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The Cognition dimension revisited: A detailed study on its added value and interactions with EQ-5D core dimensions

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INTRODUCTION

Over the last few years there has been discussion within the EuroQol Group about the development of condition specific "bolt-ons" to the standard EQ-5D. Bolt-ons are extensions of the standard five dimension instrument, implying that a dimension or multiple dimensions will be added to the EQ-5D as to broaden the coverage of the health measurement continuum. Bolt-ons can be of substantial scientific and strategic interest to the EuroQol group. There are several reasons for this interest. The most obvious and arguably most important reason is user demand. Disease specific utility measures have begun to be developed and published in the literature. Also, agencies outside the EuroQol group are interested in funding research in this area.

From a scientific point of view there are further grounds for exploring the development of condition specific bolt-ons to the EQ-5D. There is evidence that the EQ-5D does not capture all possible variations in disability caused by various conditions, in areas such as cognition (Krabbe et al, 1999), vision or hearing loss, (Espallargues et al, 2005; Brazier et al 2004), but also sexual function, incontinence or changes in someone's appearance (Kaarlola et al, 2004). Two recent studies by Pickard and Lin (2010) and Solem et al (2011) show a number of condition areas where developing bolt-ons to the EQ-5D could be justified. Moreover, more and more so-called 'mapping' algorithms to the EQ-5D are being used that are based on a link function between the EQ-5D and a condition specific non-preference based measure, often by means of a simple regression on the index values. Two recent review studies showed that many of these mappings are of very poor quality (Brazier et al, 2010, Mortimer

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et al, 2008), but the increasing use of these mappings indicates that there is an interest for index values for extensions to the EQ-5D.

There are two known studies that can be seen as initial bolt-on endeavours. The first is the addition of a cognitive dimension (Krabbe et al, 1999) and the second a sleep dimension (Yang et al, 2008). Both were not condition specific. In the cognition study valuations were performed and showed systematically different values compared to the standard EQ-5D, whereas content validity improved. It was concluded that the addition of the cognition dimension was justified. The second bolt-on valuation study showed that the sleep dimension had no significant incremental disutility and therefore adding a sleep dimension to the EQ-5D was discouraged. Two recent studies aimed at the development of bolt-ons to the EQ-5D in the areas of vision and psoriasis (Yang et al, 2012; Swinburn et al, 2012). Vision had a significant impact on the EQ-5D-3L although differences between the EQ-5D-3L states and the corresponding states including the Vision dimension were not significant. Two psoriasis related dimensions (Skin irritation and Self-confidence) had a significant impact on the EQ-5D-5L.

There are numerous ways to approach the bolt-on initiative both in practical, experimental and theoretical settings. One could think of a developing a conceptual framework, investigate measurement issues, undertake patient studies or plan valuation studies. The most challenging and decisive aspects lie in valuation, and it was therefore decided to look into a specific valuation challenge for an EQ-5D plus bolt-on for the current study.

In setting up a full blown bolt-on valuation study, it is necessary to know how the bolt-on dimension(s) affect the value function for the five core dimensions. It is to be expected that the impact of e.g. Self-Care or Usual Activities will be lower when problems in e.g. Vision get more severe. This is a logical result and is not necessarily problematic in keeping the core value function intact *relatively*. More problematic would be if adding e.g. vision would affect the *relative difference* between two core dimensions. Consider a respondent who values the disutility of Pain/Discomfort higher than the disutility for Mobility, i.e. he would rather have moderate problems in walking about than be in moderate pain. But when adding severe problems with Vision this could change so he would now find Mobility more valuable than Pain/Discomfort, since his or her vision is already so impaired. This would mean that vision has an impact on the *relative difference* between two core dimensions. In that case, more effort would be needed in accounting for all the interaction terms between dimensions in a full blown bolt-on valuation study resulting inevitably in a more comprehensive health state design. If the relative difference would not change, the core value function could remain intact and the design of health states for a full bolt-on valuation study could be much simpler. The current pilot study is tailor made to give a first insight into answering this question.

METHODS

Participants

A specialized recruitment agency organized the data collection. The interviews were conducted in Rotterdam and Groningen (the Netherlands) by a total of 12 well-trained interviewers. In total, 420 persons were invited to take part, and each were given €20 for participating.

Instruments

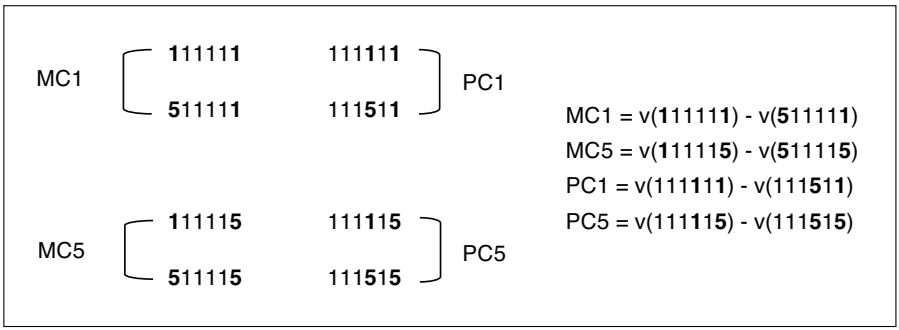
Cognition was selected as bolt-on dimension for the current study, since there is preliminary evidence that the five core dimensions do not pick up disutility in this area and because a Dutch version including Cognition ("EQ-5D+C") had been developed and psychometrically validated previously (Krabbe et al, 1999; Arons et al, 2011). The EQ-5D+C has been used in a number of studies (Wolfs et al, 2007; Noyes et al 2011; Hoeymans et al 2008; Janssen et al 2010; Melse et al; Murray et al, 2000), and in India even an unofficial five level version has been developed more than a decade ago (Mahapatra et al, 2002). The previous translation of Krabbe's Cognition dimension was be taken as point of departure for the current study. It was decided that the labels for the five levels were harmonized with the existing EQ-5D-5L dimensions (no, slight problems, moderate problems, severe problems and extreme problems). The dimension heading/descriptors were proposed by two experts (MOR; CS) and it was decided to use "memory, comprehension, concentration, thinking"[1]. The standard EQ-5D will be referred to as '5D' and the EQ-5D with Cognition as '6D'.

Research question

The main research question is to test whether adding Cognition to the 5D will affect the *relative difference* between two of the five core dimensions in relation to each other. For the current study we compared one set of paired core dimensions: Mobility in relation to Pain/Discomfort. It is to be expected that when Cognition is at level 5, the difference between level 1 and level 5 on another dimension (e.g. Pain/Discomfort) will be lower than when Cognition is at level 1, since one is already severely impaired cognitively: the extra added misery will have a lesser impact. This phenomenon can be viewed as an instance of diminishing marginal disutility. The high impact of an N3 term results from the same underlying principle. From a modelling perspective, this is not necessarily a problematic issue which can be dealt with by adjusting the core value function as a whole (e.g. by a multiplicative function). More problematic would be if the *relative* difference between the two core dimensions would differ when problems with Cognition increase, as explained below.

1. In Dutch: "onthouden, begrijpen, concentreren, denken"

EQ-5D-5L + Cognition (6D) health state profile comparison: Mobility versus Pain/Discomfort*



* For this study more realistic states were actually being used as described below

The main research question is as follows: if the distance between Pain/Discomfort levels 1 and 5 *in relation to* the distance between Mobility levels 1 and 5 is constant whether Cognition is at level 1 or at level 5, the relative difference will be constant and our main hypothesis is satisfied. If the hypothesis is accepted the impact of Cognition to the relationship between Mobility and Pain/Discomfort will be negligible and we will have evidence that the core value function can remain intact when valuing EQ-5D-5L+Cognition, at least in regard to the impact on Mobility in relation to Pain/Discomfort. If the difference is significantly different, a more complex design has to be developed for the main bolt-on valuation study, having to take these complex interactions into account.

As a means to look into more detail as to how adding Cognition will affect the core dimensions, we also add Cognition level 3. This way there are three comparisons possible, between Cognition levels 1 and 5; levels 1 and 3; and levels 3 and 5.

Study design & health states

This study made use of the EQVT software environment. As described above, nine 6D health states were needed in order to make the comparisons necessary for the main research question for which we chose slightly more realistic health states (Table 7.1). Since comparing the 6D states with the standard 5D health states will provide useful insight in the potential impact of Cognition, we added the corresponding three 5D health states to the study design. A split-half design was used with half of the sample valuing the 5D states first and the other half valuing the 6D states first. The order of the health sates was randomized within the 5D and 6D health state blocks.

Table 7.1 Mean TTO and VAS values for 5D and 6D health states (N=387 for TTO; N=400 for VAS)

5D profile	TTO	6D profile	TTO	difference	5D profile	VAS	6D profile	VAS	difference
12112	0.924	121121	0.930	-0.006*	12112	76.31	121121	78.54	-2.23
		121123	0.808	0.116			121123	63.91	12.40
		121125	0.311	0.613			121125	43.49	32.83
12152	0.228	121521	0.245	-0.017*	12152	41.04	121521	42.40	-1.36*
		121523	0.186	0.041			121523	37.31	3.73
		121525	-0.107	0.335			121525	26.51	14.53
52112	0.680	521121	0.725	-0.045	52112	56.77	521121	58.00	-1.23*
		521123	0.615	0.065			521123	48.65	8.12
		521125	0.131	0.549			521125	33.54	23.24

* Non-significant paired t-tests (all other comparisons are significant at the 0.01 level)

Valuation methods

All of these health states were tested with composite TTO (Janssen et al, 2013) and with VAS as described in the EQ-5D-5L valuation protocol using the EQ-VT software environment. Although the composite TTO is the cornerstone of the present EQ-5D-5L valuation methodology, VAS is included as an extra measure since VAS valuations have shown to be more stable and reliable than TTO valuations (Badia et al, 1999; de Boer et al, 2004; Gudex et al, 1996) which will be an asset in the current study since we are looking quite deep into the respondents' preference values.

Cognitive debriefing

A number of cognitive debriefing questions were added. It was asked how adding or leaving out Cognition (depending on the order) influenced the responses on the other dimensions. VAS scores were obtained for all six dimensions in regard to their importance, and for the five core dimensions, corresponding to the order each respondent received the health states. Further, it was asked whether only the important aspects were included in their responses and whether there was a focus on severe problems or problems in general.

Analyses

Main research question

In order to answer the main hypothesis, two different approaches were followed: looking at difference scores or looking at ratios of difference scores. The differences approach assumes an additive linear model, while ratios assume a multiplicative model including interactions. There is abundant evidence that the EQ-5D dimension structure is better explained by some kind of model including interaction terms (such as the N3 and N2 terms), implying that the ratio approach will provide a more useful perspective for testing our main hypothesis.

The descriptions for the main variables for both approaches are explained below, with D1, D3 and D5 referring to the differences approach, and R1, R3 and R5 to the ratio approach. The basic difference scores are denoted as follows: MC1, MC3, MC5 are differences scores between Mobility levels 1 and 5 while Cognition is respectively at levels 1, 3 and 5, and PC1, PC3, PC5 are differences scores between Pain/Discomfort levels 1 and 5 while Cognition is respectively at levels 1, 3 and 5. The differences approach is based on the direct differences between Mobility and Pain/Discomfort at level 5, while the ratio approach is based on the ratios of the basic differences scores.

Basic difference scores
MC1 = $v(121121) - v(521121)$
MC3 = $v(121123) - v(521123)$
MC5 = $v(121125) - v(521125)$
PC1 = $v(121121) - v(121521)$
PC3 = $v(121123) - v(121523)$
PC5 = $v(121125) - v(121525)$

Differences approach
D1= $v(521121) - v(121521)$or MC1 – PC1
D3 = $v(521123) - v(121523)$or MC5 – PC3
D5 = $v(521123) - v(121525)$or MC5 – PC3

Ratio approach
R1 = MC1 / PC1
R3 = MC3 / PC3
R5 = MC5 / PC5

Our main hypotheses were that for the differences approach:

$$D1 = D3 = D5 \text{ or } v(521121) - v(121521) = v(521123) - v(121523) = v(521125) - v(121525)$$

And for the ratio approach:

$$R1 = R3 = R5 \text{ or } \frac{v(121121) - v(521121)}{v(121121) - v(121521)} = \frac{v(121123) - v(521123)}{v(121123) - v(121523)} = \frac{v(121125) - v(521125)}{v(121125) - v(121525)}$$

Both approaches were tested by looking at the mean values as well as by performing paired samples t-tests on the individual paired D and R variables. Simple OLS regressions are applied as an alternative way to gain insight in the impact of the dimensions as well as interactions between Mobility and Cognition, and between Pain/Discomfort and Cognition.

5D versus 6D

The comparisons between the similar 5D and 6D health states were performed using paired samples t-tests. Our hypotheses were that for Cognition levels 3 and 5 a significant difference will be expected with the 5D states, with lower values for the bolt-on states. For Cognition level 1 values might be higher or equal to the EQ-5D-5L states and might be non-significant.

Ordering effects

A final test was performed looking into possible ordering effects between the group of respondents receiving 5D first and the group received 6D first. Possible effects were analysed with independent sample t-tests.

RESULTS

A total of 408 participants took part in the study. The overall sample was 53% female and had a mean age of 38 (SD 13), ranging from 11 to 75 years. A mean EQ-VAS score of 83 (SD 12) was observed, ranging from 40 to 100.

The following exclusion criteria were applied for TTO: All responses had the same value; at least 4 states were higher than the value for one of the two best states (12112 or 121121) AND the best state was <0.5; all values were <=0; according to interviewer comments (one respondent wasn't aware less than 5 years could be traded until the 10th TTO exercise, one respondent had severe difficulties with the task and showed many logical inconsistencies. This resulted in 21 respondents being excluded (5.1%). For VAS the following exclusion criterion were applied: at least 4 states were higher than value for one of the two best states (12112 or 121121) AND the corresponding best state <50, which resulted in the exclusion of 8 respondents (2.0%).

Unfortunately there were many inconsistencies resulting from the two nested sets of health states with Cognition varying between levels 1, 3 and 5: these refer to the main difference scores MC1, MC3, MC5, PC1, PC3, PC5, meaning that many respondents scored e.g. a higher value for 521125 than for 121125, or for 121523 than for 121123 which severely distorted the effects that we are looking for, leading to negative difference values where only positive difference values were expected. All these nested comparisons can be viewed as logical inconsistencies. For TTO this accounted for 126 inconsistencies and for VAS to 143. For many of these inconsistencies it appeared that one of the two health states were significantly more present at the beginning of the experiment (among the first two or three states) which might imply that this could be due to a learning effect, where respondents are still familiarizing themselves with the scale.

All analyses were performed on the full dataset as well as on the 'consistent' dataset with all respondents with inconsistencies excluded. Since the ratio approach lends itself for (extreme) outliers that can lead to seriously distorted results, these were removed from the analyses, which resulted in around 20 outliers per variable on average.

Mean TTO values for the nine 6D health states ranged from -0.107 for health state 121525 to 0.930 for 121121 (Table 7.1). When looking at the 5D values in comparison to the 6D values, our hypotheses were confirmed in all cases, with Cognition level 3 and 5 having a significant impact on all health states both for TTO and VAS, with decreasing values going from level 1 to level 3 to level 5. When comparing 5D health states with 6D health states with Cognition level 1, four out of six comparisons were non-significant, while 52112 did significantly differ from 521121 for TTO (–0.045) and 12112 did significantly differ from 121121 for VAS (–2.23). Although all differences for adding Cognition level 1 are small, there was a consistent trend that showed that values were slightly higher when compared to 5D without Cognition. Paired t-tests on the consistent dataset showed an identical pattern.

Mean TTO and VAS values for the basic difference scores (MC1, MC3, MC5, PC1, PC3, PC5) demonstrated diminishing marginal disutility, with decreasing values for Mobility and Pain/Discomfort as problems in Cognition increase: when going from MC1 to MC3 to MC5 and from PC1 to PC3 to PC5 (Tables 7.2a and 7.3a; Figures 7.1a and 7.1b). This means that when problems in Cognition are moderate and extreme, the impact of extreme problems in Mobility and Pain/Discomfort gets less. However, we see that whilst for Pain/Discomfort all differences for both TTO and VAS were significant, for the Mobility TTO values they were not (Tables 7.2b and 7.3b). For the consistent TTO dataset, interestingly a reverse effect was present for Mobility, implying that when problems in Cognition increase, the impact of more problems in Mobility leads to a higher disutility, so these seem to interact in the opposite way: not weakening but strengthening each other. Although when looking at the paired t-tests we see that these comparisons are not significant except when comparing MC1 and MC5 (Table 7.2b). Figures 7.1a and 7.1b graphically show the effect for the full dataset, the impact of both Mobility and Pain/Discomfort decreases when problems in Cognition increase, although the effect for Mobility for the TTO is very small (and non-significant)

Table 7.2a Mean (SD) basic difference scores and means for the differences and ratio approach for TTO (N=387)

Full dataset			Consistent dataset		
MC1	MC3	MC5	MC1	MC3	MC5
0.20 (0.39)	0.19 (0.40)	0.18 (0.46)	0.20 (0.37)	0.23 (0.38)	0.27 (0.42)
PC1	PC3	PC5	PC1	PC3	PC5
0.68 (0.65)	0.62 (0.65)	0.42 (0.60)	0.73 (0.68)	0.69 (0.67)	0.54 (0.58)
D1	D3	D5	D1	D3	D5
0.48 (0.70)	0.43 (0.68)	0.24 (0.60)	0.53 (0.67)	0.46 (0.68)	0.27 (0.55)
R1	R3	R5	R1	R3	R5
0.26 (0.36)	0.36 (0.49)	0.44 (0.64)	0.27 (0.35)	0.41 (0.46)	0.51 (0.54)

Dx = MCx – PCx; Rx = MCx / PCx

Table 7.2b Comparisons between basic difference scores and between variables for differences and ratio approach for TTO (paired t-tests)

	Full dataset			Consistent dataset	
	mean difference	p value		mean difference	p value
MC1 - MC5	0.026	0.328	MC1 - MC5	-0.066	0.019
MC1 - MC3	0.014	0.416	MC1 - MC3	-0.026	0.100
MC3 - MC5	0.016	0.516	MC3 - MC5	-0.039	0.122
PC1 - PC5	0.266	0.000	PC1 - PC5	0.196	0.000
PC1 - PC3	0.065	0.002	PC1 - PC3	0.044	0.093
PC3 - PC5	0.206	0.000	PC3 - PC5	0.152	0.000
D1 - D5	0.051	0.021	D1 - D5	0.262	0.000
D1 - D3	0.242	0.000	D1 - D3	0.070	0.004
D3 - D5	0.192	0.000	D3 - D5	0.192	0.000
R1 - R5	-0.144	0.000	R1 - R5	-0.188	0.000
R1 - R3	-0.079	0.003	R1 - R3	-0.115	0.000
R3 - R5	-0.053	0.197	R3 - R5	-0.059	0.124

Table 7.3a Mean (SD) basic difference scores and means for the differences and ratio approach for VAS (N=400)

Full dataset			Consistent dataset		
MC1	MC3	MC5	MC1	MC3	MC5
20.9 (20.6)	15.7 (20.4)	9.9 (17.0)	24.0 (21.6)	20.9 (20.0)	14.8 (16.0)
PC1	PC3	PC5	PC1	PC3	PC5
37.0 (23.2)	27.1 (2.4)	17.3 (18.5)	40.6 (21.8)	32.3 (20.2)	22.1 (18.0)
D1	D3	D5	D1	D3	D5
16.2 (26.7)	11.4 (22.8)	7.3 (17.1)	16.6 (26.5)	11.3 (22.4)	7.3 (16.3)
R1	R3	R5	R1	R3	R5
0.58 (0.52)	0.53 (0.58)	0.52 (0.68)	0.62 (0.50)	0.62 (0.46)	0.66 (0.49)

Dx = MCx – PCx; Rx = MCx / PCx

Table 7.3b Comparisons between basic difference scores and between variables for differences and ratio approach for VAS (paired t-tests)

	Full dataset			Consistent dataset	
	mean difference	p value		mean difference	p value
MC1 - MC5	10.965	0.000	MC1 - MC5	9.713	0.000
MC1 - MC3	5.165	0.000	MC1 - MC3	3.645	0.000
MC3 - MC5	5.799	0.000	MC3 - MC5	6.068	0.000
PC1 - PC5	19.884	0.000	PC1 - PC5	19.432	0.000
PC1 - PC3	10.070	0.000	PC1 - PC3	9.115	0.000
PC3 - PC5	9.792	0.000	PC3 - PC5	10.318	0.000
D1 - D5	8.844	0.000	D1 - D5	9.307	0.000
D1 - D3	4.894	0.000	D1 - D3	5.280	0.000
D3 - D5	3.992	0.000	D3 - D5	4.027	0.000
R1 - R5	0.072	0.076	R1 - R5	-0.031	0.385
R1 - R3	0.038	0.232	R1 - R3	-0.022	0.453
R3 - R5	0.056	0.153	R3 - R5	-0.036	0.289

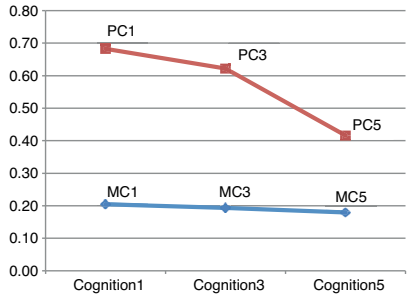


Figure 7.1a Basic difference scores for TTO (full dataset)

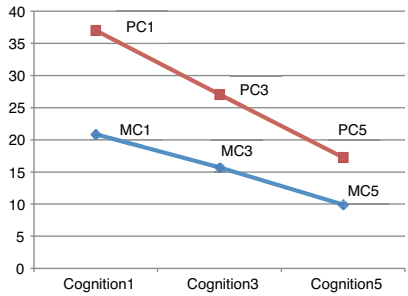


Figure 7.1b Basic difference scores for VAS (full dataset)

MC1 = v(121121) – v(521121)
MC3 = v(121123) – v(521123)
MC5 = v(121125) – v(521125)

PC1 = v(121121) – v(121521)
PC3 = v(121123) – v(121523)
PC5 = v(121125) – v(121525)

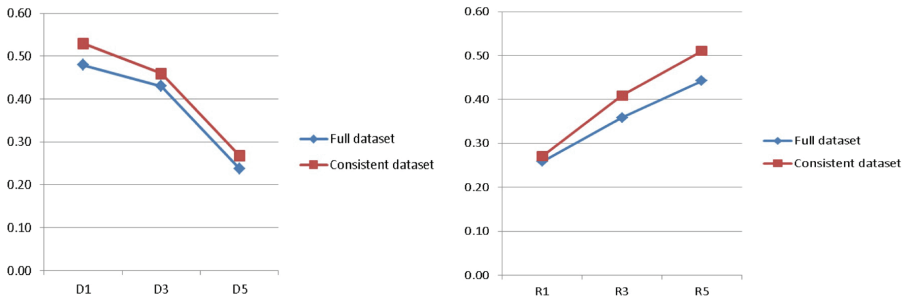


Figure 7.2a Difference and ratio scores for TTO (full and consistent datasets)

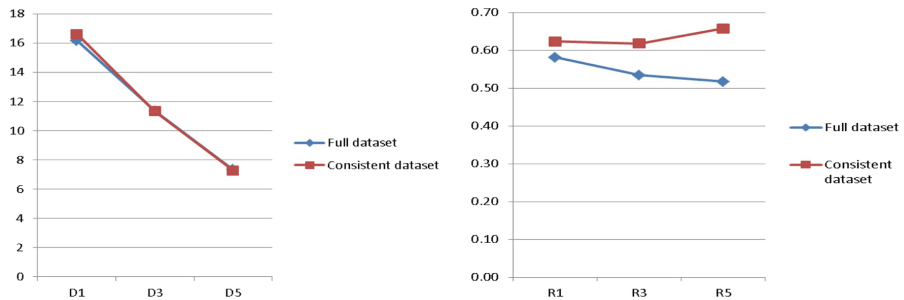


Figure 7.2b Difference and ratio scores for VAS (full and consistent datasets)

Differences approach		*Ratio approach*
D1= v(521121) – v(121521)or	MC1 – PC1	R1 = MC1 / PC1
D3 = v(521123) – v(121523)or	MC5 – PC3	R3 = MC3 / PC3
D5 = v(521123) – v(121525)or	MC5 – PC3	R5 = MC5 / PC5

The values D1 to D3 to D5 are decreasing for the full and consistent datasets for both TTO and VAS which means that when problems in Cognition increase the difference between the impact of Mobility and the impact of Pain/Discomfort decreases which can be viewed as an instance of diminishing marginal disutility (Tables 7.2a and 7.3a; Figures 7.2a and 7.2b). All these differences were significant (Table 7.2b and 7.3b).

This is also visible when looking at the scatterplots of the paired D1 – D5, D1 – D3 and D3 – D5 responses (Figure 7.3). To elaborate, D1 refers to the difference of the impact of Mobility between Pain/Discomfort when Cognition is level 1, D3 to the same difference when Cognition is at level 3 and so forth. When the dimension structure would be linear (additive main effects), all values per respondent would be identical and the fit lines would be at a 45 degree angle through the origin. Positive D values indicate respondents who value Pain/Discomfort at a lower value than Mobility, while negative values indicate respondents who value Mobility at a lower value than Pain/Discomfort. Because the lowest level (indicating least problems) of Cognition is always at the X-axis in these comparisons, the fact that the fit lines are in all cases lower than 45 degrees indicates that on average the differences between the impact of Mobility and Pain/Discomfort decreases when problems in Cognition increase, as can also be seen in the mean D values in Tables 7.2a and 7.3a. All the comparisons between the difference scores for both TTO and VAS are significant, whether on the full or the consistent dataset, implying that the main hypothesis is rejected for the differences approach, as expected. Graphically the differences approach shows clearly that both for TTO and VAS the effect of diminishing marginal disutility is small when Cognition moves from no problems (level 1) to moderate problems (level 3) as seen in the D1 – D3 scatter plots with the slope being close to 45 degrees, and the effect increases considerably when Cognition move to extreme problems, as can be seen by the declining slope for the comparisons between D1 – D5 an D3 – D5.

For the ratio approach TTO and VAS showed different results. The ratios are based on the basic difference scores with Mobility in the numerator and Pain/Discomfort in the denominator, indicating that values between 0 and 1 refer to respondents valuing Pain/Discomfort at a lower value than Mobility, and values >1 indicate respondents who value Mobility at a lower value than Pain/Discomfort. Negative values refer to inconsistent responses. Like for the differences approach, our hypothesis assumed that all values per respondent would be identical and the fit lines would be at a 45 degree angle through the origin. For TTO the ratios increase consistently and significantly for R1 – R5 and R1 – R3, both for the full and consistent datasets (Tables 7.2a and 7.2b, Figure 7.2a). Basically this can be viewed as another instance of diminishing marginal disutility since as the ratios get closer to 1, the differences between the impact of Mobility and Pain/Discomfort decrease. For the VAS ratios are similar and do not differ significantly which seems to be in favour of accepting the main hypothesis (Tables 7.3a and 7.3b, Figure 7.2b). Although a non-significant result does not necessarily mean the hypothesis can be accepted, the ratio values for the VAS are very similar when going from no problems in Cognition (R1) to moderate problems in Cognition (R3) to extreme problems in Cognition (R5). The scatter plots however (Figure 7.4) show hardly any coherence between the sets of ratio variables, both for TTO and VAS. The consistent dataset showed similar patterns. This means that any conclusions based on the ratio approach, also on the VAS results, should be taken with caution.

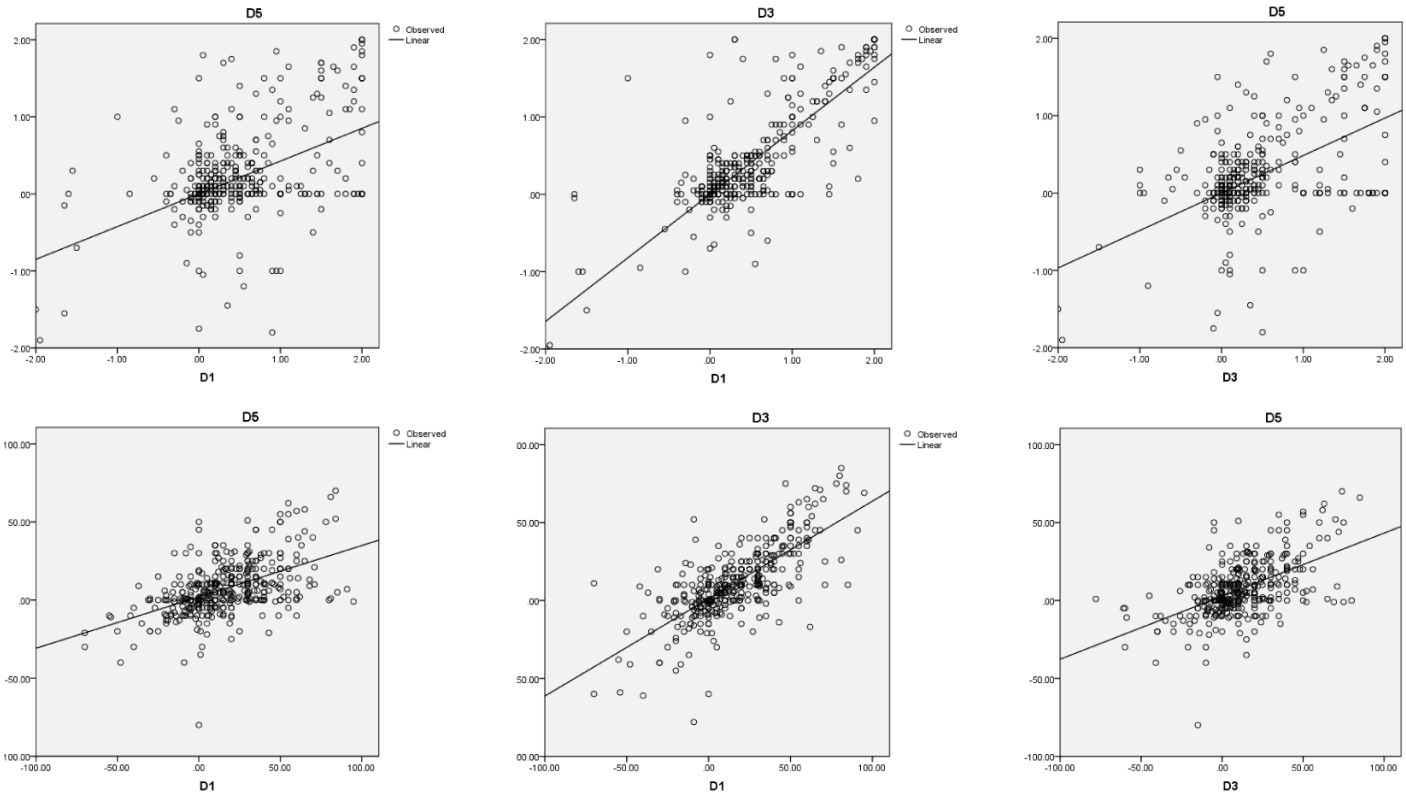


Figure 7.3 TTO (upper row) and VAS (lower row) scatter plots by respondent for the difference scores approach (full dataset)

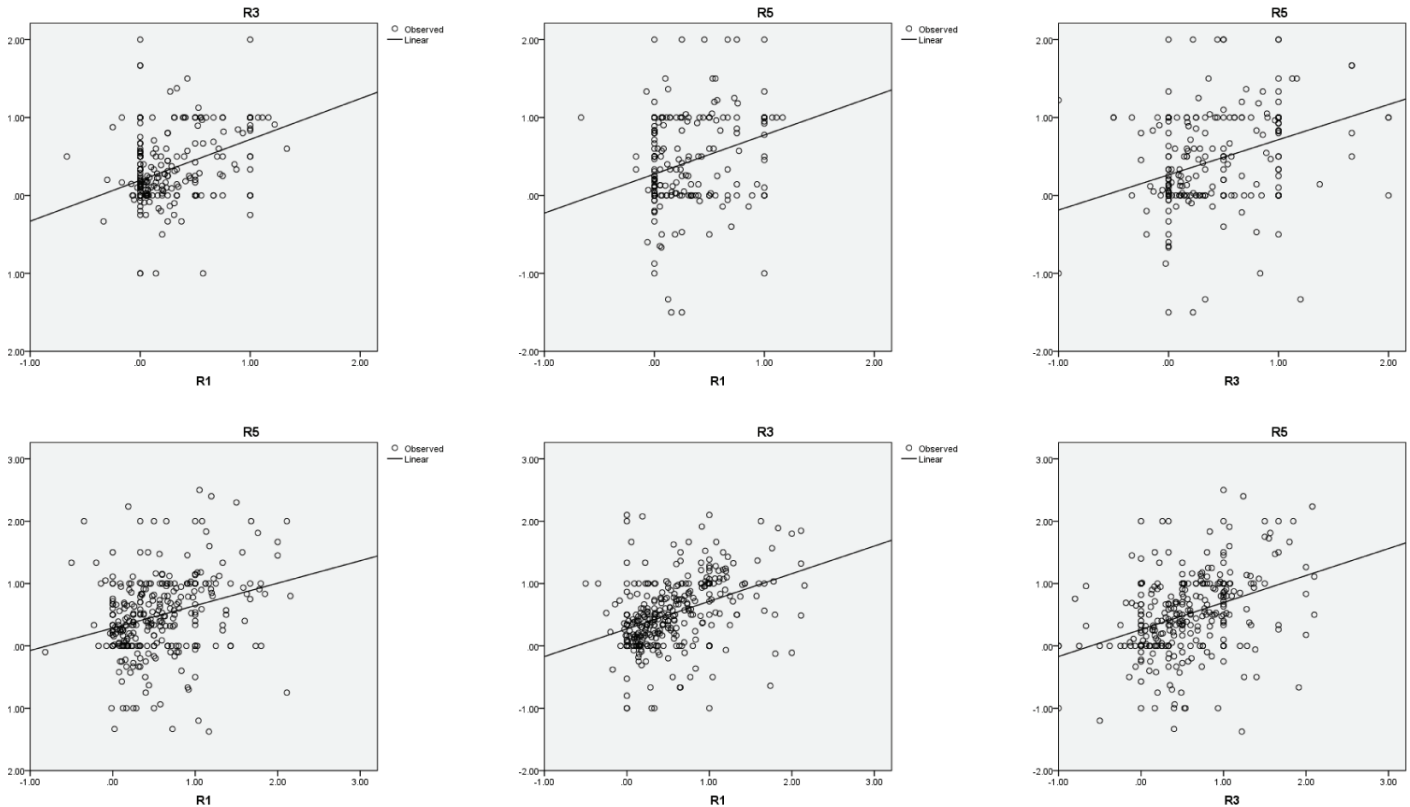


Figure 7.4 TTO (upper row) and VAS (lower row) scatter plots by respondent for the ratio approach (full dataset)

The regressions showed that Cognition had a significant impact, both for levels 3 and 5, on both TTO and VAS (Table 7.4). In regard to the interactions there were differences between both valuation methods: for TTO there was an interaction between Cognition and Pain/Discomfort level 5 but not between Cognition and Mobility or between Cognition and Pain/Discomfort level 3, while with VAS there were interactions between all pairs of dimensions (the regression on the consistent dataset shows similar results). The absolute impact of Cognition on Pain/Discomfort is higher than on Mobility, but when looking to the relative impact on the VAS, the proportion of the interaction parameter estimates on the main Mobility and Pain/Discomfort parameter estimates is almost identical: MO5CO3/MO5 = 0.23; PD5CO3/PD5 = 0.25 and MO5CO5/MO5 = 0.52; PD5CO5/PD5 = 0.53 which further seems to support our main hypothesis. For the TTO these values are not of much meaning since most of these variables are non-significant. The regressions confirm the effect of diminishing marginal disutility that was also apparent from the basic difference scores.

Table 7.4 Regression results for TTO and VAS (N=387 for TTO; N=400 for VAS)

	TTO				VAS		
	Parameter estimate	SE	p value		Parameter estimate	SE	p value
Constant	.102	.028	.000	Constant	22.63	0.73	.000
MO5	.191	.039	.000	MO5	20.10	1.03	.000
PD5	.641	.039	.000	PD5	35.82	1.03	.000
CO3	.102	.039	.009	CO3	13.55	1.26	.000
CO5	.585	.039	.000	CO5	34.06	1.26	.000
MO5CO3	-.001	.055	.989	MO5CO3	-4.64	1.78	.009
PD5CO3	-.039	.055	.474	PD5CO3	-9.15	1.78	.000
MO5CO5	-.017	.055	.763	MO5CO5	-10.37	1.78	.000
PD5CO5	-.246	.055	.000	PD5CO5	-18.85	1.78	.000

All dummy variables: MO5 – Mobility level 5; PD5 – Pain/discomfort level 5; CO3 – Cognition level 3; CO5 – Cognition level 3; MO5CO3 – Mobility level 5 AND Cognition level 3; PD5CO3 – Pain/Discomfort level 5 AND Cognition level 3; MO5CO5 – Mobility level 5 AND Cognition level 5; PD5CO5 – Pain/Discomfort level 5 AND Cognition level 5; the constant contains the impact for Self-Care level 2 and Anxiety/Depression level 2 and a term for any move away from 111111.

The ordering of 5D versus 6D did not have a significant impact for any health state for both the TTO and VAS values (mean difference for TTO was 0.010 and for VAS 1.9).

The cognitive debriefing showed that Pain/Discomfort and Cognition were considered the most important (Table 7.5). Results hardly changed when adding or leaving out Cognition. Three differences were significant but small and probably due to the relatively large sample size. Interestingly Anxiety/Depression was considered to be the least important dimension. 57% of the respondents mainly focussed on severe problems while 37% focussed on problems in general (6% had an alternative view). 52% of the respondents mainly focussed on the dimensions that were considered important by them, while 36% focussed on all dimensions. A total of 71% found the 5D states easy to value, and for the 6D states this was also 71%.

Table 7.5 Cognitive debriefing results (mean VAS scores in regard to importance)

	First 5D, then 6D (n=202)			First 6D, then 5D (n=205)		
	5D	6D	difference	6D	5D	difference
Mobility	73.1	73.3	-0.2	71.3	73.5	-2.2
Self-Care	70.8	71.5	-0.6	67.7	67.7	0.1
Usual Activities	77.3	76.2	1.1*	76.9	75.4	1.5
Pain/Discomfort	82.0	81.3	0.8	79.9	81.2	-1.2*
Anxiety/Depression	63.5	62.2	1.2*	60.4	60.3	0.1
Cognition	-	80.9	-	80.8	-	-

* Significant at the 0.05 level

CONCLUSIONS

- Cognition seemed to have a significant impact on the EQ-5D (although not all 5D dimensions were included with reported problems in the design)
- When comparing 5D and 6D adding cognition levels 3 and 5 all had a consistent and significant increasing impact in relation to 5D
- Interactions between dimensions were apparent and not linear: diminishing marginal disutility was observed for both TTO and VAS values
- When problems in Cognition were moderate, the value function approached a linear form but when problems were extreme, a multiplicative form was observed
- The VAS results seemed to support our main hypothesis when looking at the ratio approach as well as the regression results, although the raw values suggested caution is advised in making this conclusion
- Severe problems in Cognition and in Pain/Discomfort had a great impact on the value function, with Pain/discomfort being the highest. The impact of Mobility was much lower
- Interactions between dimensions are important and need to be dealt with in developing bolt-ons, but also in modelling EQ-5D-5L data
- Adding Cognition level 1 resulted in a trend upward from 5D, although differences were small and in most cases non-significant
- The TTO value scale of the upper anchor of 1 seemed identical when adding Cognition as a bolt-on dimension (judging from the almost identical values for the mild 5D and 6D states), implying the Cognition bolt-on will not require a 'new' scale continuum
- The very low coherence between the ratios might be due to too much noise in the data: based on first taking two sets of differences between a set of three health states, and subsequently taking the ratios of these differences

DISCUSSION

This study showed that Cognition as a bolt-on dimension had a significant impact on the 5D dimension structure in terms of valuation with composite TTO and VAS. When comparing 5D with 6D values, results were perfectly in line with our expectations and in favour of developing a bolt-on for Cognition. The main hypothesis was rejected in all cases for the difference approach as expected: diminishing marginal disutility was observed in all instances. Based on the ratio approach the VAS results seemed to support the main hypothesis. This was also the case when looking at the proportional impact of the regression parameters for the VAS. TTO results for the ratio approach were neither in supported nor rejected the main hypothesis. Promising for the bolt-on initiative in general was that respondents indicated they did not have more difficulties valuing the health states including Cognition over the standard 5D health states.

There were many inconsistencies in the nested pairs which might be due to an ordering effect: many of the health states causing the inconsistencies were being valued at the beginning of the experiment when respondents were still familiarizing themselves with the scale continuum. A recent adaption of the standard EQ-VT protocol is designed to correct for this, including three 'practice' health states of varying severity.

A potential weakness for comparing the 5D and 6D health states was that all respondents valued both 5D and 6D states, which could lead to a possible ordering effect, mainly for respondents who received 6D first there could still be some notion of Cognition when valuing the 5D states. Fortunately differences between the different versions were very small and all non-significant.

A limitation of this pilot study was that only one paired interaction between core dimensions was tested. Although these dimensions were selected with care, we cannot know if the outcome for interactions between other dimensions might be different. Therefore, future research is encouraged in replicating the results on a different set of two EQ-5D dimensions.

Although many interesting lessons were learned from the current study, this was only a first step in disentangling the intricate dimension structure of the EQ-5D in itself as well as the EQ-5D plus any bolt-on dimension from a valuation perspective. Future research is needed investigating interactions between the health domains, both for the 5D as well as for the 5D plus bolt-on dimensions.

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