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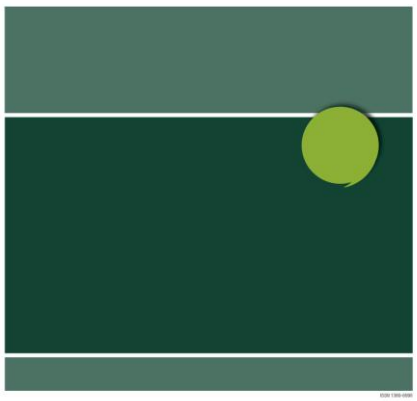

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Review article

Utilities for asthma and COPD according to category of severity: a comprehensive literature review

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Abstract

***Background*:** Asthma and COPD are incurable diseases that impact quality of life.

Objective: To summarize original research articles that measured or utilized preference-based utilities or disutilities according to disease severity.

***Methods*:** Medline and Embase were searched from inception until the end of November 2014. Two reviewers independently searched the literature with differences settled through discussion. Data extracted included utility scores as determined in original research categorized according to disease severity as well as disutilities associated with exacerbations or comorbidities. Data were tabulated and analyzed descriptively.

***Results*:** 862 articles were identified, 790 were rejected and 69 analyzed. There were 44 dealing with COPD and 25 with asthma. Average utilities determined by research were 0.828±0.062, 0.765±0.090, 0.711±0.120 and 0.607±0.120 for mild, moderate, severe and very severe COPD, respectively. Utilities used in economic analyses were 0.866±0.038, 0.770±0.024, 0.739±0.045 and 0.596±0.075, respectively. Disutilities (annual) ranged from 0.002 to 0.378; major and minor exacerbations had respective disutilities of 0.287 and 0.108. For asthma patients, utilities were for 0.86±0.32, 0.83±0.065, and 0.74±0.029, for mild, moderate, and severe disease, respectively.

***Conclusions*:** Utilities have been summarized according to severity category of asthma and COPD. These values should be useful for researchers undertaking economic analyses of these diseases.

Review article

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Utilities for asthma and COPD according to category of severity: a comprehensive literature review

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***Key words*:** asthma, COPD, utilities, preferences, severe

Introduction

It is estimated that 334 million people in the world currently suffer from asthma and almost 329 million have COPD.[1] Asthma affects from 4.3%-8.6% of all people, depending on the definition used,[2] and its prevalence is increasing worldwide.[3] Asthma is a disease that usually starts in childhood and is associated with reversible airflow obstruction that presents varying symptoms.[4] Despite the availability of a number of effective therapies, quality of life remains impaired.[5] The death rate due to this disease is 10.5 per million.[6]

On the other hand, COPD is a progressive disease with onset in mid-life characterized by dyspnea, chronic cough and sputum production, and is associated with an enhanced inflammatory response of the airways and lungs to noxious particles or gases.[7] This disease is associated with substantial mortality. In 2012, the WHO ranked COPD third highest cause of deaths.[8]

For each of these diseases, international organizations have developed guidelines as well as classification systems for disease severity. The Global Initiative for Asthma (GINA)[9] has done so for asthma and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has done the same for COPD.[7]

Respiratory diseases impose a substantial burden on society. Research has demonstrated that the burden increases with disease severity.[10-13] In addition, quality of life is decreased with increasing disease severity[14-16] as well as with decreased disease control.[17-20]

This research was undertaken to summarize results from published studies presenting original research on either asthma, COPD or both in which the authors have: 1) quantified utilities associated with the different categories of disease severity, 2) quantified disutilities associated with exacerbations of various degrees or the presence of comorbidities, and 3) utilized severity-specific utilities in cost-utility analyses.

Methods

We sought original research papers on patients with either asthma or COPD. For this research, the primary target was severe disease; however, in the absence of data for this category, it was considered acceptable if the majority of patients had at least moderate-to-severe disease. Data from patients with mild disease were also retained for comparative purposes. Disease severity could be categorized using any official definition. Most common descriptors are mild, moderate, severe and very severe and are often defined by respiratory parameters such as FEV1.

It was required that articles be original research aimed at either determining preference based patient utilities or using them as inputs into economic analyses. We accepted results derived from any instrument, provided it produced preference based scores, such as time trade-off (TTO) or standard gamble (SG). Instruments could be those in standard use such as EuroQoL (EQ-5D) or HUI-3. Alternately, we would accept scores from other instruments that were converted into preference based utilities using validated mapped equations, such as St. George's Respiratory Questionnaire.[21] Utilities could be measured for either the disease state itself or of changes in that state associated with exacerbations, comorbidities or other situations. Those utilities could be expressed in standard fashion as a decimal fraction from 1 for perfect health to 0 for death, or even lower to reflect states worse than death. Articles must have been published in English, but no restriction on date of publication.

Searches were made on Medline and Embase from inception to the end of November, 2014. Two researchers independently searched; results were compared and differences resolved through consensus discussion. Data extracted included name of first author and year of publication, countries in which the research was conducted, utility scores obtained or used, the severity of disease with which it was associated, preferences analyzed and their outcomes. Data were tabulated and analyzed descriptively.

In conducting secondary research such as this, it is important to maintain constant vigilance to avoid errors. We found apparent input errors in two published papers. In the first, Gani et al.[22] input

values of 0.787 for mild COPD, 0.750 for moderate and 0.647 for severe disease; however, in the original, those values were associated with moderate, severe and very severe disease, respectively.[23] Either the data were input incorrectly or the description of the states is wrong in their Methods. In the second, Sun et al.[24] 2011 made a similar error. Their input utilities were 0.72 for severe disease and 0.67 for very severe; however, Table 2 of the source article indicated that those values were for moderate and severe disease, respectively.[25] Utilities for exacerbations are similarly in error. We did not use any of the questionable values in our calculations.

Results

The literature search identified 862 articles, of which 793 (91.9%) were rejected and 69 (8.0%) were accepted for the analysis. Figure 1 displays the study selection process. We included 44 original studies that reported utilities related to COPD[16;21-63] and 25 studies that reported utilities related to asthma.[64-88]

Table 1 presents utility values for each category of COPD according to the GOLD classification of disease severity. Table 2 presents comparable utility values for patients with asthma, and Table 3 presents utility values according to level of control. Disutilities determined for exacerbations and comorbidities according to COPD severity category appear in Table 4. Utilities used in economic analyses appear in Table and Table for COPD and asthma, respectively.

Among the research studies that estimated utilities for COPD, average values ± SD were 0.828±0.062 for mild (GOLD-1), 0.765±0.090 for moderate (GOLD-2), 0.711±0.120 for severe (GOLD-3) and 0.607±0.120 for very severe disease (GOLD-4). In economic analyses, average utilities were 0.866±0.038, 0.770±0.024, 0.739±0.045, and 0.596±0.075 for mild, moderate, severe and very severe COPD, respectively. These rates were all within 5% of those determined in research studies.

On the other hand, the average utility values for asthma were somewhat higher than those for COPD. Mild asthma had an average utility score of 0.86 (3.9% higher), moderate was 0.83 (8.5% higher) and severe disease was 0.74 (4.1% higher). In studies that reported utility values by symptom control for asthma patients, the mean utility value was 0.641 (0.84-0.22) for moderately controlled symptoms; and 0.536 (0.17-0.84) for disease that was not controlled (Table 3). However, caution is required in making such comparisons since terminology and category definitions for asthma vary widely.[89;90]

Discussion

As expected, utilities declined with each increasing category of severity. The average decrease in utility between mild and moderate disease was 0.068 (8.4%); between moderate and severe, it declined 0.076 (10.4%) and between severe and very severe, it dropped 0.105 (15.9%). The rate of change is also increasing with increased severity. Thus, it is important to try to maintain the patient's status to avoid such impairments to quality of life.

There was a considerable amount of variation between estimates for the same severity of disease. For example, the average utility estimate for moderate COPD was 0.733, but the estimates ranged from 0.590 as determined by EQ-5D (UK Index) in the study by Pickard et al.[34] up to 0.929 as measured by Rutten-van Mölken et al.[35] using time trade-off. Due to differing input values, it is difficult to compare results across studies. Such differences also suggest that researchers should adhere to one set of values collected in the same manner when making comparisons.

A potential complicating factor is comorbidity, especially of having both asthma and COPD. GINA[39] and GOLD[7] have named the coexistence of the two diseases Asthma-COPD Overlap Syndrome (ACOS).[91] None of the papers on asthma mentioned comorbidities or ACOS. Among those that focused on COPD, one included study was based on a clinical trial that specifically excluded patients who also had asthma.[23] Five more specifically allowed the inclusion of patients with comorbid asthma.[16;27;31;33;38] Of those studies, three did not report proportions with both diseases,[16;27;31] one had separate studies in different countries for the two diseases and did not mention the proportions with comorbid disease,[38] and one conducted separate analyses on patients with overlapping diseases.[33] In that study, 6.5% (n=21) of the 322 patients enrolled had ACOS, suggesting only a small proportion of the overall population would be affected. However, the GOLD Report[92] indicates that perhaps 15-20% are affected, but the rate may approach 50% in the elderly.[93] On the other hand, the median utility for that group was lower than that of the overall group, but higher than those for patients with either comorbid bronchitis or emphysema.[33]

Thus, studies with such patients could have had some bias introduced. Authors should be diligent in documenting such information clearly and completely.

Normally, utilities are anchored between the values of 0 for death a 1 for perfect health. However, O'Reilly and colleagues[94] reported a utility value of -0.077 in a group of patients hospitalized for COPD. In that case, they valued their condition as worse than death, which reflects the serious nature of this disease and its impact on patients.

It would be quite difficult to compare utilities between diseases since definitions vary across studies. However, utilities for asthma labelled as severe were somewhat higher than those for severe COPD, suggesting that patients rate COPD as being worse than asthma. In one study, Partridge and associates[95] compared responses between patients with COPD and asthma and found that scores were much worse for COPD.

The purpose of the McTaggart-Cowan study was to validate the generic and condition specific preference-based instruments, by evaluating their ability to distinguish between different levels of asthma control. The condition-specific and VAS instruments were able to differentiate between levels of short acting beta agonist use and self-reported asthma control and severity. While the generic preference-based instruments, were able to differentiate between extreme levels of control and severity, they did not differentiate between moderate ranges of these outcomes. However, the authors did not conclude that these instruments were invalid over a moderate range, but rather suggested that more work be carried out in this area.

One study compared utility values across different countries. Utility values differ between selected European countries, the United Kingdom (UK) and the United States (US).[66] The US subjects tended to rate asthmatic health states as worse than did the Italian and French subjects.[66] Furthermore, the UK subjects reported utilities that were between those reported by the US and the French and Italian samples.[66] Consequently, country specific tariffs have been developed and used.

Lloyd et al observed that standard gamble (SG) and visual analogue scale (VAS) instruments yield instruments yielded different values for the same asthmatic health states. VAS ratings show a much larger difference between the best and worst health state.[72] The authors suggest that VAS data should not be used to inform cost-effectiveness analyses.[72] The SG data should be considered the primary source of utility data.[72]

Szende and colleagues observed that when the EQ-5D was used to derive values for asthma health states, a high proportion of patients reported a value of '1'.[70] This finding suggests that the EQ-5D was unable to differentiate between patients whose health is close to the best possible health status.[70] On the other hand, the SF-6D could distinguish between patients with worse health to a smaller extent than the EQ-5D. The most probable reason for the ceiling effect of the EQ-5D is that the EQ-5D contains three response levels: no problem, some problem and severe problem. The SF-6D instrument, however, has four to six response levels to each of its questions.

Limitations

Our search was limited to two major databases and a hand search of retrieved articles and reviews of the topic. We did not attempt to search the grey literature. As well, our findings are based only on full peer reviewed articles. Many more have appeared as abstracts or posters at scientific meetings. It is possible that results may differ or new information could exist in the literature not accessed.

In this analysis, the definition used for the GOLD categories (in all studies examined) were those from the 2011 version, which defines disease severity based on FEV1. However, a newer set of guidelines has since been released. The 2014 version proposes a different classification for severity based on symptoms, exacerbations and FEV1, since FEV1 alone is not the best predictor of severity, health status or quality of life.[92] Thus, studies appearing after the release of these new guidelines may have differing results that may not be comparable to what we report in this paper.

When examining the information on exacerbations, the reader should be aware that different definitions have been used by different authors. For example, Oostenbrink et al.[42] required symptoms be present for at least 3 days, whereas Borg et al.[39] required only 2 days. As a result, there could be differences among studies and comparisons should be made with caution.

Another issue that must be kept in mind is that it is difficult to link COPD severity with the lung function. Goossens et al. reported that, after adjusting for a number of confounding variables such as sex, age, BMI, etc., there were no longer independent associations between comorbidities, resource use or corticosteroid utilization and COPD severity.[96] Furthermore, they recommended that additional research should explore other methods to account for COPD severity. COPD and asthma patient's utilities may associated with level and number of exacerbations, regardless of level of severity.

Conclusions

This study has documented the creation of utility scores for asthma and COPD according to category of severity. These values should be of use to researchers conducting economic analyses in patients with these diseases. However, due to the large number of subgroups examined, further research needs to be done to provide more robust estimates of these utilities.

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Table 1. Utility values derived in original research in COPD, stratified by GOLD severity categories.

Author and year	Instrument	n	Patient mix	Category of severity*					Data source
				All	GOLD1	GOLD2	GOLD3	GOLD4	
Al[26] 1998	EQ-5D	425	extremely severe (lung transplant)					0.52	Dutch patients awaiting transplantation
								0.40	After 1 year on waiting list
Chen[27] 2014	EQ-5D	154	GOLD3 (65%), GOLD4 (35%)	0.644			0.686	0.565	outpatients in Hong Kong
	SF-6D			0.629			0.646	0.597	
Hajizadeh[28] 2012	Markov model	n/a	End stage - Full code					0.335	Literature based
			End stage - Do not intubate					0.310	
Jódar-Sánchez[29] 2013	EQ-5D	23	Advanced COPD (Telehealth)					0.44	Patients in Spain
	VAS							0.55	
	EQ-5D	20	Advanced COPD (controls)					0.55	
	VAS							0.55	
Kim[30] 2014	EQ5D	200	GOLD1:7%, GOLD2:57%, GOLD3:30%, GOLD4:7%		0.83	0.88	0.81	0.60	outpatients in Korea
	EQ-VAS				0.739	0.751	0.689	0.651	
Lin[31] 2014	EQ-5D-5L	670	GOLD1:15%, GOLD2:53%,	0.79	0.81	0.81	0.76	0.74	outpatients in USA

Author and year	Instrument	n	Patient mix	Category of severity*					Data source
				All	GOLD1	GOLD2	GOLD3	GOLD4	
			GOLD3:25%, GOLD4:7%						
	EQ-VAS			0.706	0.766	0.726	0.657	0.611	
Menn[32] 2010	EQ-5D	117	34 GOLD3 (29%), 83 GOLD4 (71%)				0.62	0.60	inpatients in Germany
	VAS						0.42	0.37	
	EQ-5D						0.84	0.75	patients on discharge
	VAS						0.63	0.52	
Miravitlles[33] 2014	EQ-5D-3L	346	135 GOLD2 (39%), 145 GOLD3 (42%), 66 GOLD4 (19%)	0.73		0.82	0.72	0.57	outpatients in Spain
Pickard[34] 2011	EQ-5D US Index	120	GOLD1:19%, GOLD2:44%, GOLD3:23%, GOLD4:14%	0.73	0.80	0.70	0.72	0.72	
	EQ-5D UK Index			0.63	0.73	0.59	0.63	0.63	
	EQ-5D VAS			0.653	0.743	0.662	0.601	0.587	
Rutten-van Mölken[35] 2009	TTO	229	general population†		0.974	0.929	0.717	0.522	
	VAS	236			0.811	0.678	0.457	0.303	Used regression

Author and year	Instrument	n	Patient mix	Category of severity*					Data source
				All	GOLD1	GOLD2	GOLD3	GOLD4	
Rutten-van Mölken[23] 2006	EQ-5D US values	1226	GOLD2:51%, GOLD3:42%, GOLD4:7%			0.787	0.750	0.647	UPLIFT Trial in 13 countries
	EQ-5D UK values					0.832	0.803	0.731	
	EQ-5D VAS					0.6774	0.6245	0.5784	
Schünemann[36] 2007	Standard gamble	91	patients in rehabilitation†	0.68	0.79	0.62	0.42		
	Feeling thermometer			0.61	0.80	0.61	0.36		
Solem[16] 2013	EQ-5D	314	61% severe, 39% very severe	0.674			0.707	0.623	current health
				0.552			0.59	0.494	last exacerbation
Ståhl[37] 2005	EQ-5D	159	GOLD1:16%, GOLD2:57%, GOLD3:21%, GOLD4:6%		0.84	0.73	0.74	0.52	
	EQ-5D VAS				0.73	0.65	0.62	0.37	
Starkie[21] 2011	EQ-5D	3640	36% moderate, 50% severe, 14% very severe	0.73		0.752	0.708	0.672	mapped from SGRQ
Szende[38] 2009	EQ5D	138	18% mild, 57% moderate, 18% severe, 7% very severe		0.85	0.73	0.74	0.53	Ståhl[37] 2001
	SF-6D				0.80	0.73	0.73	0.62	

COPD, Chronic Obstructive Pulmonary Disease; EQ-5D, EuroQoL 5 Dimension scale for Quality of life; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SF-6D, Short Form – 6 Dimension (Quality of Life); SGRQ, St. George's Respiratory Questionnaire; TTO, time trade-off; VAS, visual analog scale

*GOLD1= mild disease, GOLD2 = moderate, GOLD3 = severe, GOLD4 = very severe

†Not applicable; participants were asked to judge scenarios with mild, moderate and severe disease and estimate utilities

Table 2. Utility values derived in original research in asthma, stratified by severity categories.

Asthma Category	Author	Year	Method	Sample size	Mean	SD
Very mild	McTaggart-Cowan[97]	2008	EQ-5D	157	0.84	0.29
			HUI-3	157	0.82	0.22
			SF-6D	157	0.80	0.22
			AQL-5D	157	0.92	0.08
			EQ-5D VAS	157	0.79	0.18
			VAS	157	0.80	0.22
Mild	Bime[65]	2012	ASUI	453	0.83	0.17
	McTaggart-Cowan[97]	2008	EQ-5D	157	0.89	0.18
			HUI-3	157	0.88	0.18

Asthma Category	Author	Year	Method	Sample size	Mean	SD
			SF-6D	157	0.80	0.09
			AQL-5D	157	0.87	0.08
			EQ-5D VAS	157	0.80	0.15
			VAS	157	0.78	0.15
	Moy[88]	2004	SG	41	0.92	0.15
			TTO	41	0.90	0.15
			VAS	41	0.72	0.24
	Flood[66]	2006	ASUI	10	0.90	
Mild intermittent	Carroll[67]	2009	SG	324	0.91	0.18
			TTO	324	0.91	0.17
	Finnell[68]	2012	SG (TTO first)		0.91	
			TTO (TTO first)		0.88	
			SG (SG First)		0.90	
			TTO (SG First)		0.93	
Intermittent	Bime[65]	2012	ASUI	334	0.85	0.19

Asthma Category	Author	Year	Method	Sample size	Mean	SD
	Flood[66]	2006	ASUI	10	0.94	
Mild persistent	Carroll[67]	2009	TTO	383	0.91	0.18
			SG	383	0.88	0.18
Moderate	Bime[65]	2012	ASUI	298	0.80	0.19
	Flood[66]	2006	ASUI	10	0.83	
	McTaggart-Cowan[97]	2008	EQ-5D	157	0.81	0.21
			HUI-3	157	0.84	0.15
Moderate	McTaggart-Cowan[97]	2008	SF-6D	157	0.78	0.08
			AQL-5D	157	0.83	0.09
			EQ-5D VAS	157	0.76	0.15
			VAS	157	0.73	0.16
	Moy[88]	2004	SG	33	0.93	0.14
			TTO	33	0.82	0.24

Asthma Category	Author	Year	Method	Sample size	Mean	SD
			VAS	33	0.65	0.21
Moderate persistent	Carroll[67]	2009	SG	329	0.88	0.18
			TTO	329	0.91	0.15
	Finnell[68]	2012	TTO (TTO first)		0.90	
			SG (TTO first)		0.90	
			TTO (SG First)		0.91	
			SG (SG first)		0.86	
Moderate to severe	Chen[69]	2007	EQ-5D Utility Index	987	0.86	0.16
			EQ-5D VAS	987	0.74	0.20
Severe	Moy[88]	2004	SG	26	0.86	0.17
			TTO	26	0.66	0.22
			VAS	26	0.55	0.14
	Bime[65]	2012	ASUI	137	0.71	0.20
	Flood[66]	2006	ASUI	10	0.72	

Asthma Category	Author	Year	Method	Sample size	Mean	SD
	McTaggart-Cowan[97]	2008	EQ-5D	157	0.76	0.27
			HUI-3	157	0.75	0.27
			SF-6D	157	0.75	0.12
			AQL-5D	157	0.74	0.15
			EQ-5D VAS	157	0.60	0.25
			VAS	157	0.53	0.24
Severe persistent	Finnell[68]	2012	TTO (TTO first)		0.82	
			SG (TTO first)		0.84	
			TTO (SG First)		0.87	
			SG (SG first)		0.83	
	Carroll[67]	2009	TTO	350	0.85	0.20

AQL-5D: Asthma Quality of Life Utility Index; ASUI: Asthma Symptom Utility Index; EQ-5D: EuroQol; EQ-5D VAS: 'health thermometer' from EuroQol; HUI-3: Health Utility Index Mark 3; SD: standard deviation; SF-6D: Short Form 6D; SG, standard gamble; TTO, time trade-off; VAS: visual analogue scale

Table 3. Utility values derived in original research in asthma, stratified by control levels

Control	Author	Instrument	Baseline (Mean)	SD
Complete	Lloyd[72]	VAS	0.652	
		SG	0.784	
Very well controlled	McTaggart-Cowan[97]	EQ-5D	0.900	0.220
		HUI-3	0.880	0.180
		SF-6D	0.820	0.110
		AQL-5D	0.920	0.060
		EQ-5D VAS	0.810	0.150
		VAS	0.810	0.180
Well controlled		EQ-5D	0.840	0.200
		HUI-3	0.830	0.200
		SF-6D	0.790	0.090
		AQL-5D	0.880	0.100
		EQ-5D VAS	0.780	0.150
		VAS	0.770	0.170
No exacerbations	Lloyd[98]	EQ-5D	0.890	0.150

Control	Author	Instrument	Baseline (Mean)	SD
Adequate	McTaggart-Cowan[97]	EQ-5D VAS	0.761	0.155
		EQ-5D	0.810	0.220
		HUI-3	0.840	0.150
		SF-6D	0.780	0.090
		AQL-5D	0.810	0.120
		EQ-5D VAS	0.730	0.190
		VAS	0.690	0.200
Discernable but limited improvement	Lloyd[72]	VAS	0.496	
		SG	0.748	
Exacerbation w/oral steroids	Lloyd[98]	EQ-5D	0.570	0.360
		EQ-5D VAS	0.564	0.216
Good	Szende[99]	EQ-5D	0.930	
		EQ-5D	0.760	

Control	Author	Instrument	Baseline (Mean)	SD
Hospitalised	Lloyd[98]	VAS		
		SF-6D	0.800	
		EQ-5D	0.330	0.390
		EQ-5D	0.490	0.195
		VAS		
Marked improvement	Lloyd[72]	VAS	0.550	
Mildly reduced	Szende[99]	SG	0.756	
		EQ-5D	0.760	
		EQ-5D	0.670	
		VAS		
		SF-6D	0.730	
Moderate cough and dyspnea (1-3 days)	Revicki[71]	VAS	0.310	0.250
		SG	0.670	0.230
		ASUI	0.730	
Moderate cough and wheeze (4-7 days)	Revicki[71]	VAS	0.220	0.200
		SG	0.620	0.240
		ASUI	0.560	

Control	Author	Instrument	Baseline (Mean)	SD
Moderately reduced	Szende[99]	EQ-5D	0.650	
		EQ-5D VAS	0.590	
		SF-6D	0.640	
No appreciable change	Lloyd[72]	VAS	0.399	
		SG	0.705	
Not controlled	McTaggart-Cowan[97]	EQ-5D	0.800	0.210
		HUI-3	0.840	0.160
		SF-6D	0.770	0.100
		AQL-5D	0.780	0.120
		EQ-5D VAS	0.670	0.230
Not controlled	McTaggart-Cowan[97]	VAS	0.600	0.230

Control	Author	Instrument	Baseline (Mean)	SD
Poor	McCallister[73]	ASUI	0.77	0.14
		ASUI	0.73	0.16
Poor	Szende[99]	EQ-5D	0.520	
		EQ-5D VAS	0.480	
		SF-6D	0.630	
Severe cough, dyspnea, & awaken at night; moderate wheeze and	Revicki[71]	VAS	0.080	0.120
side effects (1-3 days)		SG	0.460	0.270
		ASUI	0.310	
Severe awakening at night	Revicki[71]	VAS	0.250	0.250
		SG	0.670	0.250
		ASUI	0.680	
Severe cough	Revicki[71]	VAS	0.260	0.250
		SG	0.690	0.210
		ASUI	0.700	
Severe cough; moderate wheeze & dyspnea (1-3 days)	Revicki[71]	VAS	0.200	0.200

Control	Author	Instrument	Baseline (Mean)	SD
		SG	0.600	0.210
		ASUI	0.540	
Severe cough; moderate wheeze, dyspnea, and awaken at night (1-3 days)		VAS	0.170	0.180
		SG	0.590	0.240
		ASUI	0.500	
Severe dyspnea	Revicki[71]	VAS	0.160	0.210
		SG	0.600	0.250
		ASUI	0.610	
Severe medication side effects	Revicki[71]	VAS	0.250	0.260
		SG	0.660	0.230
		ASUI	0.670	
Severe wheeze	Revicki[71]	VAS	0.240	0.250
		SG	0.660	0.210
		ASUI	0.670	
Worsening	Lloyd[72]	VAS	0.352	
		SG	0.711	

Control	Author	Instrument	Baseline (Mean)	SD

AQL-5D: Asthma Quality of Life Utility Index – 5 Dimension; ASUI: Asthma Symptom Utility Index; EQ-5D: EuroQol 5-Dimension; EQ-5D VAS: 'health thermometer' from EuroQol; HUI-3: Health Utility Index Mark 3; SD: standard deviation; SF-6D: Short Form 6-Dimension; SG: standard gamble; VAS: visual analogue scale

Table 4. Disutilities determined for exacerbations and comorbidities according to COPD severity category.

First author and year	Disease severity	Factor and its severity/frequency	Instrument	Disutility
Borg[39] 2004	GOLD1	≥1 exacerbation	Calculation, expert opinion, tariffs	0.002
	GOLD2	≥1 exacerbation		0.019
	GOLD3	≥1 exacerbation		0.022
	GOLD4	≥1 exacerbation		0.014
Goossens[40] 2011	25% moderate/ 23% severe/ 16% very severe	Difference between exacerbation and after treatment	EQ-5D	0.109
Jódar-Sánchez[41] 2014	severe (intervention)	comorbidity at baseline	EQ-5D (Spanish)	0.004
	severe (controls)	comorbidity at baseline		0.051
		comorbidity after 4 months (intervention)		0.189
		comorbidity after 4 months		0.005
Oostenbrink[42] 2005	moderate	non-severe exacerbation	Borg[39] 2004, Paterson[20] 2000, Spencer[100] 2003	0.113
		severe exacerbation		0.378
	severe	non-severe exacerbation		0.112

First author and year	Disease severity	Factor and its severity/frequency	Instrument	Disutility
		severe exacerbation		0.374
	very severe	non-severe exacerbation		0.082
		severe exacerbation		0.275
Rutten-van Mölken[35] 2009	any*	1 non-serious exacerbation in year	VAS	0.037
			TTO	0.010
	any*	2 non-serious exacerbations in year	VAS	0.068
			TTO	0.021
	any*	1 serious exacerbation	VAS	0.090
			TTO	0.042

First author and year	Disease severity	Factor and its severity/frequency	Instrument	Disutility
	any*	1 non-serious + 1 serious	VAS	0.130
			TTO	0.088
Rutten-van Mölken[23] 2006	moderate	2-5 comorbidities	EQ-5D	0.063
	moderate	>6 comorbidities		0.134
	severe	2-5 comorbidities		0.034
	severe	>6 comorbidities		0.109
	very severe	2-5 comorbidities		0.027
	very severe	>6 comorbidities		0.073
Solem[16] 2013	any	moderate exacerbation	EQ-5D	0.103
	any	severe exacerbation		0.157
	all	exacerbations		0.122
	severe	if underlying disease severe (GOLD3)		0.117
	very severe	if underlying disease very severe (GOLD4)		0.128
	any	1 moderate/severe exacerbation in last year		0.117
	any	2 moderate/severe exacerbations in last year		0.132

First author and year	Disease severity	Factor and its severity/frequency	Instrument	Disutility
	any	3+ moderate/severe exacerbation in last year		0.118
Spencer[25] 2005	mild	minor exacerbation	Brazier[101] 2002; Spencer[100] 2003	0.090
		major exacerbation		0.291
	moderate	minor exacerbation		0.062
		major exacerbation		0.273
	severe	minor exacerbation		0.195
		major exacerbation		0.262

EQ-5D: EuroQol 5-Dimension; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TTO, time trade-off; VAS: visual analogue scale

*Not applicable; participants were asked to judge scenarios with mild, moderate and severe disease and estimate utilities

Table 5. Utility values used as inputs in economic analyses involving COPD.

Author and year	Utility for COPD severity state				Country	Source
	GOLD1	GOLD2	GOLD3	GOLD4		
Al[102] 1998				0.52	Netherlands	patients (EuroQoL)
Atsou[43] 2011	0.8971	0.7551	0.7481	0.5493	UK	Borg[39] 2004, Soler[103] 2005
Borg[39] 2004	0.8971	0.7551	0.7481	0.5493	Sweden	Andersson[104] 2002
Chandra[44] 2012	0.85	0.81	0.76	0.66	Canada	Rutten-van Mölken[35;61] 2007;2009
Chuck[45] 2006	0.897	0.750	0.549		Canada	Borg[39] 2004, Oostenbrink[42] 2005
Earnshaw[46] 2009		0.755	0.748	0.549	USA	Borg[39] 2004
Gani[22] 2010*	0.787	0.750	0.647		UK	Rutten-van Mölken[23] 2006
Hertel[47] 2012			0.751	0.657	UK	Calverly[105] 2009
Hettle[48] 2012		0.787	0.750	0.647	UK	Rutten-van Mölken[23] 2006
		0.749	0.710	0.604	Belgium	
Hoogendoorn[49] 2013		0.787	0.750	0.647	Germany	Rutten-van Mölken[23] 2006, Oostenbrink[42] 2005
Hoogendoorn[50] 2011	0.8971	0.7551	0.7481	0.5493	Netherlands	Borg[39] 2004
Hoogendoorn[51] 2010	0.8971	0.7551	0.7481	0.5493	Netherlands	Borg[39] 2004
Jódar-Sánchez[41] 2014				0.4405	Spain	EQ-5D: Group 1 no comorbidity

Author and year	Utility for COPD severity state				Country	Source
	GOLD1	GOLD2	GOLD3	GOLD4		
				0.4365		EQ-5D: Group 1 with comorbidity
				0.5203		EQ-5D: Group 2 no comorbidity
				0.5704		EQ-5D: Group 2 with comorbidity
Lock[52] 2011	0.8971	0.7551	0.7481	0.5493	France, Germany, Greece, Italy, UK	Borg[39] 2004
Maniadakis[53] 2006		0.76	0.75	0.55	Greece	Oostenbrink[42] 2005
Menn[54] 2012	0.840	0.790	0.750	0.650	Germany	Rutten-van Mölken[23] 2006, Stahl[37] 2005
Miller[55] 2006				0.645	Canada	HUI-3 (lung resection)
				0.540		HUI-3 (best medical care)
Milne[56] 2014				0.66	New Zealand	EQ-5D mapped from SGRQ
Oostenbrink[57] 2008		0.755	0.748	0.549	Netherlands	Borg[39] 2004
		0.787	0.750	0.647		Rutten-van Mölken[23] 2006
Oostenbrink[42] 2005		0.755	0.748	0.549	Netherlands, Canada	Borg[39] 2004
Price[59] 2014		0.787	0.750	0.647	Sweden	Rutten-van Mölken[23] 2006
Price[58] 2013	0.82	0.80	0.77	0.74	UK	Asukai[106] 2012 (EQ-5D)
Price[107] 2011	0.82	0.80	0.77	0.74	Germany	EQ-5D from trials by Donohue[108] 2010 and Kornmann[109] 2010

Author and year	Utility for COPD severity state				Country	Source
	GOLD1	GOLD2	GOLD3	GOLD4		
Rutten-van Mölken[61] 2007		0.809	0.762	0.655	Spain	EQ-5D from UPLIFT Trial by Decramer[110] 2004
Samyshkin[62] 2014			0.751	0.657	UK	EQ-5D from Calverly[105] 2009
Samyshkin[63] 2013			0.751	0.657	Switzerland	EQ-5D from Calverly[105] 2009
Spencer[25] 2005	0.81	0.72	0.67		Canada	Prescott-Clarke[111] 1998
Sun[24] 2011[†]			0.72	0.67	USA	Spencer[25] 2005

[*]Utilities are in error; 0.787 = GOLD2, 0.750 = GOLD3 and 0.647 = GOLD4 (off by 1 category)

[†]Utilities do not match Spencer 2005 (who had GOLD2=0.72 and GOLD3=0.67); off by 1 category

EQ-5D: EuroQol 5-Dimension; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HUI-3: Health Utility Index Mark 3; SGRQ, St. George's Respiratory Questionnaire

Table 6. Utility values used as inputs in economic analyses involving asthma.

Author (Year) Country	Instrument used	Utility attribute	Utility score (SD)[SE]	Utility score (SD)[SE]	Utility data source
			Standard therapy	Omalizumab	
Brown[76] (2007)	miniAQLQ	Daily symptoms - Baseline	0.620	0.580	ETOPA[112] trial
Canada		Daily symptoms - Week 52	0.650	0.820	ETOPA[112] trial
	EQ-5D (Tsuchiya's formula)	Non-severe exacerbations	0.570 (0.36)		Price[113] 2004
		Severe exacerbations	0.330 (0.39)		Price[113] 2004
			Standard Care	Omalizumab add-on	
Campbell[77] (2010)	AQLQ	Chronic asthma	0.670 [0.15]	0.730 [0.15]	Humbert[114] 2002
United States				Omalizumab responders	
				0.780 [0.14]	
		Oral corticosteroid burst	0.570 [0.36]		Price[113] 2004
Dal Negro[78] (2011)	SGRQ mapped to EQ-5D (Stahl's formula)	Pre omalizumab add-on	0.530		Patient records in Verona Province
Italy		Post omalizumab add-on	0.700		

Author (Year) Country	Instrument used	Utility attribute	Utility score (SD)[SE]	Utility score (SD)[SE]	Utility data source
			Standard therapy	Omalizumab	
Dewilde[79] (2006)	Mapped AQLQ	Baseline	0.590(0.13)		INNOVATE[114] trial
Sweden		Week 28	0.670 (0.15)	0.780(0.14)	
	Direct health state evaluation of AQLQ	Baseline	0.720(0.13)		
		Week 28	0.780 (0.11)	0.860(0.10)	
	EQ-5D (Tsuchiya's formula)	Non-severe exacerbations	0.570 (0.36)		Price[113] 2004
		Severe exacerbations	0.33 (0.39)		
			Successful control	Suboptimal control	
Gerzeli[80] (2012)	Not specified	Baseline	0.850	0.770	Allegra[115] 2012, Briggs[116] 2006,
Italy			Outpatient managed exacerbation	Inpatient managed exacerbation	Edelen[117] 2008, Price[85] 2009, Steuten[118] 2006
			0.660	0.590	
			Pre-omalizumab	Post omalizumab	
Levy Nahon[81] (2014)	Mini-AQLQ	Pre and post 10 months	0.597	0.757	

Author (Year) Country	Instrument used	Utility attribute	Utility score (SD)[SE]	Utility score (SD)[SE]	Utility data source
Spain					
Morishima[82] (2013)	EQ-5D	Symptom free asthma	0.930		Szende[99] 2004
Japan		Day to day asthma	0.760		
		Mild exacerbation	0.650		
		Severe exacerbation	0.520		
		Hospitalization	0.520		
			Standard therapy	Omalizumab	
Norman[83] (2013)	AQRQ mapped to EQ-5D	Overall group	0.670	0.780	INNOVATE[114] Trial
United Kingdom		No exacerbations	0.890		INNOVATE[114] Trial
		Non-severe exacerbations	0.570		Lloyd[98] 2007
		Severe exacerbations	0.330		Lloyd[98] 2007
	EQ-5D measured directly	Overall group	0.720	0.770	EXALT[119] Trial
		Group requiring oral steroids	0.610	0.660	
		Hospitalized in last year	0.590	0.640	

Author (Year) Country	Instrument used	Utility attribute	Utility score (SD)[SE]	Utility score (SD)[SE]	Utility data source
		Non severe exacerbation	-0.100	-0.100	Lloyd[98] 2007
		Severe exacerbation	-0.20	-0.20	Lloyd[98] 2007
Plaza[84] (2000)	SGRQ				Patients from Osona county (Spain)
Spain		Moderate < 65 years	38 (19)		
		Moderate ≥ 65 years	44 (21)		
		Severe < 65 years	49 (20)		
		Severe ≥ 65 years	55 (13)		
Price[85] (2009)	Euro Quality of Life EQ-5D	Moderate control	0.800	0.835	Szende[99] 2004
United Kingdom					
			<u>Standard therapy and non-responder</u>	<u>Omalizumab</u>	
van Nooten[86] (2013)		Utility for omalizumab responder	0.611	0.763	PERSIST trial[74]
United States		Significant exacerbation	0.572	0.572	
		Significant severe exacerbation	0.326	0.326	

Author (Year) Country	Instrument used	Utility attribute	Utility score (SD)[SE]	Utility score (SD)[SE]	Utility data source
Willson[87] (2014)	EQ-5D	Controlled asthma	0.937	0.937	PrimoTinA-asthma trials[120]
South Africa		Partly controlled asthma	0.907	0.907	PrimoTinA-asthma trials[120]
		Uncontrolled asthma	0.728	0.728	PrimoTinA-asthma trials[120]
		Non-severe exacerbation	0.649	0.649	Assumption
		Severe exacerbation without hospitalization	0.570	0.570	Lloyd[98] 2007
		Severe exacerbation with hospitalization	0.330	0.330	Lloyd[98] 2007

AQL-5D: Asthma Quality of Life Utility Index – 5-Dimension; EQ-5D: EuroQol 5-Dimension; SD: standard deviation; SE: standard error; SF-6D: Short Form 6D; SGRQ, St. George's Respiratory Questionnaire

Figure 1. Literature search results.