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Measuring quality of life in ALS/MND: Validation of the WHOQOL-BREF

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Measuring quality of life in ALS/MND: Validation of the WHOQOL-BREF

Abstract

Objectives: The World Health Organization Quality of Life-BREF Scale (WHOQOL-BREF) is a generic QOL measure with four domains covering Physical, Psychological, Social and Environment. Providing the opportunity to contrast QoL with other conditions, or with population norms, the current study had three aims: 1) can the established domains of the WHOQOL-BREF be validated within a large ALS/MND population; 2) can a total score be validated and 3) can they provide interval level measurement?

Methods: Data were obtained from the Trajectories of Outcomes in Neurological Conditions study. Internal construct validity was determined by fit of the data to the Rasch measurement model.

Results: 636 participants with ALS/MND were included. All domains, except the Social domain, showed satisfactory fit to the Rasch model. All were unidimensional, and showed no Differential Item Functioning by age, gender, or onset type. Finally, a total score was validated from a bi-factor perspective.

Conclusions: The WHOQOL-BREF is valid for use in populations with ALS/MND and can be analysed to yield interval level measurement: It offers a range of domains that reflect QOL, which can be used for parametric analysis and for comparison with other conditions or general populations, two advantages for its inclusion as a trial outcome measure and for observational studies.

Keywords: Amyotrophic lateral sclerosis, TONiC, quality of life, Rasch, interval level measurement

Introduction

Provision of care for people with Motor Neuron Disease (MND), also known as Amyotrophic Lateral Sclerosis (ALS), is enhanced by a thorough understanding of how symptoms and functioning relate to quality of life (QOL). This relationship is expressed in the Wilson and Cleary model, which recognised that symptoms and functioning (health status) are separate to QOL (1). Many widely used HRQOL measures include items covering symptoms and functioning, potentially confounding analysis of how symptoms and functioning affect QOL (2). Furthermore, their weighting toward physical functioning can lead to the interpretation that QOL declines as the disease progresses (for review, see Simmons 2015) (3). However, studies using measures adopting a broader construct of QOL demonstrate that QOL may be preserved while physical function declines (4, 5).

The World Health Organization (WHO) designed broader QOL measures including not only the persons' physical health and psychological state, but also their level of independence, social relationships and their relationship to salient features of their environment (6). The WHO Quality of Life BREF Scale (WHOQOL-BREF) is a shortened version of the 100-item WHOQOL, with 26 items, 24 of which are scored. Its psychometric properties were analysed using data from almost 12,000 adults, with a variety of health states, recruited from hospital, rehabilitation and primary care settings (7). A multi-rater mapping process concluded that the WHOQOL-BREF has the fewest items concerning function out of five widely used generic measures of HRQOL, at 27% of items in contrast to the 83% of items concerning function for the Short Form Health Survey (SF-36) or EQ-5D, and even more for the Health Utility Index or SF-12 (2, 8).

The aims of the current study were to: a) establish if the original domains of the WHOQOL-BREF can be obtained and validated within a large ALS/MND population; b) to examine if a total score can be validated and c) describe differences in domain scores, using an interval-scaled metric, according to different demographic and clinical characteristics.

Methods

Data were obtained from an ongoing longitudinal study concerning the trajectories of outcome for those with ALS/MND, the Trajectories of Outcomes in Neurological Conditions (TONiC) study (9). Participants with ALS/MND, diagnosed according to El Escorial World Federation of Neurology criteria (10), were recruited from multidisciplinary specialist clinics across the United Kingdom. Cases with a family history of ALS/MND were eligible as were patients with only lower motor neuron (LMN) signs in 2 or more regions, or with progressive primary lateral sclerosis without spinal LMN signs, provided a consultant neurologist specialising in ALS/MND had confirmed the diagnosis.

Participants were excluded if they were unable to give informed consent, such as from cognitive deficits related to frontotemporal dementia, or if they were unable to complete self-report questionnaires even with help from a scribe. They completed a questionnaire which contained a range of Patient Reported Outcome Measures (PROMs) including the WHOQOL-BREF, Amyotrophic Lateral Rating Scale-Revised (ALSFRS-R), as well as disease duration and site of onset provided by their clinician. All participants received written information and informed consent was obtained prior to enrolment into the study. Ethical approval was granted from the relevant local research committees (reference 11/NW/0743).

Scales

The WHOQOL-BREF begins with two single summary items on quality of life and health which are not scored with the rest of the item set, and then continues with 24 items covering four domains: (a) Physical health and well-being (seven items); (b) Psychological health and well-being (six items); (c) Social relations (three items); and (d) Environment (eight items). Each item has a five-point rating scale from 0-4 (or sometimes scored 1-5); the higher the item score, the better one's 'quality of life' on the domain covered by the item. While it might be thought that items belonging to the Environment domain would be least likely to represent quality of life, they are worded in such a way that this is exactly the case, for example, "How satisfied are you with the conditions of your living place?" Even for functioning and the classical Activities of Daily Living, rather than the level of difficulty with activities, the question is "How satisfied are you with your ability to perform your daily living activities". Thus while the Physical, Psychological, Social and Environmental domains look, at first sight, to

be similar to classical 'functioning' scales as found in the Health Related Quality of Life (HRQoL) literature, their perspective is more one of appraisal of aspects related to these domains, rather than the actual 'doing' of tasks related to those domains. It is this that provides a unique perspective upon Quality of Life. Further information including a copy of the WHOQOL-BREF is available from the WHO website at https://www.who.int/mental_health/media/en/76.pdf.

The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) was developed to monitor the progression of disability in patients with ALS (11). The 12 items are scored 0-4 with a total score of 48, where lower scores indicate greater disability.

Four further scales were included to contribute towards an understanding of the external construct validity of the WHOQOL-BREF:

1. Modified Hospital Anxiety and Depression scale (mHADS), with each domain having six items, and associated clinical cuts to identify 'possible' and 'probable' anxiety or depression (12)
2. World Health Organization's Disability Assessment Schedule-2.0 (WHODAS-2.0), which summates 32 items covering communicating, getting around, self-care, getting along with others, household activities, and participation in society, analysed without the 4 work-related items (13),
3. EQ-5D-5L utility score, measured with a visual analog scale (VAS), which records the respondent's self-rated health status on a graduated (0-100) scale, with higher scores for better HRQOL (14),
4. Numeric Rating Scale (NRS) of perceived overall Quality of Life, where a high score is better.

Statistical analysis

Internal construct validity of the various domains of the WHOQOL-BREF was determined by fit of the data to the Rasch measurement model, full details of which can be found elsewhere (15, 16). Briefly, data must satisfy the requirements of the model, including local item independence, unidimensionality, and stochastic ordering of items (17). Acceptable values of these requirements are shown at the foot of the

fit table. Residual item correlations of 0.2 above the average residual correlations were indicative of local item dependency (18). These dependencies can arise from redundancy, that is, items are close replicates of one another, or from multidimensionality. Where the assumption of local item independence is breached, 'testlets' or 'super items' are formed by adding the dependent items together (19). Here we use the term testlet as a group of items which can be identified *a priori*, for example where there are subscale structures. Where empirical findings show local item dependency without *a priori* input, we refer to any such subsequent grouping of items as 'super items'. A number of strategies are available for this purpose, depending upon the pattern and extent of local dependency. For example, in the absence of any predefined underlying structure, each pair of locally dependent items can be grouped together into a super item. Also, in the RUMM2030 Rasch software, two testlets/super items absorbing all items can provide a latent estimate based upon a bi-factor equivalent solution where a (stronger) conditional test of fit becomes available (20). The explained common variance (ECV) is reported where a value of 1 indicates that all non-error variance is contained within the latent estimate. An ECV value > 0.9 is considered sufficient to indicate that the first common (in this case Rasch) factor is essentially unidimensional (21). Values marginally above 1 can be obtained, indicating that some local dependency nevertheless remains across the two testlets/super items. Finally, tests of invariance (Differential Item Functioning (DIF)) of the various domains are made for age, gender and onset type (constrained to limb and bulbar due to small numbers in other groups) (22).

In order to assess external construct validity, Spearman's correlations were analysed between the WHOQOL-BREF total and domains with four other scales: mHADS, WHODAS-2.0, EQ5D-5L utility score and NRS of QOL.

Absolute reliability was determined through the Standard Error of Measurement (SEM) and the Smallest Detectable Difference (SDD). SEM is calculated as $SEM = SD \text{ all testing scores} \times \sqrt{1 - \text{reliability}}$. SDD represents the minimal difference that a patient or group must show on the scale to ensure that the observed difference is

real and not just measurement error, and was calculated as $1.96 \times \sqrt{2} \times \text{SEM}$ where 1.96 derives from the 95% CI (23).

Results

636 patients with ALS/MND returned a baseline questionnaire by early 2018. Mean age was 65.1 years (SD 10.7) and 61.3% were male (Table 1). Over three quarters (78.6%) were married, and 40% considered themselves to be religious or spiritual. Just over three fifths (61%) were able to complete the questionnaire independently; 85% completed all the items of the WHOQOL-BREF, and 95% all but one item. Median ALSFRS-R score was 33.

Initial fit of the data to the Rasch model found that local item dependency was present throughout the scale; within the existing Physical and Psychological domains, and in a total 24-item set. Only the Environmental domain was free of local item dependency; the Social scale had too few items to detect local dependency. For example, in the 24-item set, nine pairs of items showed residual correlations above 0.2, mostly clustering within established domains. Likewise, independently, the Physical and Psychological domains also showed several pairs of locally dependent items. Consequently, items were grouped to remove the effect of the dependency.

Given this, the fit of the various domains is shown in Table 2. All but the Social domain, showed satisfactory fit to the model. All were unidimensional, and there was no DIF by age, gender, or onset type (bulbar versus limb). Indeed, in the basic 24-item analysis (not shown) only the item 'Are you able to accept your bodily appearance' showed DIF by age.

Finally, using the original four domains as testlets, a total score was validated, albeit with 8% of the variance discarded to obtain the bi-factor unidimensional latent estimate. The person item distribution of the total score is shown in Figure 1. The scale is well targeted, and its range adequately encompasses those of the sample.

Raw score to interval scale transformations for all solutions are shown in Table 3. Providing the respondent has answered all the items within the domain(s) of interest,

the raw score can be summated by adding the scores of 0-4 for each item. (If the data are scored as 1-5, then adjust the scores on the transformation table, for example, with the Physical scale of 7 items, add 7 to the raw score and the transformed score). Thus, if interval level measures of Total QOL, or QOL domains concerning Physical, Psychological and Environment are required, the raw score can be converted to an interval scale metric. The metrics have the same operational range as the raw score.

The values of the domains with respect to various demographic, clinical and other PROM-related aspects are shown in Table 4. All domains showed a significant difference and strong gradient across ALSFRS-R levels, with post-hoc analysis showing that all pairwise comparisons were significant with the exception of the comparison between the ALSFRS-R total scores 0-12 and 13-24, possibly as a result of the lowest scoring group containing only 8 cases. The Physical domain differed across onset types of limb and bulbar, while most domains did not significantly differ by gender or age.

It is instructive to look at the precision of the domains as expressed through their SEM, their SDD, and the percent of the operational range of the scale implied by the SDD (SDD%) (Table 5). The WHOQOL-BREF Total score is the most efficient in that just 8.3% of its operational range needs to be traversed to be above the error. As a contrast, the ALSFRS-R Bulbar domain requires a shift of 33.5% to be sure that any difference is meaningful and not just influenced by error.

Finally, Table 6 presents the non-parametric (Spearman's) correlations of the WHOQOL-BREF domains (excluding Social) against various other measures included in the study, in order to evaluate external construct validity. As expected, correlations were mostly of moderate strength, with the WHOQOL-BREF Psychological domain showing the strongest correlation with the mHADS Depression scale, and the Physical domain showing a strong correlation with the WHODAS-2.0. It should be noted that the Total score from the WHOQOL-BREF explains 42.2% of the variance of the NRS QoL Summary item.

Discussion

The WHOQOL-BREF has been shown to display internal construct validity for ALS/MND, with the exception of the Social scale which cannot be used as a separate domain, although its items are included in the Total score. Excluding the Social scale, all remaining domains demonstrated invariance of age, gender and onset type and showed acceptable levels of unidimensionality and fit to the Rasch model. Both the Total raw score and the Psychological domain raw score were found to be marginally multidimensional, requiring a bi-factor equivalent solution, and therefore it is necessary to use their respective interval scaled transformed scores, which are based upon a slightly reduced variance. These findings are mostly consistent with those reported by Noerholm et al., who found that in a general population study the physical, psychological and environmental domains fit a two-parameter item response theory model, but not the social domain (24). A bi-factor solution for the Total score of the WHOQOL-BREF has also been proposed elsewhere (25).

Most recently, an ALS/MND-specific QoL scale has been developed with scope for a different QoL end-point where comparability with other conditions or populations is not required (26). In contrast, the WHOQOL-BREF offers a set of domains which is built upon the appraisal of different facets of QOL and provides a distinctive generic measure of QoL.

There are several strengths emerging from the findings of the study. First, the WHOQOL-BREF is a simple, self-report measure; in this study 85% of people completed all 26 items at home without any assistance from a researcher. In addition, it appears to have good acceptability among respondents, a further 10% of people completed 25 out of 26 items. The very low amount of missing data suggests that the items are relevant for people with ALS. This is in keeping with findings in a sample of 4669 people including 27 diagnoses or healthy controls, where just 41 subjects had missing data such that the WHOQOL-BREF could not be scored (27). Secondly, interval scale latent estimates derived from fit of data to the Rasch model provide the required data quality for inclusion in parametric analysis, including path analyses and multi-level modelling. Thirdly, generic scales such as the WHOQOL-BREF, offer the advantage of enabling comparisons between conditions and with

general populations. For example less than 1% of Australian adults had WHOQOL-BREF scores comparable to ALS/MND patients with total ALSFRS-R<13/48 (28). Again, it must be remembered that the WHOQOL-BREF is not about the actual level of functioning, but rather an appraisal of, for example, whether life is thought to be meaningful, whether or not the person is able to accept their bodily appearance, how satisfied they are with their personal relationships, and how safe they feel in their daily life. It is within this perspective that contrasts should be made.

There are further limitations and strengths to the study. The use of the ordinal ALSFRS-R total score has been subjected to some criticism of late, claiming that rather it should be scored as three or four separate domains (29-31). Recently, a possible bi-factor equivalent solution to a total score for the ALSFRS-R has been put forward (32). In the current study the total ordinal score was grouped into quartiles of the operational range of the scale to allow for examination of the gradients of the WHOQOL-BREF domains over these quartiles, based upon a score familiar to most readers. The strengths of the current study include its sample size and wide range of functioning of those with ALS/MND, together with the application of the Rasch measurement model to ascertain internal construct validity.

In summary, the WHOQOL-BREF is valid for use in populations with ALS/MND and, using the transformation table, can be analysed as interval level data across several domains, providing the patient has responded to all the items within the domain(s) of interest. It can provide a Total score, and independent domains of Physical, Psychological and Environmental QOL.

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Disclosure of interest

The authors report no conflicts of interest.

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Figure 1. Person Item Distribution of WHOQOL-BREF Total Score

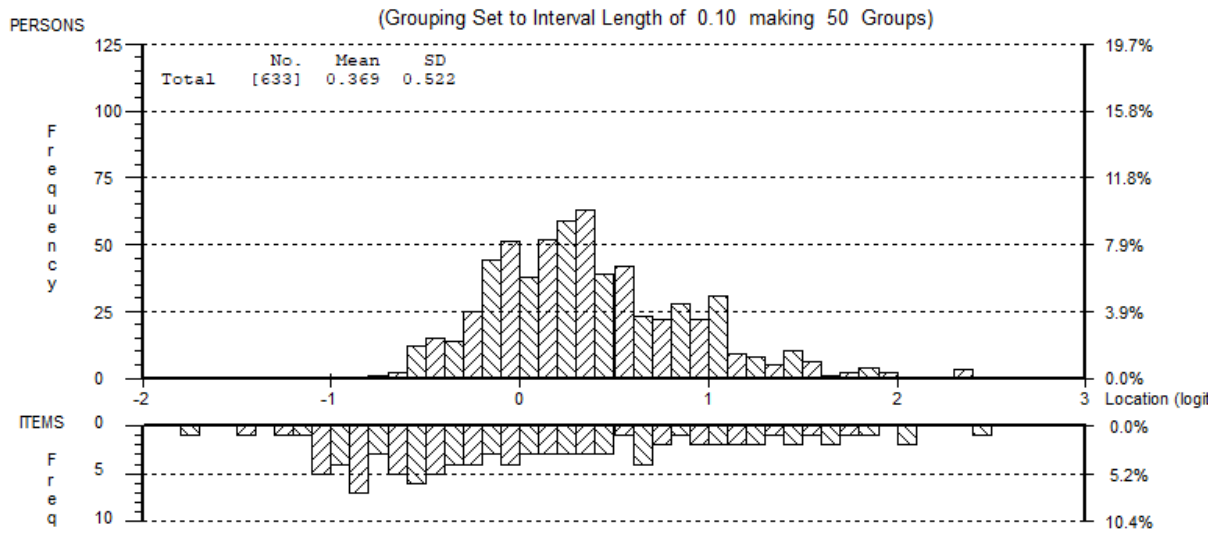


Table 1: Clinical and demographic characteristics of the ALS patients (n =636).

Characteristics	ALS patients
Gender: Males (%)	(61.3)
Mean age: years (SD)	65.1 (10.7)
Married (%):	78.6
Considered religious or spiritual (%)	40.1
Independent completion of Questionnaire (%)	61.0
Site of ALS onset (%)	
Limb	428 (67.3)
Bulbar	174 (27.4%)
Respiratory	11 (1.7%)
Unknown	23 (3.6%)
Median disease duration from diagnosis: months (IQR; range)	11.2 (4.6-29.9; 0.4-295.9)
Median ALS-FRS score (IQR: range)	33(27-38: 1-48)
Working activity (%)	
Employed	12.9
Unemployed	2.4
Retired	56.1
Unable to work because of illness or disability	22.8
Other	5.8

SD=standard deviation; IQR=Inter Quartile Range; ALSFRS-R=ALS Functional Rating Scale-Revised

Table 2: Fit of WHOQOL-BREF Domains to Rasch model.

Analysis	Scale	SD of Residuals		Chi-Square Fit statistic		Reliability		Unidimensionality	Super Item/Testlet Analysis		
		Item	Person	Value and (df)	P	PSI	Alpha		t-test; < 5% (LCI)	(Average) Latent Correlation	Explained Common Variance
1	Physical – 2 super items	0.54	0.87	11.94 (18)	0.850	0.82	0.82	3.7	1.00	1.00	0.030
2	Psychological – 2 super items	0.49	0.98	11.79 (18)	0.858	0.73	0.77	3.7	0.84	0.93	0.107
3	Social – 3 items	1.46	0.83	55.34 (20)	<0.001	0.57	0.57	1.9	-	-	-
4	Environmental - 8 items	1.37	1.06	100.0 (72)	0.016	0.77	0.78	5.6 (3.8)	-	-	-
5	Total score as 4 domain-based testlets	2.02	1.11	19.52 (36)	0.988	0.85	0.81	4.3	0.827	0.921	-
Ideal Values		<1.4*	<1.4		>0.05	>0.7	>0.7	<5.0 (LCI)	>0.8	>0.9	>0.01

*Where testlets/super items are of the same size, else can be inflated; SD= Standard Deviation; PSI=Person Separation Index; df=Degrees of Freedom ; LCI= Lower Confidence Interval

Table 3. Raw score- interval scale metric for total score, and domains.

Raw Score	Overall Total	Physical	Psychological	Environmental
0	0.0	0.0	0.0	0.0
1	8.8	2.2	2.2	2.8
2	14.2	3.7	3.7	4.7
3	17.5	4.8	4.8	6.0
4	19.8	5.6	5.6	6.9
5	21.6	6.3	6.4	7.7
6	23.0	7.0	7.1	8.4
7	24.2	7.5	7.7	9.0
8	25.2	8.1	8.3	9.5
9	26.0	8.6	8.9	10.0
10	26.8	9.1	9.5	10.5
11	27.5	9.6	10.1	11.0
12	28.1	10.0	10.7	11.4
13	28.6	10.5	11.3	11.9
14	29.1	11.1	12.0	12.3
15	29.6	11.6	12.7	12.8
16	30.0	12.2	13.4	13.2
17	30.4	12.8	14.2	13.7
18	30.8	13.5	15.1	14.2
19	31.2	14.3	16.1	14.8
20	31.5	15.1	17.1	15.4
21	31.9	16.0	18.3	16.1
22	32.2	17.0	19.7	16.8
23	32.5	18.1	21.5	17.6
24	32.9	19.4	24.0	18.4
25	33.2	20.9		19.3
26	33.5	22.6		20.4

27	33.8	24.9	21.5
28	34.1	28.0	22.8
29	34.4		24.3
30	34.8		26.1
31	35.1		28.6
32	35.4		32.0
33	35.7		
34	36.0		
35	36.4		
36	36.7		
37	37.0		
38	37.3		
39	37.7		
40	38.0		
41	38.4		
42	38.7		
43	39.1		
44	39.4		
45	39.8		
46	40.1		
47	40.5		
48	40.9		
49	41.2		
50	41.6		
51	42.0		
52	42.4		
53	42.8		
54	43.2		
55	43.6		
56	44.1		
57	44.5		

58	44.9
59	45.4
60	45.9
61	46.4
62	46.8
63	47.4
64	47.9
65	48.4
66	48.9
67	49.5
68	50.1
69	50.7
70	51.3
71	51.9
72	52.5
73	53.2
74	53.8
75	54.5
76	55.2
77	56.0
78	56.7
79	57.5
80	58.3
81	59.1
82	60.0
83	60.9
84	61.8
85	62.8
86	63.9
87	65.1
88	66.4

89	67.8
90	69.4
91	71.2
92	73.5
93	76.3
94	80.2
95	86.3
96	96.0

Table 4. Domain Scores (on interval-scaled metric) across various demographic, clinical and other factors. Mean (SD).

WHOQOL-BREF Domains	Physical	Psychological	Environmental	Total
Operational Range	0-28	0-24	0-32	0-96
Gender				
Male	14.7 (3.7)	13.9* (3.1)	19.8 (4.0)	48.3 (7.3)
Female	14.4 (3.9)	13.2* (3.4)	19.8 (4.3)	47.7 (7.7)
Age				
Up to 66	14.5 (3.9)	13.6 (3.3)	19.5 (4.3)	47.8 (7.6)
67 and above	14.7 (3.6)	13.6 (3.2)	20.1 (4.0)	48.4 (7.2)
Onset Type				
Bulbar	14.5* (4.3)	13.7 (3.5)	20.9* (4.4)	49.6* (8.4)
Limb	14.2* (3.4)	13.6 (3.2)	19.3* (3.9)	47.5* (6.9)
Respiratory	14.3 (3.2)	13.9 (3.3)	21.5 (4.3)	48.8 (7.3)
Unknown	14.6 (4.8)	13.5 (3.6)	20.2 (3.9)	48.6 (8.2)
ALSFERS-R Total**				
48-37	17.0 (3.7)	14.9 (3.1)	21.5 (4.4)	52.2 (7.6)
36-25	14.1 (3.1)	13.5 (3.0)	19.4 (3.8)	47.3 (6.5)
24-13	11.6 (2.4)	11.6 (3.0)	17.9 (3.4)	42.9 (4.6)
12-0	10.1 (2.6)	10.1 (2.6)	16.9 (3.6)	39.9 (3.2)

* Indicates statistical difference at 0.05 (posthoc tests where appropriate)

** All pairwise comparisons significant except that between the lowest two groups

Table 5. Precision of the WHOQOL-BREF domains and, for comparison, ALSFRS-R domains. All domains are on an interval scaled metric.

Domain	Mean	SD	SEM	SDC	%SDC
WHOQOL-BREF					
Physical	14.579	3.775	2.020	5.615	20.055
Psychological	13.602	3.265	1.531	4.245	17.687
Environmental	19.821	4.137	1.940	5.379	16.808
Total	48.110	7.408	2.869	7.953	8.284
ALSFRS-R					
Bulbar	8.218	3.325	1.449	4.017	33.478
Limb	13.073	5.266	2.106	5.839	24.328
Respiratory	10.341	1.922	0.838	2.322	19.352

SD=Standard Deviation; SEM= Standard Error of Measurement; SDD = Smallest Detectable Difference; %SDD is that difference as % of operational range of the scale.

Table 6. WHOQOL-BREF domains correlated with other relevant scales.

	WHODAS-32	EQ-5D-5L	mHADS Anxiety	mHADS Depression	NRS-QoL
WHOQOL-BREF					
Physical	-0.6706	0.7283	-0.3555	-0.5328	0.5567
Psychological	-0.4914	0.4791	-0.6119	-0.7329	0.6015
Environmental	-0.5107	0.5139	-0.3725	-0.4935	0.5408
Total	-0.6489	0.6651	-0.5000	-0.6787	0.6493