Meaningful and measurable health domains in Huntington's: large-scale validation of the Huntington's disease health-related quality of life questionnaire (HDQoL) across severity stages

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Large-scale validation of the Huntington's Disease health-related Quality of Life questionnaire (HDQoL) across severity stages

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Precis: The motor, cognitive and psychological domains of the Huntington's Disease health-related Quality of Life questionnaire (HDQoL) are valid for use in presymptomatic and affected patients.

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ABSTRACT (246 words)

Objectives: While 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. This study aimed 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 and forty-one participants, from pre-manifest to end-stage disease completed the HDQoL, together with generic quality of life measures, and in-person motor, cognitive and behavioural 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 two different behavioural aspects i.e. Mood-Self domain, as well as a distinct Worries domain. These domains clarify the behavioural sequelae as experienced by patients, and all showed good to excellent internal consistency. Known groups analyses illustrated significant and graded changes in clinical assesments and corresponding HDQoL domains across severity levels. Convergent and discriminant validity was demonstrated by the expected pattern of correlations between specific HDQoL domains and corresponding domain-relevant clinical assesments as well as patient-reported measures. The data demonstrate robust support for the refined HDQoL across disease stages.

Conclusions: The HDQoL with its two distinct behavioural domains of Mood-Self and of Worries, as well as a Physical-Functional and a Cognitive domain, is a relevant, reliable and valid patient-derived instrument to measure the impact of Huntington's disease across all severity stages.

Introduction

Neurodegenerative disorders have a devastating impact on individuals. The insidious nature of onset is no comfort to those confronted by the spectre 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 behavioural 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 where the protracted course of disease and gradual loss of function is in the order of decades rather than years. Due to the availability of genetic testing for HD, and the complex constellation of signs and symptoms of HD leading to the subsequent multidimensional impact on patient's lives, it is important that a disease-specific measure is used in order to adequately 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. While 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 were obtained from 281 people across Europe and Canada with different levels of HD severity, including pre-symptomatic 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 over 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 item is 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 which is consistent with the patient-centred FDA requirements for patient-reported outcomes (14). The strong patient-focused ethos and extensive multinational representation in its development sets the HDQoL apart as a patient-reported health outcome measure that truly represents the patient perspective in clinical trials and intervention studies.

In this paper, we present a large-scale psychometric evaluation of the Huntington's Disease health-related Quality of Life questionnaire (HDQoL) in order to validate its use in patients across the full spectrum of disease, and to capture the consequences of living with this disease comprehensively.

METHOD

Participants

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

Participants comprised individuals with at risk (N=14), 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, i.e. TFC 11-13 (N=80), Stage 2, i.e. TFC 7-10 (N=142), Stage 3, i.e. TFC 3-6 (N=106), and Stages 4 and 5, i.e. TFC 0-2 (N=40), and one 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 (SD 12.6) years, and mean number of expanded CAG repeat size was 43.2 (SD 4.5), ranging from 17 up to 70 repeats.

Measures

The clinician-rated Unified Huntington's Disease Rating Scale (UHDRS) (15) was performed in this study, including the following sections, i.e. Total Motor Score (TMS) motor examination (high scores indicate poorer function), Total Functional Capacity (TFC) assessment of everyday function in 5 domains (low scores indicate poorer function), Total Functional Assessment (TFA) 25-item checklist of functional tasks domains (low scores indicate poorer function), and Independence Scale (IS) 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 colour naming, word reading, and interference condition (17) and the Symbol Digit Modalities Test (18). The scoring and interpretation of these measures and of those below are summarised in the supplementary Appendix 1.

The most common neuropsychiatric symptoms in HD were determined via a semi-structured 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 five-point scale were used, where higher scores indicate poorer outcome.

Health-related quality of life was measured using two generic scales, the SF-36 (21) and the EQ-5D-3L (22). The SF-36 has been validated in HD (5) and contains 36 items that

contribute to two 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 HrQOL. The EQ-5D-3L is a generic measure which comprises five questions on mobility, self-care, pain, usual activities, pain/discomfort and psychological status using a three-point scale, and generates a summary index (0 to 1, where 1 is best).

The Huntington's Disease health-related Quality of Life questionnaire (HDQoL) (11) (see www.hdqol.info) is a disease-specific patient-reported outcome measure developed directly from interviews with HD patients (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 three overarching primary factors i.e., Primary Physical and Cognitive, Primary Emotions and Self, and Primary Services, or into six more specific scales i.e., 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 between 0 to 100 scales, higher scores indicate better health-related QoL.

Process

Building on initial pilot work (11), the objective was to obtain data from a large representative sample of HD patients, in order 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 (24), and all Rasch analyses were carried out with the RUMM2030 computer software (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 non-linearity 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, gender, 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 was available for 359 patients. Among these, the mean completion time was 22.6 minutes (SD 17.9), the median was 18 minutes (IQR 10-30), with a range of 2-120 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, 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. All items reported excellent completion rates. The item with the largest amount of missing data was item 6 (Hobby), which recorded a non-response 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 an RMSEA of 0.1, a Chi-Square p-value < 0.001, a CFI of 0.93 and a 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, Chi-Square p-value < 0.001, 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 Chi-Square p-value < 0.001, 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, Chi-Square p-value < 0.001, CFI 0.96, TLI 0.96).

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

As the CFA did not fully support the early scale structures arising from the pilot work, an Exploratory Factor Analysis was carried out in order 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 based on the conceptual framework offered by the International Classification of Functioning, Disability and Health (ICF) (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 detailed in Table 1. Within this model, two 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 & Self' set of items.

The final result to progress onto the next stage was four sets of items representing four domains which contribute towards the quality of life of a HD patient: 'Physical-Functional', 'Cognitive', 'Mood-Self' and 'Worries'.

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

- Insert Table 1 about here –

Rasch Analysis

Rasch analysis for each HDQoL domain are presented below, with preliminary and final domain fit statistics summarised in Table 2 for each domain.

- Insert Table 2 about here –

Physical Domain

In the Physical domain analysis, the twelve 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. Additionally, at this initial stage all items displayed disordered thresholds. The final item set was obtained following the rescoring of all items, and the removal of two items displaying large under-discrimination item misfit (item 5: Had difficulty maintaining your weight; and 11: Got tired easily). Within this final item set of ten, 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 twelve items. Initially, there was some misfit at the overall scale level and the individual item level, all but one of the items displayed disordered thresholds, and the item set also displayed some evidence of a lack of

unidimensionality. The final item set of eight was obtained following the removal of four items (11: Tired; 12: Sleep; 21: Remember Date; and 26: Get on with life). Items 11, 12 and 26 were initially cross-loading items (EFA factor loadings in more than one domain), and within the cognitive set these three items were all clear anomalies, displaying an under-discrimination misfit. Item 21: Remember Date was removed due to both an under-discrimination 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 & 14 into a subtest, whilst retaining all other items individually.

Mood-Self Domain

The Mood-Self domain analysis started with eleven 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 six was obtained following the rescoring of all items and the removal of three items (26: Get on with life, 30: Personal wishes and 34: Temper). Item 34 (Temper) was removed due to a large under-discrimination 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 due to large over-discriminations, meaning that these two 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 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 of the items within two subsets: Items 11, 12 and 32 (Tired, Sleep, and Financial Concerns) were combined into one 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, as this arose directly from previous qualitative work indicating that this was relevant and important to patients' health-related quality of life. As there were only three items (see Table 1 items 38, 39 and 40), the level of analysis was restricted compared to the other domains. These items were primarily concerned with the services that has been received by the individual, and therefore contribute to a set of service level indicators. Furthermore, these services-related items are extrinsic to patients and different from the other four intrinsic HDQoL domains. Therefore validation data on this separate Services domain is presented as supplemental information in Appendix 1.

DIF

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 is 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 gender, educational level and marital status groups, with the only real potential issues arising through potential bias caused by age. However, it could be argued that DIF-by-age may always be present within this sample due to 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 detailed in Table 3. As the sample included presymptomatic participants, the slightly elevated ceiling effect for the Physical and Cognitive domains was consistent with this. All of the domain SEM% values were 10.25% or lower, indicating a minimal difference between observed scores and likely true scores.

- Insert Table 3 about here –

Convergent and divergent validity

Spearman correlations between the HDQoL dimensions and generic quality of life and clinical assessments are reported below (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 and EQ-5D, relative to other non-motor measures.

The HDQoL Cognitive subscore shows the expected correlations with the cognitive assessments performed, and since these cognitive assessments are not 'pure' and encompass psychomotor skill as well due to a dependence on a speech, oculomotor and/or upper limb motor response, there are also strong correlations with motor measures as well.

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 SF36 mental component and EQ-5D Anxiety/Depression item, relative to other motor or cognitive measures. While these two domains are conceptually and statistically related (r_s=0.73,$p<0.01$), the nature of the worry-specific items captures an underlying health concern which is a more specific and distinct element of patient health, and this is reflected in the lower correlations with behavioural 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<0.01) and Physical (r_s=0.59,p<0.01) domains, than was the broader Mood-Self domain was ((r_s=0.76,p<0.01) and (r_s=0.61,p<0.01) respectively).

Overall, the pattern of correlations above are in line with expectations showing appropriate convergent and divergent validity for the HDQoL. Interestingly, while 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 domains of Mood-Self and Worries, suggesting both the distinctness and importance of tapping these more psychological HDQoL domains directly.

- Insert Table 4 about here –

Construct validity

Known groups analysis was conducted to examine HDQoL domain scores when participants were separated into different severity quartiles or levels based on key clinical assessments i.e., UHDRS total motor score, cognitive verbal fluency total correct score and Problem Behaviour Assessment-short (PBA-s) depressed mood severity score and PBA-s anxiety severity score . One-way ANOVAs 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.

- Insert new known groups validity Table 5 about here –

DISCUSSION

Data from this study demonstrate a robust validation of the refined HDQoL in a large sample of genetically verified HD patients 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 four clear and meaningful domains that reflect patients' lived experience, i.e. 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 four HDQoL domains strongly reflect the classical clinical triad of HD features, with the physical, cognitive and behavioural aspects represented. The latter is construed as two distinct domains, Mood-Self and Worries, which also map on to well-recognised psychological constructs of worry, low mood and also self-image. These two psychological domains delineate the behavioural 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 classic 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 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. However, because health care and management was nonetheless a relevant factor 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, as the extent of services may influence outcome.

In a disease like HD where impairment and loss cuts across the whole repertoire of human behaviour, the importance of a fully patient-derived instrument consistent with FDA 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 multi-faceted shadow of HD. It was also important 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. Additionally, 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 HDQoL has advantages and provides a more direct and germane measurement of health-related quality of life in HD.

Where 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 like 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 judgement 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 first hand accounts of living with HD. These direct accounts anchor the HDQoL (11, 12) and provide a strong basis to elucidate the complex psycho-emotional aspects of (anticipation of and) 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, through related to the more emotionally oriented and self-reflective elements of their experience of life with Huntington's as captured by the Mood-Self domain. These two domains provide a better understanding and conceptualisation of psychological aspects that

patients can identify with and serve to inform approaches to person-centred therapy and care. They also have a clearer clinical resonance and have implications in monitoring and intervention.

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

In conclusion, 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 in order to promote a more person-centred approach in HD.

Table 1. HDQoL factor loadings; separate Services domain in grey.

Item	HDQoL Item Descriptor ↓	Physical-Functional	Cognitive	Worries	Mood-Self	Mood-Self 'Bloated Specific' sub-factor		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	Organise 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	Socialise		0.35		0.28			
37	Support							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	Other's 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

Factor loadings <0.20 suppressed; † Items removed from final domain item set after Rasch analysis. Separate Services domain in grey.

Table 2 – Rasch Analysis Summary Results of Individual HDQoL Domains.

				Item Fit Residual		Person Fit Residual		Chi Square Interaction			PSI		Unidimensionality T-Tests (CI)	
	Analysis	Number of items	valid n	Mean	SD	Mean	SD	Value	df	p	with extrms	NO extrms	%	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	0.02	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	0.06	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	0.05	0.83	0.83	2.92%	-
Worries	Initial	6 items	516	0.5	1.7	-0.36	1.3	71.32	48	0.02	0.75	0.72	4.26%	-
	Final	6 items in 2 subtests	510	0.44	0.2	-0.5	1	19.6	16	0.24	0.58	0.53	0.59%	-
	Ideal Values		0	1	0	1			>0.05	>0.85	>0.85 >0.7	<5% >0.7	<5%	

Note: Rasch analysis summary results for the separate Services domain are presented as supplemental information in Appendix 2.

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	Min.	Max.	Floor Effect	Ceiling Effect	Cronbach's Alpha		
	Valid	Missing				25	50	75					0-10 on total score	90-100 on total score	Taken from raw scores	SEM	1.96 x SEM
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 as supplemental information in Appendix 2.

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 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[ϕ]
Perseverative thinking/behaviour (Problem Behaviour Assessment)	-0.35	-0.34	-0.25	-0.18
Disoriented behaviour (Problem Behaviour Assessment)	-0.22	-0.22	-0.17	-0.11[ϕ]
Behavioural				
Depressed Mood (Problem Behaviour Assessment)	-0.14	-0.27	-0.44	-0.39
Anxiety (Problem Behaviour Assessment)	-0.24	-0.37	-0.40	-0.34
Irritability (Problem Behaviour Assessment)	-0.19	-0.23	-0.30	-0.26
Lack of Initiative/Apathy (Problem Behaviour Assessment)	-0.37	-0.42	-0.38	-0.28
EQ-5D Anxiety/Depression	-0.31	-0.46	-0.61	-0.50
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 v.2 score	0.79	0.72	0.69	0.64
Global Clinical Impression[a] (Lower value = Less ill)	-0.70	-0.45	-0.24	-0.27
Disease Burden score[b]	-0.51	-0.29	-0.14	-0.14
Prognostic Index[c]	-0.65	-0.39	-0.16	-0.15

[b] Penney, J. B., Vonsattel, J.-P., Macdonald, M. E., Gusella, J. F., & Myers, R. H. (1997). CAG repeat number governs the development rate of pathology in Huntington's disease.*Annals of Neurology, 41*(5), 689-692. doi: 10.1002/ana.410410521

[c] Long, J. D., Langbehn, D. R., Tabrizi, S. J., Landwehrmeyer, B. G., Paulsen, J. S., Warner, J., & Sampaio, C. (2016). Validation of a prognostic index for Huntington's disease.*Movement Disorders*, n/a-n/a. doi: 10.1002/mds.26838

[a] Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

All correlations are statistically significant at $p<0.01$, except where indicated as:

[ϕ] Non-significant at $0.01<p<0.05$

ϕ ϕ Non-significant at 0.05<p

Note: Rasch analysis summary results for the separate Services domain are presented as supplemental information in Appendix 2.

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 [a,b,c,d,e,f]	87.35	72.69	61.15	50.31	132.13	<0.0001
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 [b,c,d,e]	52.47	57.01	67.84	71.59	14.56	<0.0001
PBA-s depressed mood Severity score	*1 Absent n=189*	*2 Slight n=41*	*3 Mild n=101*	*4&5 Mod&Sev n=35*	*F*	*p-value*
HDQoL Mood-Self [b,c,e,f]	69.69	62.82	57.46	45.38	29.89	<0.0001
PBA-s anxiety Severity score	*1 Absent n=165*	*2 Slight n=61*	*3 Mild n=117*	*4&5 Mod&Sev n=32*	*F*	*p-value*
HDQoL Worries [b,c,e,f]	67.53	63.39	59.24	46.25	22.56	<0.0001

Significant Tukey's pairwise comparisons ($p<0.05$) indicated by the following: [a] between Quartile 1 and Quartile 2, or between absent and slight; [b] between Quartile 1 and Quartile 3, or between absent and mild; [c] between Quartile 1 and Quartile 4, or between absent and moderate/severe; [d] between Quartile 2 and Quartile 3, or between slight and mild; [e] between Quartile 2 and Quartile 4, or between slight and moderate/severe; [f] between Quartile 3 and Quartile 4, or between mild and moderate/severe. Note, for the HDQoL (0-100) and verbal fluency scores, higher scores are better; for the UHDRS Total Motor Score and Problem Behaviour Assessment –short (PBA-s) scores, higher scores indicate poorer function.

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