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RESEARCH ARTICLE

Disparities in Huntington Disease Severity

Analysis Using the ENROLL-HD Dataset

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Abstract

Background and Objectives

Social and structural determinants of health (SDOH) have been associated with disability in neurologic diseases. However, the association between these factors and disability in Huntington disease (HD) has not been studied. This study aimed to evaluate the association of racial and sociodemographic factors with disease severity in patients with HD in North America.

Methods

We conducted a cross-sectional study of genetically confirmed participants with HD (36+ CAG repeats) in the North American region using the ENROLL-HD 2020 periodic dataset. In this analysis, our exposure variable was the participant's race/ethnicity. The main outcome measure was disease severity, as measured by the Total Functional Capacity Score (TFC), which measures the level of disability of patients with HD. We used multivariate regression models to adjust for sociodemographic factors that may mediate or moderate a causal effect between race/ethnicity and disease severity.

Results

Among 4,717 gene-positive participants in the North American region, 89.5% identified as White, 3.4% as Hispanic or Latino, and 2.3% as African American/Black. The average TFC score was 10.22 (SD 3.22); 48% of participants completed either secondary education (including college) or a professional degree, and 55% lived in a city and not in a town, village, or rural location. In multivariate regression models, we found that Black participants and those with less than a high school degree entered the ENROLL-HD study with lower TFC scores than White participants. We also found that compared with those with at least a high school degree, those who completed some form of higher education or professional degree had higher TFC scores ($p < 0.001$). This multivariate analysis did not find an association between geographic location and TFC score.

Discussion

Our study found that Black participants in North America presented to ENROLL-HD with more advanced disease than White patients. We also found that higher education was associated with less advanced disease when entering the ENROLL-HD study. The role of race/ethnicity and education in HD symptom severity warrants further investigation. These findings underscore the importance of further studying the role of social and structural determinants of health in patients with HD, particularly those from historically marginalized communities.

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Introduction

Huntington disease (HD) is a progressive rare neurogenetic disease characterized by a triad of involuntary movements (chorea), psychiatric and behavioral disturbance, and cognitive impairment. Current disease prevalence in European countries and other nations with common European ancestry is 4–7 per 100,000 persons.[1] A recent claims data set study of privately insured patients found a similar 14-year incidence rate of HD diagnosis between Black or African American (hereafter Black) and White non-Hispanic (hereafter White) insurers.[2] In the pediatric literature, a separate claim data set study found a high percentage of Black and Hispanic or Latino (hereafter Latino) patients with the disease.[2,3] In addition to claims data set studies, an analysis from the University of California Los Angeles (UCLA) HD Center of Excellence (COE) showed that between 2013 and 2021, 16% of patients identified as Latino, 5% as Black, and 11% listed race as "other."[4]

Racial and ethnic disparities in access to neurologic care are well documented. Black and Latino patients experience delays in access to acute stroke care.[5,6] Black patients with Parkinson disease also present with more advanced disease and are less likely to be provided standard-of-care treatments.[7,8] Increasing evidence refutes the notion that multiple sclerosis (MS) is more common in White people of northern European ancestry in comparison to persons of color; recent large retrospective data suggest Black patients have higher MS risk and incidence, more severe disease at diagnosis, and higher mortality rates than their White counterparts.[9] Non-Hispanic Black patients with dementia also have more cognitive deficits, neuropsychiatric symptom severity, and functional dependence.[10] Studies of racial disparities in headache suggest migraine is more frequent, severe, and likely to become chronic in Black patients.[11] Although the reasons for these disparities are varied, contributing factors include systemic racism, bias in healthcare, and social and structural determinants of health (SDOH), such as lack of health insurance and limited access to neurologic care.[12]

If communities of color report higher disability for common neurologic conditions, those with rare neurologic diseases likely experience similar disparities. In the case of amyotrophic lateral sclerosis (ALS), a disease with a similar prevalence in the United States as HD, Black patients experience delays in diagnosis and present to specialized ALS care with more advanced disease than White patients.[13,14] Given known racial and ethnic disparities in access to neurologic care, this study seeks to create a conceptual framework on the SDOH in HD and evaluate racial and ethnic differences in HD symptom severity at the time of baseline visit in ENROLL-HD as measured by the Total Functional Capacity Score (TFC), a well-validated assessment of physical and cognitive disability in Huntington disease and frequently used outcome measure in HD clinical trial design.[15]

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The Office of the Human Research Protection Program at the University of California, Los Angeles (UCLA), deemed the following study exempt from IRB review. Enroll-HD is a global clinical research platform designed to facilitate clinical research in Huntington disease. Core data sets are collected annually from all research participants in this multicenter longitudinal observational study. Data are monitored for quality and accuracy using a risk-based monitoring approach. All sites are required to obtain and maintain local ethical approval.

Study Design and Participant Selection

This study used the ENROLL-HD 2020 periodic dataset (PDS5). ENROLL-HD is a free and publicly accessible longitudinal multicenter international observational study of patients with HD.[16,17] The data set includes clinical assessment data, biological samples, and HD-specific healthcare outcome data of more than 20,000 participants, including individuals without the HD mutation (controls). Figure 1 shows the participant selection process. We reviewed data from genetically confirmed individuals with HD (36+ CAG repeats) during their baseline ENROLL-HD visit. Given worldwide differences in healthcare access, this analysis was restricted to the North American region to understand demographic and healthcare access in the United States. ENROLL-HD does not have data organized by country. As a result, it is not possible to obtain US-only data. However, the North American region includes 50 sites in the United States and 6 in Canada.

Conceptual Model

Figure 2 shows a proposed conceptual model of the relationship between race and ethnicity and disease-specific outcomes in patients with HD. In this model, we incorporate biological variables specific to HD that may directly affect the level of disability, including CAG repeat length, age, sex, and type of symptom at the time of disease onset. We also incorporate social determinants of health, which may mediate the relationship between race and disability, capturing factors associated with barriers to healthcare in minoritized communities that may indirectly lead to differences in the level of disability. The creation of this conceptual model is independent of variables available in ENROLL-HD and instead serves as a guide for future studies of SDOH in HD.

Construction of Variables

The race and ethnicity variable uses the racial categories made available through the ENROLL-HDs periodic dataset. Categorization is based on the participant's self-identification, although the baseline form includes more options than what investigators see in the periodic data set. For investigators to see the same categories participants fill out, they must contact ENROLL-HD and submit a separate data request form.[18] The level of disability in HD is measured by the TFC, a measure of physical and cognitive disability as assessed by an individual's

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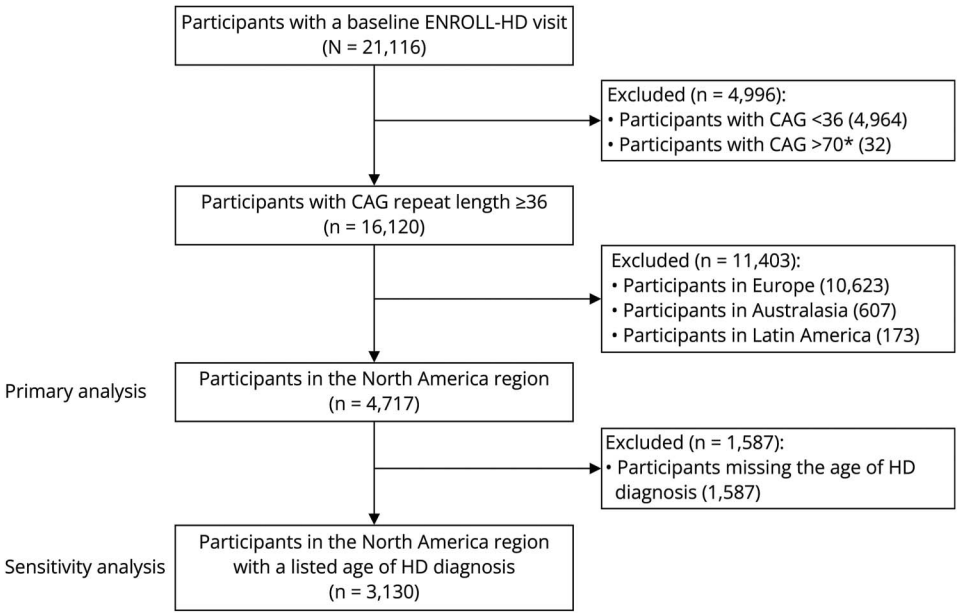
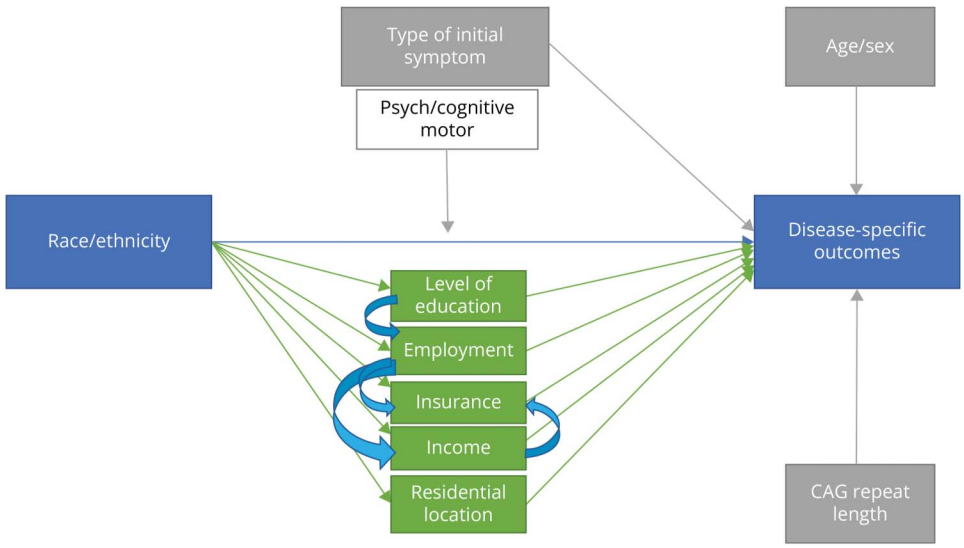
Figure 1 Participant Selection for Analysis



*ENROLL-HD aggregates data for individuals with 70 CAG repeats or more.

ability to be employed, manage finances, engage in self-care, and receive care at home (eAppendix 1, links.lww.com/CPJ/A466).[19-22] The TFC scale ranges from 0 to 13, with 13 meaning no disability and 0 meaning severe disability, and is scored by a clinician based on participant and caregiver responses. TFC is consistently used as an essential outcome measure in contemporary HD-randomized controlled trials and thus serves a critical role in developing potential disease-modifying therapies. The conceptual model in Figure 2 includes variables mediating an individual's level of disability, including SDOH, which might be barriers to healthcare access. Of these variables, ENROLL-HD has a participant's completed level of education, employment status, and the participant's residential location (listed as "geographic location"). ENROLL-HD does not collect insurance or income data, and we could not include these variables in the current multivariate analysis. Employment was ultimately not included in statistical models, given endogeneity in the TFC score, with one question in the TFC score asking about an

Figure 2 Conceptual Model of the Relationship Between Race/Ethnicity and Disease-Specific Outcomes in Huntington Disease



Moderators: Biological variables including age, sex, CAG repeat length, and the type of symptom at disease onset. Mediators: Social and structural determinants of health, including level of education, employment status, insurance, income, and geographic location.

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individual's ability to be employed. Potential moderators of the relationship between race and TFC also included biological variables such as age, sex, CAG repeat length, and symptom type at the time of disease onset. The original model did not have the age of diagnosis because of high variability in clinicians' diagnosis of HD, with a historical focus on the onset of motor symptoms (chorea) and not always considering cognitive or psychiatric symptoms, which may lead to significant disability independent of chorea.[23] Nonetheless, we did perform a sensitivity analysis including this variable.

Statistical Analysis

Descriptive statistics were used to analyze patient sociodemographic data. Linear regression models were used to assess the relationship between race/ethnicity and disease severity and disability as measured by the TFC score for available data. We used 3 sequential linear regression models. Model 1 includes a simple linear regression model of the relationship between race/ethnicity and TFC score. Models 2 and 3 include biological and SDOH variables available in ENROLL HD. Sensitivity analysis included an analysis of variance (ANOVA) testing the interaction between race/ethnicity and education (eAppendix 2, links.lww.com/CPJ/A466) and race/ethnicity and initial symptom type (eAppendix 3). We also included descriptive statistics, including the age of diagnosis and age of enrollment in baseline visits, stratified by race/ethnicity. A fourth multivariate linear regression model includes biological and SDOH variables and the age of HD diagnosis. p values were set at 0.05 with a 95% confidence interval. All analyses were performed in STATA version 17.

Data Availability

Data used in this work were generously provided by the participants in the Enroll-HD study and made available by CHDI Foundation, Inc. We used the ENROLL-HD Periodic Dataset 5 (released in 2020) for this study. The data set is publicly available and free to use by investigators.[18]

Results

Participant Demographics

Among baseline visits, we identified 4,717 participants in the North American region with genetically confirmed Huntington disease (Table 1). Only 10% (n = 494) identified as a race or ethnicity other than non-Hispanic White. A total of 3.35% (n = 158) of participants identified as Latino, 2.29% (n = 108) as Black, 1.12% as Native American (n = 53), and 0.68% (n = 32) as Asian. Most participants were women (55.9%), the mean age at the time of enrollment was 30.77 years (SD 14.2), and the average CAG repeat length was 43.5 (SD 3.8). The most common symptom type at the time of disease onset was motor (55.5%), followed by psychiatric (19.8%). However, data for this variable was missing for almost 33% of participants. Of note, the average TFC among those with missing data was 12, suggesting this group has less disability. For SDOH variables, most participants completed some form of higher education or a professional degree (44.88%), yet most reported not being employed at enrollment (58.7%). Regarding geographic location, most participants lived in a city (54.7%), and only 7.3% lived in a rural area. Except for the type of symptom at the time of disease onset, there was less than 1% of missing data for most variables, and for subgroups with missing data, the average TFC was ≤7.

Disease Severity and Level of Disability

The average TFC score in this sample was 10.22 (SD 3.22), consistent with a Shoulson-Fahn Stage II of Huntington disease. This suggests that most participants in the sample have some component of disability that prevents them from working, and they may need some assistance with activities of daily living. Table 2 shows linear regression models for the relationship between race/ethnicity and total functional capacity score. In all 3 models, Black participants with HD reported more disability than White non-Hispanic participants ($p < 0.001$). Using a marginal analysis, in this final model, Black patients have a lower TFC score (9.22) than other racial and ethnic groups. Age, sex, CAG repeat length, and initial symptom type were statistically associated with TFC scores. Higher CAG repeats were associated with more disability ($p < 0.001$), and psychiatric or cognitive symptoms as the first symptom of disease onset were also associated with more disability at the baseline ENROLL-HD visit ($p < 0.001$). Of the available SDOH, having less than a high school degree or GED equivalent was associated with more disability ($p = 0.003$), whereas higher education/professional degrees and Ph.D./doctorate degrees were associated with less disability ($p < 0.001$ and $p = 0.005$, respectively). ANOVA of the level of education based on race/ethnicity did find a higher proportion of Native American participants with less than a high school degree (41.2%) and Asian participants who completed some form of higher education or professional degree (71.9%) (eAppendix 2, links.lww.com/CPJ/A466). No significant differences were noted in comparisons of symptom type at disease onset based on race/ethnicity (eAppendix 3).

Sensitivity Analysis

To better understand the level of disability in relation to years with an HD diagnosis, we included a descriptive analysis of the age of HD diagnosis, age of baseline visit, and a new variable measuring time from HD diagnosis to time of participation in ENROLL-HD (Time-to-Enrollment, TTE). The age of HD diagnosis was missing for 33.6% of participants. For the new variable TTE, there were 174 negative values which could account for individuals who might have been asymptomatic or undiagnosed when they entered ENROLL-HD and were subsequently diagnosed in follow-up visits. Table 3 shows these data stratified by race/ethnic group. To address between-group differences, we performed a one-way ANOVA and simple linear regression analyses. Compared with White participants, Black, Latino, Native American, and mixed participants were younger at the time of HD diagnosis and entered ENROLL-HD at a younger age. There was a shorter time to enrollment across all minority groups, although this was only statistically

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Table 1 Demographics of Genetically Confirmed (CAG 36+) Huntington Disease Participants in the North America Region During Baseline Visits Using the ENROLL HD 2020 Dataset (N = 4,717)

	N (%) or mean (SD; range)	Mean total functional capacity (TFC score) (SD; range)
Age[a]	47.66 (14.2; 18–91)	—
Sex		
Female	2,637 (55.9%)	10.25 (3.26; 0–13)
Male	2,080 (44.1%)	10.17 (SD 3.17; 0–13)
Race/ethnicity (primary regressor)		
White	4,223 (89.5%)	10.26 (SD 3.19; 0–13)
Black American	108 (2.3%)	8.29 (SD 3.64; 0–13)
Hispanic or Latino origin	158 (3.4%)	10.04 (SD 3.37; 1–13)
American Indian, Native American, Amerindian	53 (1.1%)	10.13 (SD 3.68; 1–13)
Asian	32 (0.7%)	9.84 (SD 3.71; 1–13)
Mixed race	100 (2.1%)	10.71 (SD 2.92; 1–13)
Other	43 (0.9%)	10.21 (SD 3.24; 2–13)
Total functional capacity score "TFC" (0.34% missing) (mean, SD; min, max)	10.22 (3.22; 0–13)	—
CAG (36+) repeat length (mean, SD; min, max)	43.45 (3.80; 36–69)	—
Initial symptom at the time of disease onset	n = 3,156 (33% missing)	
Motor	1,736 (54.9%)	9.09 (SD 3.29; 0–13)
Cognitive	437 (13.8%)	8.81 (SD 3.08; 0–13)
Psychiatric	621 (19.7%)	9.15 (SD 3.30; 0–13)
Other	31 (1%)	9.97 (SD 2.95; 3–13)
Mixed	336 (10.6%)	9.10 (SD 3.19; 0–13)
Missing	1,553 (33%)	12.53 (SD 1.43; 2–13)
Level of education	n = 4,706 (0.23% missing)	
Less than high school/GED	122 (2.6%)	8.52 (SD 3.77; 1–13)
High school/GED	1,291 (27.4%)	9.60 (SD 3.29; 0–13)
Vocational training/some college	1,037 (22%)	10.26 (SD 3.25; 0–13)
Higher education and professional degree	2,112 (44.9%)	10.66 (SD 3.03; 0–13)
PhD/doctorate	144 (3.1%)	10.65 (SD 3.14; 1–13)
Missing	11 (0.2%)	5.67 (SD 4; 0–12)
Employment status	n = 4,708 (0.19% missing)	
Full-time employed	1,446 (30.7%)	12.71 (SD 0.88; 4–13)
Part-time employed	367 (7.8%)	11.96 (SD 1.66; 2–13)
Self-employed	125 (2.7%)	12.28 (SD 1.36; 5–13)
Not employed	2,770 (58.7%)	8.60 (SD 3.21; 0–13)
Missing	11 (0.2%)	6.33 (SD 4.63; 0–13)

Continued

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Table 1 Demographics of Genetically Confirmed (CAG 36+) Huntington Disease Participants in the North America Region During Baseline Visits Using the ENROLL HD 2020 Dataset (N = 4,717) *(continued)*

	N (%) or mean (SD; range)	Mean total functional capacity (TFC score) (SD; range)
Geographic location	n = 4,708 (0.19% missing)	
Rural	344 (7.3%)	10.07 (SD 3.32; 2–13)
Village	370 (7.8%)	10.24 (SD 3.07; 1–13)
Town	1,414 (30%)	10.02 (SD 3.19; 0–13)
City	2,580 (54.7%)	10.35 (SD 3.24; 0–13)
Missing	9 (0.2%)	7.0 (SD 4.73; 0–13)

[a] Two omitted values because of the aggregation of participants <18.

significant for Native American and mixed-race participants ($p < 0.05$). Despite a younger age at the time of diagnosis and baseline ENROLL-HD visit, Black participants had a lower TFC score than White participants ($p < 0.001$). A new multivariate linear regression model (Table 4), including the age of HD diagnosis, had similar findings to earlier models: Black participants with HD, those with psychiatric and cognitive symptoms at disease onset, and those with less than a high school degree all had more disability during the baseline ENROLL-HD visit.

Discussion

In this sample, we found that Black patients with HD and those with cognitive and psychiatric symptoms as initial symptom types present with more disability during their baseline ENROLL-HD visit. In contrast, higher educational attainment was associated with less disability. These differences remained true even when controlling for the age of HD diagnosis. Although there were no statistical differences among other racial and ethnic groups, given the low sample size, the statistical power may have been inadequate to identify statistical differences in those groups. Of note, this study suggests that despite this low sample size, Black patients with HD present with more disability at the time of participation in ENROLL-HD.

To our knowledge, this is the first study to identify racial and ethnic disparities in Huntington disease. Some of the reasons for higher disability/disease severity for Black patients in HD are likely similar to reasons for greater disability in other neurologic conditions. Black and Latino adults in the United States experience higher uninsurance rates than White non-Hispanic adults in the general population[24,25] and among hospitalized patients with neurologic disease.[26] Even if insured, Black and Latino patients are less likely to see a neurologist even if they have a documented neurologic condition.[12] Minoritized patients are also less likely to be asked to participate in clinical research studies even when interested in research participation.[27-29] Participation in ENROLL-HD requires access to a Huntington Disease Society of America COE. Although these research visits are free of cost to the patient, many community clinics and patients may be unaware, or there may be geographic barriers for patients to access these centers and be part of ENROLL-HD. In this context, higher disability for Black patients with HD during their baseline visit for ENROLL-HD may indicate a delay in access to subspecialized care or a delay in participation in the ENROLL-HD study. Sensitivity analyses suggested that Black participants with a documented age of HD diagnosis entered ENROLL-HD shortly after the diagnosis. However, these findings are difficult to interpret because of the large percentage of missing data for this variable, historical reliance on HD diagnosis based on motor symptoms, and not knowing where a participant was diagnosed. Although we postulate that social and structural determinants of health, including lack of healthcare insurance and limited referral to subspecialized neurologic care, likely contribute to higher disability in this patient cohort, larger multicenter studies are needed to understand better how communities of color access HD care, rate of participation in HD research, and to what extent disparities in access contribute to disparities in HD specific outcomes.

Consistent with previous literature, our analysis reveals that patients who presented with psychiatric symptoms as the initial symptom had lower TFC scores. Yet, the true burden of disability is likely underestimated. Several studies have reported a statistically significant relationship between depression and apathy with decreased functional capacity; however, no statistically significant association has been found between total functional capacity and anxiety, suicidality, aggression, delusions, and hallucinations—symptoms that inevitably contribute to disability.[30,31] Our findings support the hypothesis that TFC scores reflect motor and cognitive function and may underestimate the disability associated with psychiatric symptoms other than depression and apathy.[32] This inaccuracy has important clinical implications, given that psychiatric symptoms in HD may have a greater impact on disability than cognitive or motor symptoms.[33]

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Table 2 Multivariate Regression Models of Total Functional Capacity Score

	Model 1			Model 2			Model 3		
	β coefficient	Standard error	*p* Value	β coefficient	Standard error	*p* Value	β coefficient	Standard error	*p* Value
Race/ethnicity									
White non-Hispanic	Ref			Ref			Ref		
Black American	−1.977	0.313	<0.001	−1.077	0.262	<0.001	−1.024	0.319	0.001
Hispanic or Latino	−0.226	0.26	0.386	−0.300	0.218	0.169	−0.503	0.307	0.102
Other	−0.054	0.492	0.912	0.058	0.409	0.888	−0.124	0.546	0.82
Native American/ Amerindian	−0.132	0.444	0.767	−0.319	0.369	0.388	−0.33	0.63	0.60
Mixed	0.446	0.325	0.17	0.191	0.272	0.482	0.439	0.377	0.245
Asian	−0.425	0.579	0.463	−0.709	0.482	0.141	−0.771	0.674	0.253
Age				−0.136	0.003	<0.001	−0.14	0.006	<0.001
Sex									
Female				−0.199	0.079	0.012	−0.379	0.105	<0.001
Male				Ref			Ref		
CAG (36+)				−0.436	0.012	<0.001	−0.413	0.018	<0.001
Initial symptom type									
Motor				Ref			Ref		
Cognitive				−0.710	0.159	<0.001	−0.75	0.158	<0.001
Psychiatric				−0.720	0.142	<0.001	−0.739	0.141	<0.001
Other				0.867	0.542	0.110	0.75	0.539	0.164
Mixed				−0.260	0.176	0.141	−0.231	0.176	0.189
Level of education									
Less than high school/GED							−0.978	0.324	0.003
High school/GED							Ref		
Vocational training/ some college							0.046	0.148	0.755
Higher education and professional degree							0.538	0.126	<0.001
PhD/doctorate							0.895	0.32	0.005
Geographic location									
Rural							−0.018	0.206	0.93
Village							0.201	0.197	0.306
Town							−0.056	0.118	0.635
City							Ref		
Constant	10.264	0.049	<0.001	35.303	1.052	<0.001	34.715	1.067	<0.001
Sample size (N)	4701			3143			3136		

Given our noted racial disparities in HD, it is also important to better understand the relationship between race and psychiatric disease. Psychiatric symptoms are increasingly recognized as the main reason for institutionalization in patients with HD.[34] There is a paucity of epidemiologic data on the neuropsychiatric burden in racial and ethnic minority groups with HD. General population studies have explored depression in communities of color and acknowledged more

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Table 3 Average Time-to-Enrollment in ENROLL-HD Stratified by Race/Ethnicity (N = 3,130)

Race/ethnicity	Age of diagnosis (SD; range)	Age of baseline visit (SD; range)	Time-to-enrollment[a] (n = 2,955) (SD; range)	TFC score (n = 2,955) (SD; range)
White non-Hispanic	48.42 (13.0; 4–89)	52.16 (12.97; 18–91)	4.09 (4.41; 0–28)	10.48 (3.21; 0–13)
Black American	44.5 (12.3; 13–75)	47.90 (12.69; 23–83)	3.48 (3.82; 0–20)	8.24[c] (3.63; 0–13)
Hispanic or Latino	43.61 (12.49; 9–77)	46.92 (12.37; 21–80)	3.40 (3.84; 0–19)	10.01 (3.38; 1–13)
Other	51.76 (9.21; 34–75)	54.0 (9.41; 35–82)	2.48 (2.90; 0–12)	10.10 (3.28; 2–13)
Native American/Amerindian	45.07 (13.76; 15–77)	47.07 (13.71; 20–79)	2.3[b] (1.92; 0–6)	10.02 (3.71; 1–13)
Mixed	43.08 (12.46; 22–73)	45.15 (12.37; 19–73)	2.86[b] (3.79; 0–18)	10.54 (2.98; 1–13)
Asian	51.16 (14.19; 29–77)	54.37 (14.52; 30–80)	3.56 (4.53; 0–16)	9.73 (3.72; 1–13)

[a] 174 observations missing because of negative values.
[b] $p < 0.05$.
[c] $p < 0.001$ in simple linear regression and ANOVA models.

severe, chronic, and debilitating diseases in Black patients.[35] Hence, it is reasonable to suggest that Black patients with HD may have an increased burden of psychiatric illness. Furthermore, communities of color with psychiatric predominant HD symptoms may experience barriers to specialized HD care (particularly if institutionalized) or not receive an HD misdiagnosis. A study of barriers to HD access or misdiagnosis is beyond the scope of this study, yet an important hypothesis to explore in subsequent studies. Given these knowledge gaps, it is plausible that Black patients with HD may suffer from an even higher degree of disability compared with White non-Hispanic patients than our study defines.

In addition to racial and ethnic differences in the level of disability in our sample data, educational attainment had a negative linear relationship with TFC score, with higher levels of education associated with less disability. General population studies have found that educational attainment is associated with physical and functional disability, including difficulty level with activities of daily living (ADLs).[36] In these studies, individuals with less than a high school education reported more physical disability, chronic health conditions, and a higher functional decline. One challenge in interpreting these findings in ENROLL-HD is potential reverse causality because participants with less disability might have been able to complete higher levels of education. Conversely, those with higher educational attainment might have better access to health insurance, specialty care, and more educational and financial resources that can allow them to present for HD care earlier in the disease course or choose to participate in research studies such as ENROLL-HD. It is also possible that higher education attainment may provide neuroprotection and delay functional disability.[37] These associations are particularly significant in the context of education and the intersection of low-income and minority status. Racial and ethnic disparities in functional decline have been closely tied to socioeconomic advantage, including educational attainment and income.[36] In these models, controlling for income and education reduces the magnitude of these disparities between minoritized groups and White individuals. Studies suggest that the racial composition of high-poverty high schools is predominantly Black or Latino, and students in these areas had less access to advanced math and science courses.[38] Therefore, it is plausible that these racial and educational disparities may disproportionately affect minority patients with HD leading to greater disability.

There is a small number of non-White non-Hispanic patients in the ENROLL-HD dataset. There is also a lack of specificity in some racial categories, including those in an "other" racial category. Furthermore, participants can only select one race, and more racial categories are available to a participant than what investigators see in the periodic data set. The small sample size of non-White participants makes it challenging to address all racial and ethnic disparities in HD disability. This data set's lack of racial diversity likely represents an inherent participant selection bias more than true differences in disease prevalence. Although most ENROLL-HD sites are affiliated with multidisciplinary HD clinics, ENROLL-HD is a voluntary research study involving genetic testing and biosample collection. Vulnerable racial and ethnic communities who have experienced unethical medical experimentation may be less likely to agree to participate in the study, contributing to selection bias. Furthermore, several studies have found that clinicians and researchers are less likely to ask communities of color to participate in research studies.[39] With the available data in ENROLL-HD, we cannot ascertain when an individual entered the study compared with when they accessed a specialized center. To contextualize these findings, we suggest qualitative studies focused on understanding the experience of minoritized patients with HD in clinical trial recruitment and participation. In addition, lack of access to neurologic care in historically marginalized communities may lead to further delays in referrals to HD

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Table 4 Multivariate Regression Models of Total Functional Capacity Score (TFC) Including Age of HD Diagnosis (N = 2,898)

	β coefficient	Standard error	*p* Value
Race/ethnicity			
White non-Hispanic	Ref		
American Black	−1.186	0.305	<0.001
Hispanic or Latino	−0.57	0.299	0.056
Other	−0.481	0.528	0.363
Native American/Amerindian	−0.667	0.589	0.258
Mixed	0.119	0.37	0.749
Asian	−1.01	0.646	0.118
Age during baseline visit	−0.362	0.012	<0.001
Age of HD diagnosis	0.26	0.012	<0.001
Sex			
Female	−0.326	0.019	<0.001
Male	Ref		
CAG repeat length	−0.325	0.019	<0.001
Symptom type at disease onset			
Motor	Ref		
Cognitive	−0.684	0.155	<0.001
Psychiatric	−0.681	0.138	<0.001
Oculomotor	−0.639	1.115	0.566
Other	0.762	0.665	0.252
Mixed	−0.134	0.169	0.426
Level of education			
Less than high school/GED	−0.947	0.313	0.002
High school/GED	Ref		
Vocational training/some college	0.032	0.142	0.823
Higher education and professional degrees	0.442	0.122	<0.001
PhD/doctorate	0.617	0.31	0.047
Geographic location			
Rural	0.017	0.2	0.934
Village	0.132	0.19	0.486
Town	−0.108	0.115	0.348
City	Ref		
Constant	29.909	1.099	<0.001

centers, resulting in patients with HD presenting to studies such as ENROLL-HD at later disease stages and with higher levels of disability.

Age of diagnosis is another variable worth exploring, but it has significant limitations in ENROLL-HD. With more than 30% of missing data and inconsistent clinical practices in listing an age of diagnosis, we cannot accurately interpret disability in the context of the age of diagnosis. Currently, many clinicians make a diagnosis solely based on motor symptoms and not based on the onset of cognitive, behavioral, or psychiatric symptoms.[23] With the recent creation of a new disease staging and classification system for HD, we hope that future studies will better assess an HD diagnosis and help contextualize disability based on the age of symptom onset and diagnosis, with less reliance on sole motor symptoms and using biomarker data.[40] Last, our analysis has an omitted variable bias because potential mediators of the relationship between education of disability, such as income level, neighborhood deprivation index, and usual source of care, are unavailable in ENROLL-HD. This omitted variable bias limits our understanding of the true relationship between education and the level of disability. Furthermore, sociodemographic factors that affect healthcare access in the United States, such as household income and insurance type, were unavailable in ENROLL-HD. Because the current North American region also includes Canada, a country with universal healthcare independent of employment or income level, our findings may underestimate racial, ethnic, and socioeconomic disparities among the ENROLL-HD participants. The participants' country of residence may also mediate the relationship between race/ethnicity and HD's disease severity.

To understand the reasons for higher disability across different racial and ethnic groups with HD, we need improved sociodemographic data collection paired with disease-specific biological data. Multicenter quantitative studies independent of ENROLL-HD can aid in a better understanding of the interplay between social and structural determinants of health, biological factors associated with HD, and disease-specific outcomes. In addition to income, insurance payer, and neighborhood deprivation information, we must pair disease-specific outcomes with culturally appropriate neuropsychiatric evaluations of minoritized patients with HD. Demographic data reporting should also take into account racial intersectionality (e.g., Afro-Latinos), ethnic diversity that does not fall into standard categories (e.g., North African or Arab participants), and needs disaggregation to highlight the inherent cultural and economic differences within each subgroup (e.g., disaggregation of Asian demographic data). Qualitative studies can also enrich our understanding of the experiences of minoritized communities with the disease, access to specialized HD care, and participation in clinical research, including ENROLL-HD.

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TAKE-HOME POINTS

- Black individuals in North America who are gene positive for Huntington disease (HD) enter ENROLL-HD with more disability than White individuals.
- Compared with White participants, Black participants were diagnosed with HD at a younger age and entered ENROLL-HD earlier, yet they experienced more disability.
- Less than a high school degree and psychiatric manifestations as first HD symptom onset were variables associated with more disability, whereas PhD doctorate degrees were associated with less disability.
- Our findings should be interpreted with caution because we cannot disaggregate country data, race/ethnicity data collection and reporting are not comprehensive, there exists a high percentage of missing data for the age of diagnosis and the type of symptom at disease onset, and social and structural determinants of health (SDOH) such as insurance payer and income are not included in ENROLL-HD.
- Additional multicenter studies with more comprehensive SDOH data collection are needed to better understand racial and ethnic disparities in disease severity in Huntington disease.

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Alvin P. Singh, MD, MS	Department of Neurology, David Geffen School of Medicine, UCLA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Susan Perlman, MD	Department of Neurology, David Geffen School of Medicine, UCLA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Arleen Brown, MD, PhD	Division of General Internal Medicine and Health Services Research, Department of Medicine, David Geffen School of Medicine, UCLA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
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