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Severity and worsening of fatigue among individuals with multiple sclerosis

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Abstract

Background: Fatigue is associated with reduced quality of life and social participation, and poor employment outcomes. However, most studies examining fatigue are limited by small sample sizes or short follow-up periods.

Objective: To characterize the natural history of fatigue.

Methods: The North American Research Committee on Multiple Sclerosis Registry participants with ≥7 years of longitudinal data between 2004 and 2019 and a relapsing disease course were included. A subset of participants enrolled within 5 years of diagnosis was identified. The Fatigue Performance Scale assessed fatigue and ≥1-point increase in Fatigue Performance Scale sustained at the next survey defined fatigue worsening.

Results: Of 3057 participants with longitudinal data, 944 were within 5 years of multiple sclerosis diagnosis. Most participants (52%) reported fatigue worsening during follow-up. Median time to fatigue worsening ranged from 3.5 to 5 years at lower levels of index fatigue. Fatigue worsening was associated with lower annual income, increasing disability, lower initial fatigue level, taking injectable disease-modifying therapies and increasing depression levels in the relapsing multiple sclerosis participants.

Conclusion: Most multiple sclerosis participants early in their disease suffer from fatigue and at least half reported fatigue worsening over time. Understanding factors associated with fatigue may help to identify populations most at risk of fatigue worsening will be informative for the overall management of patients with multiple sclerosis.

Keywords: Multiple sclerosis, fatigue, North American Research Committee on Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is associated with many symptoms, but fatigue is one of the most debilitating symptoms experienced by individuals with MS, affecting 50%–8% of individuals.[1–5] Up to 69% of patients describe fatigue as their worst symptom.[6,7] Fatigue, often defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, is multidimensional in nature, encompassing physical and cognitive aspects, and can be influenced by multiple factors.[8,9] MS-related fatigue is adversely associated with walking ability, health-related quality of life (QoL), depression, anxiety and social participation.[9] Despite the availability of behavioral and some limited pharmacologic interventions, fatigue remains an issue.[10,11]

Longitudinal studies on fatigue in MS are limited, but most showed a high proportion of individuals with persistent fatigue.[7,12–14] One study found no association between the change in fatigue score and the change in disability measured by Expanded Disability Status Scale (EDSS).[13] Two other studies found that patients who were fatigued at baseline were not more likely than non-fatigued patients to have progression in their disability.[15,16] However, these studies followed individuals for only 1–3 years and were conducted in relatively small

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cohorts. In contrast, a study of 134 individuals enrolled in a two-year clinical trial of interferon beta-1a found that those with worsening fatigue during the initial two years had greater progressive brain atrophy over the following six years.[17] Given the varied association of fatigue with poor outcomes, a better understanding of the natural history of fatigue and the factors associated with fatigue worsening would be useful to identify when fatigue indicates someone is at risk for poor outcomes. Thus, we aimed to characterize the natural history and worsening of fatigue in MS in people with MS in a larger cohort with a longer duration of follow-up.

Methods

Study population

The North American Research Committee on Multiple Sclerosis (NARCOMS) registry is a self-report registry for persons with MS. Since 1996, the registry has collected self-reported demographic and clinical information. Participants complete an enrollment survey and update their information semi-annually thereafter. The diagnoses of MS and outcome measures used in the registry have been validated.[18–20]

This analysis included participants who were enrolled in the NARCOMS Registry, lived in the United States, reported physician-confirmed MS diagnosis with a relapsing initial course (RMS), and had at least 7 years of follow-up with at least 50% of their follow-up surveys completed to have sufficient follow-up to capture changes in fatigue over time. Additionally, participants included had a fatigue score for the initial survey. To better understand the natural history of fatigue in participants from MS diagnosis, we identified participants in this cohort who were enrolled in the NARCOMS Registry within five years of their MS diagnosis (early RMS cohort). Data from semi-annual surveys between 2004 and 2019 were utilized for this analysis and the maximum follow-up possible was 15 years.

Standard protocols, approvals and consents

Participants permit the use of their de-identified information for research purposes. The NARCOMS registry is approved by the Institutional Review Board at UT Southwestern. The datasets presented in this article are not publicly available because the datasets generated and analyzed for this study are held by the NARCOMS Registry (https://www.narcoms.org). Requests to access the datasets should be directed to MSregistry@narcoms.org. The statistical analysis plan for this work was not registered prior to being conducted.

Participant characteristics

At enrollment, participants reported date of birth, sex, race and ethnicity, education, age at onset of MS symptoms and diagnosis, and MS clinical course. Race and ethnicity were categorized as White or non-White due to the small number of participants in the African American, Asian, Hispanic and Latino, and other racial and ethnic categories. We categorized education level as > high school/GED or not.

Disability

The Patient Determined Disease Steps (PDDS) is a single-item measure of disability with response options ranging from 0 (normal) to 8 (bedridden). It correlates highly with a physician-scored EDSS score.[21] The PDDS is collected in every survey including enrollment from participants.

Fatigue

The Fatigue Performance Scale (FPS) is a single-item measure used to assess fatigue impairment in the past month. Participants evaluate their level of fatigue by selecting one of six levels: normal fatigue (0) where there are no limitations on activity or lifestyle, minimal fatigue (1), mild fatigue (2), moderate fatigue (3), severe fatigue (4) that forces the participant to modify their daily activities every day, or total fatigue disability (5), where fatigue prevents the participant from doing many of their daily activities. It is a psychometrically validated scale to measure fatigue levels in patients with MS with the FPS demonstrating a strong correlation with the Modified Fatigue Impact Scale ($r = 0.72$), Fatigue Severity Scale ($r = 0.75$) and the PROMIS Fatigue measure ($r = 0.83$), thereby indicating concurrent validity.[19,22,23] The FPS also demonstrated construct validity.[20,22] Fatigue worsening was defined as at least a 1-point increase in the FPS sustained at the next survey.

Data analysis

We summarized participant characteristics using means (SD), median (interquartile range), and frequency (percentage). The index fatigue level was the FPS at the first survey available for a participant. Comparisons between index fatigue levels of fatigue or those with and without fatigue worsening were evaluated using analysis of variance (ANOVA), Kruskal–Wallis test, as appropriate, for continuous variables and chi square test for categorical variables.

Factors associated with fatigue worsening were examined using the Kaplan–Meier method and multivariable Cox proportional hazards regression models. Total fatigue at index (FPS = 5) was excluded as worsening was not possible at this level. We evaluated the following baseline characteristics determined a priori: age at MS diagnosis (years, continuous), White race (non-White race as a reference group, binary), female sex (male sex as reference group, binary), income > $50,000 annually (income ≤$50,000 annually reference group, binary), education level (≤ high school diploma or GED reference group, binary), disease-modifying therapy used at index (none, injectable, infusion and oral), and PDDS at index (ordinal). We assessed the proportional hazards assumptions using an interaction term between each factor in the model and log(time), with time defined as the time from the index date to worsening or the end of follow-up. A sensitivity analysis was conducted including depression (ordinal) from enrollment due to an increased amount of missing data at index because the scale was not consistently included early in the registry surveys. Variable selection was conducted a priori and informed by literature review. Hazard ratios (HR) and their 95% confidence interval (95%CI) are presented. The significance level was set at 0.05. Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary, NC).

Results

Participants

As of December 31, 2019, over 12,000 RMS participants enrolled in the NARCOMS Registry had at least one follow-up survey between 2004 and 2019. Of those, 3057 had an initial FPS score and completed at least 50% of surveys for at least 7 years of follow-up (Figure 1). Participants had a mean (SD) age at their index survey of 49.8 (10.1) years and most were female (80.2%) and White (88.9%, Table 1). The average age at diagnosis was 40.3 (9.9) and the median (25th, 75th) PDDS level at the index was Moderate Disability (Minimal Disability, Late Cane). Most participants reported some fatigue with only 8.6% of the participants reporting normal fatigue levels. Increasing fatigue was associated with increasing age, disease duration and disability level and depression at enrollment (all $p < 0.001$, Table 1). Gender, education level, DMT, relapses and employment were also associated with fatigue while race was not (Figure 2).

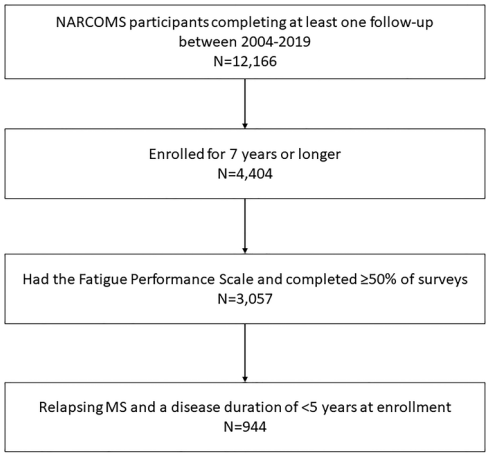

Figure 1. Participant disposition.

Fatigue at time of MS diagnosis

Of the 3057 participants, 944 (30.9%) participants enrolled within 5 years of the MS diagnosis and had a relapsing disease course, thus allowing for a more homogeneous characterization of the natural history from MS diagnosis. The early RMS cohort was also mostly female (83.5%) and White (87.5%) and had a mean (SD) age of 45.5 (9.7, Table 2 and Supplemental Table 1). The average age at diagnosis was 42.6 (9.5) and had a median disability of Mild Disability (Minimal Disability, Early Cane). A large proportion of participants in the early RMS cohort reported some level of fatigue (90.6%, Supplemental Table 1).

Fatigue worsening

Within the early RMS cohort, 491 (52%) reported worsening fatigue that was sustained over the follow-up period. The median length of follow-up in this cohort of 8 (2.5, 11.5) years. A majority of participants at lower levels of fatigue at the index had a higher proportion of worsening fatigue (Normal, 69.7%; Minimal, 71.4%) over follow-up while Mild Moderate and Severe levels of fatigue had a lower proportion of participants (60.9%, 57.4%, and 20.6%, respectively) with fatigue worsening (trend $p < 0.0001$).

The time to fatigue worsening increased for each level of index fatigue where the median (25th percentile, 75th percentile) time to worsening in those with no fatigue at index was 3.5 (2.5, 6.0) years and 4.0 (2.0, 5.0) years in those with minimal fatigue. Participants with mild fatigue at index had a median time of 5.5 (4.0, 9.0) years to fatigue worsening while those with moderate fatigue had a median time of 8.0 (6.0, 11.5) years (Figure 3). Multiple factors were associated with a faster rate of fatigue worsening in the multivariable Cox regression analyses (Table 3), including disability level, disease-

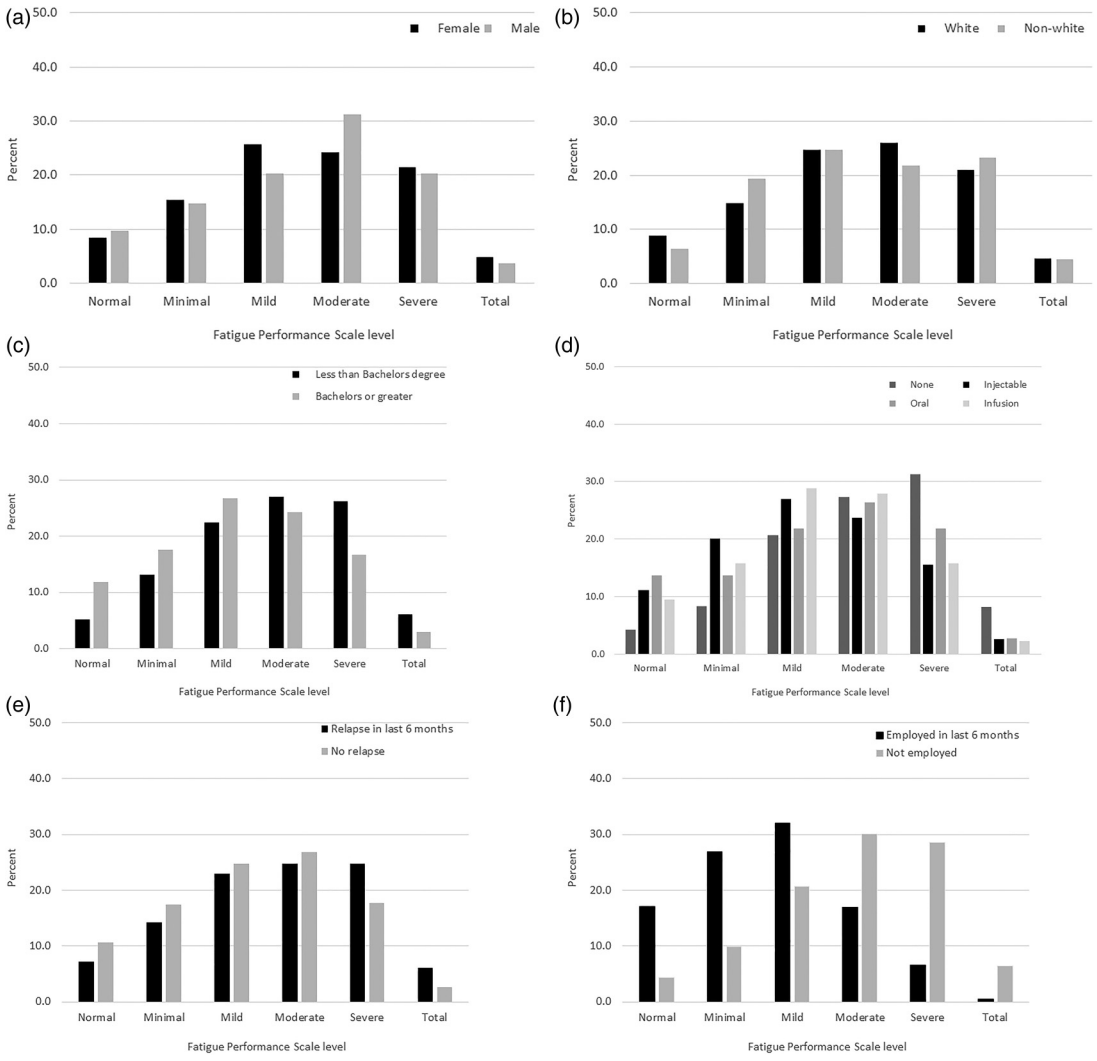

Figure 2. Proportion of fatigue levels within the cohort participant characteristics. (A) gender, (B) race, (C) education level, (D) disease-modifying therapy, (E) relapse in the past 6 month, (F) employment status in the past 6 months. The percentage shown is based on the distribution of the Fatigue Performance scale by each level of the participant characteristic.

modifying therapy type, annual income, and index fatigue level ($p < 0.001$). Increasing disability level was associated with a 9.5% increased hazard of fatigue worsening (HR (95%CI): 1.10 (1.04, 1.15), $p = 0.0005$). Compared to those on injectable disease-modifying therapies, participants on oral therapies or no DMT had a reduced hazard of fatigue worsening while those participants on an infusion DMT were not statistically significantly different (Oral: 0.49 (0.305, 0.797), $p = 0.004$; No DMT: 0.29, (0.215, 0.395), $p < 0.0001$; Infusion: 1.03 (0.7640, 1.396), $p = 0.834$). Annual household income greater than $50,000 was associated with a 30.5% decreased hazard of fatigue worsening ($p = 0.026$). No association was observed for age, race, sex, and education level with worsening fatigue. Sensitivity analyses which included depression level at enrollment were consistent, and showed an association between increased depression and worsening fatigue (HR (95%CI): 1.117 (1.014, 1.230), $p = 0.025$).

Discussion

In this longitudinal study involving 3057 participants we found over 90% of participants reported fatigue. Using over 15 years of longitudinal fatigue data, we observed that over time participants with lower reported fatigue levels initially worsened over 3.5–5.5 years. Fatigue worsening was associated with the lower initial fatigue level, lower total annual income, increasing disability, taking injectable disease-modifying therapies and increasing depression levels in the relapsing MS participants.

Table 1. Participant characteristics.

		Fatigue Performance Scale						
	Overall	Normal	Minimal	Mild	Moderate	Severe	Total	*p*-value
N (%)	3057	264 (8.6)	468 (15.3)	755 (24.7)	782 (25.6)	649 (21.2)	139 (4.5)	-
Age at index	49.8 ± 10.1	46.5 ± 10.9	48.4 ± 11.2	48.9 ± 10.1	51.2 ± 9.9	51.3 ± 8.8	50.6 ± 7.5	***<0.001***[a]
Gender								***0.003***[c]
Female	2452(80.2)	205(77.7)	379(81.0)	632(83.7)	593(75.8)	526(81.0)	117(84.2)	
Male	605(19.8)	59(22.3)	89(19.0)	123(16.3)	189(24.2)	123(19.0)	22(15.8)	
Race								0.10[c]
White	2717(88.9)	242(91.7)	402(85.9)	671(88.9)	708(90.5)	570(87.8)	124(89.2)	
Non-White	340(11.1)	22(8.3)	66(14.1)	84(11.1)	74(9.5)	79(12.2)	15(10.8)	
Level of education*								***<0.001***[c]
Less than Bachelors degree	1435(47.6)	74(28.4)	188(40.4)	322(43.2)	388(50.3)	376(58.8)	87(65.4)	
Bachelors or greater	1580(52.4)	187(71.6)	277(59.6)	423(56.8)	384(49.7)	263(41.2)	46(34.6)	
Age at symptom onset	32.3 ± 10.2	33.2 ± 10.1	33.7 ± 10.4	32.2 ± 10.0	32.4 ± 10.4	31.6 ± 9.9	29.5 ± 10.0	***<0.001***[a]
Age at diagnosis	40.3 ± 9.9	38.6 ± 10.0	40.4 ± 10.4	39.6 ± 9.6	41.1 ± 10.0	41.0 ± 9.5	39.7 ± 9.6	***<0.001***[a]
Disease duration at enrollment	7.9 ± 8.2	6.6 ± 8.4	6.5 ± 7.9	7.7 ± 8.3	8.4 ± 8.2	8.7 ± 8.3	9.0 ± 7.9	***<0.001***[a]
PDDS*	3.0[1.00,5.0]	0.00[0.00,3.0]	1.00[0.00,4.0]	3.0[1.00,4.0]	4.0[2.0,6.0]	4.0[3.0,6.0]	5.0[3.0,7.0]	***<0.001***[b]
Disease-modifying therapy								***<0.001***[c]
None	1056(34.5)	45(17.0)	88(18.8)	218(28.9)	288(36.8)	330(50.8)	87(62.6)	
Injectable	1617(52.9)	179(67.8)	324(69.2)	437(57.9)	384(49.1)	251(38.7)	42(30.2)	
Oral	110(3.6)	15(5.7)	15(3.2)	24(3.2)	29(3.7)	24(3.7)	3(2.2)	
Infusion	222(7.3)	21(8.0)	35(7.5)	64(8.5)	62(7.9)	35(5.4)	5(3.6)	
Less common DMTs	52(1.7)	4(1.5)	6(1.3)	12(1.6)	19(2.4)	9(1.4)	2(1.4)	
Any relapse in last 6 months*								***<0.001***[c]
Yes	805(43.0)	58(33.7)	115(38.2)	185(41.1)	199(41.0)	199(51.3)	49(63.6)	
No	1068(57.0)	114(66.3)	186(61.8)	265(58.9)	286(59.0)	189(48.7)	28(36.4)	
Employed in last 6 months*								***<0.001***[c]
Yes	977(34.3)	167(67.1)	263(58.7)	313(44.8)	165(22.7)	64(10.7)	5(4.0)	
No	1870(65.7)	82(32.9)	185(41.3)	386(55.2)	562(77.3)	534(89.3)	121(96.0)	

*Data not available for all subjects. Missing values: Level of Education = 42, PDDS = 49, Any relapse in last 6 months = 1184, Employed in Last 6 months = 210.
PDDS: Patient Determined Disease Step; ANOVA: analysis of variance.
Values presented as Mean ± SD, Median [P25, P75] or *N* (column %).
p-values: a = ANOVA, b = Kruskal–Wallis test, c = Pearson's chi-square test.

Table 2. Early RMS participant characteristics overall and by fatigue worsening.

	Overall ($N = 944$)	No fatigue worsening ($N = 453$)	Fatigue worsening ($N = 491$)	p-value
Age at initial survey	45.5 ± 9.7	46.2 ± 9.4	44.9 ± 9.9	***0.032***[a]
Gender				0.28[c]
Female	788(83.5)	372(82.1)	416(84.7)	
Male	156(16.5)	81(17.9)	75(15.3)	
Race				0.39[c]
White	826(87.5)	392(86.5)	434(88.4)	
Non-White	118(12.5)	61(13.5)	57(11.6)	
Level of Education*				
Less than Bachelors degree	412(44.0)	211(46.9)	201(41.3)	0.08[c]
Bachelors or greater	525(56.0)	239(53.1)	286(58.7)	
Annual income*				***0.023***[c]
<15,000	73(7.8)	35(7.7)	38(7.9)	
15,001–30K	115(12.3)	63(13.9)	52(10.8)	
30,001–50K	156(16.7)	68(15.0)	88(18.3)	
50,001–100K	245(26.3)	102(22.6)	143(29.7)	
Over 100K	196(21.0)	99(21.9)	97(20.2)	
I do not wish to answer	148(15.9)	85(18.8)	63(13.1)	
Age at symptom onset	34.0 ± 10.1	34.1 ± 10.3	33.9 ± 9.9	0.83[a]
Age at diagnosis	42.6 ± 9.5	43.1 ± 9.3	42.2 ± 9.6	0.16[a]
Disease duration diagnosis to enrollment	1.9 ± 1.6	2.0 ± 1.6	1.7 ± 1.5	***0.002***[a]
PDDS*	2.0[1.00,4.0]	2.0[1.00,5.0]	2.0[1.00,4.0]	0.13[b]
Depression, at enrollment*	1.00[0.00,2.0]	1.00[0.00,2.0]	1.00[0.00,2.0]	0.10[b]
Fatigue at index				***<0.001***[c]
Normal	89(9.4)	27(6.0)	62(12.6)	
Minimal	168(17.8)	48(10.6)	120(24.4)	
Mild	225(23.8)	88(19.4)	137(27.9)	
Moderate	230(24.4)	98(21.6)	132(26.9)	
Severe	194(20.6)	154(34.0)	40(8.1)	
Total	38(4.0)	38(8.4)	0(0.0)	
Disease-modifying therapy*				***<0.001***[c]
None	250(26.5)	196(43.3)	54(11.0)	
Injectable	559(59.2)	201(44.4)	358(72.9)	
Oral	51(5.4)	32(7.1)	19(3.9)	
Infusion	75(7.9)	20(4.4)	55(11.2)	
Less common DMTs	9(0.95)	4(0.88)	5(1.0)	
Any relapse in last 6 months*				0.54[c]
Yes	546(65.9)	255(64.9)	291(66.9)	
No	282(34.1)	138(35.1)	144(33.1)	
Employed in last 6 months*				***<0.001***[c]
Yes	409(46.0)	163(39.7)	246(51.5)	
No	480(54.0)	248(60.3)	232(48.5)	

*Data not available for all subjects. Missing values: Level of Education = 7, PDDS = 15, Depression, at enrollment = 136, Any relapse in last 6 months = 116, Disease-modifying therapy = 250, employed in last 6 months = 55.
MS: multiple sclerosis; PDDS: Patient Determined Disease Step; ANOVA: analysis of variance.
Values presented as Mean ± SD, median [P25, P75], median (min, max) or N (column %).
p-values: a = ANOVA, b = Kruskal-Wallis test, c = Pearson's chi-square test.

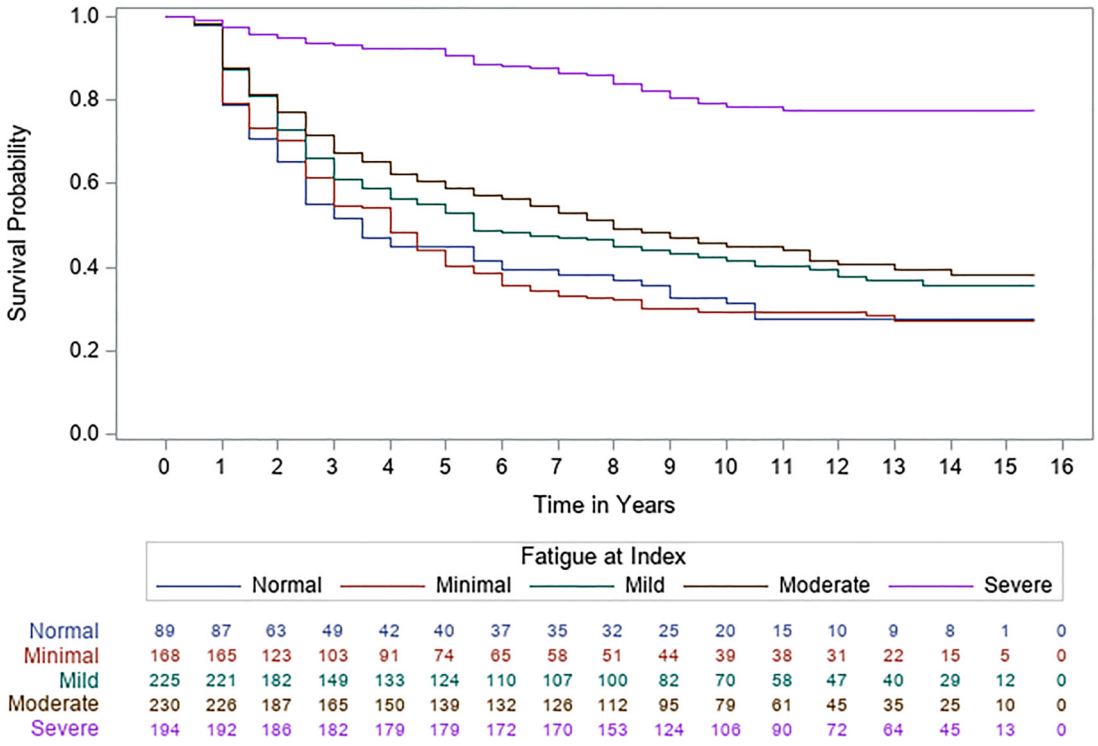

Figure 3. Fatigue worsening in early relapsing multiple sclerosis.

Early in the RMS disease course, a high proportion of participants reported at least minimal fatigue and 72.8% had mild fatigue or greater (i.e., similar to not considering borderline fatigue levels as fatigued with the FSS). This is consistent with other studies showing that fatigue is reported early and in a high proportion of persons with MS (36%–78%).[24] While literature estimates of individuals with MS who have fatigue have a wide range—possibly due to variation in study methodology, regional differences and fatigue assessments used, our estimates are within the range of reported estimates.

The rich longitudinal data in the NARCOMS Registry allowed us to characterize fatigue over time. Importantly, we observed over half of the participants early in their MS diagnosis reported worsening of their fatigue and the median time to worsening fatigue ranged between 3.5 and 5.5 years. Prior longitudinal studies showed that fatigue persisted at constant levels but was generally of 1–3 years duration. Our findings suggest that follow-up in excess of 5 years may be needed to fully understand the evolution of fatigue in people with MS. One study examined change over a 10-year period and found no statistically significant change in fatigue. Yet, the study captured fatigue at only two time points, used dichotomized fatigue levels and included a smaller number of persons with MS ($n = 96$), all of which limited power to detect change over time.[25] Over shorter time periods, efforts have focused on characterizing patterns of fatigue changes.[26,27]

We observed an association between worsening fatigue for those on an injectable DMT compared to those not taking a DMT or those on oral DMTs. Yet, the time frame of our study and the amount of follow-up needed for inclusion in the analysis, results in a limited number of DMTs other than injectable DMTs and the results regarding oral DMTs should be interpreted with caution. An older study showed no differences in fatigue or changes in fatigue over a year between those on injectable DMTs and those not taking a DMT.[28] Our results may differ from this study due to differences in the underlying measure of fatigue used, sample size, or length of follow-up. Clinical trial outcome data and their association with fatigue would be helpful for understanding the effect of DMTs on fatigue.

Other studies have also reported baseline fatigue level being associated with changes in fatigue[8,28] however, disability level has been inconsistently associated with fatigue.[13,15,16,29–31] After adjusting for multiple

Table 3. Factors associated with worsening fatigue based on multivariable Cox regression.

		Model 1				Model 2 (Sensitivity)			
Factor		Hazard ratio	95% Hazard ratio confidence limits		*p*-value	Hazard ratio	95% Hazard ratio confidence limits		*p*-value
Age at index		1.004	0.995	1.014	0.3761	1.007	0.996	1.018	0.2295
Race	White vs non-White	1.222	0.918	1.626	0.1700	1.234	0.911	1.672	0.1749
Gender	Female vs male	1.236	0.959	1.594	0.1014	1.235	0.942	1.618	0.1268
Annual income	>$50,000 vs <$50,000	0.744	0.602	0.919	0.0060	0.766	0.606	0.968	0.0255
	I do not wish to answer vs <$50,000	0.587	0.437	0.788	0.0004	0.601	0.433	0.833	0.0022
Education level	Associates/technical degrees vs less than Bachelors	1.268	0.953	1.687	0.1037	1.183	0.869	1.611	0.2866
	Bachelors/Post Bachelors vs less than Bachelors	1.028	0.815	1.297	0.8147	0.952	0.740	1.226	0.7052
Patient Determined Disease Step (PDDS)		1.093	1.043	1.147	0.0002	1.095	1.041	1.153	0.0005
Disease-modifying therapy	None vs injectable	0.261	0.195	0.350	<.0001	0.291	0.215	0.395	<.0001
	Infusion vs injectable	1.054	0.784	1.417	0.7257	1.033	0.764	1.396	0.8342
	Oral vs injectable	0.429	0.269	0.684	0.0004	0.493	0.305	0.797	0.0039
Fatigue at index		0.683	0.630	0.741	<.0001	0.647	0.589	0.711	<.0001
Depression at enrollment		-	-	-	-	1.117	1.014	1.230	0.0245

factors, there was an association between increasing disability and fatigue worsening. Little information is known regarding the association of socioeconomic status with fatigue, except that fatigue has been shown to be associated with economic outcomes in persons with MS mainly with respect to employment and should be considered as an area of future research.[24] The association between depression and fatigue has been studied frequently and similar to many of those studies we found a moderate association between depression and fatigue reported among participants.[13,29,32]

Our study is not without limitations. The NARCOMS Registry is a voluntary registry for persons with MS and participants in the NARCOMS registry may not be fully representative of the MS population. The mean age of the NARCOMS cohort is similar to the peak prevalence of MS in the US, however, representation of diverse racial/ethnic populations is limited in the registry.[33] We used a single-item scale with a 6-month recall period to measure global MS fatigue in our participants and it may not capture daily fluctuations or specific domains of fatigue as well as other measures. Yet, the NARCOMS Registry has used the validated FPS longitudinally since 2004 and the FPS strongly correlates with the MFIS and FSS.[22] Fatigue worsening was defined as at least a 1-point sustained change in the FPS, for which the minimally important difference has not been determined. However, the FPS validation study showed a linear relationship with the MFIS (MFIS = 17.8 + FPS X 10.6) where each level of the FPS corresponds to approximately 10 points on the MFIS suggesting a 1-point change likely corresponds to a meaningful change in fatigue using the FPS.[22] Last, we did not systematically capture treatment for fatigue. However, the use of medications for MS fatigue is low and limited treatments for fatigue are available with evidence that exercise and cognitive-behavioral therapy may be effective but minimal high-quality evidence for medication use.[11,34,35]

While many previous studies have shown fatigue persists over time, we found that fatigue worsening occurred frequently but often required a long follow-up time to observe these changes than most studies examine. As most individuals will experience fatigue worsening over time, there is a need for treatment management plans to address fatigue, which leads to greater social participation, higher QoL and employment. Individuals of lower SES and fatigue levels are at particular risk of worsening fatigue and warrant support from clinicians. Understanding factors associated with fatigue may help to identify populations that are most informative for future fatigue clinical trials.

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Declaration of conflicting interests

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Ethical approval

The NARCOMS registry is approved by the Institutional Review Board at UT Southwestern.

Informed consent

Participants permit the use of their de-identified information for research purposes.

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Supplemental material

Supplemental material for this article is available online.

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