantly greater than both emotional ($P < .01$) and mental fatigue ($P < .01$), which did not differ from each other (**Figure 1A**).

Differences in Fatigue Across Disease Subtypes

There was a significant 2-way interaction of disease subtype by fatigue type; within progressive MS, there was a main effect of fatigue, such that physical fatigue was greater than mental ($P < .01$) or emotional ($P < .01$) fatigue, which did not differ from each other. There were no significant differences in the severity of fatigue subtypes in RRMS. Physical fatigue in individuals with progressive MS was also significantly greater than all types of fatigue in individuals with RRMS (**Figure 1B**).

Impact of COVID-19 on Work and Self-Reported Exercise

Of those individuals with MS who were employed (53.3%), 78.7% reported that their working arrangement (remote/in-person, hybrid) remained stable from before quarantine through quarantine. Only 20.7% reported some shift from remote back to in-person or to hybrid after quarantine (**Table S1**). A greater number of persons with RRMS (60.9%) reported working than did the participants with progressive MS (23.8%) (Table 1). Regardless of MS subtype, about 50% of individuals with MS reported that the pandemic impacted the amount they exercised;

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82.7% reported that the pandemic affected the amount of social interaction they experienced weekly, but only 39.5% endorsed that the pandemic had negatively impacted their relationships (Table S2).

Discussion

The main finding of this study was that physical, mental, and emotional fatigue levels of people with MS in the United States increased during the COVID-19 lockdown, and although they declined slightly with the lifting of lockdown restrictions, these levels did not return to previous levels, which represents an overall worsening of fatigue for people with MS during this time period. Compared to the general population of adults aged 45-86 years, people with MS report 43% to 60% greater fatigue.^{11,12} Although all adults may have experienced a change in fatigue levels as a result of pandemic-related lockdowns, it is possible that the impact on people with MS was even greater. Indeed, 46% of nonhospitalized adults reported fatigue 6 months after having COVID-19. In comparison, all participants in this study reported at least some level of fatigue in the physical, mental, and emotional domains. Current evidence indicates that although fatigue is common in chronic diseases, the prevalence of severe and chronic fatigue is remarkably similar across chronic diseases, except for MS, Parkinson disease, and liver disease, in which the prevalence of severe and chronic fatigue was significantly higher.¹²

A possible explanation for the increased mental and emotional fatigue levels may be changes in routine and responsibilities. The average age of our sample was 50.9 years and 83% lived with another person, so they may have been responsible for caring for young children who were suddenly home from school while also trying to work (53% of the sample was working). The intermingling of tasks and demands on time may contribute to the perception of greater fatigue. A possible explanation for a rise in physical fatigue levels may be related to an increase in sedentary behavior. In this study, individuals reported that the pandemic changed their level of exercise (52%) and social interactions (83%) which may have contributed to leaving the house less and sitting more. In addition, a prior study showed an association between higher self-

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reported fatigue levels and low activity levels, as well as an increased fall risk and lower quality of life in people with MS.¹³ Reports of exercising less during the pandemic suggest that before the pandemic, home-based exercise was not the regular mode of most participants. Thirty-three percent of physical therapists reported that aerobic training was reduced or unavailable during the pandemic and, despite 15% of physical therapists reporting increased use of relaxation/mind-body techniques or fatigue management techniques during the pandemic,¹⁴ fatigue in our sample still rose. There is an ongoing need for exercise services and skilled therapies at major medical centers; thus, clinicians should provide resources to wellness and exercise programming that can be successfully completed at home.

There was some discrepancy in how pandemic periods were defined. We defined 3 periods: before quarantine, prior to March 2020; quarantine, March 2020 through May 2021; and easing of quarantine restrictions, June 2021 to the present (ie, the day the survey was completed). Other studies either did not define the lockdown or quarantine periods (n=6), defined a single year (ie, 2020) for consideration (n=14), or defined only the lockdown period (March 2020 to May 2020) but allowed for tests within 3 (August 2020) and 6 (November 2020) months of lockdown to be considered in the dataset (n=7). Our results build on these studies by extending the focus beyond the immediate lockdown period to determine changes in the perception of fatigue over time.

Limitations

While our sample was large, findings cannot be extrapolated to the general population of individuals with MS due to both survey bias (median PDDS score of 2 with an average age of 50.9) and participant recall bias; recall of fatigue levels over time would be more accurate with a longitudinal study design. Of course, in 2020, we did not anticipate that quarantine and restrictions would persist for such a long period of time. A longitudinal design of periodic surveys and the inclusion of a follow-up survey would potentially better capture fatigue and further our understanding of how long elevated perceptions of fatigue persist. Our data overcomes some of these limitations by capturing different types of fatigue (physical, mental,

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emotional), albeit with simple survey questions created for this study that rank fatigue on a 0 to 10 scale. We did not differentiate whether fatigue was due to the pandemic or the worsening of disease and/or symptoms due to reduced activity levels, or whether it might be due to a combination of these factors. Finally, we did not ask participants whether they had a positive COVID-19 test, so we are unable to determine if elevated fatigue levels may have been, in part, due to long-COVID.¹⁵

Conclusions

Fatigue is a common and debilitating symptom that can negatively impact quality of life. People with MS experienced increases in physical, mental, and emotional fatigue over the course of the COVID-19 quarantine and levels of fatigue did not return to baseline levels even after quarantine restrictions were lifted. Interestingly, prior work suggests that fatigue ratings tend to remain relatively stable over an 18-month period,¹⁶ which suggests that changes reported during COVID-19 lockdown may exceed natural disease progression. Persons with progressive MS reported higher levels of fatigue than those with RRMS. Providers who are attuned to the impact of fatigue can intervene with timely management strategies, but to adequately address fatigue, it is critical that health care professionals ask people with MS about all fatigue domains, which aligns with recent best-practice recommendations to use the Modified Fatigue Impact Scale to assess multiple domains of fatigue for comprehensive fatigue management in people with MS.¹⁷

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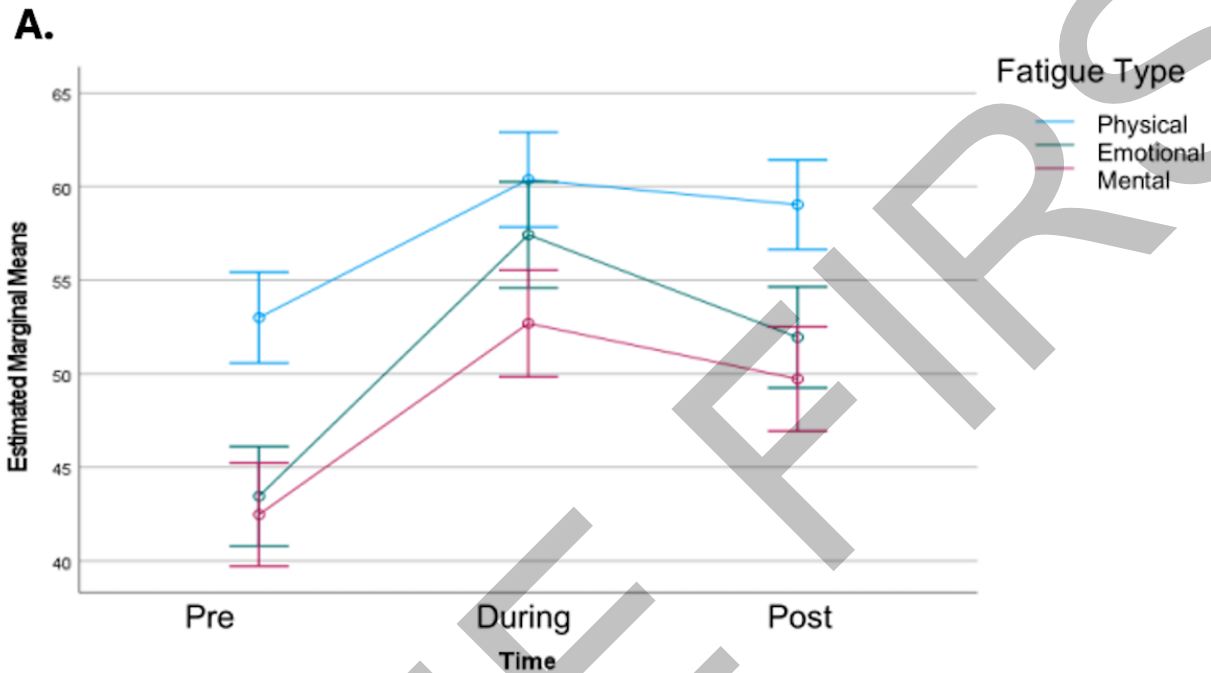
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Figure 1A. Fatigue Type by Time

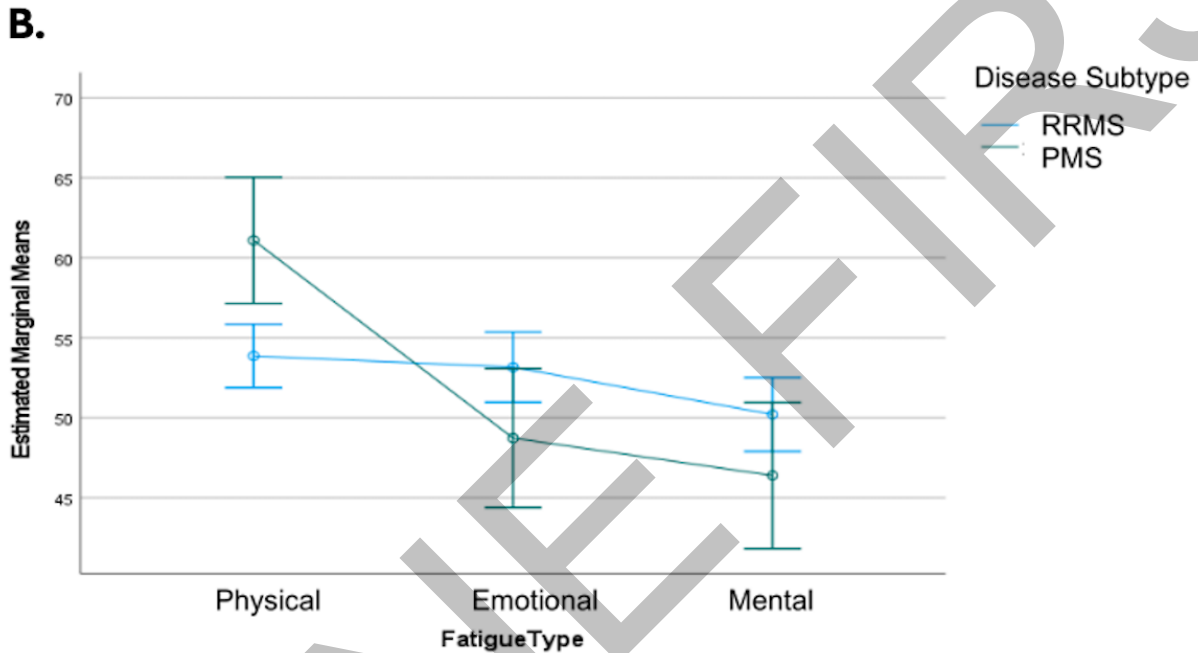


Note: Error bars 95% CI.

Physical, emotional, and mental fatigue significantly increased prior to the pandemic and during the pandemic and remained higher after the pandemic.

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Figure 1B. Fatigue Type by Disease Subtype



MS, multiple sclerosis; PMS, progressive MS; RRMS, relapsing-remitting MS

Note: Error bars 95% CI.

Individuals with progressive MS demonstrate higher levels of physical fatigue, but lower levels of emotional and mental fatigue than individuals with relapsing MS.

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Table 1. Study Demographics

	All MS (N=600)	RRMS (n=478)	Progressive MS (n=122)
Age (years) Mean (SD)	50.9 (12.5)	48.7 (12.5)	58.9 (12.2)
Sex, n			
Male	98	68	30
Female	497	405	92
Nonbinary	5	5	0
Patient Determined Disease Steps score median [range]	2 [7]	2 [7]	2 [7]
Race, n			
Asian or Pacific Islander	6	5	1
Black or African American	32	29	3
Hispanic or Latino	21	15	6
Native American or Alaskan Native	3	2	1
White or Caucasian	529	419	110
Biracial or multiracial	9	8	1
Environment, n			
Urban	116	98	18
Suburban	384	305	79
Rural	100	75	25
Live alone, n			
Yes	102	88	14
No	498	390	108
Work, n			
Yes	320	291	29
No	280	187	93
Disease-modifying therapy, n			
Yes	500	412	88
No	100	66	34
Taking fatigue medication, n			
Yes	188	146	42
No	412	332	80

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Able to walk, n	Yes	576	472	104
	No	24	6	18

MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis

Table S1. Fatigue Levels Before, During, and After COVID-19 Lockdown

	Before	During	After
Physical			
All MS	5.4 (2.4)	5.9 (2.5)	5.8 (2.3)
RRMS	5.1 (2.5)	5.8 (2.6)	5.7 (2.4)
PMS	5.4 (2.3)	6.1 (2.3)	5.9 (2.2)
Emotional			
All MS	4.4 (2.7)	6.0 (2.8)	5.5 (2.6)
RRMS	4.5 (2.7)	5.9 (2.9)	5.4 (2.7)
PMS	4.9 (2.4)	6.2 (2.6)	5.7 (2.5)
Mental			
All MS	4.5 (2.7)	5.5 (2.8)	5.2 (2.7)
RRMS	4.4 (2.8)	5.4 (2.9)	5.1 (2.8)
PMS	4.7 (2.6)	5.7 (2.7)	5.4 (2.6)

Note: All values are listed as mean (SD). Fatigue was rated on a 0 “no fatigue” to 10 “extreme fatigue” scale.

MS, multiple sclerosis; PMS, progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

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Table S2. Impact of COVID-19 Lockdown on Work, Exercise, and Relationships

	All MS N=600	RRMS N=478	PMS N=122
Was your work remote or in-person during lockdown?	320	291	29
Always remote	119	103	16
Always in-person	89	85	4
Always hybrid mix of in-person and remote	47	44	3
Initially remote, but switched to in-person	32	30	2
Initially remote, but now hybrid of remote & in-person	30	26	4
Not reported	3	3	0
Did the Covid-19 pandemic affect your amount of exercise?			
No	289	227	62
Yes	311	251	60
Has the Covid-19 pandemic affected the amount of social interaction you experience on a weekly basis?			
No	104	85	19
Yes	496	393	103
Has the Covid-19 pandemic negatively impacted your relationships?			
No	363	299	64
Yes	237	179	58

Note: All values reported as number of persons (n).

MS, multiple sclerosis; PMS, progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.