

The added effect of comorbidity on health-related quality of life in patients with asthma

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Abstract

Purpose To examine the effect of comorbidities on health-related quality of life (HRQoL) and their interaction with asthma control.

Methods In a random sample of adults with asthma, we measured generic (EQ5D) and disease-specific (AQ5D) utility scores. Asthma symptom control was determined using the 2014 Global Initiative for Asthma Management Strategy. Comorbidity scores were calculated using a validated questionnaire. We used two-part regression models to measure the adjusted difference in utility across levels of symptom control and comorbidity scores and to examine the relative role of symptom control and comorbidity in explaining the variation in HRQoL.

Results A total of 2,299 observations from 460 adult patients (mean age 52 years, 67 % women) were included.

Compared to controlled asthma, uncontrolled asthma was associated with −0.018 reduction (95 % CI −0.028, −0.009) in EQ5D and −0.076 reduction (95 % CI −0.115, −0.052) in AQ5D utilities. An increase by one standard deviation in comorbidity score relative to the mean was associated with a change of −0.029 (95 % CI −0.043, −0.016) in EQ5D and −0.010 (95 % CI −0.020, −0.004) in AQLQ utilities. The impact of comorbidity was greater than asthma symptom control in explaining EQ5D variance (12 vs. 1 %) but smaller in explaining AQ5D variance (3 vs. 12 %).

Conclusions Generic and disease-specific HRQoL instruments differentially capture the impact of symptom control and comorbidity in asthma. The selection of HRQoL instruments for asthma studies should depend on the prevalence of comorbidity in the target population and the impact of interventions on asthma control and comorbidity.

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Introduction

Asthma is a highly prevalent chronic respiratory disease [1] that has a significant impact on patients' health-related quality of life (HRQoL) [2]. As asthma is generally an incurable yet controllable condition, current evidence-based asthma management guidelines advocate achieving and maintaining asthma control, thereby decreasing the risk of adverse outcomes, most notably asthma exacerbations [3, 4]. Compared to uncontrolled asthma, controlled asthma is associated with fewer exacerbations and a better quality of life [3, 4].

Both generic (e.g., the EuroQol-5d (EQ5D) [5]) and disease-specific instruments (e.g., the Asthma Quality of Life Questionnaire (AQLQ) [6]) can be used to evaluate HRQoL in asthma. The EQ5D generates a single health state utility value (utility) to represent an individual's health state on a scale anchored at 0 for death and 1 for perfect health. Information collected from the AQLQ can be converted into a utility using a validated scoring algorithm [7]. Utility reflects a societal preferences-based valuation of quality of life and allows for the calculation of quality-adjusted life years, an essential metric for cost-effectiveness analyses [8].

Given the emphasis in asthma guidelines on achieving asthma control, reliable estimates of the impact of asthma control on utility have attracted researchers' attention [9–12]. Meanwhile, utility in asthma is also influenced by the presence of comorbid disease. In this context, comorbidity refers to either coexisting or interacting condition(s) with the primary condition. Comorbidity is generally more prevalent in patients with asthma than in the general population [13–15] and has been shown to be associated with lower HRQoL [16–18] as well as with suboptimal control of asthma [19]. The interaction between asthma control and comorbidity in influencing utility, however, is not well studied. Interventions and strategies aimed at reducing the burden of asthma can vary in scope, ranging from active treatments targeted at reducing asthma symptoms (e.g., inhaled reliever or controller medications) to broader-scope approaches, such as smoking cessation or weight reduction, that can improve not only asthma-related outcomes but the overall health [20–24]. It can be argued that for the targeted therapies, the quantification of the impact on HRQoL requires sensitive instruments focusing on changes in asthma symptoms, whereas for the latter, generic HRQoL instruments are more appropriate as they capture the broader and multifaceted impact of the intervention. Establishing cost-effectiveness profiles for such interventions requires a valid utility measure which can distinguish changes in both asthma control and its associated comorbidities. Such evidence is currently lacking because most quality-of-life studies in asthma do not consider comorbidities [9–12] and the few studies on comorbidities disregard asthma symptom control [16–18].

Using a longitudinal random sample of adults with asthma, we explored the performance of both generic and asthma-specific HRQoL instruments to simultaneously distinguish between different levels of asthma control and changes in comorbidity status. Our primary objective was to evaluate the marginal changes in utility associated with different magnitudes of comorbidity, as well as different levels of asthma symptom control. Our secondary objective was to explore the relative influence of asthma symptom

control and comorbidities on utility obtained either from generic or disease-specific instruments.

Methods

Study design and sample

Data were collected from a sample of adult asthmatics enrolled in a prospective, 1-year cohort study (University of British Columbia Human Ethics Board H10-01542). Details about the study have been described in a previous publication [25]. Between December 2010 and August 2012, 618 subjects with a self-reported physician diagnosis of asthma were recruited via random digit dialing from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (2011 population of 603,502 and 179,839, respectively [26]). Subjects who had other lung or airway diseases, were pregnant or planning to become pregnant in the next 12 months, reported a 10 pack-year smoking history or greater, or were planning to leave the study area during the follow-up period were not eligible for enrollment. Eligible subjects were followed for 1 year, with a baseline visit and four follow-up visits at 3-month intervals. The current analysis is restricted to adults 19 years and older. Patients with enough information to assess asthma symptom control, comorbidity, and quality of life for at least one visit were included in the final data set.

Outcome and exposure variables

Quality of life

At all five visits, HRQoL was measured using both a generic preference-based instrument (EuroQol-5d (EQ5D), 3-level version [27]) and an asthma-specific instrument (Asthma-related Quality of Life Questionnaire—short version (mini-AQLQ) [28]). Since Canadian valuation of utility is only available for EQ5D [29], both EQ5D and AQLQ responses were converted into utility values using UK tariffs [7, 30]. Specifically, AQLQ responses were first reduced from seven to five levels [31] which were then used to calculate EQ5D utilities, as described by Yang et al. [7].

Asthma symptom control

For each visit, patients were classified as having “controlled,” “partially controlled,” or “uncontrolled” asthma which was assessed using the 2014 Global Initiative for Asthma (GINA) Management Strategy [20]. This classification is based on patients' self-report on four asthma

symptom domains (daytime symptoms, limitation in activities, nocturnal symptoms, and need for reliever/rescue treatment) with a recall period of 3 months.

Comorbidity

Comorbidity status was measured at the final visit via the Self-administered Comorbidity Questionnaire (SCQ) with a recall period of 12 months [32]. The SCQ is a validated instrument that has been shown to have a moderately strong correlation with the Charlson index, a popular chart review-based comorbidity instrument [32], and to be equivalent to the Charlson index at predicting physical functional capacity and HRQoL impairments [33]. The SCQ includes 13 common comorbid chronic conditions [32], but this study purposefully excluded lung disorders from the assessment given that all individuals had asthma but no other respiratory diseases. Each reported condition can receive a maximum of three points (presence of disease, whether receiving treatments, and any functional limitation). The maximum overall score was therefore 36, with higher scores indicating greater comorbidity.

Covariates

Additional sociodemographic information was collected at baseline, including age, sex, ethnicity, education (categorized as postsecondary education vs. less than postsecondary education), annual household income (categorized as above vs. below \$60,000CAD), as well as baseline intensity of treatment as measured by the proportions of days covered (PDC) by any asthma controller medication in the past 12 months [34].

Statistical analysis

All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, United States). The criterion for statistical significance was a two-tailed p value of <0.05 . Descriptive statistics were calculated, and comparisons were made using Pearson Chi-square tests for categorical variables and Kruskal–Wallis tests for utility scores. An unadjusted analysis assessed the univariate association between utilities, HRQoL subdomains, symptom control, and comorbidity using Spearman's rho correlation (Online Resource 1).

The unit of observation in this study was a study visit with concomitant assessment of utility and symptom control; thus, an individual could contribute up to five observations. Comorbidity scores, measured at the last visit, were considered to be the same across all visits for an individual given that the recall period was the past 12 months and that in general the chronic comorbid

conditions included in SCQ are unlikely to significantly change over the 1-year study period.

The influence of symptom control and comorbidity on HRQoL was evaluated using regression methods with utility scores as the dependent variable and symptom control (entered as two dummy variables representing partially controlled and uncontrolled asthma, with the reference being controlled asthma), comorbidity score, and potential confounding variables as independent variables. Since the distributions of both EQ5D and AQ5D utility scores were heavily skewed to the left as well as demonstrating a ceiling effect [a considerable proportion of individuals reporting a utility score of one (perfect utility)], inference based on ordinary least square (OLS) methods could be invalid. We therefore fitted a two-part regression model with both a logistic component and an OLS component [35]. In the logistic component, we modeled the probability of reporting a utility of less than one (imperfect utility) as a function of covariates. Then, in the OLS component, we modeled the effects of covariates on utility in the subset of individuals who reported imperfect utility. To meet the assumptions of normal distribution and constant variance for regression residuals, we used logit-transformed utility scores as the dependent variable for the OLS component. For both components, we also adjusted for potential confounding variables which included age, sex, ethnicity, household income, education, intensity of asthma treatment at baseline, as well as an indicator for the study visit number. Generalized linear models with generalized estimating equations were used to fit both the logistic and logit-transformed OLS components to account for the clustering of observations within individuals [36]. Estimates from the two parts were combined to calculate the overall effect of the variables of interest [37]. Inference of association was based on parametric bootstrapping with 50 replications.

Primary objective: relationship between symptom control, comorbidity, and quality of life

We combined the regression coefficients from the logistic and logit-transformed OLS components to estimate the marginal effect of variables of interest on utilities [37]. In this context, the marginal effect of a variable is the change in the expected utility that occurs by changing the level of that variable, while keeping other variables constant. Assuming that we have controlled for all covariates that could potentially confound the relationship between the variable of interest and utility scores, such marginal effects can be interpreted causally [37]. We calculated the following marginal effects: (1) the change in expected utility scores across different levels of asthma symptom control; (2) the change in expected utility scores by increasing the comorbidity score

from zero to the sample mean and from the sample mean to one SD above the mean; and (3) the expected utility score at the whole range of comorbidity score (0–36), overall and within different levels of symptom control.

Secondary objectives: strength of association of symptom control and comorbidity with quality of life

This was assessed using the coefficient of determination (R^2), i.e., the proportion of variation in utility explained by the model with particular predictors. We first built a reference two-part model with symptom control, comorbidity, and potential confounders, as described earlier. We tested the first-order interaction between symptom control and comorbidity, but it did not further improve the goodness of the fit and thus was not included in the reference model. We then measured the change in R^2 to determine the influence of predictors when they were removed from the reference model (the more influential predictor results in the greater decrease in R^2). Using a similar framework, we examined the impact of individual comorbid conditions on HRQoL. The model for this analysis included covariates, symptom control, and all 12 comorbid conditions from the SCQ instrument as separate variables (each condition with a maximal of three points). Again, the most influential comorbid condition was the one that resulted in the greatest decrease in R^2 when it was removed from the model.

Results

Sample characteristics

The sample included 460 patients who met the inclusion and exclusion criteria with 2299 observations during the 1-year follow-up period. Three observations were removed because data on AQ5D scores were missing. Table 1 shows the characteristics of the final sample. The mean age at baseline was 52 years [standard deviation (SD) = 15], 67 % were women and 83 % were Caucasian. At baseline, 25, 39, and 36 % of the patients had controlled, partially controlled, and uncontrolled asthma, respectively. The majority of patients (70 %) reported having at least one chronic comorbid condition, with the average comorbidity score being 3.15 (SD = 3.61). The average baseline EQ5D and AQ5D utilities values were 0.91 (SD = 0.12) and 0.88 (SD = 0.12), respectively. There were 1283 (56 %) and 250 (11 %) observations with patients reporting perfect EQ5D and AQ5D utility scores, respectively, suggesting a ceiling effect especially with the EQ5D. The distribution of levels of symptom control and the mean utilities did not differ significantly across study visits (p values: symptom

control 0.22, EQ5D 0.06, AQ5D 0.92) (Table 2, Online Resource 2).

Univariate association of symptom control and comorbidity with quality of life

Distribution of utilities across levels of symptom control is shown in Fig. 1. Both asthma control (Spearman's rho correlation = -0.22 for EQ5D, $p < 0.001$; -0.44 for AQ5D, $p < 0.001$) and comorbidity (-0.40 for EQ5D, $p < 0.001$; -0.13 for AQ5D, $p < 0.001$) were inversely correlated with utilities (Online Resource 1).

Primary outcome: marginal effects of symptom control and comorbidity on quality of life

Compared with controlled asthma, uncontrolled asthma was associated with statistically significantly lower EQ5D [difference -0.018 (95 % credible interval (CI) -0.028 , -0.009)] and AQ5D [difference -0.076 (95 % CI -0.115 , -0.052)] utilities. Similarly, partially controlled asthma was associated with lower EQ5D [difference -0.012 (95 % CI -0.022 , -0.005)] and AQ5D [difference -0.029 (95 % CI -0.044 , -0.020)] utilities compared with controlled asthma (Table 3). Despite the statistical significance, however, none of the differences in EQ5D utility met the accepted minimally important differences (MID 0.074) [38].

The marginal effects of comorbidity on utility are shown in Fig. 2, showing a monotonic inverse relationship across the entire range of comorbidity scores. Increasing comorbidity scores from zero to the sample mean (3.25) was associated with both significantly lower EQ5D [difference -0.029 (95 % CI -0.043 , -0.016)] and AQ5D [difference -0.010 (95 % CI -0.020 , -0.004)] utilities. Further, an increase by one SD (3.61) above the mean was associated with significant reductions in EQ5D by -0.045 (95 % CI -0.059 , -0.031), and in AQ5D by -0.012 (95 % CI -0.024 , -0.006). The marginal effects of comorbidity stratified across levels of symptom control are displayed in Fig. 3 (95 % CIs were not provided for clarity of the figure). Across all levels of symptom control, an increase in comorbidity scores resulted in a continuous decrease in both EQ5D and AQ5D utilities. The magnitude of comorbidity-associated utility loss in EQ5D was very similar between different levels of symptom control, whereas it varied considerably as when measured using the AQ5D.

Secondary outcomes: strength of association of symptom control and comorbidity with quality of life

Table 4 shows the strength of the association between the independent variables and utilities. A model which only

Table 1 Characteristics of the study sample

	Study population (<i>N</i> = 460)
Baseline age, mean (SD)	52.01 (14.83)
Gender, % female	67 %
Ethnicity	
Caucasian	83 %
Asian	13 %
Other	4 %
Annual household income >\$60,000CAD	73 %
Postsecondary education and above	76 %
Baseline treatment intensity	
PDC < 50 %	45 %
50 % ≤ PDC < 80 %	11 %
PDC ≥ 80 %	44 %
Baseline symptom control	
Controlled	25 %
Partially controlled	39 %
Uncontrolled	36 %
Baseline EQ5D, mean (SD)	0.91 (0.12)
Baseline VAS, mean (SD)	0.74 (0.17)
Baseline AQ5D, mean (SD)	0.88 (0.12)
Overall SCQ comorbidity scores, mean (SD)	3.25 (3.61)
Reported ≥1 comorbidities in the past year	70 %
Heart diseases	7 %
Hypertension	18 %
Diabetes	7 %
Ulcer or stomach diseases	17 %
Kidney disease	2 %
Liver disease	1 %
Anemia or other blood disease	10 %
Cancer	2 %
Depression	15 %
Osteoarthritis, degenerative arthritis	28 %
Backpain	39 %
Rheumatoid arthritis	4 %

CAD Canadian dollars, *N* number counts, *PDC* proportions of days covered, *SD* standard deviation

included covariates explained 11.0 and 10.2 % of variation in EQ5D and AQ5D utilities, respectively. The full model (covariates + comorbidity + symptom control) explained 24.7 and 26.4 % of the variation in EQ5D and AQ5D utilities, respectively. Removal of symptom control from the full model decreased the explained variation in utility scores by 0.7 % for EQ5D but by 11.6 % for AQ5D, indicating the much larger sensitivity of AQ5D than EQ5D to asthma symptom control. Removal of comorbidity from the full model reduced the explained variation by 12.0 % in EQ5D and 2.9 % in AQ5D utilities, this time showing the higher sensitivity of EQ5D than AQ5D to the presence of comorbid conditions. The interaction of symptom control and comorbidity did not increase the explained variation in both utilities.

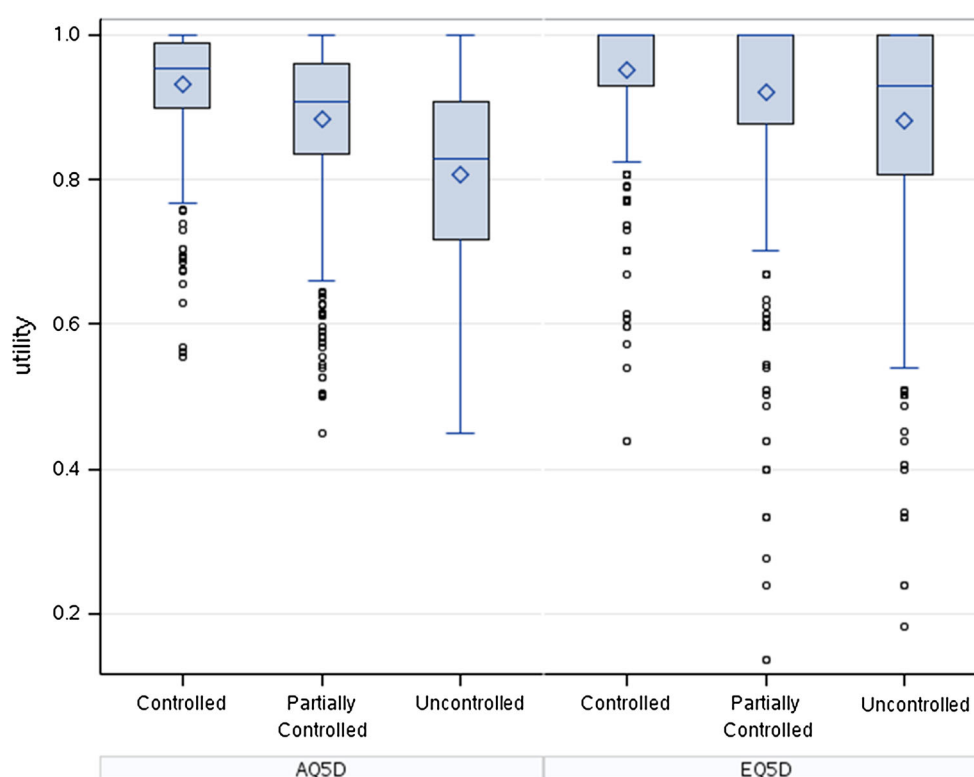
Among the twelve comorbid conditions included, depression was the most influential comorbidity on both EQ5D and AQ5D utilities; removal of depression reduced R^2 by 6.1 % for EQ5D and by 1.7 % for AQ5D.

Discussion

We evaluated popular generic and disease-specific HRQoL measures in terms of their association with changes in symptom control and comorbidity in asthma. Statistically, both EQ5D and AQ5D utilities discriminated changes in comorbidity and across all three levels of symptom control. The full regression model explained a similar proportion of variability in utility estimated from both generic and

Table 2 Utility scores and asthma symptom control across visits

	Overall	Visit					<i>p</i> value
		1	2	3	4	5	
EQ5D (<i>N</i> = 2299)							
Mean	0.92	0.91	0.91	0.91	0.92	0.92	0.0571 ^a
SD	0.13	0.12	0.13	0.13	0.12	0.13	
AQ5D (<i>N</i> = 2296)							
Mean	0.87	0.88	0.87	0.87	0.87	0.87	0.917 ^a
SD	0.12	0.12	0.11	0.12	0.12	0.11	
Asthma control (<i>N</i> = 2299)							
Controlled	28.0 %	25.2 %	27.4 %	29.4 %	27.8 %	30.3 %	0.2243 ^b
Partially controlled	39.4 %	39.1 %	42.4 %	41.1 %	36.1 %	38.1 %	
Uncontrolled	32.6 %	35.7 %	30.2 %	29.6 %	36.1 %	31.6 %	

N number counts^a Kruskal–Wallis test for between-group versus within-group differences in the means^b Pearson Chi-square for between-group versus within-group differences in the proportions**Fig. 1** Distribution of health utilities by asthma symptom control. Median values are indicated by *lines*, means are indicated by *hollow diamonds*, and outliers are indicated by *hollow circles*

asthma-specific instruments (24.7 % of variation in EQ5D and 26.4 % in AQ5D); nevertheless, the share of symptom control and comorbidity was different between the two instruments: EQ5D was much more sensitive to comorbidities than symptom control (12.0 vs. 0.7 % of variation), whereas AQ5D was much more sensitive to asthma symptom control (11.6 vs. 2.9 %). As such, we estimated that changes in asthma symptom control had a larger marginal impact on AQ5D than on EQ5D utilities.

Conversely, increase in comorbidity burden leads to a larger reduction in EQ5D than AQ5D utilities, both in general and across different levels of symptom control.

This study can be viewed as an extension of previous studies on the validity of generic and disease-specific HRQoL measures in distinguishing across levels of control in asthma [9–12]. We extended the approaches used in these studies to evaluate the sensitivity of these measures in detecting the additional effect of comorbidities on HRQoL.

Table 3 Adjusted effects of symptom control on utility: results from the two-part regression

Symptom control	Adjusted change in utility scores					
	EQ5D			AQ5D		
	Estimate	95 % CI	<i>p</i> value	Estimate	95 % CI	<i>p</i> value
Partially controlled versus controlled	−0.012	−0.022, −0.005	<0.0001	−0.029	−0.044, −0.020	<0.0001
Uncontrolled versus controlled	−0.018	−0.028, −0.009	<0.0001	−0.076	−0.115, −0.052	<0.0001
Uncontrolled versus partially controlled	−0.006	−0.009, −0.003	<0.0001	−0.047	−0.071, −0.032	<0.0001

The two-part model was adjusted for comorbidity, baseline age, sex, ethnicity, annual household income, baseline education level, baseline intensity of asthma controller therapies, and the indicator for the corresponding study visit

CI credible interval

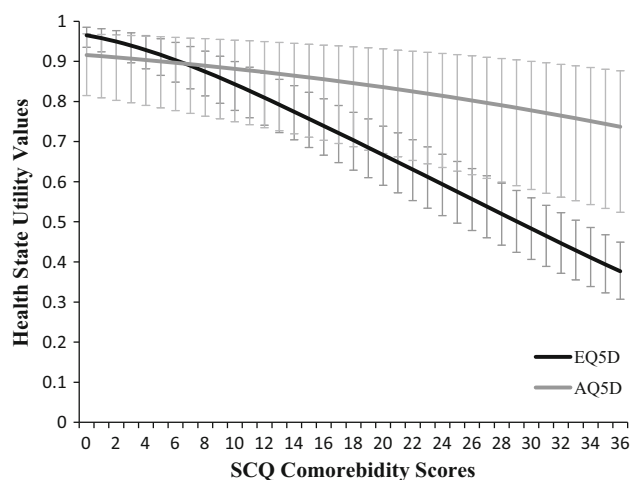


Fig. 2 Expected utility values by comorbidity. Adjusted means and 95 % CI for two utility measures: EQ5D and AQ5D. The lines denote the predicted mean scores. The bars show 95 % CI

Given the high prevalence and significant impact of comorbidity in patients with asthma (as demonstrated in our sample), our findings indicate that ignoring comorbidity may risk overestimating the benefit of asthma treatments if comorbidity affects the treatment effects. Additionally, the significance of major secondary conditions, e.g., depression, can be easily underestimated in assessing the humanistic burden of asthma if the focus is solely based on asthma symptoms. Our findings are in line with the few studies that focused on the general impact of comorbidities on HRQoL in asthma [16, 39] in that comorbidities are consistently found to greatly affect utilities measured by the generic instrument, whereas their influences on disease-specific utilities are much smaller. However, the previous two studies did not consider the effect of the primary disease (asthma symptoms). Of note, the association between different levels of asthma control and EQ5D can be easily influenced by various factors such as the assessment

Fig. 3 Expected utility values by comorbidity and asthma symptom control. The lines denote adjusted means for two utility measures, EQ5D and AQ5D, in symptomatically controlled, partially controlled, uncontrolled asthma

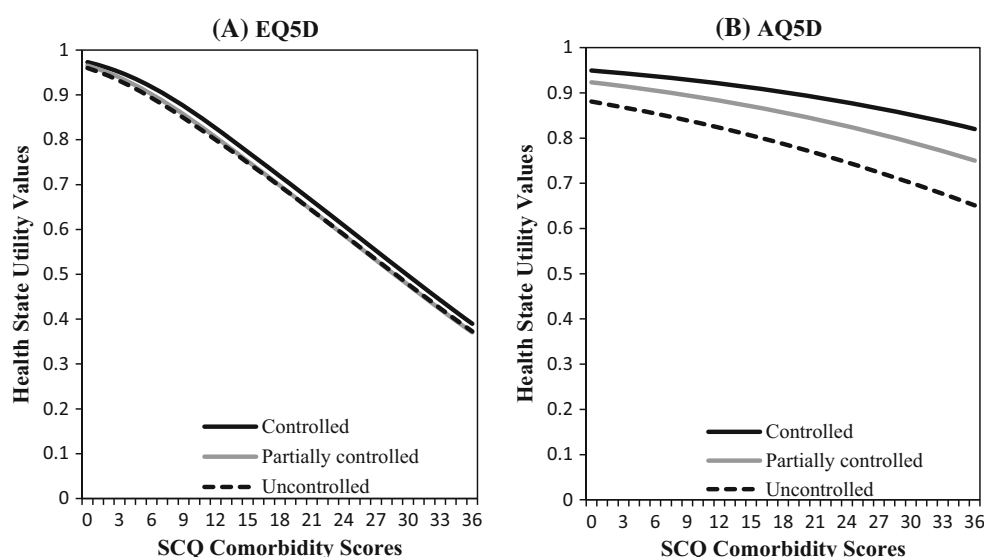


Table 4 Proportions of variance (R^2) explained by predictors

Independent variables	EQ5D (%)	AQ5D (%)
Covariates + symptom control + comorbidity + interaction ^a	24.7	26.7
Covariates + symptom control + comorbidity	24.7	26.4
Covariates + symptom control	12.7	23.5
Covariates + comorbidity	24.0	14.8
Symptom control only	9.1	17.1
Comorbidity only	22.3	7.7
Covariates only	11.0	10.2
Covariates + asthma control + comorbidity components	30.0	29.2
Excluding		
Heart diseases	29.9	29.2
Hypertension	29.7	29.1
Diabetes	29.5	28.9
Ulcer or stomach diseases	30.1	29.1
Kidney disease	29.9	29.0
Liver disease	30.0	29.2
Anemia or other blood disease	30.1	29.2
Cancer	29.9	29.2
Depression	23.9	27.5
Osteoarthritis, degenerative arthritis	29.7	29.1
Backpain	28.4	28.7
Rheumatoid arthritis	28.8	27.7

^a Interaction between levels of symptom control and comorbidity scores

method and the power of the study. For instance, in terms of statistical significance, a prior study [9] found the EQ5D to only discriminate between the best and worst levels of control measured with the Asthma Control Questionnaire, whereas another study [11] found that EQ5D discriminates between all levels of control as defined in GINA 2009 guideline.

The EQ5D has been considered valid and reliable for asthma studies [40]. However, a recent study found EQ5D unable to discriminate between the moderate levels of control [9]. Our results further showed that the marginal gain in EQ5D utility from symptomatically uncontrolled to controlled asthma was only 0.018, which is well below the MID of 0.074 for the EQ5D [38]. Meanwhile, increases in comorbidity burden led to very similar disutility based on the EQ5D, across levels of symptom control. These findings suggest that the EQ5D is rather insensitive to asthma-associated changes in utility, particularly in the high end of the utility scale (mild asthmatics) and in the presence of comorbidity. For this reason, given that symptom control is the cornerstone of contemporary evidence-based asthma management [20], EQ5D may not be appropriate for studying interventions specifically targeted at improving asthma symptoms. This may be explained by the fact that the EQ5D was designed to measure health status irrespective of underlying diseases. Compared to the overall

comorbidity burden, patients may not continuously experience asthma manifestations and can better cope with and adapt to the disease over time [41]. Despite the statistical significance, such small incremental changes in utility can potentially result in huge incremental cost-effectiveness ratios (ICERs) for targeted asthma interventions, thus rarely showing such interventions to be cost-effective. On the other hand, for broad-scope interventions such as life style modification in asthma patients, the use of generic instruments such as EQ5D may be recommended because of the substantial influences of comorbidities and their potential interaction with the treatment effect from such interventions [39].

Compared to EQ5D, AQ5D much better differentiated between levels of asthma symptom control, making it a more appropriate option for studying the effects of treatment interventions in asthma. To the best of our knowledge, the MID for the AQ5D is not yet determined; therefore, the clinical relevance of the observed associations with AQ5D utilities is unclear, yet it is expected to be lower than in EQ5D due to the generally higher sensitivity of AQ5D [9]. Though to a much smaller scale than with the EQ5D, the presence of comorbidities also affected AQ5D utility measures. There may be a dose-response relation between overall disease burden and HRQoL, as indicated by previous studies in asthma and other diseases

[16, 42, 43], even in disease-specific HRQoL measures. It is also possible that the effect of comorbidity on utility is partly attributable to their potential associations with sub-optimal asthma control. However, our results do not support this hypothesis because the interaction between asthma control and comorbidity did not significantly affect utility. Nonetheless, a prior clinical trial found that certain comorbidities (e.g., hypertension, gastrointestinal conditions) can act as mediating factors in the effects of drug treatment on asthma-specific HRQoL measures [39]. Thus, researchers should still consider comorbidity when estimating the effects of targeted asthma interventions.

This is the first study investigating the additional impact of comorbidity along with asthma control on quality of life in patients with asthma. Conclusions were drawn based on a relatively large longitudinal random sample, and thus, the results have a high level of validity. The use of validated and internationally accepted measures of HRQoL, asthma symptom control, and comorbidity further improves the validity of our findings. Moreover, associations were estimated using an efficient and rigorous statistical framework that could adjust for the skewed nature of the outcome data and clustered observations. However, the present study has several limitations. Firstly, this study sample was comprised of generally mild asthma patients, which may be attributable to the healthy volunteer bias as a result of the requirement for multiple visits to study sites. In this regard, we found the mean EQ5D utility values to be higher than those reported in the general adult population of the UK [44], USA [44], and Canada [29]. The high EQ5D score leaves less room for distinguishing small changes in symptom control and comorbidity, as it hampers our ability to extrapolate such associations to individuals with more severe asthma [45]. Secondly, there are potential biases associated with self-reported outcomes. For instance, study subjects were enrolled based on self-reported physician diagnosis of asthma, which has the potential for diagnostic mislabelling. However, asthma management in the real world is inevitably affected by such mislabelling; thus, our results can be more generalizable to clinical practice than those based on samples of diagnostically confirmed asthma patients. On the other hand, individuals with self-reported comorbidities might also tend to report more asthma symptoms and a reduced HRQoL, causing reporting bias. Finally, the marginal estimates in our results can only be interpreted causally if we have successfully controlled for all potential confounders, an assumption that cannot be easily verified [46].

With these limitations in mind, this study has important implications for assessing outcomes and comparing treatment options in asthma. Firstly, by demonstrating high prevalence and significant impact of comorbidity on HRQoL, our study highlights the importance of

considering comorbidity status in the estimation of asthma treatment effects. Secondly, it yields important information about the empirical measurement properties of generic and disease-specific instruments and their applicability to utility measurement to support cost-effectiveness analyses in asthma. Future studies should investigate the interaction of asthma interventions with asthma control and comorbidity in determining HRQoL and evaluate the within-individual changes in HRQoL as a function of changes in comorbidity over time.

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Conflict of interest Dr. Fitzgerald has severed on advisory boards for GlaxoSmithKline, AstraZeneca, Novartis, Pfizer, Boehringer-Ingelheim, Takeda, Merck. He has also been a member of speakers' bureaus for Glaxo-SmithKline, AstraZeneca, Novartis, Aerocrine, Boehringer-Ingelheim, Pfizer, and Merck. Dr. FitzGerald is a member of the Global Initiative for Asthma (GINA) and is chair of the GINA Executive and a member of its Science Committee. None of the other authors have declared any conflict of interest.

Ethical standard This study was approved by the Human Ethics board of the University of British Columbia (University of British Columbia Human Ethics No. H10-01542). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

Informed consent Informed consent was obtained from all individual participants included in the study.

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