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Psychometric properties of QI-Disability in CDKL5 Deficiency Disorder: Establishing readiness for clinical trials

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Abstract

CDKL5 Deficiency Disorder (CDD) is a rare genetic disorder with symptoms of epilepsy, developmental impairments, and other comorbidities. Currently there are no outcome measures for CDD with comprehensive evidence of validation. This study aimed to evaluate the psychometric properties of the Quality of Life Inventory-Disability (QI-Disability) in CDD. QI-Disability was administered to 152 parent caregivers registered with the International CDKL5 Disorder Database (ICDD). Confirmatory factor analysis was conducted and the goodness of fit of the factor structure was assessed. Fixed-effects linear regression models examined responsiveness of QI-Disability to reported change in child health. A subset of parent caregivers (n=56) completed QI-Disability, as well as additional health related questions, on two occasions separated by four weeks to evaluate test-retest reliability. Test-retest reliability was assessed using intra-class correlations (ICCs) calculated from QI-Disability scores. Based upon adjustments for changes in child health, ICCs were recalculated to estimate responsiveness to change. Confirmatory factor analysis, internal consistency and divergent validity were mostly satisfactory, except divergent validity was not satisfactory for the Social Interactions and Independence domains. The Physical Health, Social Interactions, Leisure and Total scores responded to changes in the child's Physical health, and the Negative Emotions and Leisure domains responded to changes in child behavior. Unadjusted and adjusted ICC values were above 0.8 for Positive Emotions, Negative Emotions, Social Interactions, Leisure, Independence domains and Total score, and above 0.6 for the Physical Health domain. Findings suggest that QI-Disability is suitable to assess the quality of life of children and adults with CDD and could be of value for upcoming clinical trials.

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Keywords

CDKL5 Deficiency Disorder; Developmental and epileptic encephalopathy; Psychometric properties; Outcome measure

1 INTRODUCTION

CDKL5 Deficiency Disorder (CDD) results from pathogenic variants in the CDKL5 gene and is characterised by epilepsy from infancy, severe developmental impairments and other comorbidities, such as cortical visual impairment, sleep and gastrointestinal issues [1, 2]. Currently, there is a lack of validated outcome measures which cater for the spectrum of symptoms in CDD and can demonstrate meaningful interventional changes in how affected individuals feel and function [3]. This is a barrier for the success of future clinical trials for CDD, where pre-clinical studies are developing promising protein and gene replacement therapies [4, 5]. Having validated measurement instruments is essential to the success of evaluating new therapeutics when they reach clinical trial testing in humans. Validity (the degree to which an instrument truly measures the construct it purports to measure) and test-retest reliability (the stability of the measure over time such that scores are consistent under similar conditions and at different time points) are important properties to assess in the population in which the instrument will be applied [6]. As per the current guidelines for best practice validation, it is recommended that an instrument is tested with the intended population to determine if the instrument is applicable for that population [7]. This has not happened with many instruments in CDD.

CDD is a complex multisystem condition and multidimensional measures have an important role in reflecting the effects of new treatments. Quality of life (QOL) is a multidimensional concept encompassing multiple components of health and well-being [8], including the influences of impairments, activities, and participation as captured in the International Classification of Functioning, Disability and Health (ICF) model [9]. Because interventions for complex conditions, particularly new gene therapies, are unlikely to impact just one domain or dimension, composite outcomes such as QOL could be suitable and efficient measures of change [10]. For everyday clinical practice, understanding QOL can be used to guide program planning and allocation of resources, contributing to optimizing the well-being of these children. Measures of QOL can also empower families to exercise choice and control over the care that their child receives and may play a role in supporting children to thrive despite the clinical severity of CDD [11].

The Quality of Life Inventory-Disability (QI-Disability) is a parent-report measure for children with intellectual disability, measuring six domains of QOL (Physical Health, Positive Emotions, Negative Emotions, Social Interaction, Leisure and the Outdoors and Independence) [12]. Initial evidence of validation and reliability was reported in 253 primary caregivers of children (5-18 years) with intellectual disability, across four diagnostic groups: Rett syndrome, Down syndrome, cerebral palsy and autism spectrum disorder [12, 13]. The domains of QOL important for children with CDD were identified in a qualitative study [14] and found to be similar to those identified in other qualitative studies [15–18] that

were the platform for the development of QI-Disability. QI-Disability was subsequently used to investigate factors affecting QOL in children and adults with CDD [19] and in children with other Developmental Epileptic Encephalopathies (DEEs) [20]. In the former study of CDD, poorer functional ability, comorbidities of poor sleep and being prescribed more than three anti-seizure medications rather than seizure frequency were related to poorer quality of life [19]. Consistently, the most recent study of children with other DEEs found lower QOL scores for children with greater disease burden and higher scores with a greater number of days minimally disrupted by seizures but not with lower seizure frequency [20]. These studies provide initial evidence of known groups validation for QI-Disability for DEE conditions.

Additional validation is needed to inform the value of QI-Disability as an outcome measure for CDD. In the current study, we aimed to 1) describe the distributions of total and subscale scores, 2) confirm the factor structure using confirmatory factor analysis, and 3) evaluate responsiveness to change, using fixed-effects linear regression models, and estimate test-retest reliability using intra-class correlations (ICCs), of QI-Disability for children and adults with CDD.

2 METHODS

2.1 Sources of Data and Procedures

The International CDKL5 Disorder Database (ICDD) served as the data source for this study [21]. The International CDKL5 Disorder Database (ICDD) was established in 2012. This unique database for CDD is the largest collection of cases worldwide and houses parent-reported and genetic data [19, 22]. Caregivers registered with the ICDD were recruited via telephone in 2018-19 to complete a follow-up questionnaire which included administration of the QI-Disability. Data were collected using Filemaker Web Capture software, with a paper format or telephone interview also available. In 2020-21, caregivers were recruited again by telephone for the new reliability study. This time, the questions were administered using the REDCap (Research Electronic Data Capture) tool, with a paper format or telephone interview also available.

2.2 Instruments

2.2.1 QI-Disability—QI-Disability is a 32-item parent-report measure evaluating QOL in children with intellectual disability [12]. The questionnaire comprises six domains: Social Interaction (7 items; e.g., “Enjoyed the social experiences of mealtimes”), Positive Emotions (4 items; e.g., “Showed cheeky or comical mannerisms”), Negative Emotions (7 items; e.g., “Been unsettled without any apparent reason”), Physical Health (4 items; e.g., “Been alert and aware during the day”), Leisure and the Outdoors (5 items; e.g., “Enjoyed spending time outdoors”) and Independence (5 items; e.g., “Made their own choices for activities or things they enjoy”). Each item is rated on a 5-point Likert scale and item scores are scaled to range from 0 to 100 with higher scores indicating better QOL. Domain scores are calculated by averaging item scores and a total score calculated by averaging domain scores.

2.2.2 Additional questions for the reliability study—

Three items regarding the child's general health, epilepsy and behavior were constructed for this study. Parents were asked to rate their child's physical health (other than due to epilepsy), the impacts of epilepsy, and emotional and behavioral difficulties over the previous month on a 5-point Likert scale at each time point, with response categories ranging from "Never" to "Very Often".

2.3 Statistical Methods

2.3.1 Distribution of scores and confirmatory factor analysis—

Families who completed the follow up questionnaire and/or who participated in the reliability study were eligible for the confirmatory factor analysis, but data from each family was only used once for this analysis. Where a child's caregiver had completed the questionnaire in both studies, we selected the source of their QI-Disability scores randomly. We refer to the resulting dataset as the confirmatory factor analysis sample. This process was chosen to increase the sample size of the confirmatory factor analysis beyond that of the original data collected between 2018/2019. Further, random selection of more than one completed QI-Disability avoided the team making any arbitrary decisions. With 32 candidate items, this sample is close to the generally recommended sample size of five participants per item [23].

Mean and standard deviation (SD) QI-Disability total and subscale scores are described and the distributions of scores presented in histograms. Confirmatory factor analysis was performed to verify the 6-factor structure of QI-Disability for children with CDD. The domains were allowed to be correlated with each other, but no correlated errors were permitted. All items were treated as ordinal variables and hence the weighted least square mean and variance adjusted (WLSMV) estimator was used [24]. Standardized factor loadings were reported, whereby factor loadings greater than 0.4 were considered stable [25]. Goodness of fit of the 6-factor model was assessed using the following statistics: Chi-square value, root mean square error approximation (RMSEA), Tucker-Lewis Index (TLI) and Comparative Fit Index (CFI). Goodness of fit is considered satisfactory if 1) the Chi-square value is smaller than three times the degrees of freedom (df); 2) the RMSEA is <0.08; and 3) the TLI and CFI are >0.9 [25]. Cronbach's alpha, the composite reliability and average variance extracted (AVE) statistics were calculated for each factor to assess internal consistency. Satisfactory internal consistency is indicated if Cronbach's alpha and composite reliability scores are >0.7. The maximum correlation squared (SCMAX) value was calculated for each factor and compared with AVE to assess divergent validity. Satisfactory divergent validity is indicated if the AVE is greater than the SCMAX. MPLUS software was used for the confirmatory factor analysis.

2.3.2 Responsiveness to change and test-retest reliability—

We used the method of Bonett [26] to derive a sample size that would give satisfactory precision for our estimates of intraclass correlation (ICC). We calculated that 51 subjects with test and retest data would lead to a 95% confidence interval width of 0.2 for an anticipated ICC value of 0.8. We refer to the resulting dataset as the reliability sample. ICC was first estimated using raw data from the test and re-test samples from the subset of caregivers who participated in the repeated administration of QI-Disability (referred to as Time 1 and Time 2). A 4-week timeframe

was chosen because the recall period for QI-Disability is one month and we therefore avoiding have data collected that referred overlapping time periods. Test-retest reliability was assessed by intra-class correlations (ICCs) using two-way mixed effects models for absolute agreement between the Time 1 and Time 2 QI-Disability scores.

Fixed-effects linear regression models were then used to explore the responsiveness of QI-Disability total score and domain scores to reported change in indicators of health, epilepsy and behavior. Independent variables in the model equations were the health, epilepsy, and behavior scores as well as a person-specific intercept (the fixed effect) which described all the between-person variation in dependent variable scores due to unobserved factors. Thus, any time invariant between-person confounding is automatically accounted for, in contrast to the alternative mixed model approach where between-person variation is described using random effects. Coefficients from the fitted models describe the degree of responsiveness to change.

Adjustment for child health, epilepsy and behavior changes was achieved by applying the following formula, $Y_2' = Y_2 - \beta_p(P_2 - P_1) - \beta_e(E_2 - E_1) - \beta_b(B_2 - B_1)$, where Y_2 is the measured QI-disability score at time 2, Y_2' is the adjusted time 2 score, P_1 and P_2 are the physical health scores at times 1 and 2 , E_1 and E_2 are the epilepsy scores at times 1 and 2, B_1 and B_2 are the behavior scores at times 1 and 2 and the [β] are the corresponding regression model coefficients. The result of this adjustment is to estimate the Time 2 score which would have been observed had levels of health, epilepsy and behavior remained the same. ICCs using two-way mixed effects models for absolute agreement between the Time 1 and Time 2 QI-Disability scores were then recalculated. Absolute agreement was used as this method does not adjust for systematic change between time 1 and 2 and is therefore more conservative. Any residual differences between the scores over time can be attributed to a lack of reproducibility and examined using test-retest reliability methodology.

Raw and adjusted ICC values are reported. ICC is the standard methodology for assessing test-retest reliability [27]. ICCs were interpreted as ≤0.40 slight agreement, 0.41-0.60 fair agreement, 0.61-0.80 moderate agreement, and 0.81-1.00 substantial agreement [28]. STATA was used to perform the regression modelling and assess test-retest reliability.

3 RESULTS

3.1 Study Sample

Descriptive statistics of clinical, genetic and demographic characteristics for the validity sample and reliability sample are presented in Table 1.

3.1.1 Confirmatory factor analysis sample—Confirmatory factor analysis data were collected from 152 caregivers of children and young people with genetically confirmed CDD, including 101 from the 2018-19 follow up study and 51 from the reliability study (2020-21). In the CFA sample, 132 had complete data, 13 had missing item, 5 had 2 missing items, 1 had 3 missing items and 1 had 5 missing items, of the 32 scale items. In this sample, nearly two thirds (61.2%) were 3 to 12 years of age, and the majority (82.2%) were female and over half (58.6%) were living in North America. The CDD variants were classified as

previously [21]. Approximately one quarter each had no functional protein (any mutation that prevents function in the catalytic domain) or a truncating variant between aa172 and aa781 (including any truncations such as nonsense or frameshift mutations that cause loss of c- terminal region whilst maintaining kinase activity). A slightly higher proportion had a missense/in-frame variant (any missense mutation within the protein kinase active region or in-frame mutation that results in loss of some kinase region (with consequent protein intact) due to deletion) and a smaller proportion had a truncating variant after aa781 (including truncations that maintains the kinase activity and a large portion of the C-terminal region). Data from the most recently completed ICDD questionnaire indicated that 66.4% were unable to walk and 61.2% communicated with gestures, signs, or vocalisations (Table 1).

3.1.2 Reliability sample—QI-Disability scores were obtained from 56 caregivers of children aged 3 years and older at Time 1 and Time 2 (2020-21). Complete datasets were used in all reliability analyses. In the reliability sample, the distributions of age, sex, mutation group, country of residence and functional abilities were similar to those in the validity sample (Table 1).

3.2 Confirmatory factor analysis

The mean (SD) total score was 58.9 (16.1), with higher domain scores for the Physical Health [74.3 (17.3)] and the Negative Emotions [73.9 (17.4)] domains, and a lower domain score for the Independence domain [29.9 (24.6)] (Table 1). The distribution of scores was left skewed for the Physical Health, Positive Emotions, Negative Emotions and Leisure and the Outdoors domains and right skewed for the Independence domain. The Social Interactions domain and total scores were normally distributed (Table 1).

Confirmatory factor analysis of the six-factor model showed satisfactory indices of relative fit using the Chi-square [963.09 (df=449)], Root Mean Squared Error of Approximation (RMSEA; 0.087), Comparative Fit and Tucker-Lewis indices (0.922). However, RMSEA was slightly higher than the recommended cut-point of 0.08. Factor loadings of all items on each domain were more than 0.5 (Table 2). The inter-domain correlation coefficients ranged from −0.350 to 0.845 (Supplementary Table 1).

Cronbach's alpha values ranged from 0.71 for the Physical Health domain to 0.91 for Social Interactions and composite reliability values ranged from 0.84 for Physical Health to 0.94 for Social Interactions. All values were >0.7 and indicative of satisfactory internal consistency (Supplementary Table 2). The average variance extracted (AVE) values for all domains were greater than 0.5 but AVE was less than the maximum correlation squared value for the Social Interactions and Independence domains, indicating that the divergent validity criteria for these domains were not met.

3.3 Reliability

3.3.1 Responsiveness to change—The QI-Disability domain scores describing Physical Health, Social Interactions and Leisure and the Outdoors varied with changes in the child's health over the 4-week interval (Table 3), including a 6.2 (95% Confidence Interval (CI) 2.3,10.1) increase in the Physical Health domain score per unit increase in the health

score. The Negative Emotions score decreased, indicating more challenging behaviors, on average 5.7 points (95%CI 2.7,8.8) per unit increase in frequency of behavior problems whereas the Leisure and the Outdoors subscale score increased on average 7.60 points (95%CI 2.6-12.6) for each unit increase in the frequency of behavior problems. None of the QI-Disability domain scores showed a significant response to reported changes in the frequency of epilepsy. The total score increased on average 3.1 (95%CI 1.2,5.0) per unit increase in the Physical Health score.

3.3.2 Test-retest reliability—Raw ICC values for each QI-Disability domain are shown in Table 4 along with ICCs adjusted for reported changes in health, epilepsy and behavior between Time 1 and Time 2. Raw and adjusted ICC values were above 0.8 indicating substantial agreement for the Positive Emotions, Negative Emotions, Social Interactions, Leisure and the Outdoors and Independence domains. ICC scores were above 0.6 indicating moderate agreement for the Physical Health domain. The total QI-Disability score also displayed substantial agreement (adjusted ICC = 0.93).

4 DISCUSSION

This is the first study to investigate the validity and reliability of QI-Disability for individuals with CDD, a measure previously validated for other neurodevelopmental conditions associated with cognitive impairment [12]. This study is part of a program of research that aims to develop and validate a suite of outcome measures for CDD, contributing to clinical trial readiness in this condition in preparation for the testing of new therapeutics [7]. We found evidence of satisfactory validity, responsiveness to change and test-retest reliability when using QI-Disability across a range of ages and abilities in the CDD population.

The QI-Disability scores found in the current study were low compared to children with Down syndrome, Rett syndrome and autism spectrum disorder [12] but similar to children with cerebral palsy and comorbid intellectual disability [12] and other DEEs [20]. In contrast to the recent study of DEEs [20], scores for most domains in CDD were skewed. For example, we observed right skew in the distributions of Independence domain scores, consistent with marked developmental impairments [1] where the marked severity of disability would contribute to limited capacity for choice and control. The Physical Health, Positive Emotions, Negative Emotions and Leisure and the Outdoors scores were somewhat left skewed. However, their mean scores were less than 75 of a total possible score of 100 and we did not observe a ceiling effect. The Social Interaction domain and Total scores were normally distributed. We note that the recent study of 176 children found normally distributed QI-Disability scores [20], possibly because this sample comprised multiple genetic disorders with a DEE and a greater breadth in phenotype than our sample with CDD.

For the original validation of QI-Disability with children with Down syndrome, Rett syndrome, autism and cerebral palsy, exploratory factor analysis consolidated the items into six domains which was confirmed in the CFA [12]. We confirmed the same factor structure for CDD. Although RMSEA was slightly higher than the recommended cut-point of 0.08,

RMSEA will tend to be biased upwards for small samples (<200) [29], therefore we still consider the model to be satisfactory because the difference between the traditional cut-off is small. We also found internal consistency to be satisfactory, but AVE was less than the maximum correlation squared value for the Social Interactions and Independence domains, suggesting less than satisfactory divergent validity. We suggest that the option of combining the Independence and Social domains would result in lost information, particularly because the distribution of scores in the Independence domain is unique, and that the validity statistics for CDD overall are satisfactory.

QI-Disability scores were responsive to the impacts of changed health status, similar to our previous report for other diagnostic groups [13]. It is feasible that the total score, and the Physical Health, Social Interactions and Leisure and the Outdoors domain scores would be lower when the child experiences episodes of poorer physical health and vice versa. It is also feasible that Negative Emotions domain scores would be lower with increased emotional difficulties and challenging behaviors. Surprisingly, increased behavioural challenges were associated with increased Leisure and the Outdoors domain scores. In CDD, behavioral problems tend to be observed in individuals with milder symptoms and greater functional abilities [19, 22] who also could more readily engage in leisure activities. We were surprised that changes in QI-Disability scores were not influenced by changes in frequency of seizures but this is consistent with our previous study where QOL varied with the number of antiseizure medications, more so than by frequency of seizures [19]. Evaluations of test-retest reliability assume that the underlying trait measured is stable over the test-retest interval. However, individuals with severe to profound developmental impairments and comorbidities experience frequent fluctuations in physical health and behaviours (e.g. due to seizures, medication changes, illness, changes in routine, sleep disruptions). Our approach also adjusted quality of life scores for changes in ratings of physical health and behaviours, to evaluate consistency independently of those effects. In doing, we can observe simultaneously some changes in health ratings in association with changes in quality of life scores. Accounting for the effects of altered health, test-retest reliability was high or satisfactory for the domain and total scores.

The QI-Disability was developed for diverse groups of children with intellectual disability who experience various impairments, comorbidities and severity [12, 13] and the validity and reliability appears comparable for CDD. Use of the QI-Disability across different diagnostic groups allows for comparison of total and domain scores across a spectrum of disorders. DEEs encompass a wide range of epilepsy syndromes, with many becoming evident in infancy and childhood [30] and QI-Disability could be applicable for those conditions also, as recently suggested [20].

A strength of our study was use of an International CDD specific database for data collection, resulting in a sample size that was well powered for this analysis. Given its extreme rarity (estimated Australian birth prevalence 0.21 cases per 100,000 live births [31], database infrastructures such as the ICDD are crucial for data collection with adequate sample size. We acknowledge that the representativeness of the ICDD is unknown. We also acknowledge that QI-Disability date are proxy-reported but child-report would be prohibitive in this disorder [32]. There are currently no validated self-report QOL measures

for children even with milder forms of intellectual disability and there is still substantial reliance on parent/proxy reports. Finally, we asked global health indicator questions to inform the stability of the individual's state of health. We acknowledge that they were rudimentary in nature but they were designed to also consider participant burden. Reliability testing took place over a one-month period during the COVID-19 pandemic and it is unlikely that pandemic conditions would have accounted for variation in QOL scores.

5 CONCLUSIONS

The development of new therapeutics such as gene therapy is accelerating. Validation of outcome measures that are important to both families [33] and the child [7] is a vital ingredient of clinical trial readiness. This study suggests that QI-Disability is a valid and reliable measure of QOL in children and adults with CDD and we present preliminary evidence that the measure is responsive to altered health states. In everyday clinical management, there is potential for quality of life measures such as QI-Disability to enable clear identification of support needs and measure responsiveness to interventions. With quality of life as a critical outcome in trials and for supports and services, families can be empowered to exercise choice and control over the care that their child receives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest:

Helen Leonard: Consultancy for Marinus, Newron, Anavex, GW Pharmaceuticals, Orion and AveXis; Clinical Trials with Newron and Anavex; All remuneration has been made to her department.

Tim A. Benke: Consultancy for AveXis, Ovid, GW Pharmaceuticals, International Rett Syndrome Foundation, Takeda, Neurogene, Ultragenyx, Zogenix, GrinTherapeutics, Alcyone and Marinus; Clinical Trials with Acadia, Ovid, GW Pharmaceuticals, Marinus and RSRT; All remuneration has been made to his department.

Scott Demarest: Consultancy for Biomarin, Neurogene, Marinus, Tysha, Ultragenyx and Ovid Therapeutics. He has funding from the NIH, project 8P and Mila's Miracle Foundation. He also serves on the advisory board for the non-profit foundations SLC6A1 Connect, Project 8P, Ring14 USA and FamilieSCN2A.

Eric Marsh: Consultancy for Stoke therapeutics, Cipla pharmaceuticals. Clinical trials with Acadia, GW pharma, Marinus, RSRT, Biopharm, Stoke therapeutics, Zogenix Pharmaceuticals.

Jenny Downs: Consultancy for Marinus, Newron, Ultragenyx, Orion and Taysha; Clinical Trials with Newron and Anavex; All remuneration has been made to her department.

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HIGHLIGHTS

- QI-Disability showed satisfactory psychometric properties with the CDD population
- QI-Disability scores were responsive to the impacts of changed health status
- QI-Disability offers a comparison of total and domain scores across a spectrum of disorders

Table 1:

Participant characteristics for the confirmatory factor analysis (CFA; n=152) and reliability (test-retest; n=56) studies

	Confirmatory Factor Analysis Sample n (%)	Reliability Sample n (%)
Mutation Group		
No functional protein	40 (26.32)	14 (25)
Missense/in-frame within the catalytic domain	43 (28.29)	19 (33.93)
Truncations between aa172 and aa781	40 (26.32)	13 (23.21)
Truncation after aa781	21 (13.82)	6 (10.71)
Not grouped	8 (5.26)	4 (7.14)
Country of residence		
Australia or New Zealand	15 (9.87)	5 (8.93)
Europe	29 (19.08)	4 (7.14)
North America	89 (58.55)	44 (78.57)
UK	10 (6.58)	2 (3.57)
Other*	9 (5.92)	1 (1.79)
Gender		
Male	27 (17.76)	11 (19.64)
Female	125 (82.24)	45 (80.36)
Age		
3-11	93 (61.18)	30 (53.57)
12+	59 (38.82)	26 (46.43)
Walking ability		
Unable	101 (66.45)	33 (58.93)
Moderate assistance	9 (5.92)	6 (10.71)
Minimal assistance	6 (3.95)	1 (1.79)
No assistance	36 (23.68)	16 (28.57)
Communication		
Simple/no communication	32 (21.05)	10 (17.86)
Gestures, signs or vocalisations	93 (61.18)	36 (64.29)
Words	27 (17.76)	10 (17.86)

QI-Disability[a]	**Confirmatory Factor Analysis Sample**		
	Mean (SD)	**Median (min,max)**	**Skew**
Physical Health	74.4 (17.3)	75 (8.3,100)	−0.76
Positive Emotions	64.5 (23.2)	68.8 (0,100)	−0.41
Negative Emotions	73.9 (17.4)	75 (25,100)	−0.95

QI-Disability[a]	Confirmatory Factor Analysis Sample		
	Mean (SD)	Median (min,max)	Skew
Social Interactions	50.0 (27.3)	50 (0,100)	0
Leisure and the Outdoors	60.9 (27.1)	70 (0,100)	−0.50
Independence	29.9 (24.6)	25 (0,95)	0.66
Total Score	58.9 (16.1)	58.3 (19.6,96.8)	−0.11

[a]Total possible scores out of 100

[*]Includes Brazil, India, Russia, Saudi Arabia, Turkey, United Arab Emirates

Table 2:

Factor loading (95% confidence interval) values from confirmatory factor analysis of QI-Disability item scores

Domain	Item	Loading (95% CI)
Physical health	Had enough energy to participate in routines and activities	0.958 (0.890, 1.000)
	Kept in good general health	0.692 (0.590, 0.794)
	Slept well through the night	0.539 (0.430, 0.647)
	Been alert and aware during the day	0.795 (0.724, 0.866)
Positive emotions	Been in a good mood	0.657 (0.573, 0.740)
	Smiled or brightened their facial expression	0.905 (0.872, 0.938)
	Showed happiness through body language	0.915 (0.882, 0.948)
	Showed cheeky or comical mannerisms	0.907 (0.867, 0.947)
Negative emotions	Been unsettled without apparent reason	0.545 (0.446, 0.644)
	Showed aggression	0.807 (0.704, 0.910)
	Appeared upset or angry	0.726 (0.637, 0.815)
	Become withdrawn with a low mood	0.598 (0.479, 0.717)
	Deliberately hurt themselves	0.831 (0.705, 0.956)
	Expressed discomfort with changes in routine	0.811 (0.706, 0.915)
	Showed signs of being anxious or agitated	0.573 (0.458, 0.688)
Social interaction	Expressed happiness when understood	0.788 (0.731, 0.846)
	Appeared relaxed when making eye contact	0.772 (0.712, 0.832)
	Initiated greetings with people verbally	0.893 (0.850, 0.936)
	Enjoyed being included	0.824 (0.771, 0.877)
	Enjoyed social experiences of mealtimes	0.776 (0.713, 0.840)
	Responded positively when others paid attention to them	0.853 (0.809, 0.897)
	Showed pleasure or excitement when looking forward to activities	0.832 (0.775, 0.890)
Leisure and the Outdoors	Enjoyed moving their body	0.864 (0.817, 0.912)
	Enjoyed feeling steady or stable during physical activities	0.852 (0.804, 0.901)
	Enjoyed physical activities	0.919 (0.887, 0.951)
	Enjoyed going on outings in the community	0.789 (0.728, 0.849)
	Enjoyed spending time outdoors	0.738 (0.669, 0.808)
Independence	Expressed their needs	0.790 (0.718, 0.862)
	Made their own choices for activities or things they enjoy	0.852 (0.799, 0.906)
	Helped to complete routine activities	0.806 (0.728, 0.884)
	Enjoyed making things with their hands – can be with help	0.648 (0.542, 0.754)
	Enjoyed using technology	0.705 (0.622, 0.787)

Table 3:

Responses of QI-Disability domain scores to reported changes in the child's health, frequency of epilepsy, and behaviour, indicated in multivariate fixed effects regression models

	Coefficient (95% CI)*		
	Health	**Frequency of Epilepsy**	**Behavior**
Physical Health	6.2 (2.3,10.1), p=0.002	−0.2 (−3.6,3.1), p=0.886	3.7 (−0.7,8.1), p=0.099
Positive Emotions	3.1 (−1.0,7.2), p=0.136	−0.6 (−4.1,3.0), p=0.749	3.5 (−1.1,8.2), p=0.133
Negative Emotions	0.4 (−2.3,3.1), p=0.788	−1.6 (−3.9,0.8), p=0.181	−5.7 (−8.8,−2.7), p<0.001
Social Interactions	4.0 (0.1,7.9), p=0.045	−0.5 (−3.8,4.9), p=0.753	0.5 (−3.8,4.9), p=0.811
Leisure and the Outdoors	6.2 (1.7,10.6), p=0.008	−0.7 (−4.6,3.2), p=0.711	7.6 (2.6,12.6), p=0.004
Independence	−1.1 (−4.6,2.4), p=0.528	2.5 (−0.5,5.5), p=0.098	−0.3 (−4.2,3.6), p=0.861
Total	3.1 (1.2,5.0), p=0.002	−0.2 (−1.9,1.5), p=0.822	1.5 (−0.6,3.7), p=0.159

* Fitted change in QID score (out of 100) per unit change in health, epilepsy, or emotional score (out of 5)

Table 4:

Intra-class correlations showing test-retest reliability of QI-Disability domains

	Intra-class correlation (ICC)	
	Raw	**Adjusted**[a]
Physical Health	0.606	0.667
Positive Emotions	0.843	0.857
Negative Emotions	0.808	0.851
Social Interactions	0.897	0.905
Leisure and the Outdoors	0.826	0.870
Independence	0.886	0.891
Total	0.912	0.928

[a]Adjusted for changes in health, epilepsy and emotional health scores