Psychometric Properties of Six EQ-5D-5L Bolt-ons in a Rare Disease Population: A Multinational, Longitudinal Study

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1. Objectives

- The EQ-5D-5L is the most widely used generic preference-accompanied measure to capture health-related quality of life data.

- Many bolt-on dimensions have been proposed to improve the validity of the EQ-5D-5L in specific conditions and populations.

- We aim to evaluate the psychometric performance of six bolt-ons (**vision, breathing, tiredness, sleep, social relationships and self-confidence**) in a myasthenia gravis (MG) patient population for whom these dimensions are particularly relevant. MG is a rare, chronic, autoimmune neuromuscular disease, occurring in every 12.4 out of 100.000 individuals.

2. Methods

- The MyRealWorld-MG (MRW) study is a digital, observational, multi-country survey among adult MG patients.

- The study was conducted in the US, UK, Canada, Japan, France, Germany, Belgium, Italy, Spain, and Denmark.

- Data collected included demographics, disease characteristics, the EQ-5D-5L, MG-Activities of Daily Living (MG-ADL), MG-Quality of Life (MG-QoL), Hospital Anxiety and Depression Survey (HADS), Health Utilities Index (HUI-3), PROMIS-Sleep Disturbance, FACIT-Fatigue and PROMIS-Dyspnea.

- The following psychometric properties of the EQ-5D-5L with bolt-on(s) were assessed: ceiling, informativity, divergent and convergent validity, known-groups validity, explanatory power and responsiveness.
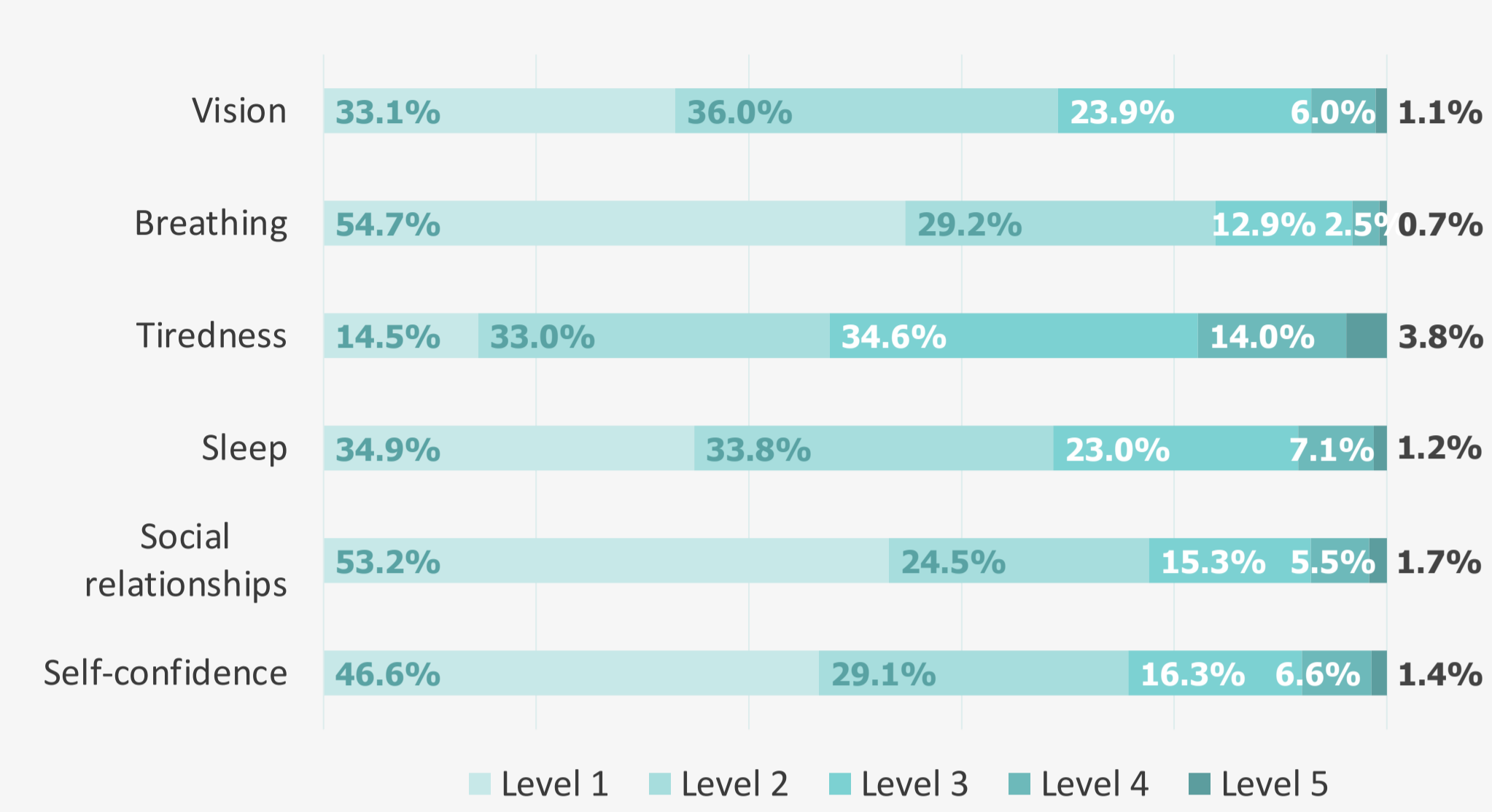
3. Results

TABLE 1. MRW Patient characteristics

		MRW (N = 1510)
Age	18-39	26.6%
	40-59	45.3%
	60-70+	28.1%
Sex	Proportion Female	67.5%
MGFA Class at enrollment	I: Ocular	16.1%
	II: Mild generalized	28.2%
	III: Moderate generalized	36.9%
	IV: Severe generalized	17.6%
	V: Intubation / myasthenic crisis	1.3%
Co-morbidities	Yes	63.7%

ABBREVIATIONS:

MG: Myasthenia Gravis, **MRW**: MyRealWorld-MG, **HADS**: Hospital Anxiety and Depression Survey, **PROMIS**: Patient-Reported Outcomes Measurement Information System, **FACIT**-fatigue: Functional Assessment of Chronic Illness Therapy, **MGFA**: Myasthenia Gravis Foundation of America, **MG-ADL**: Myasthenia Gravis Activities of Daily Living, **MGQoL**: Myasthenia Gravis Quality of Life, **HUI**: Health Utilities Index

FIGURE 1. Distribution of responses on the 6 bolt-ons

Bolt-on	Level 1	Level 2	Level 3	Level 4	Level 5
Vision	33.1%	36.0%	23.9%	6.0%	1.1%
Breathing	54.7%	29.2%	12.9%	2.5%	0.7%
Tiredness	14.5%	33.0%	34.6%	14.0%	3.8%
Sleep	34.9%	33.8%	23.0%	7.1%	1.2%
Social relationships	53.2%	24.5%	15.3%	5.5%	1.7%
Self-confidence	46.6%	29.1%	16.3%	6.6%	1.4%

- **Figure 1 shows tiredness** was the bolt-on most MG patients reported to be struggling with to some degree, with only 14.5% reporting no problems. In contrast, **breathing and social relationships** were the bolt-ons with the fewest problems.

TABLE 2. Impact of bolt-ons on ceiling, health profiles and informativity

	Ceiling	% ceiling reduction	No. of profiles	% of max profiles	Shannon H'	Shannon J'
EQ-5D-5L	14.1%	ref	574	18.4%	1.77	0.76
EQ-5D-5L + Bolt-on						
Vision	9.8%	-30%	1130	7.2%	1.79	0.77
Breathing	12.9%	-8%	1038	6.6%	1.73	0.75
Tiredness	8.1%	-43%	1062	6.8%	1.81	0.78
Sleep	9.8%	-30%	1148	7.3%	1.79	0.77
Social relationships	13.3%	-5%	1089	7.0%	1.76	0.76
Self-confidence	12.9%	-9%	1091	7.0%	1.78	0.76

- **Table 2** shows that the **tiredness, vision** and **sleep** bolt-ons proved most impactful in reducing the EQ-5D-5L's ceiling effect.

- Discriminatory power was measured with Shannon H' representing absolute informativity, and Shannon J' representing relative informativity. The highest informativity was observed in bolt-ons **tiredness, vision and sleep**.

- **Vision**, **sleep** and **self-confidence** generated the highest number of additional health profiles.

- **Table 3** illustrates that the divergent validity of bolt-ons in this population was generally modest due to strong correlations with the EQ-5D-5L dimensions. **Tiredness** was at least moderately correlated with all EQ-5D-5L dimensions (r=0.42 to r=0.66). **Breathing** was correlated with all dimensions except anxiety/depression (r=0.44 to r=0.53). **Social relationships** was correlated with all dimensions except pain/discomfort (r=0.41 to r=0.56).

- **Table 4** shows that the convergent validity of the six bolt-ons. The **breathing, tiredness and sleep** bolt-ons correlated moderately or strongly with items from other instruments intended to capture similar constructs.

TABLE 3. Divergent validity of bolt-ons

	EQ-5D-5L dimensions					Bolt-ons					
Bolt-ons	Mobility	Self-care	Usual Activities	Pain / Discomfort	Anxiety / Depression	Vision	Breathing	Tiredness	Sleep	Social relationships	Self-confidence
Vision	0.35	0.34	0.43	0.36	0.30	-	0.36	0.38	0.29	0.35	0.30
Breathing	0.50	0.47	0.53	0.44	0.32	0.36	-	0.48	0.34	0.38	0.32
Tiredness	0.58	0.52	0.66	0.57	0.43	0.38	0.48	-	0.43	0.43	0.42
Sleep	0.32	0.31	0.39	0.40	0.39	0.29	0.34	0.43	-	0.39	0.39
Social relationships	0.41	0.45	0.52	0.39	0.56	0.35	0.38	0.43	0.39	-	0.63
Self-confidence	0.35	0.37	0.43	0.37	0.64	0.30	0.32	0.42	0.39	0.63	-

TABLE 4. Convergent validity of bolt-ons

Items/Domains capturing same constructs	Spearman Rank correlation
Bolt-on: Vision	
Vision 1 (HUI3_1)	0.47
Double vision (MGADL7)	0.61
Eyelid droop (MGADL7)	0.41
I have trouble with my eyes (double vision) (MGQOL2)	0.56
Bolt-on: Breathing	
Breathing (MGADL4)	0.69
Shortness of breath in general (PROMIS Dyspnea)	0.71
Intensity (PROMIS Dyspnea)	0.69
Frequency (PROMIS Dyspnea)	0.63
Final score (PROMIS Dyspnea)	0.69
Bolt-on: Tiredness	
Inability to rise from chair (MGADL 6)	0.50
I feel fatigued (FACIT Fatigue 1)	0.75
I feel weak all over (FACIT Fatigue 2)	0.68
I feel tired (FACIT Fatigue 4)	0.76
Trouble starting things (FACIT Fatigue 5)	0.68
Trouble finishing things (FACIT Fatigue 6)	0.69
I have energy (FACIT Fatigue 7)	-0.57
I need help doing my usual activities (FACIT Fatigue 11)	0.54
Total fatigue score (FACIT Fatigue)	0.78
Bolt-on: Sleep	
My sleep quality was.. (v poor to v good) (PROMIS Sleep 1)	0.68
Sleep was refreshing (PROMIS Sleep 2)	0.59
I had a problem with my sleep (PROMIS Sleep 3)	0.71
I had difficulty falling asleep (PROMIS Sleep 4)	0.51
My sleep was restless (PROMIS Sleep 5)	0.63
I tried hard to get to sleep (PROMIS Sleep 6)	0.54
PROMIS Sleep total score (PROMIS Sleep)	0.76

Items/Domains capturing same constructs	Spearman Rank correlation
Bolt-on: Social relationships	
Emotion (HUI 3 Domain)	0.48
I have to limit my social activity because I am tired (FACIT Fatigue 13)	0.48
I am frustrated by being too tired to do the things I want to do (FACIT Fatigue 12)	0.50
Limited social activity (MGQOL 4)	0.53
Limit ability to enjoy hobbies and fun activities (MGQoL 5)	0.48
I have lost some personal independence (MGQoL 10)	0.45
Anxiety score (HADS)	0.45
Depression score (HADS)	0.56
Bolt-on: Self-confidence	
I have lost interest in my appearance (HADS 10)	0.42
Anxiety score (HADS)	0.58
Depression score (HADS)	0.60
Something awful is about to happen (HADS 3)	0.46
Worrying thought (HADS 5)	0.48
Sit at ease & feel relaxed (HADS 7)	0.45
Limitations in performing my work (at work and at home) (MGQoL 8)	0.48

Known group validity & explanatory power

- The inclusion of bolt-ons enhanced the EQ-5D-5L's ability to distinguish between known groups in groups defined by disease severity: the **vision, breathing and tiredness** bolt-ons together improved its known group validity the most with a relative efficiency of 1.29.

- The **tiredness** bolt-on contributed the most to explaining the variance of the EQ-VAS (+5.2%), while sleep contributed the least.

- **Table 5** shows that the **breathing, tiredness and sleep** bolt-ons were responsive, correlating moderately to strongly with changes in the scores of condition-specific measures.

TABLE 5. Responsiveness of bolt-ons

	Spearman correlation between total score of PROMS & bolt-ons	
Breathing	Change in PROMIS Dyspnea characteristics	Change in bolt-on
		0.49
Fatigue	Change in FACIT Fatigue	Change in bolt-on
		0.62
Sleep	Change in PROMIS Sleep disturbance	Change in bolt-on
		0.56

4. Conclusion

- The selected bolt-ons, particularly **tiredness, vision and breathing**, improved the EQ-5D-5L's ability to capture health problems in a MG patient population.

- Validity, informativity and responsiveness of these bolt-ons were established in this study, suggesting their potential for future use in MG and other relevant patient populations.