

# Common Social and Health Disparities Contribute to Racial Differences in Ambulatory Impairment in Multiple Sclerosis

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1. Describe the extent to which common social and health disparities contribute to racial differences in ambulatory impairment in MS.
2. Recognize the importance of distinguishing mediators from confounders in multivariable regression models.

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## ABSTRACT

**BACKGROUND:** We previously reported more rapid accrual of ambulatory impairments in Black compared to White individuals with relapsing remitting multiple sclerosis (RRMS) and higher body mass index (BMI). Hypertension and lower neighborhood socioeconomic status (SES) were associated with greater impairment, irrespective of race. We hypothesize that these common social and health inequities may explain a substantial portion of the racial differences in ambulation in American individuals with RRMS.

**METHODS:** Causal mediation analyses investigated baseline and change-over-time mediators of ambulatory impairment differences between 1795 Black and White individuals with RRMS using a retrospective cohort study comprised of electronic health record data from 8491 clinical encounters between 2008 and 2015 where Timed 25-Foot Walk (T25FW) speeds without assistive devices were recorded. The hypothesis was that BMI, neighborhood SES, and hypertension were possible mediators.

**RESULTS:** At baseline, Black individuals with RRMS ( $n = 175$ ) had significantly slower T25FW speeds (5.78 vs 5.27 ft/s), higher BMI, a higher prevalence of hypertension, and they were more likely to live in lower-income neighborhoods than White individuals ( $n = 1,620$ ). At baseline, a significant proportion (33.7%; 95% CI, 18.9%-59.4%) of the T25FW difference between Black and White individuals was indirectly due to a higher BMI (12.5%), hypertension burden (9.5%), and living in lower-income neighborhoods (11.2%). Once baseline mediation relationships were accounted for, there were no significant longitudinal mediation relationships.

**CONCLUSIONS:** The findings implicate social and health disparities as prominent drivers of ambulatory differences between Black and White individuals with RRMS, suggesting that wellness and health promotion are essential components of MS care, particularly for Black individuals.

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conclusions about MS in BAs.<sup>2</sup> Despite these limitations, we know that the 100,000 BAs with MS are prone to more severe disease and adverse long-term outcomes.<sup>1,3</sup>

In a retrospective cohort study of electronic health records (EHRs) that comprehensively adjusted for sociodemographic and clinical attributes, we previously reported that BAs with relapsing remitting multiple sclerosis (RRMS) were more prone to rapidly advancing ambulatory impairment than White Americans (WA) with RRMS.<sup>4</sup> We also observed that higher body mass index (BMI), lower neighborhood socioeconomic status (SES), and hypertension were independently associated with greater ambulatory impairments in individuals with RRMS, and these relationships did not differ between BAs and WAs.<sup>4,5</sup> Due to structural racism (ie, generational impact of redlining) and social and health inequities in the United States, BAs are prone to live in lower-income neighborhoods and have a greater burden of obesity and hypertension than WAs.<sup>6</sup> There are similar racial differences in MS, including evidence supporting a higher burden of uncontrolled hypertension in BAs compared with WAs with MS.<sup>4,7,8</sup> Therefore, we theorize that these common social and health inequities (ie, racial disparities) substantially contribute to the observed racial differences in MS. This is supported, in part, by a 2006 cross-sectional study of North Americans with MS, where Black compared with White participants had greater impairments, and associations attenuated when adjusted for SES.<sup>9</sup>

To date, no study has sought to identify mediators of racial disparities in MS risk or progression. In hindsight, we recognize our prior multivariable longitudinal models of ambulatory impairment that included sociodemographic and clinical attributes assumed “all else being equal”<sup>4</sup>; however, all else is not equal in the United States due to pervasive social and health inequities that disproportionately impact BAs. To characterize the true total magnitude of a racial disparity, it is important to appropriately adjust for confounders. Oftentimes mediators of the racial disparity (ie, descendants of race in a causal diagram that lead to the outcome; mechanisms through which race impacts the outcome) are included as covariates. Thus, the adjusted estimates for race from these models only reflect a portion of the true underlying relationship (ie, the effect of race independent of mediators in the model), and fail to illustrate the true magnitude of the racial difference. Here we conduct mediation analyses, hypothesizing that BMI, neighborhood

There are remarkable racial differences in multiple sclerosis (MS) risk and presentation, and data suggest racial health and social disparities may be key drivers of these observed differences.<sup>1</sup> A decade ago, Black/African Americans (BA) were shown to be the most at-risk American subpopulation for MS, yet contemporary research characterizing racial differences and racial disparities have been notably sparse.<sup>1</sup> This evidence gap is compounded by continued underrepresentation of diverse populations in clinical trials, further impeding efforts to make generalizable

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SES, and hypertension are prominent mechanisms of the observed racial difference in ambulatory impairment between BAs and WAs with RRMS.

## METHODS

We revisited our retrospective cohort study to examine cross-sectional and longitudinal mediators of baseline and change-over-time racial disparities in ambulatory impairment in patients with RRMS. These analyses were approved by the institutional review boards at the Cleveland Clinic Foundation and Case Western Reserve University. The source population consisted of RRMS patients seeking extended care at a tertiary MS referral center in the United States between 2008 and 2015.<sup>4,5</sup> We excluded patients requiring unilateral or bilateral assistive devices at baseline as their distribution of Timed 25-Foot Walk (T25FW) speed at baseline was right-skewed with wide standard deviations (data not shown), which would introduce heterogeneity in the subsequent models. There were 1795 individuals with RRMS who reported that they did not require an assistive device and T25FW (objective measure of ambulation) was recorded in 8491 clinical encounters, which spanned an average interval of 2.5 years (SD = 0.8). Diagnosis of MS was confirmed by chart review.<sup>10</sup> Age, sex, race (Black or White only), disease duration, disease-modifying therapy (DMT) status (yes/no), smoking status (ever/never), BMI, hypertension (yes/no), and 9-digit ZIP code of residence (mapped to 520 census tracts and linked to 2010 US Census median household income data) were abstracted from EHRs, as previously described.<sup>4,5</sup> To determine a hypertension diagnosis, 4 EHR domains were inspected (progress notes, problem list, past medical history, medication list) and a patient was classified as having hypertension based on evidence from at least 2 domains (eg, listed in the medical history and having an antihypertensive prescription).<sup>5</sup>

Baseline attributes were compared using Fisher's exact and Wilcoxon rank-sum tests for categorical and continuous variables, respectively. Mediation analyses were informed by path diagrams that illustrate the directionality of the associations of interest (FIGURE S1, available online at IJMSc.org), and direct acyclic graphs were used to identify confounders to be included as covariates (FIGURE S2). Mediators of interest were baseline measures of BMI, hypertension, and median household income of ZIP code of residence. Other abstracted variables were covariates.

Mediation analyses were conducted to investigate mediators of racial disparities in T25FW, informed by directed acyclic graphs (Figure S2). Mediators of interest were baseline measures of BMI, hypertension, and median household income, and covariates included age, sex, disease duration, smoking status, and DMT status. First, a latent growth model evaluated linear growth over time in T25FW using maximum likelihood to estimate

the parameters with robust Huber-White sandwich estimation to calculate standard errors (MLR option in MPlus v8.2).<sup>11,12</sup> Robust approaches are insensitive to departures from parametric assumptions that may exist in the data, and the model effectively handled ignorable missing data dependent on the data in hand (ie, following a missing at random assumption) via full information maximum likelihood. Therefore, all patients were included in the trajectory analysis for unbiased inference. Second, the latent growth model was extended to include the hypothesized causal pathways, and accounting for covariates, to investigate mediation relationships (Figure S1).<sup>13,14</sup> That is, the growth of the T25FW (via a latent intercept and linear slope) was regressed on all baseline measures (the mediators, race and covariates), while baseline measures of the multiple mediators were regressed on race and the covariates in a single analysis. There was no significant growth in T25FW after accounting for the baseline mediation relationships; thus, the model was reduced to evaluate cross-sectional mediation alone. Given the cross-sectional setting, we were able to explicitly address nonlinearity that may arise due to hypertension being a binary mediator employing a Bayes estimator and a Markov chain Monte Carlo algorithm based on the Gibbs sampler with a noninformative prior. Direct, specific indirect, total indirect, and total effects were then calculated (IND option in MPlus v8.2) with 95% Bayesian credibility intervals (CI) to test for mediation. A 2-sided alpha of 5% determined statistical significance in our frequentist modeling (ie, latent growth modeling approaches). Data analyses took place in April 2022.

## RESULTS

There were 175 BAs and 1620 WAs with RRMS who did not differ by sex or age (TABLE 1). At baseline, BAs had significantly slower T25FW speeds (5.78 vs 5.27 ft/s), shorter disease duration, lower DMT usage, and were less likely to have ever smoked than WAs. Black/African American patients also had significantly higher BMI, a higher prevalence of hypertension, and they were more likely to live in lower-income neighborhoods than WAs seen at the same tertiary institution.

There was significant worsening in T25FW over time (FIGURE S3; intercept = 5.3s, SE = 0.035,  $P < .001$ ; slope = 0.012s/month, SE = 0.001,  $P < .001$ ). However, there was no change-over-time once baseline mediation relationships were accounted for (intercept = 3.4s, SE = 0.205,  $P < .001$ ; slope = -0.011s/month, SE = 0.008,  $P = .170$ ). At baseline, the total direct effect of being a BA was a 0.56s (95% CI, 0.35-0.77) increase in T25FW compared to WAs, which encompasses a direct effect and hypothesized indirect effects adjusted for other covariates (TABLE 2). This total effect is very similar to the unadjusted difference (Table 1), which illustrates that BAs take, on average, about 10% longer to complete the T25FW. A significant proportion (33.7% [95% CI, 18.9%-59.4%]; 0.19s [95% CI, 0.11s-0.27s])

**TABLE 1.** Study Population Attributes at Baseline

Variable	All RRMS	Black Americans	White Americans	P
Participants	1795	175 (9.8%)	1620 (90.2%)	
T25FW (seconds)	5.32	5.78	5.27	8.1 × 10 <sup>-8</sup>
Slow ambulators (T25FW > 8s)	98 (5.5%)	11 (6.3%)	87 (5.4%)	0.60
BMI (mean; kg/m <sup>2</sup> )	28.6	30.7	28.4	3.4 × 10 <sup>-5</sup>
Hypertension	323 (18.0%)	52 (29.7%)	271 (16.7%)	6.9 × 10 <sup>-4</sup>
Median household income by ZIP code (2010)	\$55,300	\$44,100	\$56,500	3.0 × 10 <sup>-19</sup>
Female	1329 (74.0%)	136 (77.7%)	1193 (73.6%)	0.28
Age (years)	42.9	41.6	43.0	0.06
Never smoker	730 (40.7%)	94 (53.7%)	636 (39.3%)	0.0013
Disease duration (years)	9.4	7.6	9.6	0.014
On DMT	1265 (70.5%)	108 (61.7%)	1157 (71.4%)	0.0088

BMI, Body Mass Index; DMT disease-modifying therapy; RRMS, relapsing remitting multiple sclerosis; T25FW, Timed 25-Foot Walk.

**TABLE 2.** Cross-Sectional Mediation Statistics Using Bayes Estimator for Racial Disparity in Timed 25-Foot Walk

Effect of identifying as Black for individuals with RRMS	Coefficient (95% CI)	Percent of total effect (95% CI)
Total effect	0.558s (0.349, 0.768)	100%
Total direct effect	0.369s (0.151, 0.585)	66.3% (40.6, 81.1)
Total indirect effect	0.187s (0.113, 0.269)	33.7% (18.9, 59.4)
Indirect effect	Body mass index	12.5% (5.7, 23.2)
	Hypertension	9.5% (1.1, 23.4)
	Lower income neighborhood	11.2% (3.2, 23.6)

of this racial difference in ambulation speeds was due to racial health disparities as a result of a higher burden of social and health inequities in BAs with RRMS compared to WAs with RRMS, specifically of a higher BMI, a greater burden of hypertension, and a greater likelihood of living in a lower-income neighborhood (Table 2). Higher BMI mediated 12.5% (95% CI, 5.7-23.2) of the racial difference, followed by 11.2% (95% CI, 3.2-23.6) for living in a lower-income neighborhood, and 9.5% (95% CI, 1.1-23.4) for hypertension. The direct effect of being a BA on ambulation, after accounting for the mediated relationships and adjusting for covariates, was 0.37s (95% CI, 0.15-0.58); thus, 66.1% (95% CI, 40.6-81.1) of the racial difference in ambulation between Black and White individuals with RRMS remains unexplained and it is likely that other common drivers of racial disparities may further explain these differences (ie, differential prescribing patterns, allostatic load, earning potential).

## DISCUSSION

There are substantial racial differences in MS, and inequities that drive racial health disparities play a prominent role in these observed patterns. Here, we demonstrate that, on average, Black individuals with RRMS take about 10.5% (0.558s/5.32s) longer to complete a timed ambulatory task compared to their WA counterparts. A third of this difference is due to racial health and social disparities that can be attributed to higher BMI (12.5%), a higher burden of hypertension (9.5%), and living in lower-income

neighborhoods (11.2%). Had we treated these 3 mediators as confounders (covariates in a multivariable model), we would have reported that BAs with RRMS were, at most, 6.9% slower (0.369s/5.32s)—an underestimate of 33%. This work highlights the need to judiciously consider which potential covariates may be mediators (downstream of the exposure of interest [being BA in this study] and leading to the outcome) and how it may impact the interpretation of findings. In the case of our prior study of longitudinal change in T25FW, we should have said that the reported difference between BAs and WAs was *only* the direct effect and likely an underestimate of the true difference, which would mean that the accrual of ambulatory impairment in BAs is even greater than we previously reported.

The presented work is not comprehensive, but it is a start to the conversations that must take place because contemporary race-specific or race-comparative studies of MS outcomes continue to be sparse and often rely on multivariable models that may treat mediators as confounders. Our prior study, like most other findings, likely failed to quantify the true underlying racial difference (via direct and indirect effects) in MS outcomes, much less the extent to which disparities drive these relationships. As a result, the prior findings were likely dampened, diminishing the urgency to address them.

While this work is meant to start the discourse, there are several limitations to acknowledge. First, we were only able to focus on 3 common social and health inequities and were unable to examine other individual-level social





As common social and health disparities in the United States contribute to racial differences in ambulatory impairment, clinicians should view wellness and health promotion strategies as essential components of multiple sclerosis care, particularly for Black individuals. ■

determinants of health (eg, financial insecurity, changes in insurance status, housing instability) and other systemic health care biases (ie, that a greater proportion of BAs are not on a DMT). We only examined these relationships in a study population that originated from a single tertiary care setting; although the ratio of BA to WA in this study sample is reflective of the ratio observed within the MS population in the United States, it is not reflective of the racially diverse metropolitan setting (Cleveland, 47% BA)<sup>15</sup> nor the relatively moderately diverse region (Northeast Ohio, 17% BA)<sup>16</sup> of the tertiary facility. It is plausible that selection bias may have factored into the study sample, such that the included patients only represent a subset of the source population, for example, those with specific health-care-seeking behaviors (ie, having health insurance, which facilitates referral to a tertiary care facility) and more active/aggressive disease (therefore, more likely to seek specialty care). We also excluded those participants who required an assistive device at baseline, limiting our generalizability to individuals with RRMS who ambulate without assistance. A notable strength of the study is that we were able to account for key correlates of disease activity/progression and health-care-seeking behaviors (ie, age, sex, smoking, disease duration, and treatment status), as well as examine whether there were cross-sectional and longitudinal mediation effects.

## CONCLUSIONS

In summary, racial disparities matter in MS, as illustrated in this first-of-its-kind mediation analysis. We demonstrate that a higher BMI, a higher hypertension burden, and living in a lower-income neighborhood explained a third of the ambulatory impairment difference between BA and WA individuals with RRMS. How neighborhood SES and hypertension may contribute to ambulatory impairments are not directly clear and merit further investigation, particularly

in BA individuals with RRMS. It is critical that future work should further illuminate the extent to which other inequities and racial disparities impact observed clinical relationships in MS, which together can be leveraged to advocate for investing more resources in health promotion and preventive care as integral components of MS care. Such efforts will have the most benefit for the most vulnerable individuals with MS. ■

**CONFLICTS OF INTEREST:** On behalf of all authors, the corresponding author states that there is no conflict of interest.

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