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Humanistic Burden of Huntington Disease

Evidence From the Huntington Disease Burden of Illness Study

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Abstract

Background and Objectives

Huntington disease (HD) is a rare, inherited, and highly complex neurodegenerative disorder with no currently approved disease-modifying treatments. We investigated the effect of HD on health-related quality of life and other patient-reported outcomes in the Huntington's Disease Burden of Illness (HDBOI) study.

Methods

The HDBOI study is a retrospective, cross-sectional study conducted between September 2020 and May 2021 in France, Germany, Italy, Spain, the United Kingdom, and the United States. People with symptomatic onset HD (PwHD) were recruited by their HD-treating physicians and categorized as early (ES), mid (MS), or advanced stage (AS) HD. Physicians provided sociodemographic and clinical information from the participant's medical records in electronic case report forms (eCRF); participants or their proxies completed online Patient Public Involvement Engagement questionnaires (PPIE-P). Patient-reported outcomes included the 5-level EQ-5D version (EQ-5D-5L), Short-Form-(SF)-36 v2 (and SF-6-Dimension [SF-6D] utility), Huntington Quality of Life Instrument (H-QoL-I), and the Work Productivity and Activity Impairment Specific Health Problem. All outcomes were summarized using descriptive statistics, and differences between disease stages were assessed by Kruskal-Wallis tests.

Results

A total of 2,094 PwHD were enrolled with completed eCRFs (100%) and PPIE-P forms (n = 482, 23%). Participants' mean age was 47.3 years; they were generally evenly distributed across countries, with the majority being ES (40%) followed by MS (33%) and LS (26%). The mean EQ-5D-5L (n = 336) utility score was 0.59 (SD, 0.27), with the highest mean utility scores [SD] in ES (0.72 [0.22]) followed by MS (0.62 [0.18]) and AS (0.37 [0.30]), $p < 0.001$. The mean SF-6D score (n = 482) was 0.57 (SD, 0.10), with mean values decreasing with advanced disease (ES, 0.61; MS, 0.56; AS, 0.50, $p < 0.001$). H-QoL-I mean scores (n = 482) also worsened with more advanced disease, from 0.58 for ES to 0.49 for MS and 0.37 for AS, $p < 0.001$. Impairment in daily activities and in work productivity also increased with more advanced disease. Overall proxy respondents reported on average worse outcomes than PwHD (self-reported) across all outcomes and disease stages suggesting a possible unawareness of deficits by PwHD.

Discussion

The HDBOI study provides new insights into the characteristics and humanistic burden of PwHD and offers a meaningful contribution to this underserved research area.

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Huntington disease (HD) is a rare, inherited, and highly complex neurodegenerative disorder, affecting all aspects of an individual's life. Over time, HD has a substantial effect on physical, cognitive, and behavioral processes[1] and universally leads to disability and death.[2] The estimated prevalence of HD in North America and Europe ranges from approximately 6–14 cases per 100,000 people and has been shown to be increasing in the Western world following the provision of diagnostic testing.[3] Life expectancy from HD onset varies, but typically ranges from approximately 15–20 years after diagnosis of motor symptoms.[4]

HD is caused by a DNA expansion of repeating cytosine, adenine, and guanine (*CAG*) triplets in the huntingtin gene (*Htt*). *CAG* repeats of more than 39 will result in a person developing HD in a normal lifespan, reduced penetrance is seen between 36 and 39 repeats, and longer repeats are associated with earlier disease onset.[5-7] *CAG* repeats are also correlated with the progression of motor and cognitive deficits.[8] Several studies have contributed to understanding the predictors of disease progression.[9-12] Symptoms can vary widely: early signs and symptoms often include personality changes, mood swings, chorea, irritability, and dementia.[13] Progressive neurologic damage can affect movement, cognition (perception, awareness, thinking, and judgment), and behavior, leading to PwHD becoming dependent on caregivers for activities of daily living.[2] As such, the mean annual costs of care for PwHD have been shown to increase dramatically with disease progression, particularly those related to informal care services, hospital/residential and nursing home care, and outpatient services.[13,14]

There are currently no approved disease-modifying treatments to slow, halt, or reverse the course of HD. Clinical management aims to reduce the burden of symptoms, maximize functionality, improve health-related quality of life (HRQoL), and prevent complications.[15] In recent years, promising research exploring molecular regulation of gene expression via antisense oligonucleotides, small molecules, and gene therapies has offered the potential for meaningful, durable clinical response, and clinical trials are ongoing.

In the context of novel emerging therapeutic pathways for PwHD, it is important to understand the burden of HD and the unmet needs of existing management options. HD is known to have a substantial effect on both PwHD and their families, but little tangible information is available on the humanistic burden on PwHD,[16] and very few studies have assessed HRQoL in HD using validated instruments.[17] The Huntington's Disease Burden of Illness Study (HDBOI) was conducted to characterize the clinical, humanistic, and economic burden of disease on PwHD and their caregivers. In this article, we report findings from the HDBOI study related to humanistic burden on PwHD across disease stages within 6 countries, including the effect of HD on participant's quality of life (HRQoL) and work productivity and activity impairment measured by means of validated instruments.

Methods

HDBOI is a retrospective, cross-sectional, international burden of illness study of people with diagnosed HD in France, Germany, Italy, Spain, the United Kingdom, and the United States. The study was overseen by an Expert Reference Group consisting of key stakeholders, including clinicians (neurologists, psychiatrists, and allied health professionals), patient advocates, and health economists. The study collected information related to the clinical, humanistic, and economic burden of HD on participants and caregivers; this analysis focused on patient-focused humanistic burden outcomes. HDBOI data were collected between September 2020 and May 2021.

Physician Participants

HD-treating physicians were invited via a fieldwork agency to recruit eligible PwHD during routine clinical consultations. To be eligible to participate in the HDBOI study, physicians had to be neurologists, psychiatrists, general practitioners, internists, geriatricians, or geneticists; they had to be the main point of contact for patients with HD and they had to have access into the patient's medical records. Sampling also considered the geographic distribution of physicians within each country to ensure a mix of metropolitan and rural areas.

Participants

Eligible participants were adults (aged ≥18 years) clinically diagnosed with symptomatic motor HD disease ≥12 months before the date of clinical consultation that was used for study recruitment (defined as the index date). Participants who participated in a clinical trial for an HD treatment in the 12 months before the index date were not eligible. PwHD were categorized as early (ES), mid (MS), or advanced (AS), as per Wild and Tabrizi descriptors[18] manifest HD disease stage at the consultation date (index date) based on the opinion of the treating physician.

Variables and Outcomes

Data were collected from an electronic Case Record Form (eCRF) completed by the HD-treating physician and a voluntary Patient Public Involvement Engagement (PPIE-P) questionnaire completed by the PwHD. For participants with a severe cognitive deficit, the caregiver was asked to provide consent and to complete the PPIE-P on the participant's behalf as a proxy respondent. All questionnaires were administered via an online platform.

Physicians retrospectively extracted sociodemographic and clinical information related to diagnosis, disease history, and symptomatology from the participants' medical records to complete the eCRF. In parallel, PwHD and caregivers completed sociodemographic and clinical information and lifestyle changes and cross-sectional self-reported outcomes in the PPIE-P questionnaire.

Cross-sectional participant-reported outcomes in the PPIE-P and analyzed in this piece included the Short-Form (SF)-36 v2, EQ-5D-5L, the Huntington Quality of Life Instrument

(H-QoL-I) (Clay 2012), and the Work Productivity and Activity Impairment Specific Health Problem (WPAI-SHP).[19]

1. The SF-36 v2 is a standardized instrument used to measure physical and mental health.[20] From this, preference-based utility scores can be calculated using an algorithm specifically developed for this purpose (SF-6-Dimension [SF-6D]). Utility scores range from 0.291 to 1.000, where a score of 1 represents full health.
2. The EQ-5D-5L is a generic measure of self-reported health comprising 5 dimensions: mobility, usual activities, self-care, pain and discomfort, and anxiety and depression. Each dimension has 5 levels of severity (from no problems to extreme problems).[21] A health state index utility score based on country-specific value sets is derived through an amalgam of the 5 responses; in this case, the England value set was used for all participants for comparability purposes. Scores generally range from 0 (equivalent to dead) to 1 (perfect health), although scores of less than zero (worse than dead) can also be derived.
3. The H-QoL-I is a disease-specific tool that assesses the humanistic and clinical burden of living with HD. It comprises 11 items that are divided into 3 dimensions: motor functioning, psychology, and socializing. The H-QoL-I index is calculated by summing all the item scores, which are then normalized to a scale ranging from 0 to 100, with 100 indicating the best possible health and 0 indicating the worst.[22]
4. The WPAI-SHP is a validated and widely used instrument for measuring the effect of a condition on an individual's work and activities during the previous 7 days.[19] It consists of 6 questions, from which 4 main outcomes can be generated: percent work time missed due to health, percent impairment while working due to health, percent overall work impairment due to health, and percent activity impairment due to health.

Table 1 Participants With Completed eCRFs and PPIE-Ps by Country and Disease Stage

Participants, n (%)	All participants	ES	MS	AS
Completed eCRFs				
Total	2094 (100)	846 (40)	701 (34)	547 (26)
Total by country				
Italy	492 (24)	190 (22)	182 (26)	120 (22)
United States	492 (24)	213 (25)	154 (22)	125 (23)
Spain	354 (17)	152 (18)	107 (15)	95 (17)
United Kingdom	272 (13)	91 (11)	111 (16)	70 (13)
Germany	264 (13)	96 (11)	85 (12)	83 (15)
France	220 (11)	104 (12)	62 (9)	54 (10)
Total	2094 (100)	846 (100)	701 (100)	547 (100)
Completed PPIE-P questionnaires				
Total	482 (100)	204 (42)	164 (34)	114 (24)
Participant (PwHD)	440 (91)	192 (94)	155 (95)	93 (82)
Proxy respondent	42 (9)	12 (6)	9 (5)	21 (18)
Total by country				
Spain	207 (43)	103 (50)	58 (35)	46 (40)
Italy	126 (26)	55 (27)	49 (30)	22 (19)
United Kingdom	56 (12)	6 (3)	26 (16)	24 (21)
France	43 (9)	20 (10)	14 (9)	9 (8)
United States	37 (8)	15 (7)	12 (7)	10 (9)
Germany	13 (3)	5 (2)	5 (3)	3 (3)
Total	482 (100)	204 (100)	164 (100)	114 (100)

Abbreviations: AS = advanced stage; eCRF = electronic Case Report Form; ES = early stage; MS = mid stage; PPIE-P = Patient Public Involvement Engagement Patient.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics for the overall study population and by subgroups based on HD stage. Humanistic burden data were analyzed descriptively overall, by disease stage and by country using measures of central tendency. Univariate comparisons were conducted when appropriate. No imputation of missing data was performed. Differences between outcomes were explored by disease stage, and the statistical significance of these differences was assessed by Kruskal-Wallis tests. All data were analyzed using STATA 16 (StataCorp LLC, College Station, TX; stata.com) and R (r-project.com).

Standard Protocol Approvals, Registrations, and Participant Consents

The study protocol and materials were approved by the University of Chester Ethics Committee. Electronic informed consent was obtained from all participants (or proxies for participants) in the study.

Data Availability

The data that support the findings of this study may be available from HCD Economics, Ltd, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may be available from the authors on reasonable request and with permission of HCD Economics Ltd.

Results

A total of 2,094 PwHD were enrolled in the study, with completed eCRFs for all 2,094 (100%) participants and completed optional PPIE-P forms from 482 (23%) patients. Forty-two (9%) of the PPIE-P responses were completed by proxy respondents (of these, 29% ES, 21% MS, and 50% AS). The total sample was generally evenly distributed across participating countries, with adequate representation across disease stages (Table 1). The greatest proportions of participants were from Italy and the United States (n = 492, 24% each), and the majority of participants had ES HD (40%) followed by MS (33%) and AS (26%).

Table 2 shows the distribution of PwHD sociodemographic and clinical characteristics. The mean age of the overall sample was 47.3 years (SD, 13.7).

Effect of HD on HRQoL

As HD is a chronic and degenerative disease, standardized tools measuring HRQoL are important to provide information on PwHD personal everyday experiences and to assess the burden of disease.[22,23] Of the 482 PwHD completing the PPIE-P, 336 (70%) completed the EQ-5D-5L, and 482 (100%) completed the SF-36 and the H-QoL-I. Results are displayed in Table 3.

HRQoL Measured by the EQ-5D

After normalization to the England value set, the total mean EQ-5D-5L utility score for the overall PPIE-P sample of 336

Table 2 Participant Sociodemographic and Clinical Characteristics (eCRF Population, n = 2094)

eCRF population				
Participant, n (%) unless noted	**All participants (n = 2094)**	**ES (n = 846)**	**MS (n = 701)**	**AS (n = 547)**
Sex				
Female	1,253 (60)	492 (58)	397 (57)	365 (67)
Male	799 (38)	334 (39)	288 (41)	177 (32)
Prefer not to answer	42 (2)	20 (2)	16 (2)	6 (1)
Age, mean (SD)	47.3 (13.7)[a]	43.2 (12.9)[a]	48.1 (13.6)	52.3 (13.3)
BMI, mean (SD)	23.9 (3.5)[b]	23.7 (3.5)[b]	24.1 (3.4)[b]	23.8 (3.7)[b]
PPIE-P sample				
Participant, n (%) unless noted	**All participants (n = 482)**	**ES (n = 204)**	**MS (n = 164)**	**AS (n = 114)**
Sex				
Female	164 (35)	76 (37)	63 (38)	30 (26)
Male	313 (65)	128 (63)	101 (62)	84 (74)
Age, mean (SD)	47.0 (12.4)	43.4 (12.2)	48.9 (11.6)	50.7 (12.3)
BMI, mean (SD)	24.2 (3.3)[c]	23.9 (3.2)[c]	24.3 (3.6)[c]	24.2 (3.3)[c]

Abbreviations: AS = advanced stage; eCRF = electronic Case Report Form; ES = early stage; MS = mid stage.
[a] Available responses in the total sample, n = 2093; early stage, n = 845.
[b] Available responses in the total sample, n = 1151; early stage, n = 487; mid stage, n = 376; advanced stage, n = 288.
[c] Available responses in the total sample, n = 337; early stage, n = 151; mid stage, n = 108; advanced stage, n = 78.

Table 3 EQ-5D-5L, SF-6D, and H-QoL-I Utility Scores Overall and by HD Disease Stage

Participants, n (%)	All participants	ES	MS	AS
EQ-5D-5L, mean (SD)				
Sample size (N) all participants/self-reported/proxy	336/309/27	129/122/7	119/115/4	88/72/16
All participants[a]	0.59 (0.27)	0.72 (0.22)	0.62 (0.18)	0.37 (0.30)
Self-reported (PwHD)[a]	0.62 (0.24)	0.74 (0.19)	0.62 (0.18)	0.42 (0.27)
Proxy respondent[c]	0.26 (0.35)	0.34 (0.31)	0.66 (0.26)	0.13 (0.31)
EQ-5D-5L, dimensions—all participants (N = 336)				
Mobility (1–5)	2.50 (1.11)	1.85 (0.81)	2.52 (0.87)	3.42 (1.11)
Self-care (1–5)	2.42 (1.11)	1.78 (0.89)	2.49 (0.85)	3.28 (1.10)
Usual activities (1–5)	2.49 (1.08)	1.94 (0.89)	2.51 (0.85)	3.28 (1.12)
Pain (1–5)	2.41 (0.87)	1.99 (0.81)	2.46 (0.75)	2.94 (0.79)
Anxiety/depression (1–5)	2.66 (0.92)	2.37 (0.95)	2.62 (0.79)	3.13 (0.87)
SF-6D, mean (SD)				
Sample size (N) all participants/self-reported/proxy	482/440/42	204/192/12	164/155/9	114/93/21
Utility score—all participants[a]	0.57 (0.10)	0.61 (0.12)	0.56 (0.07)	0.50 (0.08)
Self-reported (PwHD)[a]	0.57 (0.10)	0.61 (0.11)	0.56 (0.07)	0.51 (0.08)
Proxy respondent[b]	0.49 (0.10)	0.54 (0.11)	0.55 (0.06)	0.44 (0.09)
H-QoL-I				
Sample size (N) all participants/self-reported/proxy	482/440/42	204/192/12	164/155/9	114/93/21
Total H-QoL-I score—all participants[a]	0.50 (0.20)	0.58 (0.21)	0.49 (0.15)	0.37 (0.17)
Self-reported (PwHD)[a]	0.52 (0.19)	0.60 (0.20)	0.50 (0.15)	0.41 (0.15)
Proxy respondent[b]	0.31 (0.19)	0.40 (0.20)	0.40 (0.15)	0.22 (0.17)
H-QoL-I domains—all participants (N = 482)				
Motor scoring	0.51 (0.23)	0.61 (0.24)	0.49 (0.17)	0.34 (0.19)
Psych scoring	0.45 (0.21)	0.52 (0.22)	0.45 (0.17)	0.35 (0.19)
Socializing scoring	0.55(0.24)	0.63 (0.25)	0.54 (0.08)	0.46 (0.23)

Abbreviations: AS = advanced stage; eCRF = electronic Case Report Form; ES = early stage; HD = Huntington disease; H-QoL-I = Huntington Quality of Life Instrument; MS = mid stage; PwHD = people with symptomatic onset HD; SF-6D = Short-Form-6–Dimension.
To assess the significance of differences between disease stages, Kruskal-Wallis tests were conducted for the H-QoL-I total score and the EQ-5D-5L and SF-6D utility scores.
[a] $p < 0.001$.
[b] $p < 0.01$.
[c] $p < 0.05$.

responders was 0.59 (SD, 0.27). The total mean normalized scores were highest (indicating more favorable HRQoL) among the subgroup of ES disease (mean [SD]) (0.72 [0.22]) compared with MS (0.62 [0.18]) and AS (0.37 [0.30]), $p < 0.001$. The observed trend of decreasing score with disease progression was found for self-reported and proxy-reported responses. However, proxy responders reported on average worse EQ-5D-5L scores vs self-reported scores. In the AS group, the mean utility score for proxy respondents was just 0.13 (SD 0.31) compared with the self-reported score of 0.42 (SD 0.27), $p < 0.001$.

The anxiety and depression dimension was the main driver of poor EQ-5D-5L scores in ES and MS participants. In the AS group, mobility, followed by the self-care and usual activities dimensions were the main drivers of lower scores (Table 3).

HRQoL Measured by the SF-6D

After normalization to the England value set, the mean SF-6D utility score (all participants) was 0.57 (SD, 0.10), with mean values appearing to decrease with advanced disease. The mean (SD) SF-6D scores for participants with ES (n = 204),

MS (n = 164), and AS HD (n = 114), respectively, were 0.61 (0.12), 0.56 (0.07), and 0.50 (0.08), $p < 0.001$ (Table 3). A similar trend was observed for self-reported responses; however, as with EQ-5D, proxy responders reported on average worse SF-6D scores, in particular for the AS group (0.51 vs 0.44, $p < 0.001$).

HRQoL Measured by the H-QoL-I

The total H-QoL-I scores also reflected worse participant-reported HRQoL with advanced disease, as the mean (SD) overall scores decreased from 0.58 (0.21) for those with ES HD to 0.49 (0.15) with MD and 0.37 (0.17) with AS, $p < 0.001$. As with the other HRQoL outcomes, there are large disparities between self-reported and proxy-reported responses across the 3 disease stages.

Results for the motor, psychology, and socializing dimensions display a similar trend to the observed for the total score: mean H-QoL-I motor scores were 0.61, 0.49, and 0.34, psychology scores were 0.52, 0.45, and 0.35, and socializing scores were 0.63, 0.54, and 0.46 for ES, MS, and AS, respectively.

Effect of HD on Activity Impairment and Work Productivity

The symptoms associated with HD have a strong effect on functional capacity and affect a person's ability to perform daily activities, work functions, and maintain employment and may lead to reduced work hours or cessation of work.[24,25] The effect on work and productivity was captured in the WPAI-SHP. Overall impairment in daily activities increased with disease severity for both PwHD ($p < 0.001$) and proxy respondents ($p < 0.05$), as displayed in Table 4. Proxy respondents reported worse impairment in daily activities for PwHD than self-reported (79% vs 58% respectively, $p < 0.001$). A total of 134 PwHD (28%) reported being employed for pay (all self-reported). Of these (n = 134) PwHD, overall work productivity loss increased with disease severity: 43% in ES, 55% in MS, and 57% in AS.

Discussion

The HDBOI study provides insights into the patient characteristics and humanistic burden by means of a set of patient-reported outcomes that aim at capturing the effect of living with HD. Moreover, the HDBOI study contributes to the literature providing insight on participant's HRQoL across all stages of disease and from a multinational perspective. The HDBOI is one of the largest studies capturing quality of life using general and specifically validated HRQoL tools for PwHD.

Overall results show that PwHD bear a substantial humanistic burden that increases with disease advancement. For each tool (EQ5D-5L, SF-6D, and H-QoL-I), results in general show poor HRQoL scores, which worsen with disease progression. Standardized tools are important for capturing HRQoL as they allow us to compare the experience of PwHD with other populations. For example, results for EQ-5D-5L utility scores highlight how PwHD experience a much worse HRQoL (ES 0.72, MS 0.62, and AS 0.37) than that observed for the general population (general population 45–54 age group average EQ-5D-5L utility is 0.84).[26] For SF-6D (ES 0.61, MS 0.56, and AS 0.50), similar results are observed (0.79 general population 45–54 age group).[27]

The HRQoL tools used in this study were able to capture the effect of both physical and psychological decline on HRQoL. For example, PwHD experienced worse scores on each dimension of the EQ5D-5L; however, anxiety and depression dimension was the main driver of poor utility scores in ES and MS participants. In the AS group, the main drivers were mobility, followed by the self-care and usual activities. Likewise, for the the HD-specific tool, H-QoL-I, the psychology dimension for ES and MS participants displayed the worst outcomes, whilst for AS participants, motor was the dimension with the lowest score. Our results for EQ5D-5L, H-QoL-I, and SF-6D fall within the ranges reported by other studies,[17,22,27,28] although due to differences in the version of the tool used (EQ5D-3L vs 5L) and the composition of the study populations, they are not directly comparable.

Although this study demonstrates the substantial effect of HD on HRQoL, it is also important to highlight the observed discrepancies between self-reported and proxy respondent outcomes, as the latter group reported on average worse outcomes across all disease stages. Our findings are consistent with previously published studies for HD[29] and for other chronic diseases.[30] One rationale for this discrepancy could be that PwHD who were able to complete the self-reported forms have higher levels of HRQoL than those who had a proxy respondent completing the survey on their behalf. However, this discrepancy may be due to the well-documented lack of insight, unawareness of deficits, and overestimation of abilities often displayed by PwHD.[31,32] In particular, one of the studies finds that PwHD have higher self-ratings of their own competency (i.e., behavioral control, emotional control, and activities of daily living) than the ratings provided by the PwHD when asked to measure the competence of another person not affected by HD.[32] This is important as although overall the HDBOI study reports a substantial effect on HRQoL for PwHD, taking only into account the self-reported HRQoL might have underestimated the HRQoL and therefore the humanistic burden of HD.

Similarly, the WPAI tool also shows a significant effect of HD on the work and productivity of PwHD. Overall impairment in daily activities is large and increases with disease severity. Impairment in daily activities for all participants was 59% and 79% for self- and proxy-reported groups, respectively, highlighting discrepancies between patient and proxy groups. For work productivity loss, we observe higher-than-anticipated employment levels among MS and AS groups in the self-reported group (none in employment in the proxy reported),

Table 4 Activity Impairment and Work Productivity, Overall and by Disease Stage

Participants, n (%) unless noted	All participants	ES	MS	AS
Completed PPIE-P, n (%)	482 (100)	204 (42)	164 (34)	114 (24)
PwHD	440 (91)	192 (94)	155 (95)	93 (82)
Proxy respondent	42 (9)	12 (6)	9 (5)	21 (18)
Percent overall activity impairment due to health, mean-PwHD (SD)[a]	58.1 (25)	46.4 (26)	63.6 (21)	72.9 (20)
Percent overall activity impairment due to health, mean–proxy respondent (SD)[b]	78.8 (19)	68.3 (23)	80 (12)	84.3 (16)
Employed in the last 7 d, n (%)				
PwHD	**134 (28)**	**83 (41)**	**35 (21)**	**16 (14)**
Proxy respondent	—	—	—	—
Percent overall work productivity loss due to health (WPL), mean (SD)	47.6 (27)	42.8 (29)	54.8 (23)	56.9 (20)
Percent work time missed: absenteeism, mean (SD)[b]	11.5 (0.2)	9.1 (0.1)	13.9 (0.3)	18.3 (0.2)
Percent impaired productivity at work: presenteeism, mean (SD)	42.2 (0.2)	38.3 (0.3)	49.1 (0.2)	47.5 (0.2)

Abbreviations: AS = advanced stage; ES = early stage; HD = Huntington disease; MS = mid stage; PPIE-P = Patient Public Involvement Engagement; PwHD = people with symptomatic onset HD; WPAI = Work Productivity and Activity Impairment; WPL = Work Productivity Loss.
To assess the significance of differences between disease stages, Kruskal-Wallis tests were conducted for the 4 WPAI outcomes.
[a] $p < 0.001$.
[b] $p < 0.05$.

which may be associated with impaired awareness often displayed by PwHD. Our results for proxy-reported impairment in daily activities are similar to those reported by Goh et al. 2020[33]; however, they do not include advanced-stage PwHD in their analysis. This further supports the hypothesis about PwHD overestimating their abilities as we would expect the WPAI results from this study to be higher considering that AS PwHD were included. WPAI-SHP may not be the most appropriate tool for assessing productivity outcomes due to the self-reported nature of this tool and the difficulties with insight in the HD population; hence, it may not reflect the actual work productivity loss at later stages of disease.

The findings of this study should be interpreted in the context of certain strengths and limitations. To minimize bias and to provide representative estimates of the burden of HD, we aimed to enroll a generalizable sample with adequate proportions of patients in each disease stage; however, these proportions were not available in the published literature. Because recruitment was driven through the clinician office visits, very advanced-stage patients may have been underrepresented if they were admitted to long-term residential or nursing care homes. As such, the HRQoL in AS participants may be overestimated. In addition, the assessment of participants' disease stage was based on the opinion of the treating physicians. As such, we cannot be certain that our disease stage classification fully corresponds with standardized measures. Furthermore, although patient-reported outcomes are particularly valuable in the context of burdensome, lifelong conditions such as HD, data collection may have been influenced by a selection bias in participation and completion of the questionnaires. In addition, given that the number of proxy respondents accounts for less than 10% of the total PPIE-P responses, findings for this group might not be generalizable. Finally, there may have been a potential recall bias for self/proxy respondents completing the PPIE-P, although the recall periods were relatively recent (e.g., past 7 days).

This HDBOI study offers an up-to-date picture of the large burden of HD across disease stages. Moreover, it increases the evidence base for the international HD community by capturing a large set of patient-reported outcomes and improving the knowledge about the course of disease, information that will enable stakeholders to make fully informed decisions and can lead to improvements in the management of HD. Results show a substantial humanistic burden that increases as diseases progress, emphasizing the need for intervention at earlier stages of HD. Overall, it is difficult to contextualize these findings as there is little information available on the humanistic burden of HD in the literature. As such, the HDBOI study offers a meaningful contribution to this underserved research area by offering a detailed description of the burden of HD by severity levels. Future work should further explore the source of differences between self-reported and proxy-reported outcomes and the unawareness of deficits displayed by PwHD as solely focusing on self-reported measures might be underestimating the true burden of HD.

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Humanistic Burden of Huntington Disease: Evidence From the Huntington Disease Burden of Illness Study

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