ONLINE RESOURCES

Associations between the EQ-5D-5L and exacerbations of chronic obstructive pulmonary disease in the ETHOS trial

Journal: *Qual Life Res*

Dan Jackson,[1] Martin Jenkins,[1] Enrico de Nigris,[2] Debasree Purkayastha,[1] Mehul Patel,[1] Mario Ouwens[3]

[1]AstraZeneca, Cambridge, UK; [2]Formerly of AstraZeneca, Cambridge, UK; [3]AstraZeneca, Gothenburg, Sweden

Correspondence to: Dan Jackson, Academy House, 136 Hills Rd, Cambridge CB2 8PA, UK; daniel.jackson1@astrazeneca.com

Sensitivity analysis methods

The sensitivity analysis was based on a data not missing at random assumption. It is possible that EuroQoL 5-dimension 5-level (EQ-5D-5L) and St. George's Respiratory Questionnaire (SGRQ) scores are more likely to be missing for patients with poorer health-related quality of life, so multiple imputation was used to impute scores at patient-visits where values were missing. This imputation model included all variables from Models 1, 2, and 3 (including the outcomes) as well as patient-visit EQ-5D-5L utility scores. Predictive mean matching was used for continuous outcomes to ensure valid values were imputed.

Overall, 100 imputed datasets were created. The 5% and 95% EQ-5D-5L utility scores and SGRQ scores across the 100 missing values were singly imputed as a sensitivity analysis. SGRQ scores were not used in the analysis. This sensitivity analysis did not enforce the relationship between SGRQ total score and the squared valued of the SGRQ total score (the squared value was imputed as another variable), and it did not consider the interaction between exacerbation and disease severity. Due to the complexity of the model, only baseline

and information from the same patient-visit were used in the imputation model. Multiple imputation creates complete datasets for all variables, but only EQ-5D-5L and SGRQ scores were then singly imputed using the 5% and 95% quantiles across the 100 imputed datasets to capture the possibility that missing values for the two patients reported outcomes may be lower than assumed when assuming missing at random. Current forced expiratory volume in 1 second (FEV_1) severity was not imputed so that information from patient visits where this is missing was not recovered in the sensitivity analysis. Current FEV_1 severity was not imputed.

Online resource 1 Listing of regression coefficients used across models

Model 1[a]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.705	0.710	0.714	
Visit_two	0.030	0.037	0.044	
Visit_three	0.036	0.044	0.051	
Visit_four	0.042	0.049	0.057	
Visit_five	0.036	0.044	0.052	
Visit_six	0.042	0.050	0.059	
Moderate exacerbation	–0.062	–0.055	–0.048	Figure 1a
Severe exacerbation	–0.055	–0.035	–0.014	Figure 1a
Previous moderate exacerbation	–0.016	–0.014	–0.011	Figure 1a
Previous severe exacerbation	–0.018	–0.011	–0.003	Figure 1a
Visit_two: 160 µg BGF	–0.006	0.003	0.012	
Visit_two: 320 µg BGF	–0.002	0.008	0.017	
Visit_two: GFF	–0.005	0.005	0.014	
Visit_three: 160 µg BGF	–0.010	0.000	0.010	
Visit_three: 320 µg BGF	–0.004	0.006	0.016	
Visit_three: GFF	–0.007	0.003	0.013	
Visit_four: 160 µg BGF	–0.013	–0.003	0.007	
Visit_four: 320 µg BGF	–0.004	0.006	0.016	
Visit_four: GFF	–0.006	0.004	0.015	
Visit_five: 160 µg BGF	–0.005	0.006	0.017	
Visit_five: 320 µg BGF	–0.009	0.002	0.013	
Visit_five: GFF	0.000	0.011	0.022	
Visit_six: 160 µg BGF	–0.010	0.001	0.012	
Visit_six: 320 µg BGF	–0.005	0.006	0.017	
Visit_six: GFF	–0.002	0.009	0.020	

Model 2[a,b,c]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.824	0.862	0.901	
Visit_two	0.030	0.036	0.043	
Visit_three	0.035	0.043	0.050	
Visit_four	0.040	0.048	0.055	
Visit_five	0.034	0.042	0.050	
Visit_six	0.039	0.047	0.056	
Moderate exacerbation	–0.061	–0.053	–0.046	Figure 1b
Severe exacerbation	–0.054	–0.034	–0.014	Figure 1b
Previous moderate exacerbation	–0.015	–0.013	–0.010	Figure 1b
Previous severe exacerbation	–0.016	–0.008	0.000	Figure 1b
Age (years)	–0.0006	–0.0002	0.0002	
Male	–0.003	0.003	0.009	
US & Canada	–0.002	0.006	0.013	
Asia	0.079	0.093	0.106	
Australia & New Zealand & South Africa	0.031	0.045	0.059	
Eastern Europe	0.050	0.061	0.071	
Mexico & Central America & South America	0.018	0.027	0.037	
LOG eosinophil count	0.004	0.009	0.014	
Number of exacerbations previous year	–0.006	–0.002	0.001	
FEV_1 continuous	0.001	0.001	0.001	
CAT score	–0.013	–0.013	–0.012	
ICS use	–0.007	–0.001	0.006	
Severe exacerbation previous year	–0.030	–0.023	–0.015	
Visit_two: 160 µg BGF	–0.006	0.003	0.012	
Visit_two: 320 µg BGF	0.000	0.009	0.018	
Visit_two: GFF	–0.005	0.004	0.013	
Visit_three: 160 µg BGF	–0.009	0.001	0.011	
Visit_three: 320 µg BGF	–0.002	0.008	0.018	

	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
Visit_three: GFF	–0.008	0.002	0.012	
Visit_four: 160 µg BGF	–0.012	–0.002	0.008	
Visit_four: 320 µg BGF	–0.002	0.008	0.018	
Visit_four: GFF	–0.007	0.004	0.014	
Visit_five: 160 µg BGF	–0.005	0.006	0.017	
Visit_five: 320 µg BGF	–0.006	0.004	0.015	
Visit_five: GFF	–0.001	0.010	0.021	
Visit_six: 160 µg BGF	–0.009	0.002	0.013	
Visit_six: 320 µg BGF	–0.003	0.009	0.020	
Visit_six: GFF	–0.003	0.008	0.020	

Model 2a[a,b,c,d]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.891	0.929	0.967	
Visit_two	0.030	0.036	0.043	
Visit_three	0.035	0.043	0.050	
Visit_four	0.040	0.048	0.055	
Visit_five	0.034	0.042	0.050	
Visit_six	0.039	0.047	0.056	
Moderate exacerbation	–0.061	–0.053	–0.046	Figure 1c
Severe exacerbation	–0.054	–0.034	–0.014	Figure 1c
Previous moderate exacerbation	–0.015	–0.013	–0.010	Figure 1c
Previous severe exacerbation	–0.016	–0.008	0.000	Figure 1c
Age (years)	–0.0006	–0.0002	0.0002	
Male	–0.003	0.003	0.009	
US & Canada	–0.002	0.006	0.013	
Asia	0.079	0.092	0.105	
Australia & New Zealand & South Africa	0.031	0.045	0.059	
Eastern Europe	0.050	0.060	0.071	
Mexico & Central America & South America	0.018	0.027	0.037	

	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
LOG eosinophil count	0.004	0.009	0.014	
Number of exacerbations previous year	−0.006	−0.002	0.002	
Severe COPD	−0.024	−0.018	−0.011	
Very severe COPD	−0.050	−0.040	−0.029	
CAT score	−0.013	−0.013	−0.012	
ICS use	−0.007	−0.001	0.006	
Severe exacerbation previous year	−0.030	−0.023	−0.016	
Visit_two: 160 µg BGF	−0.006	0.003	0.012	
Visit_two: 320 µg BGF	0.000	0.009	0.018	
Visit_two: GFF	−0.005	0.004	0.013	
Visit_three: 160 µg BGF	−0.009	0.001	0.010	
Visit_three: 320 µg BGF	−0.002	0.008	0.018	
Visit_three: GFF	−0.008	0.002	0.012	
Visit_four: 160 µg BGF	−0.012	−0.002	0.008	
Visit_four: 320 µg BGF	−0.002	0.008	0.018	
Visit_four: GFF	−0.007	0.004	0.014	
Visit_five: 160 µg BGF	−0.005	0.006	0.017	
Visit_five: 320 µg BGF	−0.006	0.004	0.015	
Visit_five: GFF	−0.001	0.010	0.021	
Visit_six: 160 µg BGF	−0.009	0.002	0.013	
Visit_six: 320 µg BGF	−0.003	0.009	0.020	
Visit_six: GFF	−0.003	0.008	0.020	

Model 3[a,c,d]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.955	0.986	1.017	
Visit_two	0.000	0.006	0.012	
Visit_three	0.000	0.006	0.012	
Visit_four	0.003	0.010	0.016	
Visit_five	−0.006	0.001	0.008	

Visit_six	–0.002	0.005	0.012	
Moderate exacerbation	–0.019	–0.012	–0.005	Results text (as disutility)
Severe exacerbation	–0.039	–0.021	–0.002	Results text (as disutility)
Previous moderate exacerbation	–0.004	–0.001	0.001	Results text (as disutility)
Previous severe exacerbation	–0.009	–0.003	0.004	Results text (as disutility)
Age (years)	–0.0004	–0.0001	0.0002	
Male	0.001	0.006	0.011	
US & Canada	0.000	0.006	0.013	
Asia	0.040	0.051	0.062	
Australia & New Zealand & South Africa	0.019	0.030	0.041	
Eastern Europe	0.027	0.036	0.044	
Mexico & Central America & South America	0.006	0.014	0.021	
LOG eosinophil count	0.002	0.006	0.010	
Number of exacerbations previous year	–0.003	0.000	0.003	
Severe COPD	–0.005	0.000	0.006	
Very severe COPD	–0.010	–0.002	0.007	
CAT score	–0.005	–0.004	–0.004	
ICS use	–0.005	0.000	0.006	
Severe exacerbation previous year	–0.018	–0.013	–0.007	
SGRQ total	–0.0030	–0.0027	–0.0023	Results text (as disutility)
SGRQ total squared	–0.000039	–0.000035	–0.000031	Results text (as disutility)
Visit_two: 160 µg BGF	–0.011	–0.003	0.005	
Visit_two: 320 µg BGF	–0.006	0.002	0.010	
Visit_two: GFF	–0.004	0.004	0.012	
Visit_three: 160 µg BGF	–0.014	–0.005	0.003	
Visit_three: 320 µg BGF	–0.009	–0.001	0.008	
Visit_three: GFF	–0.006	0.003	0.011	
Visit_four: 160 µg BGF	–0.017	–0.008	0.000	
Visit_four: 320 µg BGF	–0.009	0.000	0.008	

	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
Visit_four: GFF	−0.007	0.001	0.010	
Visit_five: 160 µg BGF	−0.008	0.001	0.010	
Visit_five: 320 µg BGF	−0.009	0.000	0.009	
Visit_five: GFF	0.000	0.009	0.018	
Visit_six: 160 µg BGF	−0.012	−0.002	0.007	
Visit_six: 320 µg BGF	−0.007	0.002	0.011	
Visit_six: GFF	0.000	0.010	0.019	

Model 4[a,c]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.798	0.864	0.930	
Visit_two	0.026	0.037	0.048	
Visit_three	0.016	0.028	0.040	
Visit_four	0.023	0.036	0.048	
Visit_five	0.011	0.025	0.038	
Visit_six	0.022	0.036	0.050	
Moderate/severe exacerbation	−0.036	−0.024	−0.012	Figure 2a
Previous moderate/severe exacerbation	−0.012	−0.008	−0.005	Figure 2a
Age (years)	−0.0002	0.0004	0.0011	
Male	−0.020	−0.010	0.000	
US & Canada	−0.006	0.006	0.017	
Australia & New Zealand & South Africa	0.015	0.041	0.067	
Mexico & Central America & South America	−0.041	0.062	0.165	
LOG eosinophil count	−0.006	0.002	0.011	
Number of exacerbations previous year	−0.008	−0.002	0.004	
FEV_1 continuous	−0.001	−0.001	0.000	
CAT score	−0.014	−0.013	−0.013	
ICS use	−0.014	−0.003	0.008	
Severe exacerbation previous year	−0.024	−0.012	0.001	
FEV_1 continuous current	0.002	0.0023	0.003	Figure 2a

	Lower 95% CI	Estimate	Upper 95% CI	
Visit_two: 160 µg BGF	–0.022	–0.007	0.008	
Visit_two: 320 µg BGF	–0.021	–0.006	0.010	
Visit_two: GFF	–0.016	–0.001	0.015	
Visit_three: 160 µg BGF	–0.011	0.005	0.021	
Visit_three: 320 µg BGF	–0.009	0.007	0.023	
Visit_three: GFF	–0.007	0.010	0.026	
Visit_four: 160 µg BGF	–0.013	0.004	0.020	
Visit_four: 320 µg BGF	–0.013	0.004	0.021	
Visit_four: GFF	–0.007	0.010	0.027	
Visit_five: 160 µg BGF	–0.005	0.012	0.030	
Visit_five: 320 µg BGF	–0.015	0.003	0.020	
Visit_five: GFF	–0.009	0.009	0.028	
Visit_six: 160 µg BGF	–0.017	0.002	0.020	
Visit_six: 320 µg BGF	–0.024	–0.005	0.014	
Visit_six: GFF	–0.019	0.000	0.019	

FEV_1 continuous current is the current FEV_1 percent predicted continuous.

Model 4a[a,c,d]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.880	0.945	1.010	
Visit_two	0.028	0.040	0.051	
Visit_three	0.020	0.031	0.043	
Visit_four	0.026	0.039	0.051	
Visit_five	0.014	0.028	0.041	
Visit_six	0.025	0.039	0.053	
Moderate/severe exacerbation	–0.038	–0.027	–0.015	Figure 2b
Previous moderate/severe exacerbation	–0.012	–0.009	–0.005	Figure 2b
Age (years)	–0.0002	0.0004	0.0011	
Male	–0.021	–0.011	–0.001	
US & Canada	–0.005	0.006	0.018	
Australia & New Zealand & South Africa	0.013	0.039	0.065	

	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
Mexico & Central America & South America	−0.042	0.061	0.165	
LOG eosinophil count	−0.006	0.003	0.011	
Number of exacerbations previous year	−0.007	−0.001	0.005	
Severe COPD	−0.013	−0.001	0.011	
Very severe COPD	−0.028	−0.010	0.009	
CAT score	−0.014	−0.013	−0.012	
ICS use	−0.014	−0.003	0.008	
Severe exacerbation previous year	−0.025	−0.013	0.000	
Severe COPD current	−0.025	−0.018	−0.010	Figure 2b
Very severe COPD current	−0.056	−0.045	−0.035	Figure 2b
Visit_two: 160 μg BGF	−0.020	−0.005	0.010	
Visit_two: 320 μg BGF	−0.018	−0.002	0.013	
Visit_two: GFF	−0.014	0.001	0.016	
Visit_three: 160 μg BGF	−0.010	0.006	0.022	
Visit_three: 320 μg BGF	−0.007	0.010	0.026	
Visit_three: GFF	−0.006	0.011	0.027	
Visit_four: 160 μg BGF	−0.011	0.006	0.023	
Visit_four: 320 μg BGF	−0.011	0.006	0.023	
Visit_four: GFF	−0.006	0.011	0.029	
Visit_five: 160 μg BGF	−0.003	0.015	0.032	
Visit_five: 320 μg BGF	−0.014	0.004	0.022	
Visit_five: GFF	−0.009	0.010	0.028	
Visit_six: 160 μg BGF	−0.015	0.003	0.021	
Visit_six: 320 μg BGF	−0.022	−0.003	0.016	
Visit_six: GFF	−0.019	0.000	0.019	

Model 4b[a,c,d]				
	Lower 95% CI	Estimate	Upper 95% CI	Data reported in:
(Intercept)	0.917	0.973	1.029	
Visit_two	0.003	0.013	0.023	

Visit_three	–0.010	0.001	0.011	
Visit_four	–0.002	0.009	0.020	
Visit_five	–0.016	–0.004	0.008	
Visit_six	–0.009	0.004	0.017	
Moderate/severe exacerbation	–0.007	0.004	0.015	Results text (as disutility)
Previous moderate/severe exacerbation	–0.005	–0.002	0.001	Results text (as disutility)
Age (years)	0.0000	0.0006	0.0011	
Male	–0.011	–0.003	0.006	
US & Canada	–0.004	0.005	0.015	
Australia & New Zealand & South Africa	0.000	0.021	0.043	
Mexico & Central America & South America	–0.016	0.071	0.159	
LOG eosinophil count	–0.005	0.001	0.008	
Number of exacerbations previous year	–0.004	0.001	0.006	
Severe COPD	–0.007	0.003	0.013	
Very severe COPD	–0.011	0.005	0.020	
CAT score	–0.005	–0.005	–0.004	
ICS use	–0.012	–0.003	0.006	
Severe exacerbation previous year	–0.019	–0.008	0.002	
Severe COPD current	–0.011	–0.004	0.003	Results text (as disutility)
Very severe COPD current	–0.022	–0.012	–0.002	Results text (as disutility)
SGRQ total	–0.0033	–0.0026	–0.0019	Results text (as disutility)
SGRQ total squared	–0.000039	–0.000032	–0.000025	Results text (as disutility)
Visit_two: 160 µg BGF	–0.026	–0.013	0.001	
Visit_two: 320 µg BGF	–0.020	–0.006	0.008	
Visit_two: GFF	–0.012	0.002	0.016	
Visit_three: 160 µg BGF	–0.014	0.000	0.014	
Visit_three: 320 µg BGF	–0.013	0.002	0.016	
Visit_three: GFF	–0.003	0.011	0.026	
Visit_four: 160 µg BGF	–0.015	–0.001	0.014	
Visit_four: 320 µg BGF	–0.017	–0.002	0.012	

Visit_four: GFF	−0.004	0.011	0.026	
Visit_five: 160 µg BGF	−0.006	0.009	0.024	
Visit_five: 320 µg BGF	−0.012	0.004	0.019	
Visit_five: GFF	−0.005	0.011	0.027	
Visit_six: 160 µg BGF	−0.016	0.000	0.016	
Visit_six: 320 µg BGF	−0.023	−0.006	0.010	
Visit_six: GFF	−0.011	0.006	0.022	

[a]Indicators for each post baseline visit (Visit_two, Visit_three, Visit_four, Visit_five, Visit_six); visit:treatment terms model post-baseline treatment effects; the reference treatment group is budesonide/formoterol fumarate dihydrate

[b]All additional covariates to those included in Model 1 are baseline covariates

[c]Western Europe is the reference group for geographical region

[d]Moderate COPD is the reference category for baseline FEV_1 percent predicted versus severe COPD and very severe COPD

160 µg BGF 160/14.4/10 µg budesonide/glycopyrronium/formoterol fumarate dihydrate, *320 µg BGF* 320/14.4/10 µg budesonide/glycopyrronium/formoterol fumarate dihydrate, *CAT* COPD Assessment Test, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *FEV$_1$* forced expiratory volume in 1 second, *GFF* 14.4/10 µg glycopyrronium/formoterol fumarate dihydrate, *ICS* inhaled corticosteroid, *SGRQ* St. George's Respiratory Questionnaire

Online resource 2 Demographics and clinical characteristics of the mITT population from the ETHOS study (N=8509)

Variable	
Age, years, mean (SD)	64.7 (7.6)
Female, n (%)	3428 (40.3)
Male, n (%)	5081 (59.7)
Exacerbations during the 12 months prior to screening, n (%)	
1	3699 (43.5)
≥2	4810 (56.5)
COPD severity (based on GOLD FEV$_1$ % predicted)[a] at screening, n (%)	
Moderate	2427 (28.5)
Severe	5151 (60.5)
Very severe	924 (10.9)
Missing	7 (0.1)
Post-rescue medication FEV$_1$ % predicted, mean (SD)	43.4 (10.3)

[a]Moderate FEV$_1$ % predicted was defined as ≥50% and <80%; severe FEV$_1$ % predicted was defined as ≥30% and <50%; very severe FEV$_1$ % predicted was defined as <30%

COPD chronic obstructive pulmonary disease, *FEV$_1$* forced expiratory volume in 1 second, *FEV$_1$ % predicted* forced expiratory volume in 1 second percentage of predicted normal value, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *mITT* modified intent-to-treat, *SD* standard deviation

Online resource 3 Sensitivity analysis based on data not missing at random assumption for predictors of EQ-5D-5L based on FEV_1 levels and exacerbations (Question 3; Model 5)[a,b]

Variable	Coefficient (95% CI)
Predicted baseline EQ-5D-5L utility score for patients with currently moderate COPD with no current or previous exacerbation	0.726 (0.717, 0.735)
Covariate adjustment from baseline (currently moderate COPD severity with no current or previous exacerbation during the ETHOS trial) in EQ-5D-5L utility score	
Severe COPD	−0.015 (−0.023, −0.008)**
Very severe COPD	−0.044 (−0.054, −0.033)**
Current exacerbation	−0.021 (−0.053, 0.010)
Current exacerbation, additional effect if severe COPD	−0.002 (−0.037, 0.033)
Current exacerbation, additional effect if very severe COPD	−0.014 (−0.051, 0.024)
Previous exacerbations	−0.017 (−0.021, −0.013)**

Data represent estimates (95% CI)

Wald p-values; **$p<0.01$

[a]Model includes covariates as described in Table 1

[b]Based on 3316 patients

CI confidence interval, *EQ-5D-5L* EuroQoL 5-dimension 5-level, *FEV_1* forced expiratory volume in 1 second