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Racial Disparities in Time to Huntington Disease Diagnosis in North America

An ENROLL-HD Analysis

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Abstract

Background and Objectives

There are well-documented racial and ethnic disparities in access to neurologic care and disease-specific outcomes. Although contemporary clinical and neurogenetic understanding of Huntington disease (HD) is thanks to a decades-long study of a Venezuelan cohort, there are a limited number of studies that have evaluated racial and ethnic disparities in HD. The goal of this study was to evaluate disparities in time from symptom onset to time of diagnosis of HD.

Methods

Using the ENROLL-HD periodic data set 5 (PDS5), we performed sequential multivariate linear regressions to evaluate sociodemographic factors associated with disparities in time to diagnosis (TTD) for gene-positive individuals (CAG repeats 36+) in the North America region. Sensitivity analyses included imputed multivariate regression analysis of individuals with a total motor score (TMS) of 10 or higher and those with 40+ CAG repeats. We also used descriptive statistics to present TTD data in other ENROLL-HD participating regions.

Results

Among 4717 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 TTD in the group was 3.78. When adjusting for clinical and sociodemographic variables, Black participants were diagnosed with HD 1 year later than White participants ($p < 0.05$). Additional factors associated with a later diagnosis included psychiatric symptoms as initial HD symptom, unemployment during baseline ENROLL visit, and higher educational attainment. Sensitivity analysis of gene-positive (36+ CAG) participants with a TMS of 10 or higher and of those with 40+ CAG repeats yielded similar findings.

Discussion

Across multiple statistical models, Black ENROLL-HD participants were diagnosed with HD 1 year later than White participants. Clinical factors suggesting a delay in HD diagnosis included psychiatric symptoms at disease onset and a negative family history of HD. Unemployment during baseline visit and higher educational attainment were sociodemographic factors suggestive of a later diagnosis. Additional multicenter qualitative and quantitative studies are needed to better understand reasons for delays in HD diagnosis among Black individuals, and the role of social and structural determinants of health in obtaining a timely HD diagnosis.

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Introduction

Huntington disease (HD) is a rare neurogenetic condition characterized by a triad of cognitive, behavioral, and motor abnormalities including chorea, dystonia, and ataxia,. Traditionally, clinicians made a definitive diagnosis based on the onset of chorea in the setting of a family history and supported by genetic testing.[1,2] However, cognitive and behavioral symptoms can predate motor onset by 10 years, which may lead to misdiagnoses.[1,3] Although disease prevalence varies worldwide, in the United States, the estimated prevalence has been reported as 7–10 per 100,000 persons, with a recent claims data study suggesting it could be as high as 15 per 100,000 persons.[4-7] Regarding racial and ethnic patient diversity in HD, older studies suggested a lower incidence or prevalence in Black, Latino, and Asian communities compared with White-Non Hispanic groups (hereafter White).[4] However, recent claims data studies suggest that disease estimates in Black individuals may be comparable with White individuals.[7,8] Despite the suggested epidemiologic similarities, racial and ethnical disparities in HD diagnosis have not been well described. Furthermore, there are a limited number of published studies evaluating social and structural determinants of health (SDOH) in HD.[9]

There are well-documented racial and ethnic disparities in access to neurologic care in the United States. Black and Latino patients are less likely to receive outpatient neurologic care despite having a chronic neurologic condition.[10] These differences are true even when controlling for socioeconomic status and insurance payer factors associated with lack of access to health care. Similarly, Black and Latino patients are less likely to receive specialist care for Parkinson disease and present for dementia care with more advanced disease.[11-14] In addition to disparities in access to neurologic care, Black patients are more likely to be misdiagnosed or underdiagnosed with common neurologic conditions such as dementia and headache.[15,16]

Given the known disparities in access to neurologic care in the United States, this study aimed to evaluate racial and ethnic disparities in receiving an HD diagnosis, as measured by the time from symptom onset to the time of HD diagnosis, in a cohort of individuals part of the ENROLL-HD observational study.

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 HD. 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.

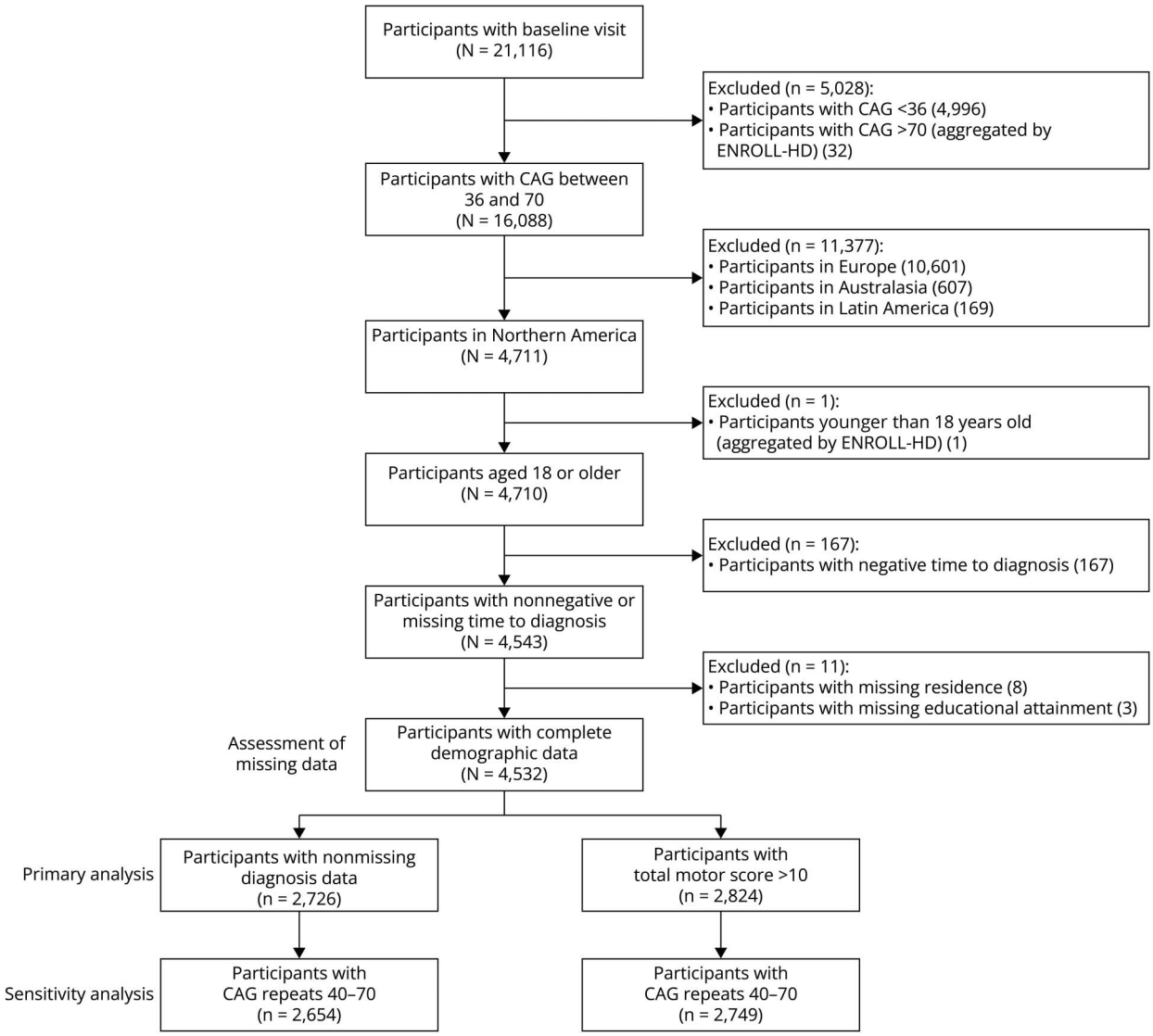
Study Design

This cross-sectional study used the ENROLL-HD periodic data set (PDS) 5, publicly available in December 2020. ENROLL-HD is a free and publicly accessible longitudinal multicenter international observational study of individuals affected by HD.[17] ENROLL-HD takes place at HD Centers worldwide, and any patient with HD or at risk of developing HD can participate in the study. The data set includes clinical assessment data, biosamples, and HD-specific health care outcome data of more than 20,000 participants. A small percentage of the data set also comprises controls such as caregivers. Figure 1 shows the participant selection process for this analysis. We used data from HD gene-positive individuals (36 CAG+) during their baseline visit. To maintain participant confidentiality, ENROLL-HD aggregates data for participants with 70 CAG repeats or more and those younger than 18 years. Given well-documented racial and ethnic disparities in health care in the United States and worldwide differences in health care access and insurance payer systems, this analysis mainly focused on participants in North America, including 50 sites in the United States and 6 in Canada. Nonetheless, we also provide some descriptive data for other regions.

Conceptual Model and Construction of Variables

In this analysis, our independent variable was race/ethnicity and our outcome variable was time-to-HD diagnosis (TTD). Race and ethnicity are based on participant self-identification. However, participants can see more race and ethnicity options than those available in the periodic data set, suggesting that certain racial and ethnic groups may be lumped into the "Other" category.[18] The race and ethnicity categories included in this analysis are based on racial categories made publicly available through the periodic data set. TTD was a constructed variable that consisted of the participant's age of HD diagnosis (as reported by a clinician) and age of symptom onset as reported by the patient's family. We chose the age of symptom onset as reported by the family because many participants with HD may experience cognitive impairment and be unable to provide this information. For the analysis, we excluded individuals with a negative TTD, which could account for those receiving an HD diagnosis based on genetic testing and before the development of symptoms. Figure 2 shows a conceptual model of the proposed relationship between race/ethnicity and time to diagnosis. Potential mediators of this relationship include social and SDOH. SDOH variables available through ENROLL HD include the participant's education, employment status, and residential location (i.e., rural vs urban, listed as "geographic location"). Moderators of the relationship include age at the time of symptom onset, sex, family history of

Figure 1 Participant Selection for Study Analysis



HD, type of initial symptom at the time of disease onset, and CAG repeat length.

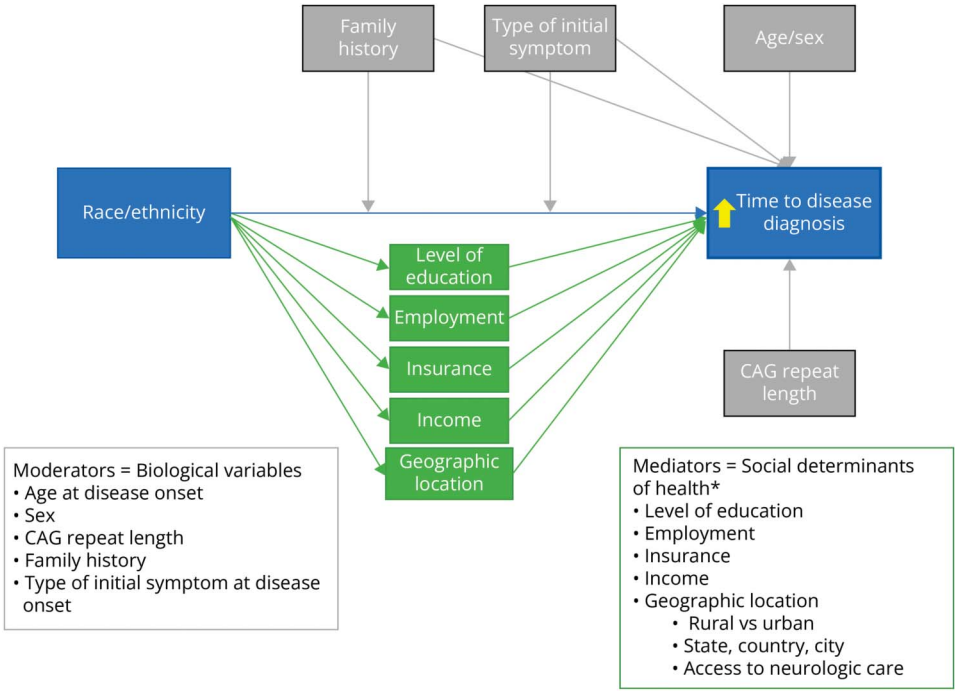
Statistical Analysis

Descriptive statistics were used to analyze patient sociodemographic data. Linear regression models were used to assess the relationship between race/ethnicity and TTD for available data. We used 3 separate linear regression models, including an unadjusted model, an adjusted model including confounding biological variables such as age, sex, CAG repeat length, and symptom type at the time of disease onset, and a third model including biological variables and sociodemographic variables such as residential location and level of education. These 3 models included all available data. p values were set at 0.05 with a 95% confidence interval. All analyses were performed in STATA version 17 by the first author (A.M.) and verified by a second author (A.O.) in R version 4.2.1.

Sensitivity Analyses

We used ANOVA and χ^2 tests to analyze patterns of missingness based on race/ethnicity. Since many participants in the data set may be HD positive, but be presymptomatic or minimally symptomatic, we further restricted the analysis to participants with a total motor score (TMS) of 10 or greater. In a separate analysis, we looked at participants with a diagnostic confidence level (DCL) of 4, another commonly used criterion to identify symptomatic individuals. The results were similar between DCL of 4 and TMS of 10 or greater. We ultimately used the TMS criteria because, compared with DCL, TMS is less likely to be subject to rater or clinician subjectivity or bias. In the final multivariate linear

Figure 2 Conceptual Model of the Relationship Between Race/Ethnicity and Time-to-Diagnosis in Individuals With Huntington Disease



*Of these variables, ENROLL-HD only has data on level of education, employment status during each visit, and individuals' geographic location (ex: urban vs rural).

regression model, we used multiple imputations (assuming missing data at random) to account for missing data. Last, we conducted a similar analysis of missing data and multivariate regression models in participants with 40+ CAG repeats and TMS of 10 or greater.

Although our primary analysis focused on disparities in the North America region, for comparative purposes, we performed a descriptive analysis of other regions worldwide (Figure 3).

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. The data set is publicly available and free to use by investigators.[18]

Results

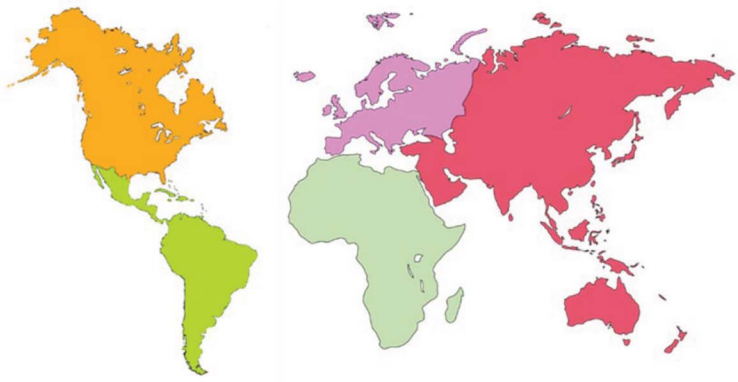
Participant Demographics

Table 1 presents patient demographic data for all genetically confirmed (36+ CAG repeats) participants with HD in North America. Of 4717 participants, most identified as White (89.5%), followed by Hispanic or Latino (hereafter, Latino) (3.4%) and Black (2.3%). The average age at symptom onset, as reported by the family, was 44.6, and the age of HD diagnosis was 48.08. As a result, the average time-to-diagnosis (TTD) was 3.78 years. However, 41.8% of these initial analysis's TTD data was missing. In those with available data, the average time to diagnosis for Black participants was 4.6 years, 4.2 years for Latino participants, 4.2 years for Asian participants, and 4.1 years for Native American participants (Table 2). Black, Latino, Native American, and mixed-race individuals were younger in age ($p < 0.001$) and had higher CAG repeats ($p < 0.001$). In Black and Latino participants, motor symptoms at disease onset were far more common than cognitive symptoms. Psychiatric symptoms at onset were less common in Black participants than in White and Latino participants. There were also racial differences in educational attainment within this cohort, with Asian participants more likely to report higher education and professional degrees than any other group and Native American participants more likely to have less than a high school degree or GED equivalent. Most participants lived in a city, although Black, Latino, Asian, and mixed-race, more so than White participants. By contrast, residential locations were evenly distributed for Native American participants. Across all groups, most participants were unemployed during the baseline visit.

Multivariate Regression Analysis of Genetically Confirmed HD Participants (36–69 CAG repeats)

Table 3 presents 3 separate linear regression models of TTD analyzing available data. An unadjusted linear regression analysis of TTD and race/ethnicity yielded no statistically significant differences. However, in sequential models including biological variables and sociodemographic data, Black participants were diagnosed with HD over a year later than White participants

Figure 3 Participant Characteristics and Time-to-Diagnosis in Latin America, Europe, and Australasia



Latin America: 173 participants
(Argentina, Chile, Colombia)

113 (65.3%) Female participants

Race/ethnicity (n; %):
• White: (46; 26.6%)
• Hispanic or Latino: (123; 71.1%)

Time to HD diagnosis (mean, SD, % missing):
• 4.98 (6.07), 30.1%

Initial symptom at time of disease onset (n = 129; 25.43% missing) (n; %):
• Motor: (89; 69%)
• Psychiatric: (36; 27.9%)

Level of education (n; %):
• Less than high school: (47; 27.2%)
• High school/GED equivalent (72; 41.6%)
• Some college or higher: (54; 31.2%)

Employment (n; %):
• Full-time: (40; 23.3%)
• Unemployed: (116; 67.4%)

Location of residence (n; %):
• Town: (15; 8.7%)
• City: (154; 89%)

Europe: 10,263 participants
(Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Switzerland, UK)

5,646 (53.1%) Female participants

Race/ethnicity (n; %):
• White: (10,365; 97.6%)
• Hispanic or Latino origin: (53; 0.5%)

Time to HD diagnosis (mean, SD, % missing):
• 3.54 (4.27), 36.3%

Initial symptom at time of disease onset (n = 7,343; 30.9% missing) (n; %):
• Motor: (4,108; 55.9%)
• Psychiatric: (1,684; 22.9%)
• Mixed: (980; 13.4%)

Level of education (n; %):
• Less than high school: (2,837; 2.6%)
• High school/GED equivalent (3,525; 27.4%)
• Some college or higher: (4,194; 70%)

Employment (n; %):
• Full-time: (2,839; 26.8%)
• Unemployed: (6,579; 62.1%)

Location of residence (n; %):
• Rural: (548; 5.2%)
• City: (3,501; 33%)

Australasia: 607 participants
(Australia and New Zealand)

331 (54.3%) Female participants

Race/ethnicity (n; %):
• White: (468; 77.1%)
• Other: (125; 20.6%)

Time to HD diagnosis (mean, SD, % missing):
• 3.54 (4.66), 58%

Initial symptom at time of disease onset (n = 294; 51.57% missing) (n; %):
• Motor: (161; 54.8%)
• Psychiatric: (56; 19.1%)
• Mixed: (47; 16%)

Level of education (n; %):
• Less than high school: (63; 10.4%)
• High school/GED equivalent (173; 28.5%)
• Some college or higher: (371; 61.1%)

Employment (n; %):
• Full-time: (179; 29.5%)
• Unemployed: (310; 51.1%)

Location of residence (n; %):
• Rural: (23; 3.8%)
• City: (280; 46.1%)

($p < 0.01$). We did not see statistically significant differences among Latino, Asian, Native American, or other racial and ethnic minority groups. In these models, compared with female participants, male participants were diagnosed 0.4 years later ($p < 0.05$ in model 2 and $p = 0.01$ in model 3). In both models, participants with psychiatric symptoms as the initial symptom type were diagnosed 1 year later compared with those with motor symptoms ($p < 0.001$). Although 93% of participants reported a known family history of HD, those with no family history of HD, or unknown family history, were diagnosed with HD 1.6 and 2 years later than those with a known family history ($p < 0.001$). In SDOH, participants who were unemployed at the time of baseline visit were diagnosed 1.3 years later than those employed full-time ($p < 0.001$), and those with PhD/doctorate degrees were diagnosed 1.7 years later than those with a high school degree or GED equivalent ($p = 0.001$).

Sensitivity Analyses

Owing to 41.8% missing data with the creation of the TTD variable, we restricted our analysis to individuals with a TMS greater than 10 and a DCL of 4. Patient demographic data and patterns of missingness based on TMS and DCL can be found in eAppendix 1. TTD missing data were 9.4% when restricting the group based on TMS and 8.4% when restricting based on DCL. Given the high collinearity between TMS and DCL (Pearson correlation = 0.738), we ultimately used the TMS score due to less subjectivity than with DCL. Table 4 presents a final imputed multivariate regression analysis of TTD. Like the earlier analysis, Black participants were diagnosed with HD 1.2 years later than White participants ($p = 0.015$), male participants were diagnosed 0.4 years later than female participants ($p = 0.017$), and those with psychiatric symptoms at disease onset were diagnosed a year later than those with motor symptoms ($p < 0.001$). This

Table 1 Patient Demographics of Huntington Disease Participants in the North America Region During Baseline Visits Using the ENROLL HD 2020 Data Set (N = 4,717)

Age (mean, SD)[a]	(min, max)
47.65 (14.15)	18, 91
Sex	n (%)
Female	2,637 (55.9)
Male	2,080 (44.1)
Race/ethnicity (primary regressor)	n (%)
White	4,223 (89.5)
American Black	108 (2.3)
Hispanic or Latino origin	158 (3.4)
American Indian, Native American, Amerindian	53 (1.1)
Asian	32 (0.7)
Mixed	100 (2.1)
Other	43 (0.9)
Age at symptom onset (mean, SD, % missing)	min, max
44.60 (13.11) 33.3%	3,85
Age of HD diagnosis (mean, SD, % missing)	
48.08 (13.00), 33.6%	4,89
Time-to-HD diagnosis (mean, SD, % missing)	
3.78 (4.66), 41.8%	0,46
CAG (36+) repeat length (mean, SD)[b]	
43.45 (3.80)	3,669
Family history of HD (0.2% missing)	n (%)
Yes	4,383 (93.1)
No	132 (2.8)
Unknown	193 (4.1)
Initial symptom at time of disease onset (33% missing)	n (%)
Motor	1,736 (54.9)
Cognitive	437 (13.8)
Psychiatric	621 (19.7)
Oculomotor	7 (0.2)
Other	24 (0.8)
Mixed	336 (10.6)
Level of education (0.2% missing)	n (%)
Less than high school/GED	122 (2.6)
High school/GED	1,291 (27.4)
Vocational training/some college	1,037 (22.0)
Higher education and professional degree	2,112 (44.9)
PhD/doctorate	144 (3.1)
Employment status (0.2% missing)	n (%)
Full-time employed	1,446 (30.7)
Part-time employed	367 (7.8)
Self-employed	125 (2.7)
Not employed	2,770 (58.8)
Geographic location (0.2% missing)	n (%)
Rural	344 (7.3)
Village	370 (7.9)
Town	1,414 (30)
City	2,580 (54.8)

[a] Two omitted values due to aggregation of participants <18.
[b] Six omitted values due to aggregation of participants >70.

analysis also showed similar findings for SDOH. Unemployed participants during baseline visits were diagnosed 1.4 years later than those employed, and those with PhD/doctorate degrees were diagnosed close to 1.7 years later than those with a high school degree or GED equivalent. We found no statistically significant differences associated with the participant's residential location. Last, we used the Fisher exact test to compare educational attainment and type of initial symptom at disease onset (eAppendix 2) and found a higher proportion of participants with higher educational attainment levels reporting cognitive and psychiatric symptoms, in contrast to those with high school and less than high school degrees who more commonly reported motor symptoms as first symptom type ($p < 0.001$).

Given the new proposed HD classification and staging system,[19] we also performed an imputed multivariate linear regression analysis of participants with 40+ CAG repeats (eAppendix 3). In this new analysis, we had similar findings with statistically significant differences in TTD noted for Black participants, those with psychiatric symptoms at the time of disease onset, participants with no or unknown HD family history, unemployed participants, and those with PhD/doctorate degrees: all these groups were diagnosed 0.9–2.2 years later.

For all the imputed analyses, we attempted to control for race/education and race/employment interaction. However, given the small subgroups within each category, we could not make meaningful interpretations.

Table 2 Characteristics of Participants for Primary Analysis by Race/Ethnicity (N = 2,719)

	White non-Hispanic	American Black	Hispanic or Latino	Native American/Amerindian	Asian	Mixed	Other	
	N = 2435	N = 81	N = 80	N = 22	N = 18	N = 56	N = 27	*p* Value
Time to diagnosis	3.7 (4.6)	4.6 (5.8)	4.2 (5.0)	4.1 (3.6)	4.2 (5.8)	3.5 (4.0)	4.1 (5.1)	0.680
Age	52.44 (13.02)	48.2 (12.8)	48.4 (12.4)	47.2 (14.3)	54.4 (14.9)	45.5 (12.4)	53.9 (9.7)	<0.001
Sex, male	1201 (49.3)	40 (49.4)	34 (42.5)	8 (36.4)	9 (50.0)	24 (42.9)	15 (55.6)	0.652
CAG repeat length	43.91 (4.17)	46.6 (5.0)	45.4 (4.3)	45.8 (6.1)	44.1 (3.9)	45.9 (4.8)	43.5 (2.6)	<0.001
Family history of HD								0.207
Yes	2211 (90.8)	70 (86.4)	73 (91.2)	20 (90.9)	16 (88.9)	48 (85.7)	21 (77.8)	
No	97 (4.0)	3 (3.7)	1 (1.2)	1 (4.5)	1 (5.6)	3 (5.4)	1 (3.7)	
Unknown	127 (5.2)	8 (9.9)	6 (7.5)	1 (4.5)	1 (5.6)	5 (8.9)	5 (18.5)	
Education								<0.001
Less than high school/GED	61 (2.5)	3 (3.7)	7 (8.8)	11 (50.0)	0 (0.0)	0 (0.0)	1 (3.7)	
High school/GED	760 (31.2)	34 (42.0)	27 (33.8)	6 (27.3)	1 (5.6)	20 (35.7)	5 (18.5)	
Vocational training/some college	511 (21.0)	27 (33.3)	16 (20.0)	2 (9.1)	2 (11.1)	17 (30.4)	7 (25.9)	
Higher education and professional degrees	1029 (42.3)	16 (19.8)	28 (35.0)	3 (13.6)	15 (83.3)	19 (33.9)	12 (44.4)	
PhD/doctorate	764(3.0)	1 (1.2)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)	
Residence								<0.001
Rural	194 (8.0)	1 (1.2)	2 (2.5)	6 (27.3)	0 (0.0)	3 (5.4)	1 (3.7)	
Village	206 (8.5)	4 (4.9)	4 (5.0)	6 (27.3)	1 (5.6)	4 (7.1)	3 (11.1)	
Town	829 (34.0)	12 (14.8)	7 (8.8)	5 (22.7)	4 (22.2)	13 (23.2)	4 (14.8)	
City	1206 (49.5)	64 (79.0)	67 (83.8)	5 (22.7)	13 (72.2)	36 (64.3)	19 (70.4)	
Employment status								0.052
Full-time	371 (15.2)	6 (7.4)	12 (15.0)	1 (4.5)	1 (5.6)	9 (16.1)	6 (22.2)	
Part-time	134 (5.5)	3 (3.7)	8 (10.0)	2 (9.1)	2 (11.1)	5 (8.9)	0 (0.0)	
Self-employed	43 (1.8)	0 (0.0)	1 (1.2)	0 (0.0)	2 (11.1)	0 (0.0)	1 (3.7)	
Not employed	1887 (77.5)	72 (88.9)	59 (73.8)	19 (86.4)	13 (72.2)	42 (75.0)	20 (74.1)	
Age at symptom onset as reported by family members	45.2 (13.0)	40.5 (11.9)	41.4 (11.9)	40.9 (13.5)	47.4 (13.2)	39.8 (12.9)	47.4 (9.7)	<0.001
Age at clinical diagnosis	49.0 (12.9)	45.1 (12.4)	45.6 (11.7)	45.0 (14.5)	51.7 (14.4)	43.3 (12.5)	51.5 (9.4)	<0.001
Symptom type at disease onset								0.509
Motor	1352 (55.5)	59 (72.8)	51 (63.7)	11 (50.0)	12 (66.7)	35 (62.5)	20 (74.1)	
Cognitive	334 (13.7)	6 (7.4)	7 (8.8)	4 (18.2)	1 (5.6)	6 (10.7)	2 (7.4)	
Psychiatric	469 (19.3)	5 (6.2)	13 (16.2)	4 (18.2)	4 (22.2)	8 (14.3)	5 (18.5)	
Oculomotor	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	13 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Mixed	261 (10.7)	11 (13.6)	9 (11.2)	3 (13.6)	1 (5.6)	6 (10.7)	0 (0.0)	

Global Demographics

Figure 3 summarizes patient demographics in regions other than North America. ENROLL-HD primarily comprises data from individuals in Europe (N = 10,623). Latin America had the lowest participant enrollment (N = 173). Australasia includes Australia and New Zealand. There were no

ENROLL-HD sites in Africa or Asia. Across all regions, there was more than 30% of missing data for TTD. Australasia had the highest percentage (58% missing), and Latin America had the lowest (30.1% missing). Using available data, the TTD was about 3.5 years in Europe and Australasia. Latin American participants reported the longest TTD averaging close to 5 years. Across all regions, there were more female participants than men. The most common initial symptom type was motor, although, in Latin America, a higher percentage of participants reported motor symptoms at disease onset compared with other regions (69% vs ~55.5%). Psychiatric symptoms were the second most common symptom at disease onset, followed by mixed symptoms. Across all regions, ~90% of participants reported a known family history of HD (data available on request). Regarding SDOH, 61% of participants in Australasia and 70% in Europe reported at least some college education. Only 31% of Latin American participants reported at least some college education. Over 50% of all baseline participants in all regions were unemployed at the time baseline visit. In Australasia and Europe, most participants did not reside in a city, whereas in Latin America, 89% lived in a city.

Discussion

This study examined the role of race, ethnicity, and other clinical and sociodemographic factors in time to an HD diagnosis. Despite a small percentage of non-White participants in North America, across different statistical models, we found that Black participants with HD were diagnosed a year later than White participants. Other factors associated with a later diagnosis included psychiatric symptoms as the first symptom at the time of disease onset, not having a family history of HD or unknown family history, unemployment, and having a PhD/doctorate degree. The findings in this study are similar to emerging health equity literature in HD using ENROLL-HD and that has identified that Black participants in the cohort enter this natural history study with more disease-associated disability, and that has also found relationships between educational attainment and nonmotor symptoms, and HD-related disability.[20,21] Our study also compared TTD among ENROLL-HD participants worldwide. The average TTD was about 3.5 years from symptom onset, although participants in Latin America were diagnosed 5 years after symptom onset. Furthermore, Australasia and Latin America had a small number of participants compared with the population size in each region.

Although we have identified disparities within ENROLL-HD, the study's limited racial diversity highlights health equity issues in clinical research participation and access to specialized HD care. Despite the small percentage of ENROLL-HD participants who identify as an ethnicity other than White, many Centers of Excellence (COEs) across the United States report seeing a more diverse patient population than in ENROLL-HD.[22] Reasons for the lack of diversity in ENROLL-HD may include limited recruitment of minoritized individuals, community mistrust of investigators/research, and limited access to an ENROLL-HD site. There are data to suggest that even if interested, historically minoritized groups in the United States are less likely to be asked to participate in research.[23] Another challenge is that ENROLL-HD participation involves biosample collection. Decades of unethical experimentation in Black, Latino, and Native American communities in the United States may make patients from these groups hesitant to participate in research studies, including ENROLL-HD.[24-27] In addition, many research studies in the United States lack language or culturally concordant research staff, which creates additional barriers to the participation of Limited English Proficient participants.[27] In the case of ENROLL-HD, it is not clear what are the specific methods by which sites across the United States ensure recruitment of a diverse patient population or what percentage of patients from minoritized groups from individual HD COEs are part of the ENROLL-HD study. Furthermore, most HD research in the United States, including ENROLL-HD, occurs at COEs, and we do not know how many non-White patients with HD receive care outside COEs.

Despite the limited patient diversity in ENROLL-HD, we found that Black participants were diagnosed a year later than White non-Hispanic participants. One explanation for these findings is that these patients may experience delays in accessing specialized HD centers with experience diagnosing HD and access to confirmatory genetic testing and counseling. Studies in general neurology, dementia, Parkinson disease, and stroke have found racial and ethnic disparities in access to a general neurologist and subspecialists, misdiagnosis, and that minoritized groups present for neurologic care with more advanced disease.[13,16,28-32] In the case of rare diseases, racial disparities have been reported in testing and interpretation of newborn screenings, as well as concerns of stigmatization of children with genetic conditions such as sickle cell or cystic fibrosis.[33] Regarding genetic testing and counseling, oncology literature has also found that minority groups are less likely to be referred for genetic testing and counseling for BRCA1 and BRCA2 mutations associated with breast cancer.[34] Based on the experiences of minoritized groups with access to genetic testing and counseling for rare pediatric disorders and common conditions such as breast cancer, we suspect that patients with HD in historically marginalized communities experience similar disparities.[35] Considering the associated stigma with HD and the condition's rarity, the delay in diagnosis may be even more pronounced than what we found in this study. Furthermore, the lack of statistically significant findings in other minoritized groups, including Latino participants, may be due to a small sample size and not representative of real-world disparities in HD diagnosis. Additional quantitative and qualitative studies on these groups are needed to understand cultural views surrounding

Table 3 Multivariate Regression Models of Time-to-HD Diagnosis in ENROLL-HD Participants (36–70 CAG Repeats) in North America (N = 2,719)

	Model 1			Model 2			Model 3		
	β Coefficient	SE	*p* Value	β Coefficient	SE	*p* Value	β Coefficient	SE	*p* Value
Race/ethnicity									
White non-Hispanic	Ref			Ref			Ref		
American Black	0.882	0.528	0.095	1.335	0.493	0.007	1.248	0.494	0.012
Hispanic or Latino	0.440	0.531	0.407	0.500	0.493	0.311	0.513	0.494	0.300
Other	0.339	0.904	0.708	0.317	0.840	0.705	0.302	0.835	0.717
Native American/Amerindian	0.401	1.000	0.688	0.537	0.928	0.563	0.260	0.955	0.785
Mixed	−0.217	0.631	0.731	−0.362	0.587	0.538	−0.280	0.584	0.632
Asian	0.487	1.105	0.659	0.890	1.024	0.385	0.954	1.022	0.351
Age at symptom onset				−0.181	0.010	<0.001	−0.188	0.010	<0.001
Sex									
Female				Ref			Ref		
Male				0.319	0.167	0.056	0.370	0.167	0.027
CAG (36–70)				−0.456	0.029	<0.001	−0.467	0.029	<0.001
Initial symptom type									
Motor				Ref.			Ref		
Cognitive				−0.041	0.256	0.873	−0.142	0.255	0.577
Psychiatric				1.083	0.230	<0.001	1.046	0.229	<0.001
Oculomotor				1.018	1.772	0.566	0.753	1.762	0.669
Other				1.765	1.164	0.130	1.884	1.156	0.103
Mixed				0.141	0.278	0.613	0.098	0.277	0.723
Family history of HD									
Yes				Ref			Ref		
No				2.270	0.434	<0.001	2.225	0.431	<0.001
Unknown				1.770	0.369	<0.001	1.654	0.367	<0.001
Employment status									
Full-time employed							Ref		
Part-time employed							0.429	0.410	0.296
Self-employed							0.186	0.666	0.780
Not employed							1.343	0.237	<0.001
Level of education									
Less than high school/GED							0.224	0.510	0.660
High school/GED							Ref		
Vocational training/some college							−0.156	0.232	0.501
Higher education/professional degree							0.057	0.200	0.776
PhD/doctorate							1.711	0.511	0.001
Geographic location									
Rural							0.139	0.324	0.669
Village							0.290	0.309	0.348
Town							−0.098	0.187	0.600
City							Ref.		

Table 4 Imputed Multivariate Linear Regression Model of Time-to-Diagnosis in ENROLL-HD Participants (36–70 CAG) With a Total Motor Score >10 (N = 2,815)

	β Coefficient	SE	*p* Value
Race/ethnicity			
White non-Hispanic	Ref		
American Black	1.187	0.485	0.015
Hispanic or Latino	0.643	0.506	0.204
Other	0.226	0.820	0.783
Native American/Amerindian	−1.321	0.880	0.136
Mixed	−0.161	0.605	0.791
Asian	0.769	1.048	0.463
Age at symptom onset	−0.185	0.010	<0.001
Sex			
Female	Ref		
Male	0.401	0.168	0.017
CAG repeat length	−0.467	0.030	<0.001
Symptom type at disease onset			
Motor	Ref		
Cognitive	−0.050	0.265	0.852
Psychiatric	1.023	0.244	<0.001
Oculomotor	0.483	1.727	0.780
Other	1.800	1.161	0.123
Mixed	0.158	0.281	0.575
Family history of HD			
Yes	Ref		
No	2.325	0.456	<0.001
Unknown	1.617	0.374	<0.001
Employment status			
Full-time employed	Ref		
Part-time employed	0.778	0.434	0.074
Self-employed	0.440	0.700	0.530
Not employed	1.432	0.244	<0.001
Level of education			
Less than high school/GED	0.539	0.503	0.284
High school/GED	Ref		
Vocational training/some college	−0.121	0.240	0.615
Higher education and professional degrees	0.114	0.201	0.571
PhD/doctorate	1.666	0.514	0.001
Geographic location			
Rural	0.228	0.329	0.489
Village	0.256	0.308	0.406
Town	−0.087	0.192	0.653
City	Ref.		

HD and HD diagnosis and evaluate potential barriers to accessing specialized HD care.

A second explanation for the difference in TTD is that the interaction between race/ethnicity and other SDOH drives this difference, along with the interplay between types of symptoms at disease onset. This analysis found that higher educational attainment and unemployment were associated with later diagnosis. A separate study using a 2017 version of ENROLL-HD found that individuals with higher educational attainment had an earlier age of symptom onset and diagnosis, although it did not measure "time-to-diagnosis" in the cohort, and thus, we cannot make direct comparisons between both studies.[36] Of interest, the analysis found that those with higher educational attainment had lower motor scores, less disability, and higher scores in cognitive assessments, including the Stroop test, suggesting that higher educational attainment may serve a neuroprotective role in HD. In the dementia literature, higher educational attainment has been associated with a lower rate of functional decline and cognitive impairment.[37] This may also be true in patients with HD. Our sensitivity analyses also showed that those with higher education were more likely to report cognitive and psychiatric symptoms as first symptom at the time of disease onset. Considering that current standards for definitive HD diagnosis are based on the presence of motor symptoms, those with higher educational attainment (and possibly higher health literacy) may be more aware of nonmotor symptoms or more likely to attribute cognitive and psychiatric symptoms to HD. These findings also align with some of our own clinical experiences, where highly educated patients are more aware of the disease and present earlier for specialized HD care. Additional studies evaluating education and HD disease onset, progression, and access to specialized care are needed to better understand education as a primary predictor for time to diagnosis.

Another SDOH associated with a later diagnosis was unemployment. Unemployed individuals may experience barriers to general health care access, leading to a later diagnosis. Symptoms related to HD, including cognitive impairment

and severe behavioral disturbances, may limit someone's employment ability. Considering that in the United States, most individuals receive employer-based health insurance and individuals unable to work may lose health insurance benefits, leading to delays in diagnosis.[38] In this analysis, the timing of unemployment in relation to symptom onset and diagnosis is unknown. Subsequent longitudinal analysis using ENROLL-HD should look at TTD based on a participant's change in employment status. Other factors, including insurance payer and income level, may mediate this relationship. These are not data typically collected in ENROLL-HD; an analysis with other databases or multicenter collaborations is needed to understand the role of SDOH in TTD.

The third major finding in this study was that those with psychiatric symptoms at the time of disease onset were diagnosed later than those with motor symptoms. This is not surprising considering that an HD diagnosis has been traditionally made based on the presence of chorea or confirmatory genetic testing. However, it has been well established that cognitive, behavioral, and psychiatric symptoms can predate the onset of chorea by 10 years or more.[1] The new International Classification System, introduced in 2022, provides a framework for diagnosing and staging HD at earlier stages and independent of the onset of motor symptoms.[19] Nonetheless, it is important to recognize that individuals with psychiatric disease experience disparities in health care access and outcomes. Individuals with severe mental illness experience delays in general medical care and have higher mortality rates for common chronic conditions such as diabetes, cardiovascular disease, and cancer.[39-41] In the case of HD, psychiatric symptoms can range from common conditions such as anxiety and depression to less common symptoms such as psychosis and mania.[42] Medications associated with drug-induced chorea, including dopamine blockers, are now frequently used to manage treatment-resistant depression.[43] In this context, we suspect that delays in diagnosis in this group could be due to delays in access to health care due to the existence of a mental health illness, possible lack of recognition of psychiatric symptoms as part of HD, and the use of dopamine blockers for a primary psychiatric indication, which could lead to a possible misdiagnosis of a drug-induced movement disorder. We suggest additional studies to evaluate how psychiatric disease delays access to HD care.

A significant limitation in analyzing racial disparities in this study is the small sample of non-White participants in ENROLL-HD. The limited diversity in ENROLL-HD likely represents an inherent participant selection bias more than differences in disease prevalence. There may be many reasons for the limited patient diversity in ENROLL-HD, ranging from barriers to recruitment of minority groups into the study, willingness to participate, and access to specialized HD centers. There is also a need for standardized practices for recruiting participants to ENROLL-HD. SDOH, including distance from a COE, may limit patients' ability to participate in the study. To truly understand delays in HD diagnosis, we need qualitative studies to understand how minoritized communities access HD care. There are also concerns with the racial terminology used by ENROLL-HD, particularly the use of the term "American Black." This term may not be representative of Black individuals from Caribbean, African, and other national and ethnic backgrounds who may not identify as American. Furthermore, current race/ethnic reporting and classification in ENROLL-HD are incomplete because it limits participants to select 1 race category and fails to account for intersectionality (ex: Afro Latinos), ethnic diversity that does not fall into standard categories (ex: Arab participants) and needs disaggregation to highlight inherent cultural and economic differences within each subgroup (ex: disaggregation of Asian demographic data). The ENROLL-HD data set can improve racial and ethnic data collection and reporting by adhering to commonly used nomenclature (ex: Black race), expanding the number of categories, and allowing participants to select multiple racial and ethnic categories.

The data set also had more than 30% missing data for the age of diagnosis and type of symptom at disease onset. Based on our sensitivity analyses, we suspect that missingness for these variables is due to a lack of motor symptoms, suggesting a group that is either asymptomatic or minimally symptomatic. This limitation also highlights concerns raised by the HD community with traditional reliance on motor symptoms for HD diagnosis and staging.[2] Although we hope that the newly proposed 2022 disease classification and staging system will help in the early diagnosis of HD participants, it may not improve disease recognition, particularly in underserved communities. Furthermore, the new staging system relies on biomarker data, specifically imaging studies.[19] This will likely incur additional costs and barriers in access to neuroimaging to already underserved communities. The study of blood biomarkers and ongoing education of patients, families, and community providers will be vital in ensuring appropriate early diagnosis and staging of HD in underserved communities in the United States and worldwide.

With the rapid development of clinical trials for disease modification in HD, it is essential to ensure the early recognition of HD and referral to specialized HD care, particularly among historically marginalized racial and ethnic groups. To improve early disease identification and diagnosis, we must understand the barriers to an early diagnosis and access to specialized HD care for minority groups. Additional studies evaluating the role of SDOH in early disease recognition, diagnosis, and referral to specialized care are critical. Furthermore, there is a need to identify barriers to specialized HD care among patients with HD outside of HD COEs. A complete understanding of these factors will allow better design of interventions to improve the early diagnosis of HD

TAKE-HOME POINTS

- Despite a small sample size, Black patients in North America with Huntington disease (HD) and who participated in ENROLL-HD experienced a delay in receiving an HD diagnosis, as measured by time from symptom onset to time of a formal HD diagnosis.
- Other factors associated with a later HD diagnosis included (1) psychiatric symptoms as initial symptom type, (2) lack of family history of HD or unknown family history, (3) being unemployed during baseline ENROLL-HD visit, and (4) completing PhD/doctorate degrees.
- Worldwide, the average TTD was 3.5 years, yet there was a large percentage of missing data for the variables of age of symptom onset or age of HD diagnosis. Missing data for these variables may represent presymptomatic individuals.
- Due to barriers in health care access in the United States, we suspect that true delays in diagnosis are likely underestimated in our study, considering ENROLL-HD only takes place in HD Centers of Excellence which are mostly affiliated with academic institutions in urban settings.
- Additional multicenter studies outside of HD Centers of Excellence are needed to better understand potential disparities in HD diagnosis and access to specialized HD care.

worldwide while ensuring worldwide equitable access to HD care and emerging therapies.

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