Performance of the EQ-5D-5L plus respiratory bolt-on in the Birmingham chronic obstructive pulmonary disease cohort study

Hoogendoorn, Martine ; Jowett, Sue; Dickens, Andy; Jordan, Rachel; Enocson, Alexandra; Adab, Peymane; Versteegh, Matthijs ; Rutten-van Mölken, Maureen

DOI:
10.1016/j.jval.2021.05.006

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Hoogendoorn, M, Jowett, S, Dickens, A, Jordan, R, Enocson, A, Adab, P, Versteegh, M & Rutten-van Mölken, M 2021, 'Performance of the EQ-5D-5L plus respiratory bolt-on in the Birmingham chronic obstructive pulmonary disease cohort study', *Value in Health*, vol. 24, no. 11, pp. 1667-1675. https://doi.org/10.1016/j.jval.2021.05.006


ScienceDirect

Contents lists available at **sciencedirect.com**
Journal homepage: **www.elsevier.com/locate/jval**

Preference-Based Assessments

Performance of the EQ-5D-5L Plus Respiratory Bolt-On in the Birmingham Chronic Obstructive Pulmonary Disease Cohort Study

Martine Hoogendoorn, PhD, Susan Jowett, PhD, Andrew P. Dickens, PhD, Rachel Jordan, PhD, Alexandra Enocson, PhD, Peymane Adab, PhD, Matthijs Versteegh, PhD, Maureen Rutten-van Mölken, PhD

ABSTRACT

Objectives: A respiratory bolt-on dimension for the EQ-5D-5L has recently been developed and valued by the general public. This study aimed to validate the EQ-5D-5L plus respiratory dimension (EQ-5D-5L+R) in a large group of patients with chronic obstructive pulmonary disease (COPD).

Methods: Validation was undertaken with data from the Birmingham COPD Cohort Study, a longitudinal UK study of COPD primary care patients. Data on the EQ-5D-5L+R were collected from 1008 responding participants during a follow-up questionnaire in 2017 and combined with (previously collected) data on patient and disease characteristics. Descriptive and correlation analyses were performed on the EQ-5D-5L+R dimensions and utilities, in relation to COPD characteristics and compared with the EQ-5D-5L without respiratory dimension. Multivariate regression models were estimated to test whether regression coefficients of clinical characteristics differed between the EQ-5D-5L+R utility and the EQ-5D-5L utility.

Results: Correlation coefficients for the EQ-5D-5L+R utility with COPD parameters were slightly higher than the EQ-5D-5L utility. Both instruments displayed discriminant validity but analyses in clinical subgroups of patients showed larger absolute differences in utilities for the EQ-5D-5L+R. In the multivariate analyses, only the coefficient for the COPD Assessment Test score was higher for the model using the EQ-5D-5L+R utility as outcome.

Conclusions: This study showed that the addition of a respiratory domain to the EQ-5D-5L led to small improvements in the instrument's performance. Comparability of the EQ-5D across diseases, currently considered one of its strengths, would have to be traded off against a modest improvement in utility difference when adding the respiratory dimension.

Keywords: COPD, EQ-5D, respiratory dimension, validation.

VALUE HEALTH. 2021; 24(11):1667–1675

Introduction

The EQ-5D (EQ-5D™ is a trade mark of the EuroQol Research Foundation)[1,2] has been often used to evaluate health-related quality of life of patients with respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD).[3–5] Several studies concluded that the EQ-5D is a valid and reliable measure of health status in asthma and COPD.[3,6,7] Nevertheless, correlations of the EQ-5D and other generic health-related quality of life measures with lung function and respiratory markers are usually low or moderate.[6,8] Other studies also argued that the responsiveness of the EQ-5D to changes in health in patients with asthma and COPD over time seems rather limited,[9,10] which might lead to an underestimation of the number of quality-adjusted life-years (QALYs) gained by a treatment or intervention. It is hypothesized that important aspects of these respiratory diseases, such as shortness of breath, coughing, wheezing, and fatigue, are not covered by the current 5 dimensions of the EQ-5D, causing a suboptimal sensitivity to change. Several examples of COPD trials are available that reported significant and relevant changes in clinical and patient-reported outcomes, but very low gains in QALYs.[11–15] An underestimation of the number of QALYs gained results in an overestimation of the cost per QALY, reducing the likelihood that the treatment or intervention will be funded or reimbursed. Nevertheless, it has not been possible to demonstrate whether the small QALY gains are due to insensitivity of instruments or a low valuation by the general public of the observed gains in health-related quality of life.

Recently, a respiratory bolt-on dimension has been developed for the EQ-5D-5L as a potential solution to improve its responsiveness in patients with respiratory symptoms.[16] The pilot valuation study for the additional respiratory dimension demonstrated a significant effect for the moderate to very severe levels of the dimension, indicating that the new item is associated with additional disutility.

This study aimed to apply the EQ-5D-5L plus respiratory dimension (EQ-5D-5L+R) to a large primary care COPD population, to explore the response distribution over the levels of the respiratory dimension and its association with patient and COPD disease characteristics.

Methods

COPD Patient Population

The EQ-5D-5L+R was validated using data from the large Birmingham COPD Cohort Study (BCCS). This 3-year longitudinal study was designed to aid the understanding of the natural history of COPD in primary care and to develop a prognostic index for predicting hospital admissions specifically in a primary care COPD population.[17] Participants in the BCCS were recruited from 71 general practices across the West Midlands in the UK. The cohort included 3 patient groups: (1) patients with a diagnosis of COPD in the GP records at the start of the study (n = 1558), (2) patients with no COPD diagnosis who reported respiratory symptoms and had spirometry-confirmed airflow obstruction in a linked case-finding trial (n = 331),[18] and (3) patients reporting respiratory symptoms having normal lung function in the linked case-finding trial (n = 413). The first 2 patient groups were included in the analyses for the current study.

BCCS data were collected at baseline (2012-2014) and follow-up (2015-2016) study assessments. An additional questionnaire including the EQ-5D-5L+R (Reproduced by permission of EuroQol Research Foundation) was sent out to all surviving cohort participants in the spring of 2017. Data collected during this survey in combination with previously collected data were used for the current analysis.

Measurements

To measure the EQ-5D-5L+R, the original questions of the EQ-5D-5L were kept unchanged and printed on 1 page in the regular format.[2] The sixth question about the respiratory dimension[16] was printed on the next page and was formulated as follows:

Breathing problems (eg, shortness of breath, wheezing, coughing, sputum)

☐ I have no breathing problems.
☐ I have slight breathing problems.
☐ I have moderate breathing problems.
☐ I have severe breathing problems.
☐ I have extreme breathing problems.

Relevant patient and disease characteristics that were collected in the same questionnaire included the COPD Assessment Test (CAT),[19] dyspnea (Medical Research Council [MRC] dyspnea scale),[20] current smoking status, and self-reported exacerbations and respiratory-related hospitalizations in the past 12 months. Additional patient-level information on patient and clinical characteristics was obtained from the last available follow-up time point before completion of the EQ-5D-5L+R. Sociodemographic data available were sex, age, ethnicity, employment status, and deprivation score (Index of Multiple Deprivation).[21] Clinically relevant parameters collected at previous time points included medical history based on self-reported diagnosed comorbidities, lung function (forced expiratory volume in 1 second [FEV_1] and FEV_1% predicted), body mass index, disease-specific quality of life (COPD St. George's Respiratory Questionnaire [SGRQ] score),[22] physical activity level (International Physical Activity Questionnaire short form),[23] exercise capacity (sit-to-stand test), and grip strength (handgrip strength test). Table 1 shows all the variables available in the BCCS with their last time point measured.[17]

Statistical Analysis

First, the response distribution of the EQ-5D-5L+R was explored using frequency tables. Second, the mean and SD of demographic and clinical variables for different levels of the respiratory dimension and the other EQ-5D dimensions were calculated. The chi-square test was used to test differences in categorical data, which were summarized by frequencies and percentages. Analysis of variance was used to test differences in means for continuous variables with a normal distribution, while the Kruskal-Wallis test was used to test differences for variables with a skewed distribution. Third, the utility index value for the EQ-5D-5L+R was calculated based on the preliminary tariff for all 6 dimensions estimated in a Dutch pilot study (range, −0.78 to 1.0).[16] This was compared with the utility value for the standard EQ-5D-5L calculated based on the published Dutch tariff (range, −0.45 to 1.0).[24] The correlation between the utility index values and several clinical parameters was assessed using the Spearman correlation coefficient. To investigate known-group validity, the discriminatory ability of the EQ-5D and EQ-5D+R was compared across 5 clinical subgroups: (1) history of exacerbations (<2 vs ≥2), (2) history of severe exacerbations defined as hospital admission for COPD (no vs yes), (3) lung function impairment (Global Initiative for Chronic Obstructive Lung Disease [GOLD] I/II vs GOLD III/IV), (4) level of dyspnea (MRC 1/2 vs 3/4/5), and (5) CAT score (<10 vs ≥10). Cutoff values for these different subgroups were obtained from the GOLD COPD guidelines.[25] Differences in utilities between the clinical subgroups for the EQ-5D-5L and EQ-5D-5L+R were tested using the Mann-Whitney *U* test. Finally, regression models were estimated with either the EQ-5D-5L utility index or the EQ-5D-5L+R utility index as the dependent variable. Seven disease-specific parameters (MRC dyspnea, SGRQ total score, CAT score, history of exacerbations, history of severe exacerbations, handgrip test, and sit-to-stand test) were added as independent variables one at a time to a basic model that included covariates for sex, age, ethnicity, deprivation score, work status, smoking status, history of several diseases, body mass index, and FEV_1% predicted to show the isolated effect of the disease-specific parameters on the utilities. Several types of generalized linear models were explored using different distributions (normal/log/gamma) and assessed based on their goodness of fit (Akaike information criterion, Bayesian information criterion, and root mean squared error). The coefficients of the parameters were compared between the EQ-5D-5L and the EQ-5D-5L+R model. Comparison was done by assessing whether the mean estimates of the coefficients of the EQ-5D-5L+R model were included in the confidence interval (CI) around the coefficients of the EQ-5D-5L model or not. All analyses were conducted using SPSS version 25 (IBM Corp, Armonk, NY).

Results

Response Distribution of the Respiratory Bolt-On

Of the 1889 BCCS participants potentially eligible for this study, 1032 responded to the additional questionnaire sent in 2017 and 1008 provided data for the respiratory bolt-on dimension. The responses on the respiratory bolt-on were distributed as follows: 17% no breathing problems, 37% slight breathing problems, 32% moderate breathing problems, 12% severe breathing problems, and 1.8% extreme breathing problems. The ceiling effect was less

Table 1. Variables available in the British COPD Cohort Study.

Variable	Time of last measurement*	Percent missing
Sex	Baseline	0%
Age	Additional 2017 questionnaire	0%
Ethnicity	Baseline	3.9%
Employment status	Additional 2017 questionnaire	2.3%
Deprivation score	Additional 2017 questionnaire	0.8%
Smoking status	Additional 2017 questionnaire	5.2%
Number of comorbidities	Baseline + 36-month follow-up	0%
Diabetes	Baseline + 36-month follow-up	0%
High blood pressure	Baseline + 36-month follow-up	0%
Coronary heart disease	Baseline + 36-month follow-up	0%
Other heart disease	Baseline + 36-month follow-up	0%
Stroke	Baseline + 36-month follow-up	0%
Heart failure	Baseline + 36-month follow-up	0%
Asthma	Baseline + 36-month follow-up	0%
Depression	Baseline + 36-month follow-up	0%
FEV_1 (litre/min)	36-month follow-up	0.7%
FEV_1% predicted	36-month follow-up	0.7%
Body mass index (BMI)	36-month follow-up	1.9%
MRC score	Additional 2017 questionnaire	0%
SGRQ impact score	Baseline	21%
SGRQ activity score	Baseline	19%
SGRQ symptom score	Baseline	20%
SGRQ total score	Baseline	38%
Total exacerbations in the past year[†]	Additional 2017 questionnaire	5.1%
Respiratory hospitalizations in the past year[‡]	Additional 2017 questionnaire	2.8%
CAT score	Additional 2017 questionnaire	6.3%
IPAQ score	36-month follow-up	7.5%
Sit-to-stand test	36-month follow-up	10.2%
Handgrip test	36-month follow-up	1.3%
EQ-5D-5L+R	Additional 2017 questionnaire	1.2%

CAT indicates COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EQ-5D-5L+R, EQ-5D-5L plus respiratory dimension; FEV_1, forced expiratory volume in 1 second; IPAQ, International Physical Activity Questionnaire; MRC, Medical Research Council; SGRQ, St. George's Respiratory Questionnaire.
*Baseline, 2012-2014; 36-month follow-up, 2015-2016. The additional 2017 questionnaire was administered after the 36-month follow-up.
[†]Self-reported number of periods with worsening of symptoms requiring steroids and/or antibiotics in the past 12 months.
[‡]Self-reported number of hospital admissions for lung problems.

in the EQ-5D-5L+R; 7.2% of the patients reported no problems on all dimensions compared with 15.5% in the EQ-5D-5L.

Association Between Responses on Respiratory Bolt-On and Patient/Disease Characteristics

Table 2 shows the patient and disease characteristics of the study population stratified by response level of the respiratory bolt-on. Worse levels of the respiratory dimension were associated with a higher deprivation score, higher percentage of current smokers, more comorbidities, lower lung function values (FEV_1), less physical activity (International Physical Activity Questionnaire), and worse disease-specific quality of life (SGRQ, CAT) and dyspnea scores. The same pattern was observed for the 5 dimensions of the EQ-5D (Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.006).

Impact of Respiratory Bolt-On on Utilities

The mean utility based on the EQ-5D-5L+R was 0.675 (SD 0.33) with a minimum value of −0.67 and a maximum value of 1.00. For the utility based on the standard EQ-5D-5L, these values were 0.695 (SD 0.29), −0.45, and 1.00, respectively. Figure 1 shows the mean utilities based on the EQ-5D-5L with and without respiratory bolt-on specified by response level of the respiratory bolt-on. Utilities based on the EQ-5D-5L and EQ-5D-5L+R varied substantially for patients with level 4 or 5 of the respiratory bolt-on. For example, for patients with severe breathing problems, the

Table 2. Demographic and comorbidity characteristics by response on the respiratory bolt-on.

Variable	Total population (N = 1008)	No problems (n = 171)	Slight problems (n = 372)	Moderate problems (n = 323)	Severe/extreme problems (n = 142)	*P* value (ANOVA, Kruskal-Wallis, or χ^2)
Males, n (%)	589 (58)	94 (55)	213 (57)	191 (59)	91 (64)	.39
Age, mean (SD)	71.0 (8.7)	68.9 (9.3)	70.5 (8.9)	71.7 (8.0)	72.5 (9.0)	<.001
Ethnicity British/mixed British, n (%)	887 (91)	147 (89)	321 (92)	294 (93)	125 (91)	.38
Smoking status, n (%)						
- Current smoker	180 (19)	23 (14)	56 (16)	69 (23)	32 (24)	<.001
- Ex-smokers	609 (64)	95 (59)	225 (63)	94 (64)	94 (69)	
- Never smokers	167 (18)	42 (26)	76 (21)	40 (13)	9 (7)	
Employment status, in work n (%)	159 (16)	42 (26)	81 (23)	26 (8)	10 (7)	<.001
Deprivation score, mean (SD)*	26.3 (16.3)	23.5 (14.8)	24.4 (15.3)	27.5 (16.6)	31.8 (18.2)	<.001
Number of comorbidities, mean (SD)		1.08 (0.9)	1.12 (0.9)	1.43 (1.0)	1.51(1.0)	<.001
Diabetes, n (%)	180 (19)	24 (14)	55 (16)	69 (24)	32 (26)	.007
High blood pressure, n (%)	490 (51)	72 (43)	154 (44)	191 (62)	73 (57)	<.001
Coronary heart disease, n (%)	156 (17)	14 (9)	46 (14)	69 (24)	27 (22)	<.001
Other heart disease, n (%)	149 (17)	20 (12)	51 (15)	52 (19)	26 (22)	.09
Stroke, n (%)	79 (9)	10 (6)	17 (5)	33 (12)	19 (17)	<.001
Heart failure, n (%)	83 (9)	8 (5)	20 (6)	38 (14)	17 (15)	<.001
Asthma, n (%)	362 (39)	36 (22)	128 (37)	127 (43)	71 (58)	<.001
Depression, n (%)	247 (27)	34 (21)	82 (24)	88 (31)	43 (36)	.009
FEV_1 (litre), mean (SD)	2.0 (0.8)	2.5 (0.7)	2.2 (0.7)	1.8 (0.6)	1.5 (0.7)	<.001
FEV_1 (% predicted, mean (SD)	81 (26)	99 (21)	86 (22)	73 (24)	60 (26)	<.001
GOLD stage, n (%)						
- Mild/moderate	874 (87)	167 (98)	354 (95)	270 (84)	83 (60)	<.001
- Severe/very severe	127 (13)	4 (2)	17 (5)	51 (16)	55 (40)	
Body mass index, mean (SD)	29 (5.9)	28 (5.3)	28 (5.2)	29 (6.4)	31 (6.5)	
SGRQ-C total score, mean (SD)*	32 (22)	12 (11)	22 (14)	42 (18)	59 (20)	<.001
- Impact subscore	19 (20)	5 (8)	11 (13)	28 (19)	44 (24)	<.001
- Activity subscore	39 (30)	13 (17)	28 (23)	53 (25)	74 (23)	<.001
- Symptom subscore	51 (24)	28 (19)	43 (20)	58 (21)	73 (18)	<.001
CAT score, mean (SD)*	16 (9)	6.6 (4.9)	12 (5.7)	21 (6.5)	29 (5.8)	<.001
MRC dyspnea scale, n (%)						
- Grade 1-2	485 (48)	152 (89)	258 (69)	70 (22)	5 (4)	<.001
- Grade 3-5	523 (52)	19 (11)	114 (31)	253 (78)	142 (96)	
Exacerbations in the past 12 months, n (%)						
- None	532 (54)	146 (86)	228 (63)	129 (41)	29 (21)	<.001
- 1 exacerbation	148 (15)	11 (7)	63 (18)	61 (20)	13 (10)	
- 2 exacerbations	121 (12)	5 (3)	41 (11)	57 (18)	18 (13)	
- 3 exacerbations	91 (9)	3 (2)	19 (5)	39 (13)	30 (22)	
- More than 3 exacerbations	88 (9)	4 (2)	10 (3)	27 (9)	47 (34)	
Severe exacerbations in the past 12 months, yes, n (%)	50 (5)	3 (2)	6 (2)	15 (5)	26 (19)	<.001
IPAQ score, n (%)						
- Low activity	328 (35)	41 (24)	102 (29)	124 (42)	61 (54)	<.001

continued on next page

Table 2. Continued

Variable	Total population (N = 1008)	No problems (n = 171)	Slight problems (n = 372)	Moderate problems (n = 323)	Severe/extreme problems (n = 142)	*P* value (ANOVA, Kruskal-Wallis, or χ^2)
- Moderate activity	344 (37)	66 (39)	132 (38)	112 (38)	34 (30)	
- High activity	260 (28)	61 (36)	118 (33)	62 (21)	19 (17)	
Sit-to-stand test, mean (SD)	20 (7.4)	24 (7.4)	21 (7.1)	18 (6.6)	16 (5.7)	<.001
Handgrip test, mean (SD)	28 (11)	30 (11)	29 (11)	27 (11)	26 (12)	.007

ANOVA indicates analysis of variance; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IPAQ, International Physical Activity Questionnaire; MRC, Medical Research Council; SGRQ-C, COPD St. George's Respiratory Questionnaire.
*In contrast to other scores, higher scores for deprivation, SGRQ-C, and CAT indicate a worse score.

utility value was 0.319 based on the EQ-5D-5L and 0.163 based on the EQ-5D-5L+R, a difference of 0.156.

Association Between Respiratory Bolt-On Utilities and Disease Characteristics

Table 3 shows the correlation coefficients between clinical COPD characteristics and the utility values based on the EQ-5D-5L with and without respiratory bolt-on. The utility value based on the EQ-5D-5L+R correlated slightly better with virtually all respiratory-related parameters than the standard EQ-5D-5L.

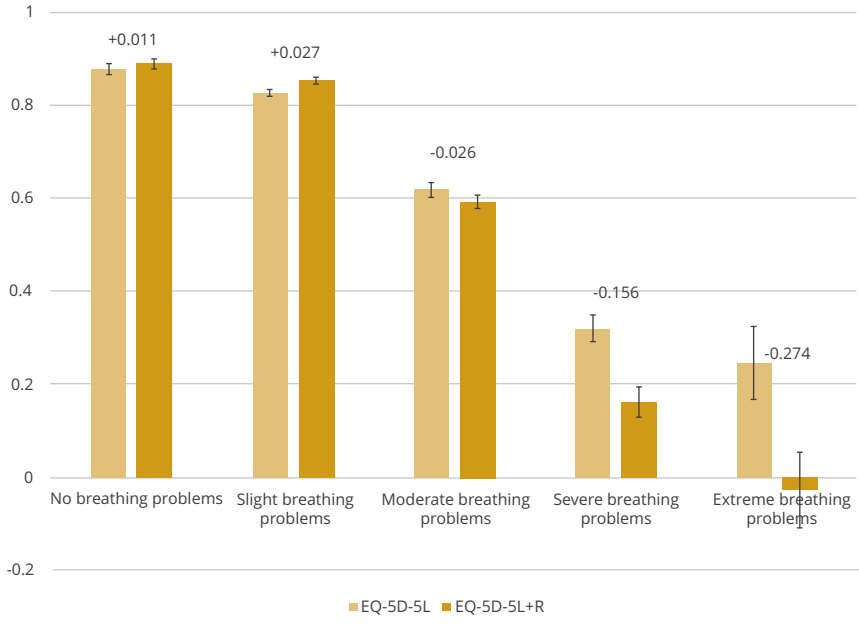
The EQ-5D-5L+R also displayed more marked differences in utility values between clinical subgroups of patients than the EQ-5D-5L (Table 4), with the largest difference (0.078) relating to a history of severe exacerbations. Subgroup results for lung function impairment and MRC specified by 4 and 5 categories, respectively, are shown in the Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.006.

Results of the multivariate regression analysis showed that generalized linear models using a normal distribution had the best fit with the data (Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.006). For the multivariate regression models using the EQ-5D-5L+R utility value as the outcome, the coefficients for the clinical parameters were higher (Table 5), but remained within the CI around the coefficients of the EQ-5D-5L models, with the exception of the CAT score (EQ-5D-5L model, −0.018 [95% CI −0.020 to −0.017]; EQ-5D-5L+R model, −0.021(95% CI −0.023 to −0.019]).

Discussion

This study aimed to validate the EQ-5D-5L+R in a large primary care COPD population. Descriptive analyses showed that COPD disease characteristics worsened with worse levels of the respiratory dimension and the standard 5 EQ-5D dimensions. The utility based on the EQ-5D-5L had a fair correlation ($0.2 < r < 0.5$) with the majority of COPD characteristics and a moderate correlation ($0.5 < r < 0.7$) with SGRQ total score, CAT, and MRC. All but one correlation with the EQ-5D-5L+R utility were slightly higher. There were strong correlations ($r > 0.7$) with the CAT and MRC. Absolute mean differences in utility between clinical subgroups of

Figure 1. Mean (SE) EQ-5D-5L and EQ-5D-5L+R utilities for patients with a different response on the respiratory dimension.



EQ-5D-5L+R indicates EQ-5D-5L plus respiratory dimension; SE, standard error.

Table 3. Correlation coefficients between COPD characteristics and utility values based on the EQ-5D-5L with and without respiratory bolt-on.

Variable	Spearman correlation coefficients	
	EQ-5D-5L utility value without respiratory dimension	EQ-5D-5L utility value with respiratory dimension
FEV_1, litre	.26*	.32*
FEV_1% predicted	.24*	.32*
Body mass index	−.17*	−.17*
SGRQ-C total score	−.63*	−.67*
- Impact subscore	−.58*	−.61*
- Activity subscore	−.63*	−.65*
- Symptom subscore	−.46*	−.51*
Cough (yes/no)	−.35*	−.39*
Phlegm (yes/no)	−.35*	−.39*
Chest tightness (yes/no)	−.45*	−.50*
CAT score	−.69*	−.71*
MRC dyspnea scale	−.69*	−.72*
Exacerbations in the past 12 months	−.32*	−.36*
Respiratory hospitalization in the past 12 months	−.12*	−.14*
IPAQ score, n (%)	.22*	.24*
Sit-to-stand test	.38*	.38*
Handgrip test	.17*	.16*

CAT indicates COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; IPAQ, International Physical Activity Questionnaire; MRC, Medical Research Council; SGRQ-C, COPD St. George's Respiratory Questionnaire.
*$P<.01$.

patients were significantly larger for the EQ-5D-5L+R, ranging from +0.037 for the CAT score to +0.077 for history of severe exacerbations. Although regression coefficients for COPD parameters were higher when using the EQ-5D-5L+R rather than the EQ-5D-5L utility value as outcome, the differences in coefficients were small and not significant for all clinical variables except the CAT score. Because the EQ-5D-5L+R was only measured once, the responsiveness of the instrument to changes in clinical parameters could not be assessed within the current data set. Therefore, it is not yet possible to determine the impact of using the EQ-5D-5L+R on the number of QALYs gained of an intervention or treatment. Comparable with the standard EQ-5D dimensions, utility decrements for the respiratory dimension are highest for the more severe levels. Decrements for moderate, severe, and extreme breathing problems are −0.086, −0.219, and −0.327, respectively.[16] For example, if a treatment improves the symptoms of a respiratory patient from severe to moderate breathing problems, this substantially increases the utility and can result in an additional gain in QALYs compared with the EQ-5D-5L if according to patients the impact of the improvement in symptoms is not fully captured by the other 5 dimensions. Future research is needed on the responsiveness of the EQ-5D-5L+R. In addition, it should be emphasized that the current validation study should be repeated in other patient populations such as asthma and cardiovascular patients before conclusions on the final validity of the respiratory bolt-on could be drawn.

Although important aspects of respiratory diseases might not be included in the descriptive system of the EQ-5D, one could argue that their impact on physical functioning might be captured by the standard EQ-5D dimensions mobility, self-care, and usual activities. A study from Finch et al[26] showed that, when using an item pool based on generic preference-based measures, both in principal component analysis and confirmatory factor analysis, the breathing item of the 15D questionnaire loaded on the construct of physical function, showing a high correlation between a respiratory item and physical functioning. Similar results were found by Engel et al[27] when examining items from generic measures and a capability measure using exploratory factor analysis. These high correlations were not observed in our study, where the item pool included items from condition-specific measures. In the development phase of the respiratory bolt-on, we observed that items on respiratory symptoms were included in separate constructs in the principal component analysis not including EQ-5D physical function dimensions. Nevertheless, adding a respiratory or other dimension to the EQ-5D always increases the risk of overlap with the standard 5 dimensions, which could be an explanation for the limited sensitivity of the EQ-5D-5L+R in the current study. Results of the current study are specific for the respiratory bolt-on and should not be generalized to other bolt-ons.

The larger differences in utility value between the important clinical subgroups and the higher regression coefficients for the EQ-5D-5L+R can mainly be explained by the increased length of the utility scale for the EQ-5D-5L+R utility value (range, −0.78 to 1.0; total length, 1.78) compared with the EQ-5D-5L utility value (range, −0.45 to 1.0; total length, 1.45). This was also observed in a study of Versteegh et al[28] that explored the relevance of condition-specific preference-based measures. In this study, health states based on (simplified) disease-specific questionnaires were valued by the general population resulting in utilities, which were compared with the utilities obtained from the EQ-5D-3L questionnaire. Absolute differences in utility score between levels of severity of the diseases were larger for the EQ-5D than the disease-specific instruments, because the range of the utility scale for the EQ-5D utility was greater.[28] This implies that the absolute differences in utility value between subgroups of patients are strongly affected by the length of the utility scale. An increased length of the utility scale results in larger differences between health states and therefore larger gains in QALYs. In the current study, the assumption that results could be explained by a larger scale was tested by performing an analysis using the normalized score for the EQ-5D-5L and EQ-5D-5L+R (Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.006). Results showed that absolute differences in utility between subgroups of patients became smaller and even nonsignificantly different between the EQ-5D-5L and EQ-5D-5L+R using normalized utilities. This illustrates that the length of the scale has an impact on the results, but the longer range of the EQ-5D-5L+R scale is justified by the additional disutility that breathing problems add.

The results of the study were in line with previous studies. Other studies exploring the correlation between either EQ-5D-3L or EQ-5D-5L and clinical COPD parameters[29–31] found that, in general, the EQ-5D utility had a poor correlation with lung function, that is, FEV_1% predicted (r, 0.14-0.19).[6,7,31] Despite this low correlation, the EQ-5D-3L was found to be able to discriminate between different stages of lung function impairment.[6,31] The correlation with lung function in our study was fair and higher for

Table 4. Differences in utility value in clinical subgroups of patients with COPD (in-between subject analysis).

Subgroup	Mean EQ-5D-5L utility value without respiratory dimension	Mean EQ-5D-5L utility value with respiratory dimension	Difference
History exacerbations:			
<2 exacerbations	.753	.749	
≥2 exacerbations	.573	.515	
Difference	.179*	.235*	.055*
History severe exacerbations:			
No respiratory hospitalization	.708	.692	
1 or more respiratory hospitalizations	.530	.436	
Difference	.179*	.256*	.078*
Lung function impairment:			
GOLD 1/2	.716	.706	
GOLD 3/4	.561	.473	
Difference	.156*	.233*	.077*
Symptoms MRC			
MRC 1/2	.855	.859	
MRC 3/4/5	.547	.504	
Difference	.308*	.355*	.047*
Symptoms CAT			
CAT <10	.874	.881	
CAT ≥10	.630	.600	
Difference	.244*	.281*	.037*

CAT indicates COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council.
*P<.001.

the EQ-5D-5L+R utility. Correlation between MRC score and utility has been reported to be around 0.5 in previous studies,[6,7,29,30] compared with approximately 0.6 in this study. In line with this analysis, the CAT score was reported to have a moderate-to-strong correlation with utility values in previous studies.[7,29,30] Other studies exploring the performance of bolt-on dimensions for the EQ-5D also found larger differences in utility between subgroups of patients for the EQ-5D with additional

Table 5. Multivariate analysis showing the isolated effect of 7 clinical parameters on utilities (generalized linear model with normal distribution).

Type of analysis	EQ-5D-5L utility value without respiratory dimension	EQ-5D-5L utility value with respiratory dimension
	Coefficient clinical Parameter (95% CI)	Coefficient clinical Parameter (95% CI)
1. Basic model* + MRC (≥3 vs <3)	−.252 (−.288 to −.215)	−.274 (−.315 to −.232)
2. Basic model + SGRQ total score (per point)	−.007 (−.008 to −.006)	−.008 (−.009 to −.007)
3. Basic model + CAT score (per point)	−.018 (−.020 to −.017)	−.021 (−.023 to −.019)
4. Basic model + any exacerbation (yes vs no)	−.082 (−.120 to −.045))	−.111 (−.153 to −.069)
5. Basic model + severe exacerbation (yes vs no)	−.143 (−.222 to −.064)	−.206 (−.294 to −.117)
6. Basic model + handgrip test	.005 (.003-.007)	.005 (.003-.008)
7. Basic model + sit-to-stand test	.009 (.007-.012)	.010 (.007-.013)

BMI indicates body mass index; CAT, COPD Assessment Test; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MRC, Medical Research Council; SGRQ, St. George's Respiratory Questionnaire.
*The basic model included sex, age, ethnicity, deprivation score, work status, smoking status, history of several diseases, BMI and FEV_1% predicted. A check for multicollinearity in the basic and other models showed that all variance inflation factors (VIPs) were well below 10.

dimension.[32,33] A study by de Graaf et al[32] reported slightly larger differences in utility with the EQ-5D-5L plus cognitive dimension than the standard EQ-5D-5L in patients with stroke with different levels of modified Rankin Scale and patients with and without a decrease in health or daily activities. Luo et al[33] found that absolute mean differences in utility values between mutually exclusive subgroups of patients with different vision problems were larger for the EQ-5D-3L plus vision bolt-on than the standard EQ-5D-3L.

The strengths of this study were that the BCCS study collected a wide range of patient characteristics, physiological measures, and clinical outcomes from a large, well-characterized primary care COPD population.[17] A limitation of the study was that the EQ-5D-5L+R was measured during a follow-up questionnaire, while some of the clinical parameters were obtained from earlier measurements. Nevertheless, with the exception of a deterioration in grip strength and a slight improvement in lung function, the majority of clinical parameters remained stable during the 3-year study period, thus minimizing the impact of using data from different time points. In addition, the design of this study would have been most optimal when half of the patients would have completed the EQ-5D-5L+R and half the regular EQ-5D-5L, because self-reporting on a dimension of the EQ-5D may depend on the response on the other dimensions. Another limitation was that English patients completed the descriptive system, whereas EQ-5D-5L+R utilities could only be calculated based on a Dutch tariff. An English tariff for the EQ-5D-5L+R is not available.

Conclusion

This study showed that the addition of a respiratory bolt-on to the EQ-5D-5L led to a modest improvement in performance of the utility instrument. Although differences in utilities between clinical subgroups of patients were larger with the EQ-5D-5L+R than the EQ-5D-5L, clinical COPD variables correlated only slightly better with EQ-5L-5D+R utilities. Adding a respiratory dimension to the EQ-5D might improve its responsiveness in certain diseases. Nevertheless, the main disadvantage is that it reduces the comparability of the outcomes of the EQ-5D across diseases, which is currently one of the strengths of the instrument. This study showed that comparability would be traded off against a modest improvement in the absolute difference in utility. The final impact on the QALY gained, however, would depend on the time horizon used in the evaluation. On the basis of our findings, we would recommend future intervention studies to calculate both the standard QALYs to allow comparison with other diseases and the "bolt-on" QALYs to measure the impact of adding a symptom- or disease-specific dimension on the cost-effectiveness ratio.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.05.006.

Article and Author Information

Accepted for Publication: May 10, 2021

Published Online: August 4, 2021

doi: https://doi.org/10.1016/j.jval.2021.05.006

Author Affiliations: Institute for Medical Technology Assessment (IMTA), Erasmus University Rotterdam, Rotterdam, The Netherlands (Hoogendoorn, Versteegh, Rutten-van Mölken); Health Economics Unit, University of Birmingham, Birmingham, England, UK (Jowett); Institute of Applied Health Research, University of Birmingham, Birmingham, England, UK (Dickens, Jordan, Enocson, Adab); Erasmus School of Health Policy and Management (ESHPM), Erasmus University Rotterdam, Rotterdam, The Netherlands (Rutten-van Mölken).

Correspondence: Martine Hoogendoorn, PhD, Institute for Medical Technology Assessment, Erasmus University Rotterdam, PO Box 1738, 3000 DR, Rotterdam, The Netherlands. Email: hoogendoorn@imta.eur.nl

Author Contributions: *Concept and design*: Hoogendoorn, Jordan, Rutten-van Mölken
Acquisition of data: Dickens, Jordan, Enocson, Adab
Analysis and interpretation of data: Hoogendoorn, Jowett, Jordan, Versteegh, Rutten-van Mölken
Drafting of the manuscript: Hoogendoorn, Jowett, Dickens, Adab, Versteegh, Rutten-van Mölken
Critical revision of the paper for important intellectual content: Hoogendoorn, Jowett, Dickens, Jordan, Versteegh, Rutten-van Mölken
Statistical analysis: Hoogendoorn, Rutten-van Mölken
Provision of study materials or patients: Dickens, Jordan, Enocson, Adab
Obtaining funding: Hoogendoorn, Jordan, Adab, Rutten-van Mölken
Administrative, technical, or logistic support: Enocson
Supervision: Rutten-van Mölken

Conflict of Interest Disclosures: Dr Hoogendoorn reported receiving grants and in kind support from the EuroQol group for the development of the respiratory bolt-on during the conduct of this study; and an unrestricted grant for the development of the respiratory bolt-on from Boehringer Ingelheim during the conduct of the study. Dr Jordan reported receiving grants from the National Institute for Health Research during the conduct of the study; and personal fees from Boehringer Ingelheim outside the submitted work. Dr Adab reported receiving grants from the National Institute for Health Research Program Grants for Applied Research during the conduct of the study; grants from the National Institute for Health Research and the Medical Research Council outside the submitted work; and chairing the National Institute for Health Research Public Health Research Funding Committee during the conduct of this study. Dr Versteegh reported receiving grants and nonfinancial support from the EuroQoL research foundation as well as being a member during the conduct of the study, and grants from Boehringer Ingelheim during the conduct of the study. Dr Rutten-van Mölken reported receiving in kind support from the EuroQol group for the development of the respiratory bolt-on followed by a grant from the EuroQol group for the current validation study; and an unrestricted grant for the development of the respiratory bolt-on during the conduct of the study. No other disclosures were reported.

Funding/Support: This work was supported by grant 20190850 from the EuroQol Foundation. The paper presents independent research using the Birmingham COPD Cohort Study which is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0109-10061). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The Birmingham COPD Cohort study is part of The Birmingham Lung Improvement StudieS – BLISS.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgment: The authors thank Tosin Lambe for his help in designing the study. The authors would also like to acknowledge the patients that participated in the Birmingham COPD Cohort study, as well as the support of their general practices.

REFERENCES

1. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53–72.
2. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727–1736.
3. Pickard AS, Wilke C, Jung E, Patel S, Stavem K, Lee TA. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. *Respir Med*. 2008;102(4):519–536.

4. Moayeri F, Hsueh YS, Clarke P, Hua X, Dunt D. Health state utility value in chronic obstructive pulmonary disease (COPD); the challenge of heterogeneity: a systematic review and meta-analysis. *COPD*. 2016;13(3):380–398.
5. Tarride JE, Burke N, Bischof M, et al. A review of health utilities across conditions common inpaediatric and adult populations. *Health Qual Life Outcomes*. 2010;8:12.
6. Lin FJ, Pickard AS, Krishnan JA, et al. Measuring health-related quality of life in chronic obstructive pulmonary disease: properties of the EQ-5D-5L and PROMIS-43 short form. *BMC Med Res Methodol*. 2014;14:78.
7. Nolan CM, Longworth L, Lord J, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax*. 2016;71(6):493–500.
8. Pickard AS, Yang Y, Lee TA. Comparison of health-related quality of life measures in chronic obstructive pulmonary disease. *Health Qual Life Outcomes*. 2011;9:26.
9. Petrillo J, van Nooten F, Jones P, Rutten-van Molken M. Utility estimation in chronic obstructive pulmonary disease: a preference for change? *Pharmacoeconomics*. 2011;29(11):917–932.
10. Sullivan PW, Ghushchyan VH, Campbell JD, Globe G, Bender B, Magid DJ. Measurement of utility in asthma: evidence indicating that generic instruments may miss clinically important changes. *Qual Life Res*. 2016;25(12):3017–3026.
11. Gillespie P, O'Shea E, Casey D, et al. PRINCE study team. The cost-effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: the PRINCE cluster randomised trial. *BMJ Open*. 2013;3(11):e003479.
12. Hoogendoorn M, van Wetering CR, Schols AM. Rutten-van Mölken MPMH. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? *Eur Respir J*. 2010;35(1):79–87.
13. Brown C, Austin G, McGowan J, Chakravorty I. Is the EuroQol general health status questionnaire sensitive to the impact of pulmonary rehabilitation in COPD? *Am J Respir Crit Care Med*. 2009;179:A3852.
14. van den Boom G, Rutten-van Mölken MP, Molema J, Tirimanna PR, van Weel C, van Schayck CP. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. *Am J Respir Crit Care Med*. 2001;164(11):2057–2066.
15. Briggs AH, Glick HA, Lozano-Ortega G, et al. TOwards & Revolution in COPD Health (TORCH) investigators. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. *Eur Respir J*. 2010;35(3):532–539.
16. Hoogendoorn M, Oppe M, Boland MRS, Goossens LMA, Stolk EA, Rutten-van Mölken MPMH. Exploring the impact of adding a respiratory dimension to the EQ-5D-5L. *Med Decis Making*. 2019;39(4):393–404.
17. Adab P, Fitzmaurice DA, Dickens AP, et al. Cohort profile: the Birmingham chronic obstructive pulmonary disease (COPD) cohort study. *Int J Epidemiol*. 2017;46(1):23.
18. Jordan RE, Adab P, Sitch A, et al. Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (TargetCOPD): a cluster-randomised controlled trial. *Lancet Respir Med*. 2016;4(9):720–730.
19. Jones PW, Hardin G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648–654.
20. Fletcher CM. The clinical diagnosis of pulmonary emphysema; an experimental study. *Proc R Soc Med*. 1952;45(9):577–584.
21. Department for Communities and Local Government. *The English Indices of Deprivation 2010*. London, United Kingdom: Department for Communities and Local Government; 2011.
22. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George respiratory questionnaire. *Chest*. 2007;132(2):456–463.
23. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381–1395.
24. Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Health*. 2016;19(4):343–352.
25. Global Strategy for Prevention, Diagnosis and Management of COPD [Report: 2020]. www.goldcopd.com. Accessed April 6, 2020.
26. Finch AP, Brazier JE, Mukuria C, Bjorner JB. An exploratory study on using principal-component analysis and confirmatory factor analysis to identify bolt-on dimensions: the EQ-5D case study. *Value Health*. 2017;20(10):1362–1375.
27. Engel L, Mortimer D, Bryan S, Lear SA, Whitehurst DGT. An investigation of the overlap between the ICECAP-A and five preference-based health-related quality of life instruments. *Pharmacoeconomics*. 2017;35(7):741–753.
28. Versteegh MM, Leunis A. Uyl-de Groot CA, Stolk EA. Condition-specific preference-based measures: benefit or burden? *Value Health*. 2012;15(3):504–513.
29. Esquinas C, Ramon MA, Nuñez A, et al. Correlation between disease severity factors and EQ-5D utilities in chronic obstructive pulmonary disease. *Qual Life Res*. 2020;29(3):607–617.
30. Szentes BL, Schwarzkopf L, Kirsch F, Schramm A, Leidl R. Measuring quality of life in COPD patients: comparing disease-specific supplements to the EQ-5D-5L. *Expert Rev Pharmacoecon Outcomes Res*. 2020;20(5):523–529.
31. Rutten-van Mölken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? *Chest*. 2006;130(4):1117–1128.
32. de Graaf JA, Kuijpers M, Visser-Meily J, Kappelle LJ, Post M. Validity of an enhanced EQ-5D-5L measure with an added cognitive dimension in patients with stroke. *Clin Rehabil*. 2020;34(4):545–550.
33. Luo N, Wang X, Ang M, et al. A vision "bolt-on" item could increase the discriminatory power of the EQ-5D index score. *Value Health*. 2015;18(8):1037–1042.