Linguistic and Psychometric Validation of the "Cognition" Bolt-on Version of the Japanese EQ-5D-5L (EQ-5D-5L+C) by Adding a Cognitive Dimension for the Elderly

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BACKGROUNDS

- Over the past decades, there have been discussions among researchers on the requirement for a "bolt-on" version of the EQ-5D as well as a condition-specific "bolt-on" version of the EQ-5D to better capture disability caused by various conditions, such as cognition[1)-4)] .
- With the advanced aging society in Japan and bearing in mind the expected prevalence of dementia in this aging population, an instrument which is capable of evaluating HRQOL, including cognitive function, will be of benefit for people with cognitive impairment. No previous research has, however, been conducted for adding a cognition dimension in the Japanese EQ-5D.

OBJECTIVES

- To develop a cognition bolt-on proxy version of the Japanese 5-level EQ-5D (EQ-5D-5L+C) by referring to a previously published bolt-on version[4)] , we linguistically validated a cognition dimension and psychometrically validated the EQ-5D-5L+C.

METHODS

- EQ-5D-5L modification and its use were granted by the EuroQol group.
- This study was approved by the ethics committee of the Graduate School of Pharmaceutical Science, Faculty of Pharmaceutical Science, The University of Tokyo.

Linguistic validation

- Linguistic validation of the cognition dimension was performed according to a standard process via forward and back translations and using a pilot test[5)6)].
- A pilot test using the preliminary EQ-5D-5L+C proxy version was conducted for five professional/family caregivers who were 20 years or older in July 2021.

Psychometric validation

- Psychometric validation utilized data collected from residents of six nursing homes managed by Life Group, Inc. in Japan, every three months between October 2021 to April 2022. The following anonymized data were extracted at baseline, 3 months and 6 months: background information, EQ-5D-5L+C and EQ-5D-5L (both proxy versions with responses provided by the nursing home staff), and Mini-Mental State Examination (MMSE).
- Ceiling and floor effects were analyzed, calculating the percentage of participants scoring the best and worst status. Above 70% was considered to be adverse[7)] .
- Construct validity was analyzed, using Spearman's rank order correlation coefficients between each of the EQ-5D-5L+C dimensions and MMSE scores at baseline.
- Test-retest reliability was evaluated by assessing agreements in the cognition dimension between baseline and 3 months; and between baseline and 6 months, among participants whose MMSE category had not changed between the two time points.
- Sensitivity to change in the EQ-5D-5L+C cognition dimension was evaluated based on the correlation with changes in the MMSE score between two sets of time points: baseline and 3 months; and baseline and 6 months, using Spearman's rank order correlation coefficients. Additionally, to evaluate whether the addition of the cognition dimension improves the sensitivity to change in the EQ-5D-5L+C, we estimated the sensitivity to change in both EQ-5D-5L and EQ-5D-5L+C. As value sets for EQ-5D-5L+C are not yet developed, total scores of EQ-5D-5L and EQ-5D-5L+C were each calculated by summing the level of five or six dimensions.

RESULTS

Linguistic validation

- The Japanese EQ-5D-5L+C was finalized after forward and back translations of the cognition dimension and cognitive interviews where five professional/family caregivers who fully understood the cognition dimension along with the Japanese EQ-5D-5L without major difficulty. Both original and Japanese versions of the cognition dimension are shown in **Figure 1**.

Figure 1. Original and Japanese versions of the cognition dimension

Original cognition dimension

COGNITION *(memory, comprehension, concentration, thinking)*

I have no problems with cognition ☐
I have slight problems with cognition ☐
I have moderate problems with cognition ☐
I have severe problems with cognition ☐
I have extreme problems with cognition ☐

Japanese cognition dimension developed in this study

認知機能 ***(例：記憶力[物忘れ]、理解力、集中力、思考力)***

認知機能に問題はない ☐
認知機能に少し問題がある ☐
認知機能に中程度の問題がある ☐
認知機能にかなり問題がある ☐
認知機能に極度の問題がある ☐

Psychometric validation

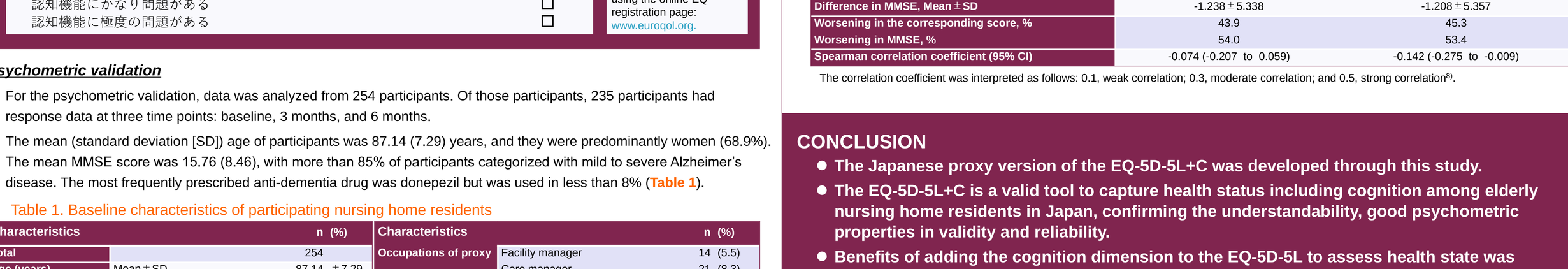
- For the psychometric validation, data was analyzed from 254 participants. Of those participants, 235 participants had response data at three time points: baseline, 3 months, and 6 months.
- The mean (standard deviation [SD]) age of participants was 87.14 (7.29) years, and they were predominantly women (68.9%). The mean MMSE score was 15.76 (8.46), with more than 85% of participants categorized with mild to severe Alzheimer's disease. The most frequently prescribed anti-dementia drug was donepezil but was used in less than 8% (**Table 1**).

Table 1. Baseline characteristics of participating nursing home residents

Characteristics		n (%)	Characteristics		n (%)
Total		254	Occupations of proxy	Facility manager	14 (5.5)
Age (years)	Mean ± SD	87.14 ± 7.29		Care manager	21 (8.3)
Sex	Men	79 (31.1)		Registered nurse	101 (39.8)
	Women	175 (68.9)		Other staff	117 (46.1)
Criteria for determination of the daily life independence level of the elderly with dementia*	I	9 (3.5)	MMSE	n	246
	II	9 (3.5)		Mean ± SD	15.76 ± 8.46
	IIa	20 (7.9)	MMSE category	Normal: 30	6 (2.4)
	IIb	68 (26.8)		Mild Cognitive Impairment: 26-29	21 (8.3)
	III	38 (15.0)		Mild AD: 21-25	54 (21.3)
	IIIa	41 (16.1)		Moderate AD: 11-20	105 (41.3)
	IIIb	26 (10.2)		Severe AD: 0-10	60 (23.6)
	IV	23 (9.1)		Missing	8 (3.1)
	M	4 (1.6)	Barthel index	n	247
	Not applicable	15 (5.9)		Mean ± SD	52.47 ± 30.58
	Missing	1 (0.4)	Prescribed anti-dementia drugs	Donepezil	19 (7.5)
				Galantamine	5 (2.0)
				Rivastigmine	4 (1.6)
				Memantine	16 (6.3)
				Yokukansan/YiganSan	14 (5.5)

Note: Data are presented as frequencies and percentages unless otherwise indicated. Percentages may not sum to 100% due to rounding.
* Ranks are categorized as I, II, IIa, IIb, III, IIIa, IIIb, IV, and M; the higher rank indicates the presence of more severe symptoms that interfere with daily life and more frequent difficulties in behavior and communication.

Figure 2. Distribution of EQ-5D+C response at baseline, 3 months, and 6 months



- No ceiling or floor effects (>70%) were found in the cognition dimension (**Figure 2**).
- For construct validity, the strongest correlation (95% confidence interval, CI) with the MMSE score was found in the cognition dimension (r_s= -0.640 [CI: -0.730 to -0.550]), followed by strong and moderate correlations in the self-care and usual activities dimensions (r_s= -0.530 [-0.632 to -0.429] and -0.497 [-0.598 to -0.395], respectively) (**Table 2**).

Table 2. Correlations between EQ-5D+C dimensions and MMSE at baseline

EQ-5D+C dimensions	N	Spearman's correlation coefficient	(95% CI)
Mobility	245	-0.330	(-0.447 to -0.213)
Self-care	246	-0.530	(-0.632 to -0.429)
Usual activities (e.g. work, study, housework, family or leisure activities)	246	-0.497	(-0.598 to -0.395)
Pain / discomfort	246	-0.026	(-0.153 to 0.102)
Anxiety / depression	246	-0.033	(-0.161 to 0.094)
Cognition (memory, comprehension, concentration, thinking)	244	-0.640	(-0.730 to -0.550)

The correlation coefficient was interpreted as follows: 0.1, weak correlation; 0.3, moderate correlation; and 0.5, strong correlation[8)] .
Note: The number of participants varied due to missing data among each dimension.

- Of all participants, the MMSE category was unchanged from baseline for 138 participants at 3 months and for 119 participants at 6 months.
- Of these participants, a good level of test-retest reliability of the cognition dimension was observed both between baseline and 3 months; and between baseline and 6 months (κ=0.644, 95%CI, 0.541 to 0.746; and κ=0.656, 0.549 to 0.763, respectively) (**Table 3**).

Table 3. Agreement of the cognition dimension between baseline and 3 months and between baseline and 6 months

	No problems	Slight problems	Moderate problems	Severe problems	Extreme problems	Weighted kappa coefficient*	(95% CI)
Baseline response	Response at 3 months (n=138), n, (%)						
No problems	9 (6.5)	1 (0.7)	2 (1.4)	0 (0.0)	0 (0.0)		
Slight problems	8 (5.8)	20 (14.5)	20 (14.5)	2 (1.4)	0 (0.0)		
Moderate problems	1 (0.7)	5 (3.6)	17 (12.3)	7 (5.1)	2 (1.4)	0.644	(0.541 to 0.746)
Severe problems	2 (1.4)	3 (2.2)	2 (1.4)	13 (9.4)	8 (5.8)		
Extreme problems	0 (0.0)	1 (0.7)	2 (1.4)	10 (7.2)	3 (2.2)		
Baseline response	Response at 6 months (n=119), n (%)						
No problems	7 (5.9)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)		
Slight problems	1 (0.8)	19 (16.0)	17 (14.3)	5 (4.2)	0 (0.0)		
Moderate problems	1 (0.8)	9 (7.6)	19 (16.0)	5 (4.2)	0 (0.0)	0.656	(0.549 to 0.763)
Severe problems	0 (0.0)	2 (1.7)	9 (7.6)	9 (7.6)	3 (2.5)		
Extreme problems	0 (0.0)	0 (0.0)	1 (0.8)	6 (5.0)	3 (2.5)		

The kappa coefficient was interpreted as follows: poor, < 0.20; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and very good, 0.81–1.00[9)].
* Fleiss-Cohen weights were used.

- The mean MMSE score changed by -1.207 (SD: 5.346) at 3 months; and by -1.149 (5.899) at 6 months from baseline among 237 and 221 participants, respectively (**Table 4**).
- Similar but weak correlations between changes in the cognition dimension and those in the MMSE scores were observed for both two time point sets (3 months: r_s= -0.191, 95%CI, -0.325 to -0.058; 6 months: r_s= -0.267, -0.396 to -0.138).

Table 4. Sensitivity to MMSE change in the cognition dimension

Change	3 months vs baseline	6 months vs baseline
n	237	221
Difference in EQ-5D-5L+C cognition, Mean ± SD	0.017 ± 0.916	0.140 ± 0.945
Difference in MMSE, Mean ± SD	-1.207 ± 5.346	-1.149 ± 5.899
Worsening in EQ-5D-5L+C, %	29.1	33.9
Worsening in MMSE, %	53.6	48.4
Spearman correlation coefficient (95% CI)	-0.191 (-0.325 to -0.058)	-0.267 (-0.396 to -0.138)

The correlation coefficient was interpreted as follows: 0.1, weak correlation; 0.3, moderate correlation; and 0.5, strong correlation[8)].

- A correlation with changes in the MMSE score at 3 months was higher when the cognition dimension was added to the EQ-5D-5L (EQ-5D-5L+C 6 dimensions) compared to the EQ-5D alone (EQ-5D-5L 5 dimensions) (r_s= -0.142, -0.275 to -0.009; vs. r_s= -0.074, -0.207 to 0.059) (**Table 5**), indicating that the EQ-5D-5L+C better captures change in cognitive function compared to the EQ-5D-5L alone, although the correlation was weak.

Table 5. Sensitivity to MMSE change in EQ-5D-5L (5 dimensions) and EQ-5D-5L+C (6 dimensions)

Change	Total levels (1-5) of EQ-5D-5L 5 dimensions	Total levels (1-5) of EQ-5D-5L+C 6 dimensions
n	239	236
Difference in the corresponding score, Mean ± SD	0.464 ± 3.175	0.395 ± 3.140
Difference in MMSE, Mean ± SD	-1.238 ± 5.338	-1.208 ± 5.357
Worsening in the corresponding score, %	43.9	45.3
Worsening in MMSE, %	54.0	53.4
Spearman correlation coefficient (95% CI)	-0.074 (-0.207 to 0.059)	-0.142 (-0.275 to -0.009)

The correlation coefficient was interpreted as follows: 0.1, weak correlation; 0.3, moderate correlation; and 0.5, strong correlation[8)].

CONCLUSION

- **The Japanese proxy version of the EQ-5D-5L+C was developed through this study.**
- **The EQ-5D-5L+C is a valid tool to capture health status including cognition among elderly nursing home residents in Japan, confirming the understandability, good psychometric properties in validity and reliability.**
- **Benefits of adding the cognition dimension to the EQ-5D-5L to assess health state was suggested, although careful consideration may be needed to assess cognitive changes over time.**
- **Future research is needed to develop value sets for the EQ-5D-5L+C.**

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Abbreviations

the cognition bolt-on version of the Japanese 5-level EQ-5D, EQ-5D-5L+C; Mini-Mental State Examination, MMSE; standard deviation, SD; Alzheimer's disease, AD; confidence interval, CI

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