Association between functional endpoints and quality-of-life outcomes in Huntington's disease gene carriers: Results from a real-world data analysis of the Enroll-HD global registry

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Background

- Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder that leads to progressive loss of functional capacity and shortened life.[1,2]
- The clinical features of HD typically emerge in the peak productive age (i.e., between 30 and 50 years), after which the disease progresses relentlessly over the next 15–20 years.[3]
- Loss of functional capacity coupled with impaired cognition are major causes of decline in health-related quality of life (HRQoL) in patients with HD.[4] However, the relationship between functional capacity and HRQoL is less explored.

Objective

- To assess the associations between HD functional endpoints measured by the Unified HD Rating Scale (UHDRS) Total Functional Score (TFC) and other scales (i.e., Total Motor Score [TMS] , Verbal Fluency Test [VFT], Problem Behavior Assessment [PBA]-Apathy), and quality-of-life outcomes (QoL) measured by Short-Form Survey12 (SF-12) and other QoL scales (Euro-QoL-5D [EQ-5D], Work Productivity and Activity Impairment-Overall Work Impairment due to HD [WPAI-OWIHD]) in HD gene carriers.

Methods

Study design & participants

- This was a non-interventional, retrospective, registry-based cohort study that used data from Enroll-HD global registry periodic dataset.
- The Enroll-HD database contains longitudinal data on diagnosis, treatments, and HD-related measures for HD gene carriers across 19 countries spanning North America, Europe, Australasia, and Latin America.
- Adult HD patients (≥18 years) with a positive HD genetic test (i.e., either pre-manifest HD or manifest HD) and having ≥1 on-site visit with TFC assessment were included.

Key variables

- Data on manifest HD, functional endpoints (i.e., UHDRS-TFC), other endpoints (i.e., UHDRS-TMS, VFT, PBA-Apathy) and QoL outcomes (i.e., SF-12 PCS & MCS, EQ-5D [derived from SF-12], WPAI-OWIHD) were used for this analysis.
  - UHDRS TFC is used to measure capacity to work, handle finances, perform domestic chores and self-care tasks, and live independently. TFC is measured between 0-13, with higher value indicating least severity.[5]
  - UHDRS TMS is a 31-item tool used to assess oculomotor, bradykinesia/rigidity, dystonia, chorea, and gait/balance, with varying response options ranging from 0-4 (0 indicating normal findings; 4 indicating severe abnormalities).[5]
  - UHDRS VFT is used to measure cognitive performance. It has a score range of 0 to no upper bound, with higher scores indicating higher cognitive performance.[5]
  - PBA-Apathy subscale is used to assess psychiatric abnormalities. The subscale is measured between 0-16, with higher scores indicating more severe psychiatric abnormalities.[5]
  - SF-12 PCS & SF-12 MCS are generic QoL assessment tools standardised to a mean of 50 and standard deviation (SD) of 10, with higher scores indicating better quality of life.[6]
  - WPAI-overall work impairment due to HD (OWIHD) is used measure ability to work and perform regular activities. WPAI-OWIHD is measured between 0-100%, with higher score indicating greater impairment.[7]
- In addition, baseline characteristics (i.e., age, gender, Charlson comorbidity index, and visit number) were analysed.

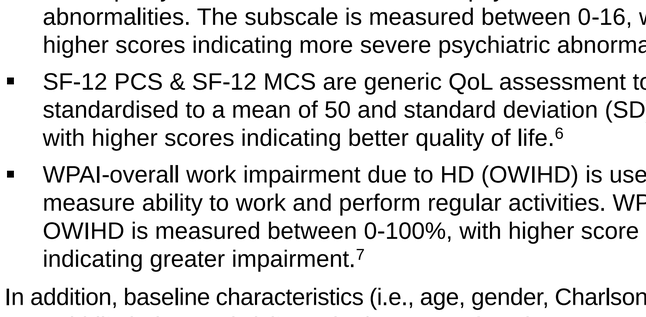
Data analysis

- All study variables were summarised using descriptive statistics. Categorical measures were presented as frequencies and percentages while continuous measures were presented as mean and standard deviation (SD).
- The association between functional endpoints and QoL outcomes were assessed using descriptive analysis, inferential statistics including but not limited to distribution of endpoints, and linear mixed models.
- The association modelling results were presented as coefficients and their respective 95% confidence intervals (CIs). A p<0.05 was defined *a priori* as statistically significant.

Results

- Overall, 15,300 patients and their family controls were retrieved from the Enroll-HD periodic dataset (released in October 2018). Of these, 11,553 were adult HD gene carriers, where 8,387 (73%) had manifest HD, and 3,544 (27%) had pre-manifest status (**Figure 1**).

Figure 1. Patient selection



HD, Huntington's disease; UHDRS, Unified Huntington's Disease Rating Scale.

Notes: *After attrition, there were 8,009 manifest HD patients at Enroll study first visit. During the follow-up 378 pre-manifest patients progressed to manifest.

- Baseline demographic and clinical characteristics stratified by cohort are presented in **Table 1**.

Table 1. Baseline characteristics of HD cohort

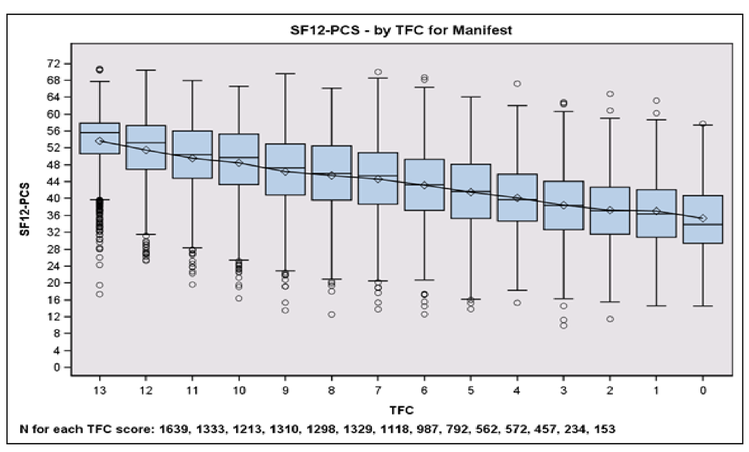
Characteristics	HD gene carriers (N=11,553)	Pre-manifest HD (N=3,544)	Manifest HD (N=8,387*)
Mean (SD) age (in years)	48.9 (13.9)	39.8 (12.1)	52.7 (12.7)
Age group (in years), n (%)			
<18	0 (0%)	0 (0%)	0 (0%)
18-50	6,129 (53.1%)	2,807 (79.2%)	3,550 (42.3%)
51-75	5,145 (44.5%)	725 (20.5%)	4,567 (54.5%)
76+	279 (2.4%)	12 (0.3%)	270 (3.2%)
Female, n (%)	6,229 (54%)	2,110 (59.5%)	4,343 (51.8%)
Mean (SD) number of CAG repeats (High allele)	43.6 (3.8)	42.4 (2.8)	44.0 (4.0)
CCI score			
Mean (SD) at entering the HD stage	0.2 (0.51)	0.1 (0.46)	0.2 (0.53)
CCI distribution, n (%)			
0-1	11,134 (96.4%)	3469 (97.9%)	8033 (95.8%)
2-3	405 (3.5%)	69 (1.9%)	344 (4.1%)
4+	14 (0.1%)	6 (0.2%)	10 (0.1%)
Region			
Europe	7,526 (65%)	2,039 (57.5%)	5,685 (67.8%)
North America	3,526 (31%)	1,285 (36.3%)	2,402 (28.6%)
Latin America	76 (0.7%)	7 (0.2%)	69 (0.8%)
Australasia	425 (3.7%)	213 (6%)	231 (2.8%)
Mortality	474 (4.0%)	13 (0.4%)	462 (5.5%)

CAG, cytosine-adenine-guanine; CCI, Charlson Comorbidity Index; SD, standard deviation; HD, Huntington's disease.

Notes: *After attrition, there were 8,009 manifest HD patients at Enroll study first visit. During the follow-up 378 pre-manifest patients progressed to manifest.

- Results from the regression analysis showed that TFC contributed significantly to the model while deriving SF-12 PCS score (coefficient: 0.822; 95% CI: 0.695 to 0.950; p<0.0001) and SF-12 MCS score (coefficient: 0.490; 95% CI: 0.317 to 0.663; p<0.0001) among manifest HD patients (**Figures 2 & 3**). Further, age and gender contributed significantly to both the models (p<0.05).

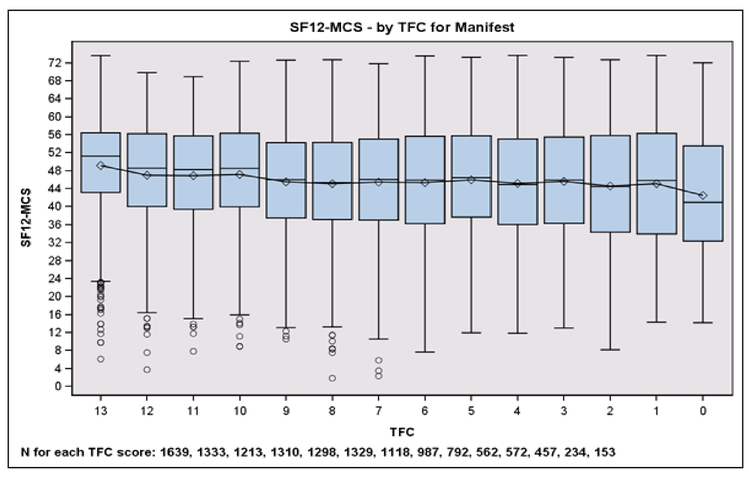
Figure 2. Distribution of observed SF-12 PCS by TFC for manifest HD patient visits



HD, Huntington's disease; PCS, physical component score; SF-12, Short Form Survey 12; TFC, Total Functional Capacity.

Notes: Box-and-whisker plots – black horizontal line = median; horizontal edges of box depict Q1 and Q3 (interquartile range); the end of whiskers represent minimum and maximum values

Figure 3. Distribution of observed SF-12 MCS stratified by TFC for manifest HD patient visits

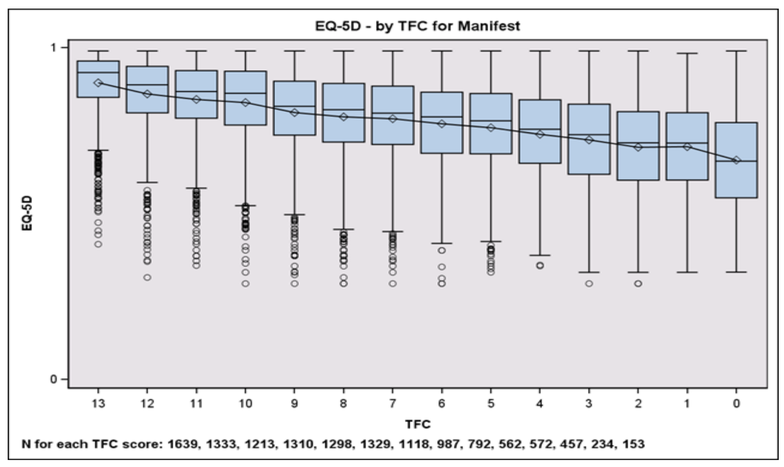


HD, Huntington's disease; MCS, mental component score; SF-12, Short Form Survey 12; TFC, Total Functional Capacity.

Notes: Box-and-whisker plots – black horizontal line = median; horizontal edges of box depict Q1 and Q3 (interquartile range); the end of whiskers represent minimum and maximum values

- Time-lag analysis between TFC and SF-12 PCS from next visit was found to be statistically significant (coefficient: 0.260; 95% CI: 0.097 to 0.423; p=0.0018).
- The association of TFC with SF-12 derived EQ-5D (coefficient: 0.011; 95% CI: 0.009 to 0.013; p<0.0001) and WPAI-OWIHD (coefficient: -8.388; 95% CI: -10.758 to -6.018; p<0.0001) was found to be significant (**Figures 4 & 5**). No other independent variables were found to be significant.

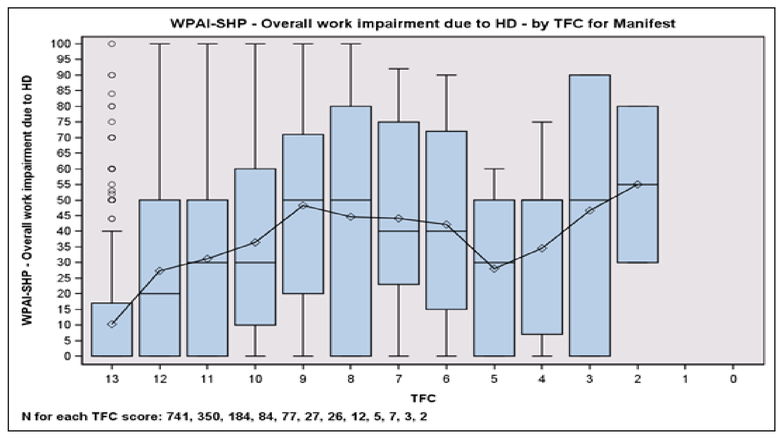
Figure 4. Distribution of observed EQ-5D scores stratified by TFC for manifest HD patient visits



EQ-5D, EuroQol- 5 dimension; HD, Huntington's disease; TFC, Total Functional Capacity.

Notes: Box-and-whisker plots – black horizontal line = median; horizontal edges of box depict Q1 and Q3 (interquartile range); the end of whiskers represent minimum and maximum values

Figure 5. Distribution of observed WPAI-OWIHD scores stratified by TFC for manifest HD patient visits



HD, Huntington's disease; TFC, Total Functional Capacity; WPAI-OWIHD, Work Productivity and Activity Impairment Questionnaire: Overall work impairment due to HD.

Notes: Box-and-whisker plots – black horizontal line = median; horizontal edges of box depict Q1 and Q3 (interquartile range); the end of whiskers represent minimum and maximum values

- The potential association between other three functional endpoints and QoL outcomes was explored. With certain exceptions (SF-12 MCS ~ VFT, WPAI-OWIHD ~ VFT), we observed that the other HD functional endpoints contributed significantly to the QoL outcomes (**Table 2**).

Table 2. Association of other endpoints with QoL outcomes

	SF-12 PCS	SF-12 MCS	EQ-5D	WPAI-OWIHD
	Coefficient (95%CI)			
TMS	-0.102 (-0.125 to -0.079)**	-0.050 (-0.081 to -0.018)*	-0.001 (-0.002 to -0.001)**	0.455 (0.125 to 0.785)*
VFT	0.226 (0.168 to 0.284)**	0.064 (-0.012 to 0.141)	0.002 (0.002 to 0.003)**	0.129 (-0.475 to 0.732)
PBA-Apathy	-0.136 (-0.202 to -0.071)**	-0.641 (-0.724 to -0.558)**	-0.006 (-0.007 to -0.006)**	1.540 (0.881 to 2.200)**

CI, Confidence interval; EQ-5D, EuroQol- 5 dimension; HD, Huntington's disease; PCS, physical component score; SF-12, Short Form Survey 12; PBA, Problem Behavior Assessment; TMS, Total Motor Score; VFT, Verbal Fluency Test; WPAI-OWIHD, Work Productivity and Activity Impairment Questionnaire: Overall work impairment due to HD.

Notes: *p<0.05; **p<0.0001

Limitations

- EQ-5D values would have to be constructed from SF-12 since they are not measured in Enroll-HD dataset.
- Constructing one metric using another does not compare favourably to measuring the respective quantity empirically, which is not possible in this retrospective data set.

Conclusions

- Overall, the demographic characteristics of the study population was in line with previously published studies.[1,8,9]
- TFC was found to have significant and seemingly linear relationship with SF-12 (PCS and MCS) and other QoL outcomes (EQ-5D and WPAI-OWIHD) among manifest HD patients suggesting that TFC can be used as a proxy of QoL.
- A stronger significant relationship was found between TFC and SF-12 PCS at next visit, and between TFC and SF-12 MCS at next visit, indicating a time lag effect.
- Higher age and CCI was found to negatively impact SF-12 PCS. Additionally, females with manifest HD appear to be worse off in terms of physical health than males with manifest HD.

References

1. Walker FO. *Lancet.* 2007;369(9557):218–28; **2.** Mochel F & Haller RG. *J Clin Invest.* 2011;121(2): 493–9; **3.** Riley BE & Lang AE. *Neurol Clin Pract.* 2008;1585–6; **4.** Ross CA, et al. *Mov Disord.* 2014;29(11):1351–8; **5.** Winder JY, et al. *Mov Disord Clin Pract.* 2018;5(5):527–33; **6.** Shah RM, et al. *Health Qual Life Outcomes.* 2018;16(1):1–11; **7.** Morrisroe K, et al. *Clin Exp Rheumatol.* 2017;106(4):130–7; **8.** Frank S. Neurotherapeutics, 2014, 11(1): 153-160; **9.** https://www.ninds.nih.gov/health-information/disorders/huntingtons-disease (accessed October 2022).

Disclosures

This study was funded by Novartis Pharma AG, Basel, Switzerland. Valery Risson, Vladimir Bezlyak, Anusha Malepati, and Santosh Tiwari are employees of Novartis. Ming Zou and Smieszek Timo at the time of performing this study, had been employees of IQVIA.

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