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Patient-Reported Outcomes

Meaningful and Measurable Health Domains in Huntington's Disease: Large-Scale Validation of the Huntington's Disease Health-Related Quality of Life Questionnaire Across Severity Stages

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ABSTRACT

Background: Although health-related quality of life is key for patients with long-term neurodegenerative conditions, measuring this is less straightforward and complex in Huntington's disease (HD).

Objectives: To refine and validate a fully patient-derived instrument, the Huntington's Disease health-related Quality of Life questionnaire (HDQoL), and to elucidate health domains that are meaningful to patients' lived experience.

Methods: Five-hundred forty-one participants, from premanifest to end-stage disease, completed the HDQoL, together with generic quality-of-life measures and in-person motor, cognitive, and behavioral assessments. The psychometric properties of the HDQoL were examined using factor analysis and Rasch analysis.

Results: Four HDQoL domains emerged, reflecting the classical triad of HD features; they were Physical-Functional, Cognitive, and 2 different behavioral aspects, that is, the Mood-Self domain and a distinct Worries domain. These domains clarify the behavioral sequelae as experienced by patients, and all showed good to excellent internal consistency. Known-groups analyses illustrated significant and graded changes in clinical assessments and corresponding HDQoL domains across disease severity levels. Convergent and discriminant validity was demonstrated by the expected pattern of correlations between specific HDQoL domains and corresponding domain-relevant clinical assessments as well as patient-reported measures. The data demonstrate robust support for the refined HDQoL across disease stages.

Conclusions: The HDQoL, with its 2 distinct behavioral domains of Mood-Self and Worries as well as the Physical-Functional and Cognitive domains, is a relevant, reliable, and valid patient-derived instrument to measure the impact of HD across all severity stages.

Keywords: Huntington's disease, patient-reported outcome, presymptomatic/preclinical Huntington's disease, quality of life, questionnaire

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Introduction

Neurodegenerative disorders have a devastating impact on individuals. The insidious nature of onset is no comfort to those confronted by the specter of progressive losses, often at the prime of their lives. The multidimensionality of the concept of quality of life is particularly relevant in chronic and degenerative disease.[1] Health-related quality of life is an important concept that provides insight into the wider impact of disease on everyday life. It is crucial to the evaluation of interventions from the patients' perspective, and is of paramount importance to the individual and their families.[2]

Huntington's disease (HD) is a fully penetrant neurodegenerative disorder characterized by motor, cognitive, and behavioral disturbances that typically occur in mid-life.[3] Accurate and meaningful measurement of health-related quality of life to capture the true impact of HD on personal well-being and life satisfaction is key, especially in the absence of proven disease-modifying treatment, and when the protracted course of disease and gradual loss of function is in the order of decades rather than years. Because of the availability of genetic testing for HD, and the complex constellation of signs and symptoms of HD leading to the subsequent multidimensional impact on patients' lives, it is important that a disease-specific measure be used to adequately

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capture the impact of living with HD. Data from our studies[4,5] and others[6,7] provide indications that generic scales are unlikely to comprehensively capture the true impact of living with all aspects of a medically complex condition such as HD, which has profound genetic and psychological ramifications. Although there has been some HD-specific work,[8–11] there is still need for a psychometrically robust and fully patient-derived instrument that comprehensively captures and measures the full impact of HD in patients' lives.

The Huntington's Disease health-related Quality of Life questionnaire (HDQoL) has been generated directly from in-depth individual interviews[11,12] with patients representing the full spectrum of HD from presymptomatic to late stage. Feedback on the pertinence of these initial interview items was obtained from 281 people across Europe and Canada with different levels of HD severity, including presymptomatic and at-risk individuals. The resultant 40-item HDQoL was shown to be a reliable instrument with high test-retest correlation coefficients of 0.7 and higher for all domains.[11,13] Development of the HDQoL was therefore fully driven by patients from the ground up to allow concepts to emerge from patients' views, so that each domain and each item are directly relevant to the lived HD experience and perspective. This facilitated maximal capture of relevant health concepts for a fully coherent and patient-derived framework that is consistent with the patient-centered Food and Drug Administration requirements for patient-reported outcomes.[14] The strong patient-focused ethos and extensive multinational representation in its development set the HDQoL apart as a patient-reported health outcome measure that truly represents the patient perspective in clinical trials and intervention studies.

In this article, we present a large-scale psychometric evaluation of the HDQoL to validate its use in patients across the full spectrum of disease, and to comprehensively capture the consequences of living with this disease.

Methods

Participants

This cross-sectional multicenter study involved a total of 541 English-speaking individuals living with HD. They were recruited through 29 UK centers of the European Huntington's Disease Network REGISTRY observational study and also directly through 6 care homes in the United Kingdom. In addition to family history records, 93.2% of the participants had cytosine adenine guanine (CAG) repeat information regarding individual HD genetic status confirming HD diagnosis.

Participants comprised individuals with at-risk (n = 14) and gene-positive presymptomatic status (n = 158) as well as patients with clinically manifest motor symptoms spanning the full trajectory of HD severity, from Stage 1 (ie, total functional capacity [TFC] 11-13; n = 80), Stage 2 (ie, TFC 7-10; n = 142), Stage 3 (ie, TFC 3-6; n = 106), and Stages 4 and 5 (ie, TFC 0-2; n = 40), and 1 participant without this information recorded. Of the 541 participants, 280 (51.8%) were female patients, 238 (44.0%) were married or living with a partner, and 107 (19.8%) were in paid employment. The mean age was 50.1 ± 12.6 years, and the mean number of expanded CAG repeat size was 43.2 ± 4.5, ranging from 17 to 70 repeats.

Measures

The clinician-rated Unified Huntington's Disease Rating Scale[15] was used in this study, including the following sections: Total Motor Score motor examination (high scores indicate poorer function), Total Functional Capacity assessment of everyday function in 5 domains (low scores indicate poorer function), Total Functional Assessment 25-item checklist of functional task domains (low scores indicate poorer function), and Independence Scale 0-100 score (low scores indicate poorer function and greater dependency). Measures of cognitive performance used were psychomotor tasks that tap executive function, namely, verbal (letter/phonemic) fluency,[16] Stroop color naming, word reading, interference condition,[17] and the Symbol Digit Modalities Test.[18] The scoring and interpretation of these measures and of those described later herein are summarized in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.016.

The most common neuropsychiatric symptoms in HD were determined via semistructured interviews of patients (with partners acting as informants where present) by a clinician, using the 11-item short version of the Problem Behaviours Assessment Scale (PBA-s).[19] The more robust severity (rather than frequency) scores[20] on a 5-point scale were used, with higher scores indicating poorer outcome.

Health-related quality of life was measured using 2 generic scales, the short form 36 health survey (SF-36)[21] and the 3-level EuroQol 5-dimensional questionnaire (EQ-5D).[22] The SF-36 has been validated in HD[5] and contains 36 items that contribute to 2 summary scales, the physical summary score and the mental summary score, on a 0 to 100 scale, with 100 being no impairment and 0 being severe impairment; scores are standardized using a norm-based mean of 50 and standard deviation of 10, with higher scores indicating better health-related quality of life. The 3-level EQ-5D is a generic measure that comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, and psychological status using a 3-point scale and generates a summary index (0-1, where 1 is best).

The HDQoL[11] (see www.hdqol.info) is a disease-specific patient-reported outcome measure developed directly from interviews with patients with HD.[12] Therefore, each item comprises a relevant aspect of health-related quality of life for which participants provide a self-reported response on a Likert scale. Initial pilot work suggested that the HDQoL items could be clustered into 3 overarching primary factors (ie, Primary Physical and Cognitive, Primary Emotions and Self, and Primary Services) or into 6 more specific scales (ie, Specific Physical and Functional, Specific Cognitive, Specific Hopes and Worries, Specific Mood State, Specific Self and Vitality, and Specific Services). On each of these scales, scoring was on 0 to 100 scales, with higher scores indicating better health-related quality of life.

Process

Building on initial pilot work,[11] the objective was to obtain data from a large representative sample of patients with HD to carry out a robust validation of the HDQoL, using both factor analysis and Rasch analysis.[23] This combination of analytic approaches provides information to enable the scale domains to undergo a full psychometric evaluation and to be refined as appropriate. All factor analyses were carried out using the MPlus 6 computer software (Muthén & Muthén, Los Angeles, California),[24] and all Rasch analyses were carried out with the RUMM2030 computer software (Perth, Western Australia).[25] Rasch analysis is based on a unidimensional mathematical model, used to evaluate the legitimacy of summing items to generate measurements in logit units.[25] The difference between observed raw scores and the Rasch model estimated measurement indicates the extent of nonlinearity in the ordinal raw score.[26] Rasch analysis was used

within each domain to evaluate response category structure, individual item fit, overall scale fit and reliability, relative item-person distribution (targeting), response dependency, unidimensionality, and item group bias (differential item functioning [DIF]) by age, sex, education level, and marital status.[27,28]

For known-groups validity, we expected synchrony between HDQoL domains and the corresponding clinical measures used, where both would reduce with increasing disease severity levels.

Results

Scale Descriptive Data

Data regarding scale completion time were available for 359 patients. Among these, the mean completion time was 22.6 ± 17.9 minutes and the median was 18 minutes (interquartile range 10-30), with a range of 2 to 120 minutes, where late-stage patients were allowed breaks throughout the questionnaire. When examined by disease stages, the full 40-item HDQoL was completed, on average, in 11.6 minutes for at-risk/presymptomatic participants and 22.4 minutes for Stage 1, 24.7 minutes for Stage 2, 27.2 minutes for Stage 3, and 36.4 minutes for Stages 4 and 5 patients. All items reported excellent completion rates. The item with the largest amount of missing data was item 6 (Hobby), which recorded a nonresponse rate of 2.8%.

Analysis—Scale Refinement

Initially, a confirmatory factor analysis (CFA) was carried out to test the original factorial structure(s) as proposed by the pilot work. The Primary Scale Structure (3 factors) was not fully supported, with the 3-factor model displaying a root mean square error of approximation (RMSEA) of 0.10, a χ^2 P value of less than .001, a comparative fit index (CFI) of 0.93, and a Tucker-Lewis index (TLI) of 0.92. Additional error correlations were included to account for the dependency within each factor, but the structure was still not fully supported (RMSEA 0.08; χ^2 P value $<$.001; CFI 0.96; TLI 0.95).

The Specific Scale Structure (6 factors) fared slightly better, with the 6-factor model displaying an RMSEA of 0.08, a χ^2 P value of less than .001, a CFI of 0.94, and a TLI of 0.94. Additional error correlations were included to account for the dependency within each factor, but the structure was still not fully supported (RMSEA 0.07; χ^2 P value $<$.001; CFI 0.96; TLI 0.96).

Each individual domain subscale was also assessed, in both the 3- and 6-factor structures. Within this analysis, very few subscales were fully supported by the results of the CFA, and a lot of error correlation was necessary to account for apparent dependency. In addition, the Primary Physical and Cognitive Function Scale immediately fractured into the 2 elements of "Physical" and "Cognitive."

Because the CFA did not fully support the early scale structures arising from the pilot work, an exploratory factor analysis was carried out to provide guidance as to the likely number of relevant factors (domains) within the item set, and how these aligned with the conceptual underpinning of the item set on the basis of the conceptual framework offered by the International Classification of Functioning, Disability, and Health.[29] This analysis was based on a polychoric correlation matrix (to best account for the ordinal polytomous items) using a promax rotation.

The alignment of the statistical and conceptual models served as a guide to allow for the identification of the potential constituent items of each individual domain. The basis of this was the exploratory factor analysis model with 6 factors (RMSEA 0.048), as presented in Table 1. Within this model, 2 of the items appeared to be loading as a "bloated specific," which occurs when highly dependent items, which are often paraphrases of each other, appear to look like a separate factor, but are really just a display of specific variance.[30,31] This bloated specific was a single factor containing mainly items 33 (Irritated) and 34 (Temper). These items were therefore grouped, on a conceptual basis, with the factor representing the "Mood and Self" set of items.

The final result to progress onto the next stage was 4 sets of items representing 4 domains that contribute toward the quality of life of a patient with HD: "Physical-Functional," "Cognitive," "Mood-Self," and "Worries."

In addition, "Services" is identified as a potential domain, but this should be treated as distinctly separate from the rest of the domains because service provision is not a property of the individual.

Rasch Analysis

Rasch analysis for each HDQoL domain is presented herein, with preliminary and final domain fit statistics presented in Table 2 for each domain.

Physical domain

In the Physical domain analysis, the 12 HDQoL items were initially included. There was some misfit at the overall scale level and the individual-item level, although the item set did display evidence of unidimensionality. In addition, at this initial stage all items displayed disordered thresholds. The final item set was obtained after the rescoring of all items and the removal of 2 items displaying large underdiscrimination item misfit (item 5: Had difficulty maintaining your weight; and item 11: Got tired easily). Within this final item set of 10, a degree of dependency was still present, which was subsequently accounted for through a subtest procedure.[32]

Cognitive domain

The Cognitive domain analysis started with 12 items. Initially, there was some misfit at the overall scale level and the individual-item level, all but 1 of the items displayed disordered thresholds, and the item set also displayed some evidence of a lack of unidimensionality. The final item set of 8 was obtained after the removal of 4 items (item 11: Tired; item 12: Sleep; item 21: Remember date; and item 26: Get on with life). Items 11, 12, and 26 were initially cross-loading items (exploratory factor analysis factor loadings in more than 1 domain), and within the cognitive set, these 3 items were all clear anomalies, displaying an underdiscrimination misfit. Item 21 (Remember date) was removed because of both an underdiscrimination misfit and a dependency with item 18 (Everyday memory), and a problematic interaction between these issues. One significant dependency was accounted for through combining items 13 and 14 into a subtest while retaining all other items individually.

Mood-Self domain

The Mood-Self domain analysis started with 11 items. Initially, there was some misfit at the overall scale level and the individual-item level and 7 of the 11 items displayed disordered thresholds, although the item set did display evidence of unidimensionality. The final item set of 6 was obtained after the rescoring of all items and the removal of 3 items (item 26: Get on with life; item 30: Personal wishes; and item 34: Temper). Item 34 (Temper) was removed because of a large underdiscrimination misfit and a large dependency with item 33 (Irritated), and a problematic interaction between these issues. Items 26 (Get on with life) and 30 (Personal wishes) were both removed because of large

Table 1. HDQoL factor loadings.

Item	HDQoL item descriptor	Physical-Functional	Cognitive	Worries	Mood-Self	Mood-Self "bloated specific" subfactor	Services
1	Carrying things	**0.77**					
2	Balance	**0.83**					
3	Walking	**0.96**					
4	Jobs around the house	**0.78**					
5	Weight	0.36					
6	Hobby	**0.55**			0.33		
7	Dressing	**0.90**					
8	Swallowing	**0.65**					
9	Eating	**0.80**					
10	Operate television	**0.74**					
27	Independence	**0.58**			0.35		
13	Multitask	0.30	**0.67**				
14	Slow	0.29	**0.68**				
15	Use words		**0.61**				
16	Concentration		**0.77**				
17	Decision making		**0.85**				
18	Everyday memory		**0.75**				
19	Organize day		**0.73**				
20	Follow conversation		**0.57**				
21	Remember date		0.62				*0.21*
26	Get on with life		0.22		0.65		
24	Hope			0.34	**0.55**		
25	Motivation		0.45		**0.51**		
28	Confidence		0.31		**0.56**		
29	Low mood				**0.62**	0.27	
30	Personal wishes				0.73		
31	Role in family				**0.58**		
33	Irritated				**0.20**	0.70	
34	Temper					0.95	
35	Socialize		0.35		**0.28**		
37	Support				**0.18**		*0.52*
11	Tired	0.35	0.34	**0.19**			
12	Sleep		0.37	**0.34**			
22	HD family worry			**0.84**			
23	HD worry			**0.93**			
32	Financial concerns			**0.28**		0.23	
36	Others' attitude to HD	0.25		**0.37**			
38	Services for HD						*0.87*
39	Management of HD						*0.88*
40	Information on HD						*0.82*

Note. Factor loadings <0.20 mostly suppressed.
HD indicates Huntington's disease; HDQoL, Huntington's Disease health-related Quality of Life questionnaire.
Items removed from final domain item set after Rasch analysis in light grey. Separate Services domain column in grey.

overdiscriminations, meaning that these 2 items have a certain dependency with the overall domain score, which means that they cannot be validly included within the item set as individual items. There was no significant dependency within the remaining item set.

Worries domain

Six items were included in the Worries domain analysis. Initially, the fit at the overall scale level and the individual-item level was reasonably good, and the item set also displayed

Table 2. Rasch analysis summary results of individual HDQoL domains.

Domain	Analysis	Number of items	Valid, n	Item fit residual, mean ± SD	Person fit residual, mean ± SD	χ^2 interaction			PSI		Unidimensionality *t* tests	
						Value	*df*	*P*	With extremes	Without extremes	%	Lower bound 95% CI
Physical	Initial	12 items	481	−0.55 ± 2.8	−0.4 ± 1.4	287	96	0	0.82	0.86	3.33	–
	Final	10 items in 6 subtests	453	−0.03 ± 1.8	−0.47 ± 1.2	69.47	48	.020	0.81	0.84	3.31	–
Cognitive	Initial	12 items	499	−0.02 ± 3.9	−0.56 ± 1.9	356.8	96	0	0.88	0.9	7.47	5.60%
	Final	8 items in 7 subtests	463	0.07 ± 1.6	−0.55 ± 1.4	65.23	49	.060	0.88	0.88	2.38	–
Mood-Self	Initial	11 items	505	0.04 ± 3.2	−0.51 ± 1.7	272.3	88	0	0.86	0.88	4.39	–
	Final	8 items	483	0.17 ± 1.5	−0.4 ± 1.3	83.94	64	.050	0.83	0.83	2.92	–
Worries	Initial	6 items	516	0.5 ± 1.7	−0.36 ± 1.3	71.32	48	.020	0.75	0.72	4.26	–
	Final	6 items in 2 subtests	510	0.44 ± 0.2	−0.5 ± 1	19.6	16	.240	0.58	0.53	0.59	–
	Ideal values		0	1 ± 0	1		>0.05	>.850	>0.85	<5%	<5	
									>0.7	>0.7		

Note. Rasch analysis summary results for the separate Services domain are presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.016.
CI indicates confidence interval; HDQoL, Huntington's Disease health-related Quality of Life questionnaire; PSI, person separation index; SD, standard deviation.

evidence of unidimensionality, although at this stage all items displayed disordered thresholds. The final item set remained the same, but all items were rescored, and the optimal approach to account for the dependency within the domain was to combine all the items within 2 subsets: items 11, 12, and 32 (Tired, Sleep, and Financial concerns) were combined into 1 subtest, and items 22, 23, and 36 (HD family worry, HD worry, and Other's attitude to HD) were combined into the other subtest.

Services domain

A small set of items regarding services was identified in the exploratory factor analysis as a separate Services factor, because this arose directly from previous qualitative work indicating that this was relevant and important to patients' health-related quality of life. Because there were only 3 items (see items 38, 39, and 40 in Table 1), the level of analysis was restricted compared with the other domains. These items were primarily concerned with the services that have been received by the individual, and therefore contribute to a set of service level indicators. Furthermore, these service-related items are extrinsic to patients and different from the other 4 intrinsic HDQoL domains. Validation data on this separate Services domain are presented in Appendix 1 in Supplemental Materials.

Differential Item Functioning

Overall, for the final analysis stage of each domain, only 4 out of 92 (4.3%) separate uniform DIF tests displayed evidence of some DIF.

Although some evidence of DIF has been found, the extent and magnitude of the present DIF are unlikely to have any significant impact on any domain scores that are obtained. Throughout the analysis, at the individual-item level the entire item set is very stable among different sexes, educational levels, and marital status groups, with the only real potential issues arising through potential bias caused by age. Nevertheless, it could be argued that DIF-by-age may always be present within this sample because of the interaction of the age of the patients and the pattern of disease progression.

Psychometric Data

The psychometric properties of the HDQoL were found to be acceptable, as presented in Table 3. Because the sample included presymptomatic participants, the slightly elevated ceiling effect for the Physical and Cognitive domains was consistent with this. All the domain standard error of the mean percentage values were 10.25% or lower, indicating a minimal difference between observed scores and likely true scores.

Convergent and Divergent Validity

Spearman correlations between the HDQoL dimensions and generic quality of life and clinical assessments are presented in Table 4. The HDQoL Physical domain shows strong correlations with the motor and functional clinical assessments as well as the motor-related elements of the SF-36 and the EQ-5D, relative to other nonmotor measures.

The HDQoL Cognitive domain shows the expected correlations with the cognitive assessments performed, and because these cognitive assessments are not "pure" and encompass psychomotor skills as well because of a dependence on a speech, oculomotor, and/or upper limb motor response, there are strong correlations with motor measures as well.

The HDQoL Mood-Self domain correlated most highly with the SF-36 Mental Component Summary Score which includes the Mental Health subscale containing items on mood and emotions. The narrower HDQoL Worries domain representing disease-related concerns also correlated with the SF-36 Mental Component Summary Score (particularly the Vitality subscale) but to a slightly lesser extent. The HDQoL Mood-Self domain and to a lesser extent the Worries domain also show higher correlations with relevant items from the PBA such as depressed mood, anxiety, irritability, and apathy as well as the EQ-5D anxiety/depression item, relative to other motor or cognitive measures. Although these 2 domains are conceptually and statistically

Table 3. Descriptive data and psychometric properties of the HDQoL.

Scale 0-100 scores (higher score = better QOL)	N		Mean ± SD	Median	Percentiles			Skewness	Range	Minimum	Maximum	Floor effect (0-10 on total score)	Ceiling effect (90-100 on total score)	Cronbach α (taken from raw scores)	SEM	1.96 × SEM
	Valid	Missing			25	50	75									
Physical-Functional domain	541	0	66.77 ± 21.07	62.97	51.15	62.97	81.94	0.05	93.69	6.31	100	0.2%	15.9%	0.92	9.18	18.00
Cognitive domain	528	13	62.91 ± 20.74	61.55	49.98	61.55	76.09	−0.04	100	0	100	1.3%	15.0%	0.94	7.18	14.08
Mood-Self domain	526	15	61.74 ± 18.02	59.25	50.8	59.25	70.41	0.21	100	0	100	0.4%	7.8%	0.89	7.43	14.56
Worries domain	535	6	61.23 ± 15.81	59.92	50.67	59.92	68.96	−0.06	100	0	100	0.4%	3.7%	0.79	10.25	20.08

Note. Rasch analysis summary results for the separate Services domain are presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.016.
HDQoL indicates Huntington's Disease health-related Quality of Life questionnaire; QOL, quality of life; SD, standard deviation; SEM, standard error of the mean.

related (r_s = 0.73; P<.010), the nature of the worry-specific items in the HDQoL Worries domain captures an underlying concern about disease impact that is a more specific and distinct element of patient health, and this is reflected in the lower correlations with general behavioral measures relative to the broader Mood-Self domain. Consistently, the more discrete Worries domain was also slightly less strongly correlated with the Cognitive (r_s = 0.66; P<.010) and Physical (r_s = 0.59; P<.010) domains than was the broader Mood-Self domain (r_s = 0.76, P<.010 and r_s = 0.61, P<.010, respectively).

Overall, the aforementioned pattern of correlations is in line with expectations showing appropriate convergent and divergent validity for the HDQoL. Interestingly, although there were generally strong correlations between the global/general scores with the Physical-Functional domain, and to a lesser extent also the Cognitive domain, this was not so much the case for the Mood-Self and Worries domains, suggesting both the distinctness and importance of tapping these more psychological HDQoL domains directly.

Construct Validity

Known-groups analysis was conducted to examine HDQoL domain scores when participants were separated into different severity quartiles or levels on the basis of key clinical assessments (ie, Unified Huntington's Disease Rating Scale Total Motor Score, cognitive verbal fluency total correct score, and PBA-s depressed mood severity score and PBA-s anxiety severity score). One-way analyses of variance showed that participants in different quartiles and severity levels had significantly different HDQoL domain scores (Table 5). There were significant Tukey pairwise comparisons between levels of severity, such that poorer motor, verbal fluency, and PBA-s scores corresponded with poorer HDQoL scores on the relevant domains, thereby demonstrating robust known-groups validity.

Discussion

Data from this study demonstrate a robust validation of the refined HDQoL in a large sample of genetically verified patients with HD spanning the full trajectory of disease stages. The substantial body of data from this psychometric evaluation allowed for a definitive consolidation and refinement of the putative HDQoL structure,[11] revealing 4 clear and meaningful domains that reflect patients' lived experience (ie, Physical-Functional, Cognitive, Mood-Self, and Worries). The separate Services domain is an external aspect that reflects patients' ongoing navigation of the health system.

The 4 HDQoL domains strongly reflect the classical clinical triad of HD features, with the physical, cognitive, and behavioral aspects represented. The latter is construed as 2 distinct domains, Mood-Self and Worries, which also map on to well-recognized psychological constructs of mood, self-esteem, as well as worry and anxiety. These 2 psychological domains delineate the different behavioral aspects of HD from the patient perspective in the context of living with a complex and progressive long-term condition. The natural emergence of this classical triad within the HDQoL reflects the strength of the fully patient-derived heritage of the HDQoL, and its simultaneous relevance to care from both patient and clinician perspectives.

Within the HDQoL, DIF was largely absent across domains, and where it was manifest, such as age, it made sense at a conceptual level, with its link to progression, and therefore to correct for this DIF may not actually be optimal to the measurement process.[33]

The small Services domain is a somewhat separate and external element of the HDQoL. Nevertheless, because healthcare and management were nonetheless relevant factors in the experience of the patients' disease journey in the underpinning qualitative work, this domain can be used for information to get an indication of care and service evaluation. It may have value as a useful moderator for any model, because the extent of services may influence outcome.

In a disease such as HD where impairment and loss cut across the whole repertoire of human behavior, the importance of a fully patient-derived instrument consistent with Food and Drug Administration patient-reported outcome measure guidance[14] becomes even more crucial. To be relevant, the content and structure of a scale must stem from the unique perspective of patients, drawing from their everyday lived experience. Each and every item within the refined HDQoL domains originated directly from the experience of patients living in the complex and multifaceted shadow of HD. It was also important to use clinical measures to validate HD-specific scales using a large sample of patients across the full trajectory of disease at a higher level of granularity, to fully capture the impact of disease. In addition, use of the Rasch measurement model and robust evidence of the validity and reliability presented here supports the value and meaningfulness of the HDQoL scores. It is for these reasons the

Table 4. Spearman correlations between HDQoL dimensions, clinical and questionnaire measures.

	Domain 0-100 score (100 = high QOL)			
	Physical-Functional	Cognitive	Mood-Self	Worries
Motor/Functional				
UHDRS Total Motor Score	−0.68	−0.42	−0.17	−0.18
UHDRS Total Functional Assessment Score	0.76	0.55	0.32	0.29
UHDRS Independence Scale	0.76	0.54	0.30	0.29
EQ-5D mobility	−0.73	−0.50	−0.31	−0.36
EQ-5D self-care	−0.63	−0.39	−0.25	−0.28
EQ-5D activity	−0.68	−0.56	−0.39	−0.40
EQ-5D pain/discomfort	−0.35	−0.25	−0.18	−0.28
SF-36 Physical Functioning (PF)	0.79	0.51	0.33	0.38
SF-36 Role-Physical (RP)	0.73	0.60	0.48	0.47
SF-36 Bodily Pain (BP)	0.31	0.25	0.25	0.29
SF-36 PCS	0.73	0.46	0.30	0.37
Cognition				
Symbol Digit Modalities Test	0.63	0.43	0.22	0.18
Stroop interference task	0.61	0.43	0.18	0.21
Verbal fluency task	0.56	0.38	0.18	0.15*
Perseverative thinking/behavior (PBA)	−0.35	−0.34	−0.25	−0.18
Disoriented behavior (PBA)	−0.22	−0.22	−0.17	−0.11†
Behavioral				
Depressed mood (PBA)	−0.14	−0.27	−0.44	−0.39
Anxiety (PBA)	−0.24	−0.37	−0.40	−0.34
Irritability (PBA)	−0.19	−0.23	−0.30	−0.26
Lack of initiative/apathy (PBA)	−0.37	−0.42	−0.38	−0.28
EQ-5D anxiety/depression	−0.31	−0.46	−0.61	−0.50
SF-36 Vitality (VT)	0.53	0.62	0.64	0.58
SF-36 Social Functioning (SF)	0.56	0.65	0.67	0.56
SF-36 Role-Emotional (RE)	0.52	0.63	0.64	0.55
SF-36 Mental Health (MH)	0.36	0.49	0.67	0.52
SF-36 MCS	0.38	0.59	0.73	0.57
General				
EQ-5D index value (UK)	0.71	0.58	0.48	0.49
SF-36 General Health (GH)	0.60	0.56	0.56	0.56
SF-36 v.2 score	0.79	0.72	0.69	0.64
Global Clinical Impression[35] (lower value = less ill)	−0.70	−0.45	−0.24	−0.27
Disease burden score[36]	−0.51	−0.29	−0.14	−0.14
Prognostic index[37]	−0.65	−0.39	−0.16	−0.15

Note. All correlations are statistically significant at $P < .010$, except where indicated otherwise. Rasch analysis summary results for the separate Services domain are presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.016.
EQ-5D indicates EuroQol 5-dimensional questionnaire; HDQoL, Huntington's Disease health-related Quality of Life questionnaire; MCS, mental component score; PBA, Problem Behaviours Assessment; PCS, physical component score; QOL, quality of life; SF-36, short form 36 health survey; UHDRS, Unified Huntington's Disease Rating Scale.
*Nonsignificant at $.010 < P < .050$.
†Nonsignificant at $P < .050$.

HDQoL has advantages and provides a more direct and germane measurement of health-related quality of life in HD.

When HD genetic testing uptake remains the exception rather than the norm, contrary to initial expectations, there is no valid replacement for confidentially disclosed patients' experiences in a complicated and all-encompassing disease such as HD. Especially where changes in cognition and psychological emotion regulation are part and parcel of the disease, this phenomenological experience is most authentically elicited using individual interviews conducted in the privacy of patients' homes to allow for free expression of personal experiences that are uncontaminated by external influences.[34] Non–HD-specific items, general HD focus group discussions, theoretical discourse, clinical judgment, or academic analysis cannot really provide a substitute for the actual words and expressions embodied in the HDQoL, which were derived from authentic individually elicited firsthand accounts of living with HD. These direct accounts anchor the HDQoL[11,12] and provide a strong basis to elucidate the complex psychoemotional aspects of (and anticipation of) decades of life with a degenerative condition as understood by patients. The Worries domain taps into specific concerns about the health impact on patients' lives and families, and is indeed separable, though related to the more emotionally oriented and self-reflective elements of their experience of life with HD as captured by the Mood-Self domain. These 2 domains provide a better understanding and conceptualization of psychological aspects that patients can identify with and serve to inform approaches to person-centered therapy and care. They also have a clear clinical resonance and implications for care, monitoring and intervention.

The 4 key HDQoL domains provide a meaningful profile of scores that cover the triad of HD symptomatology as perceived by the patient. Although this profile reflects the multidimensional concept of health-related quality of life and allows for measuring discrete areas, this also means the absence of an overall composite score. Another practical limitation of this UK-wide study means

Table 5. Mean HDQoL domain scores for different quartiles or levels of clinical measures demonstrating known-groups validity.

UHDRS Total Motor Score	Quartile 1 (0-5) (n = 125)	Quartile 2 (6-22) (n = 122)	Quartile 3 (23-41) (n = 121)	Quartile 4 (42-124) (n = 123)	*F*	*P* value
HDQoL Physical-Functional*,†,‡,§,‖,¶	87.35	72.69	61.15	50.31	132.13	<.0001
Verbal fluency Total correct	**Quartile 1 (0-8) (n = 69)**	**Quartile 2 (9-13) (n = 79)**	**Quartile 3 (14-19) (n = 77)**	**Quartile 4 (20+) (n = 71)**	***F***	***P* value**
HDQoL Cognitive†,‡,§,‖	52.47	57.01	67.84	71.59	14.56	<.0001
PBA-s depressed mood severity score	**1 (absent) (n = 189)**	**2 (slight) (n = 41)**	**3 (mild) (n = 101)**	**4/5 (moderate/ severe) (n = 35)**	***F***	***P* value**
HDQoL Mood-Self†,‡,‖,¶	69.69	62.82	57.46	45.38	29.89	<.0001
PBA-s anxiety severity score	**1 (absent) (n = 165)**	**2 (slight) (n = 61)**	**3 (mild) (n = 117)**	**4/5 (moderate/ severe) (n = 32)**	***F***	***P* value**
HDQoL Worries†,‡,‖,¶	67.53	63.39	59.24	46.25	22.56	<.0001

Note. For the HDQoL (0-100) and verbal fluency scores, higher scores are better; for the UHDRS Total Motor Score and PBA-s scores, higher scores indicate poorer function.
HDQoL indicates Huntington's Disease health-related Quality of Life questionnaire; PBA-s, short version of the Problem Behaviour Assessment; UHDRS, Unified Huntington's Disease Rating Scale.
*Significant Tukey pairwise comparisons ($P<.050$) between quartile 1 and quartile 2 (or between absent and slight).
†Significant Tukey pairwise comparisons ($P<.050$) between quartile 1 and quartile 3 (or between absent and mild).
‡Significant Tukey pairwise comparisons ($P<.050$) between quartile 1 and quartile 4 (or between absent and moderate/severe).
§Significant Tukey pairwise comparisons ($P<.050$) between quartile 2 and quartile 3 (or between slight and mild).
‖Significant Tukey pairwise comparisons ($P<.050$) between quartile 2 and quartile 4 (or between slight and moderate/severe).
¶Significant Tukey pairwise comparisons ($P<.050$) between quartile 3 and quartile 4 (or between mild and moderate/severe).

that future work beyond this sample would be helpful to strengthen the applicability of the HDQoL more globally. The strengths of the study include the representation across severity levels, including later stage patients up to Stage 5 who were in care homes, and also the clinical measures used to establish the validity of the HDQoL.

Conclusions

This study provides robust psychometric support for the refined HDQoL across disease stages, showing that it is fit for purpose in measuring the impact of disease in patients' lives in a meaningful way. This underpins its suitability for use in clinical intervention trials, where any effects on the triad of HD symptoms can be investigated from the patients' perspective to examine the felt impact on patients' lives. In this way, patients' perspectives can more formally contribute to decision making in clinical management and care to promote a more person-centered approach in HD.

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Supplemental Materials

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