Title: How Multiple Sclerosis Symptoms Vary by Age, Sex, and Race/Ethnicity

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Take-Home Points

- Men and women with MS have similar total symptoms burden. Women were more symptomatic earlier in the disease, and reported higher levels of fatigue and anxiety, while men scored worse on domains of mobility and dexterity.

- African-American and Hispanic-Americans reported higher symptom burden in all 12 domains compared to Whites. Hispanic-Americans had higher scores than African-Americans on domains of pain, cognition, depression, and anxiety.

- Self-rated health was not predicted by sex or race/ethnicity, but only by scores in domains of body pain, depression, fatigue, and, to a lesser extent, overall disability (PDDS).

- It is plausible that more effective management of pain, depression, and fatigue in MS will lead to a decrease in disparities in self-rated health among race/ethnic groups and improvements in quality of life across all groups.
Abstract (250/250 words)

Background: Little is known about how symptom severity in the various neurologic domains commonly affected by MS vary by age, sex and race/ethnicity.

Methods: This was a retrospective study of MS patients attending two tertiary centers in the NYC metropolitan area, who self-identified as White, African-American (AA), or Hispanic-American (HA). Disability was rated with Patient-determined Disability steps (PDDS) and symptom severity - with SymptoMScreen (SyMS), a validated battery for assessing symptoms in 12 domains. Analyses comparing race, sex, and age groups were carried out using ANOVA Models and Tukey’s HSD multiple comparison tests to control the overall Type I error. A multivariable model was constructed to predict good self-rated health (SRH) that included demographic variables, PDDS and SyMS domain scores.

Results: Sample consisted of 2,622 MS patients (age 46.4 years; 73.6% female; 66.4% White, 21.7% AA, 11.9% HA). Men had higher adjusted PDDS than women (p=0.012), but similar total SyMS score. Women reported higher fatigue and anxiety scores (more botheration), while men had higher walking and dexterity scores. AA and HA had higher symptom domain scores than Whites in each of the 12 domains and worse SRH. In a multivariable logistic model, only pain, walking, depression, fatigue, and global disability (PDDS), but not sex or race/ethnicity predicted good SRH.

Conclusions: AA and HA race/ethnicity was associated with higher overall disability, higher symptom severity in each of the 12 domains commonly affected by MS, and worse self-rated health relative to Whites. However, only symptom severity and disability, and not demographic variables, predicted good self-rated health.
Introduction:

Much has been written about symptoms of multiple sclerosis [1][2], but relatively little about how symptoms of MS vary by age, sex and race/ethnicity. We have previously assessed symptom severity as a function of disease duration in MS [3]. Here, we compare MS symptom severity across the age spectrum in men and women of the three race/ethnic groups most represented in our practice – Whites, African-Americans (AA), and Hispanic-Americans (HA). Minority populations are increasingly affected by MS [4][5], but less than 1% of all MS studies have been devoted to them [6]. A better understanding of similarities and differences in symptomatology of the different race/ethnicity groups is necessary to fully address the disparities that may exist in the care of non-White patients with MS [7][8][9].

Methods:

Consecutive patients from the New York University (NYU) MS Care Center (New York City, NY) and Barnabas MS Care Center (Livingston, NJ) self-identified their sex (but not gender), race/ethnicity (White, African-American, Hispanic-American, Other) and rated their disability, symptom severity and quality of health at the time of their scheduled doctor visit. Disability was rated with Patient-Determined Disability Steps (PDDS), an eight-point scale that measures global neurological impairment in MS [10] (available at https://9369df97-4fc0-4f79-b0e9-183aa5f01c36.filesusr.com/ugd/826c66_b39d4958805541efbdf3dd2b81ec80d5.pdf). PDDS strongly correlates with the Expanded Disability Status Scale (EDSS) [11]. Symptom severity was assessed with SymptoMScreen (SyMS, available at www.symptomscreen.org), a validated battery of seven-point Likert scales for 12 domains commonly affected by MS: mobility, dexterity, vision, fatigue, cognition, bladder function, sensory function, spasticity, pain, dizziness, depression, and anxiety [12], with higher scores indicating more impact of that domain on patients’ functioning. Self-rated health (SRH) was assessed with a single-response question used by the World Health Organization for the study of aging and global health: ‘In general, how would you rate your health today? -Very good

Inclusion criteria were age 18 or above and diagnosis of MS, which was confirmed by the treating clinician at the time of visit. We restricted analyses to the three main racial/ethnic groups in our sample, whites (WA), African Americans (AA), and Hispanic-Americans (HA). Visits took place between June 2010 and December 2018. When there was more than one record for the patient, we used only the last available record for the analyses.

Analyses included descriptive statistics (means, median, standard deviation) and plots of mean scores by age group, sex, and race, and means adjusted for the other variables. Analyses comparing race, sex, and age groups were calculated using ANOVA Models and Tukey’s HSD multiple comparison tests to control the overall Type I error. A multivariable logistic model to predict good self-rated health (defined as response of ‘Very good’ (=1) or ‘Good’ (=2) on SRH) included demographic variables (age, sex, race/ethnicity), disability (PDDS), and individual SyMS domain scores. All analyses were carried out using JMP 14.2.0 and SAS 9.4 software; p<0.05 was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The retrospective study used de-identified data and received an exemption determination from the institutional review boards (IRBs) of NYU Langone Medical Center (New York) and Barnabas Medical Center (Livingston, NJ). Patient consent was not required.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results:

Demographic and disease-related characteristics
Of the 2,851 consecutive patients who met the initial inclusion criteria, 229 patients (8% of the sample) were excluded because they either declined to provide race/ethnicity or reported ‘other race’. Thus, the final sample consisted of 2,622 MS patients from NYU (n = 1,556) and Barnabas (n = 1,066) MS Care Centers. Out of 2,622 patient records, one domain was missing in 505 patients (19%) and 2 domains were missing in 50 patients (1.9%). The most common reason for ‘missing’ domain was that ‘Dizziness’ (n=259), which was added later to the instrument than the other domains. For individuals with the missing scores, we used imputation by calculating the average score for the items present and scaling these values to a 12-domain score. Demographics and disease-related characteristics of the sample are summarized in Table 1.

Differences in disability and symptom severity between men and women

Men had higher disability (PDDS) than women (p=0.012 adjusted for Race and Age), but the total SyMS scores were similar for the two sexes (p=0.39, adjusted for Race and Age). Unadjusted SyMS scores in men and women stratified by age are shown in Figure 1: there was a tendency toward higher scores in women in 18-29 group (p=0.09) and were significantly higher scores in women in 30-39 group (p=0.047), while scores in the three older age brackets were similar; the interaction test was not significant (p=0.15).

Men and women showed an increase in PDDS and total SyMS score with age (p<0.0001 for both, adjusted for race and sex), with the highest change between ages 40 and 59 in both sexes (Figure 1). Age group, race, and sex were all significant effects in the models and no two-way interactions were significant. With respect to individual domain scores, men had worse scores in the domains of walking (mean difference of 0.19, p<0.013, adjusted for age and race) and dexterity (mean difference of 0.15, p<0.028), but better scores on the domains of fatigue (mean difference of 0.17, p=0.020) and anxiety (mean difference 0.19, p=0.0071). There were no significant differences between sexes in the other 8 domains. Self-rated health was similar among men and women (p=0.84).
Differences in disability and symptom severity among Whites, African-Americans and Hispanic-Americans

The age-adjusted mean PDDS for AA and HA men and women were higher than for their White counterparts of the respective sex (p<0.0001). Figure 2 (top panel) shows the unadjusted mean PDDS scores for each sex/race/age subgroup, and the numbers of patients in each sex/race/age subgroup. The mean total SyMS scores among the three race/ethnic group were also significantly higher in AA and HA than Whites after adjusting for age and sex (p-values <0.05 via post hoc t-tests on the least squares adjusted means) (Figure 2, bottom panel). With respect to individual domains, AA had significantly worse scores than Whites on all domains: walking (mean difference of 0.67, p<0.001), dexterity (0.40, p<0.0001), spasticity (0.50, p<0.0001), pain (0.57, p<0.0001), sensory (0.43, p<0.0001), bladder function (0.53, p<0.0001), fatigue (0.44, p<0.0001), vision, (0.39, p<0.0001), dizziness (0.39, p<0.0001), cognition (0.39, p<0.0001), depression (0.35, p<0.0001), anxiety (0.21, p=0.0054). HA also had worse scores than Whites in all domains: walking (0.49, p<0.0001), dexterity (0.43, p<0.0001), spasticity (0.60, p<0.001), pain (0.81, p<0.0001), sensory (0.51, p<0.0001), bladder function (0.55, p<0.0001), fatigue (0.58, p<0.0001), vision (0.58, p<0.0001), dizziness (0.58, p<0.0001), cognition (0.79, p<0.0001), depression (0.60, p<0.0001), anxiety (0.56, p<0.0001). HA higher scores than AA on domains of pain (0.24, p<.0001), cognition (0.40, p<0.0001), depression (0.25, p<0.023) and anxiety (0.25, p<0.026). Figure e-1, http://links.lww.com/CPJ/A299 shows unadjusted domain scores stratified by age and sex for each of the three race/ethnic groups. Self-rated health was worse in AA (mean=1.43) compared to Whites (1.15, p<0.0001), and was similar in AA and HA (mean=1.48, p=0.43).

Age-related trends of domain scores

Age-related domain trends showed significant increases in men and women of each race/ethnic group (with the exception for anxiety, for which a decrease with age was observed). We therefore compared the age-related trends for the 12
domains to each other irrespective of sex and race/ethnicity. Fatigue scores were markedly higher than scores in any other domain throughout the age spectrum, and especially in the younger patients, and were only overtaken by walking scores in the oldest age group (Figure 3). Continuous increase in symptom scores throughout the age spectrum in the mostly ‘spinal’ domains of walking, bladder, and, to a lesser degree, dexterity, stood in contrast to the relative ‘flattening’ with age in the ‘cerebral’ domains of depression and cognition, which increased only before age 40, but not thereafter.

Predictors of good self-rated health

We started with a logistic model to predict good self-rated health (‘Very good’ or ‘Good’ responses) based only on age, race and sex, and overall disability (PDDS). This model was able to achieve an area under the ROC curve of 0.78 with race (p<0.0005) and PDDS (p<0.0001) being the two statistically significant predictors in the multivariable model. This model achieved 69% sensitivity and 77% specificity. When the individual domain predictors were added to the model, the area under the ROC curve was improved to 0.88 In the expanded model, only four disease-related factors – body pain, depression, fatigue, and PDDS (in the order of decreasing contribution) were significant predictors of good SRH, while age, sex and race/ethnicity were not. The model had sensitivity of 81.9% (95% CI 76.8 - 87.2%), specificity of 76.0% (95% CI 69.6%-82.9%), positive likelihood ratio of 3.4 (95% CI 3.0 – 3.9), negative likelihood ratio of 0.2 (95% CI 0.2 to 0.3), positive predictive value was 85.4% (95% CI 83.6%, 87.0%) and negative predictive value of 71.0% (95% CI 68.3% 73.6%).

Discussion:

Disability and symptom burden increased with age in men and women of every race/ethnicity groups, as would be expected in a progressive neurologic disorder. The largest increase occurred between ages of 40 to 60, perhaps a reflection of the transition from relapsing to progressive phase during this period in most patients. The change in symptom burden score between 50-60 and 60+ age
groups was less pronounced, possibly due to the relatively slower progression in the older patients, or to psychologic accommodation to physical limitations (as reflected in lower anxiety and depression scores in 60+ age patients compared to 50-60 age group). 'Immortal time bias', whereby older and severely disabled patients would be more likely to have died or be too impaired to follow up in the clinic, may also have contributed to the apparent flattening in total SyMS scores in the older groups. With the exception of anxiety, individual domain scores all showed increase with age, but the pattern of increase differed between 'spinal' domains, such as walking and bladder function, which steadily increased, and cognitive and affective domains, which tended to increase before age 40, but not thereafter. Worsening of physical disability with age and stabilization of mental health scores has been observed by others as well [3][13][14].

Men and women had similar total symptom scores and similar self-rated health. Younger women (<40 years old) tended to have higher total symptom scores than men of same age, perhaps a reflection of higher rate of relapse and enhancing lesion formation in women compared to men [15][16][17]. Higher anxiety score among women with MS may reflect a well-known predisposition of women to anxiety disorders [18]. Women also had higher fatigue score than men; a similar findings of higher fatigue in women were reported in recent multi-center study of Chinese patients with MS [19]. Men had higher overall disability (PDDS), and worse walking and dexterity scores, which is also consistent with the survey of Chinese MS patients [19] and the literature documenting higher burden of ‘spinal’ disability and higher load of the destructive, T1-hypointense lesions in men as compared to women (reviewed in [20]).

African ancestry is a known risk factors for worse outcomes in MS [21][22]. African Americans have faster disease progression [23], especially early in the disease [24], and more brain [25][26], spinal cord [27], and optic nerve [28] atrophy. In line with these reports, we found that symptom scores were higher in AA compared to Whites in every domain even after adjusting for age and sex. Literature on MS in Hispanic Americans is sparse. Our prior work showed that HA have higher disability scores than Whites [29]. In the present work, we show that HA had worse scores than Whites in every domains, and even higher than in
AA in several domains of invisible disability - pain, cognition, depression and anxiety.

Given the differences in symptom burden across race/ethnic groups, we hypothesized that race would be an independent predictor of good self-rated health (SRH). However, race/ethnicity was only a strong predictor of SRH if domain scores are not taken into account. In a multivariable model that accounted for age, sex, race/ethnicity, self-reported disability and individual domain symptom scores, only body pain, depression, fatigue, and PDDS - in the order of decreasing contribution - were predictive of good SRH. Sensitivity of the model was 82% and specificity - 76%. Thus, what determines how patients view their health is not their demographics but by symptom severity in domains of invisible disability and, to a much lesser extent, their overall physical disability score (PDDS).

One limitation of our study is that the racial self-identification does not reveal the extent of genetic admixtures in patients’ ancestry [30], and may even conflict with the genetic data [31]. One can overcome this limitation by using ancestry informative genetic markers, but this approach is not feasible in a retrospective, clinic-based study. Another limitation is that clinician-rated measures were not available for our sample; prior studies have validated domain SyMS scores against clinician-rated metrics [12][32][33]. Thirdly, we did not collect information on patients’ socioeconomic status (SES), and are not able determine how much of variance in symptom burden among race/ethnic groups maybe due to differences in SES. In our prior work on disability differences in MS patients from the different racial groups, adjusting for insurance status as a surrogate for SES, did not change results [29]. However, others have found that failure to account for SES differences may lead to overestimation of differences between racial groups [34]. We propose that the future observational studies comparing outcomes across ethno-ancestries use 'Area Deprivation Index' (ADI), which can be derived from patient’s address (https://www.neighborhoodatlas.medicine.wisc.edu/), as a more nuanced surrogate of SES, and also address social determinants of health which may disproportionately impact minoritized populations that extend beyond SES [35].
Another limitation is that we did not systematically collect data on disease-modifying (DMT) and symptomatic therapies. In our prior work, we did not find differences in overall rates of DMT use across ethnic groups [27] and in a recent audit of NYU MS Center data, higher proportion of AA were receiving high-efficacy therapies (natalizumab and anti-CD20 therapies) than Whites (data on file) likely in response to their higher disease severity. Thus, it is highly unlikely that observed differences in disease severity are due to under-treatment of minority populations. Finally, the potential impact of various forms of selection bias must be considered. If the more disabled minority patients are preferentially referred to tertiary centers, while milder cases are managed by community neurologists, our minority populations maybe skewed toward the more severe end of the spectrum [8]. Conversely, if the more impaired minority patients are less likely to follow up in the referral center given socio-economic disparities, the results would be skewed in the opposite direction. The racial representation in our clinics with respect to Whites, AA, and HA is reflective of our catchment area, so a considerable referral bias is not likely. Still, clinic MS patients may differ from the general MS population, and population-based studies covering diverse geographic locales are needed to confirm whether our findings are generalizable.

In conclusion, AA and HA race/ethnicity was associated with higher overall disability, higher symptom severity in each of the 12 domains commonly affected by MS, and with lower self-rated health scores relative to Whites. Importantly, race/ethnicity was not a predictor of self-rated health, rather SRH was mainly predicted by severity of body pain, depression and fatigue. Our work suggests that improvement in managing these symptoms will be most likely to improve patients’ quality of life and to reduce the disparities in self-rated health among race/ethnic groups. High symptom burden in non-White minorities with MS warrants investigation into its biologic and sociologic causes.
References:


36.
Table 1. Demographic and Disease-related Characteristics

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<table>
<thead>
<tr>
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<tbody>
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<td><strong>Number of patients</strong></td>
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<td><strong>NYU MS Center</strong></td>
<td>1,556</td>
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<tr>
<td><strong>Barnabas MS Center</strong></td>
<td>1,065</td>
</tr>
<tr>
<td><strong>Age; Mean, SD</strong></td>
<td>46.4 ±13.0</td>
</tr>
<tr>
<td><strong>Sex; %Female</strong></td>
<td>73.6%</td>
</tr>
<tr>
<td><strong>Race; %</strong></td>
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<td><strong>White</strong></td>
<td>66.4%</td>
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<tr>
<td><strong>African-American</strong></td>
<td>21.7%</td>
</tr>
<tr>
<td><strong>Hispanic-American</strong></td>
<td>11.9%</td>
</tr>
<tr>
<td><strong>MS Subtype; % Relapsing</strong></td>
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<td><strong>PDDS, mean, [median], SD</strong></td>
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<tr>
<td><strong>Total SymptomScreen, mean [median], SD</strong></td>
<td>19.0 [16], ±14.6</td>
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<tr>
<td><strong>Self-Rated Health score, mean, SD</strong></td>
<td>1.3 ±0.9</td>
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Abbreviations: PDDS - Patient-determined Disability Steps; SD – standard deviation
Figure Legends:

Figure 1. Total SyMS score in women (blue) and men (red) stratified by age.

Figure 2. Patient-determined Disability Steps (PDDS) score in women (left) and men (right) stratified by age and race/ethnicity is shown on the top panel and total symptoMScreen score in women (left) and men (right) stratified by age and race/ethnicity is shown on the bottom panel. The number of patients in each age group, stratified by sex and race/ethnicity is shown below. Abbreviations: W – white (green); AA – African-American (blue); HA – Hispanic-American (red)
Figure 3. Symptom domain scores across age span for the entire sample stratified by age.
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