RESEARCH ARTICLE   **Open Access**

Health-related quality of life associates with change in FEV_1 in COPD: results from the COSYCONET cohort

Johanna I. Lutter[1]* , Rudolf A. Jörres[2], Kathrin Kahnert[3], Larissa Schwarzkopf[1], Michael Studnicka[4], Stefan Karrasch[2,5,6], Holger Schulz[5], Claus F. Vogelmeier[6], Rolf Holle[1,7] for the COSYCONET Study Group

Abstract

Background: Forced expiratory volume in one second (FEV_1) characterizes the pathophysiology of COPD and different trajectories of FEV_1 decline have been observed in patients with COPD (e.g. gradual or episodic). There is limited information about the development of patient-reported health-related quality of life (HRQL) over the full range of the natural history of COPD. We examined the longitudinal association between change in FEV_1 and change in disease-specific and generic HRQL.

Methods: We analysed data of 1734 patients with COPD participating in the COSYCONET cohort with up to 3 years of follow-up. Patients completed the Saint George's Respiratory Questionnaire (SGRQ) and the EQ-5D Visual Analog Scale (EQ VAS). Change score models were used to investigate the relationship between HRQL and FEV_1 and to calculate mean changes in HRQL per FEV_1 change categories [decrease (≤ -100 ml), no change, increase (≥ 100 ml)] after 3 years. Applying hierarchical linear models (HLM), we estimated the cross-sectional between-subject difference and the longitudinal within-subject change of HRQL as related to a FEV_1 difference or change.

Results: We observed a statistically significant deterioration in SGRQ (total score + 1.3 units) after 3 years, which was completely driven by the activity component (+ 4 units). No significant change was found for the generic EQ VAS. Over the same period, 58% of patients experienced a decrease in FEV_1, 28% were recorded as no change in FEV_1, and 13% experienced an increase. The relationship between HRQL and FEV_1 was found to be approximately linear with decrease in FEV_1 being statistically significantly associated with a deterioration in SGRQ (+ 3.20 units). Increase in FEV_1 was associated with improvements in SGRQ (− 3.81 units). The associations between change in FEV_1 and the EQ VAS were similar. Results of the HLMs were consistent and highly statistically significant, indicating cross-sectional and longitudinal associations. The largest estimates were found for the association between FEV_1 and the SGRQ activity domain.

(Continued on next page)

* Correspondence: johanna.lutter@helmholtz-muenchen.de
[1]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, GmbH – German Research Center for Environmental Health, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany
Full list of author information is available at the end of the article

(Continued from previous page)

Conclusions: Difference and change in FEV_1 over time correlate with difference and change in disease-specific and generic HRQL. We conclude, that deterioration of HRQL should induce timely re-examination of physical status and lung function and possibly reassessment of therapeutic regimes.

Trial registration: NCT01245933. Date of registration: 18 November 2010.

Keywords: COPD, Cohort, Longitudinal, Patient reported outcome, Health status, Physical activity

Background

Chronic obstructive pulmonary disease (COPD) is defined by the presence of post-bronchodilator airways obstruction, respiratory symptoms such as breathlessness, cough, and sputum production and a history of exposure to inhalational injury [1]. Patients with COPD experience an accelerated decline in FEV_1 compared to healthy never smoking individuals, where a decline of about 20 ml per years was shown [2]. However, the natural history of COPD is not always characterized by a gradual accelerate decline but can also present as episodic accelerated decline of FEV_1. Here, episodes of deteriorated and improved lung function mark the overall downward trajectory of lung function over time [3]. Accordingly, patients with declining or rapidly declining FEV_1 but also patients with stable or even improved FEV_1 over time have been identified in large COPD cohorts [4–6].

While measures like FEV_1 and blood gases reflect the pathophysiology of COPD, measures of health-related quality of life (HRQL) reflect the patient's perspective of his/her disease. They are meaningful instruments to monitor the course of COPD as they cover the severity of symptoms, the impact of the disease on daily life and have also been found to predict mortality [7–9]. The longitudinal association between change in FEV_1 and change in HRQL is not fully understood. Estimates based on RCTs and only few observational studies range from only a weak correlation [10] to strong correlations [11–13] and often focus on one direction of FEV_1 change– i.e. decrease only [14] or increase only [11, 13]. Furthermore, the transferability of findings from RCTs to routine care is limited, because of highly selected patient samples.

In summary, there is limited information about the development of HRQL over the full range of the natural history of COPD, which includes FEV_1 decrease in the context of exacerbations, FEV_1 increase as a consequence of treatment, as well as unchanged FEV_1. We therefore analysed data from a large, real-world observational cohort of COPD patients followed for 3 years, with the aim to analyse and possibly quantify the association between longitudinal FEV_1 change and change in generic and disease-specific HRQL.

Methods

Study design and study population

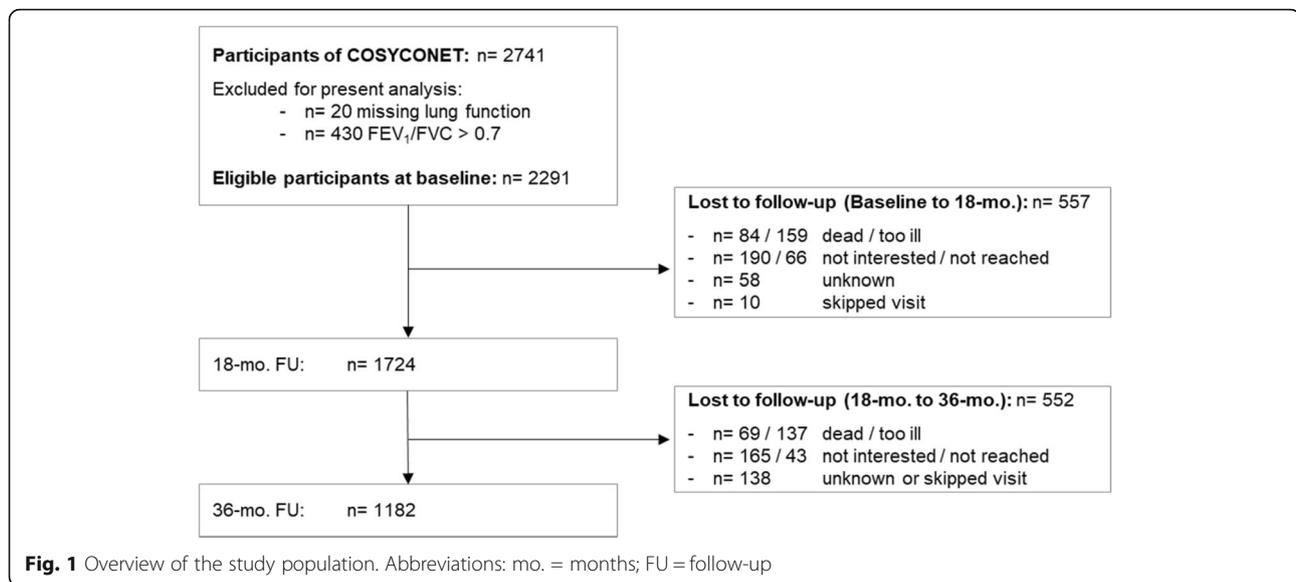Between September 2010 and December 2013, the prospective, multicentre COSYCONET ("German COPD and Systemic Consequences – Comorbidities Network") study recruited 2741 participants in 31 study centres across Germany and re-examinations took place after 18- and 36-months. Briefly, baseline inclusion criteria of COSYCONET were age ≥ 40 years and a physician's diagnosis of COPD. Detailed information about the inclusion and exclusion criteria and the recruitment process are available elsewhere [15].

For the present analysis, we excluded patients with (a) missing FEV_1 values at baseline, (b) $FEV_1/FVC \geq 0.7$ at baseline, and (c) no further study participation after baseline. Patients with alpha-1-antiythrypsin deficiency were not excluded, since their HRQL was found to be comparable to patients without the immune deficiency in a cross-sectional analysis [16]. An overview of the study population is given in Fig. 1.

COPD definition and HRQL assessment

Participants underwent standardized post-bronchodilator spirometry at each visit. GOLD grades 1–4 were assigned at baseline based on FEV_1 predicted, whereby reference values were taken from the Global Lung Initiative [17]. For the stratified analysis, GOLD grades were further aggregated in two groups (GOLD 1/2 and 3/4) because of limited numbers of patients in GOLD grades 1 and 4 (each less than 10% of the total sample).

At each visit, HRQL was assessed using two self-administered questionnaires: the generic 3-level version of Euro-Qol 5D (EQ-5D-3 L) and the disease-specific Saint George's Respiratory Questionnaire for COPD (SGRQ) [18, 19]. The generic instrument EQ-5D is designed to assess HRQL regardless of a specific disease and consists of two parts, the descriptive section and the valuation section. For the present analysis, we used the descriptive section only, i.e. the Visual Analogue Scale (EQ VAS), since this descriptive section was found to better discriminate between COPD grades compared to the EQ-5D valuation section. Furthermore, the VAS was preferred as a simple measure of generic HRQL since the EQ-5D utility index requires a country-dependent tariff and is less sensitive due to its skewed distribution [20]. When using the EQ VAS, participants value their current health status on a scale between 0 (worst possible) and 100 (best imaginable) and a 6.9 units change

Participants of COSYCONET: n= 2741

Excluded for present analysis:
- n= 20 missing lung function
- n= 430 FEV$_1$/FVC > 0.7

Eligible participants at baseline: n= 2291

Lost to follow-up (Baseline to 18-mo.): n= 557
- n= 84 / 159   dead / too ill
- n= 190 / 66   not interested / not reached
- n= 58   unknown
- n= 10   skipped visit

18-mo. FU: n= 1724

Lost to follow-up (18-mo. to 36-mo.): n= 552
- n= 69 / 137   dead / too ill
- n= 165 / 43   not interested / not reached
- n= 138   unknown or skipped visit

36-mo. FU: n= 1182

Fig. 1 Overview of the study population. Abbreviations: mo. = months; FU = follow-up

has been proposed as the minimal clinically important difference [21]. To assess disease-specific HRQL, we used the SGRQ in its COPD specific version. This questionnaire consists of 40 questions related to three components of HRQL (symptoms, activity, and impacts). The total score ranges between 0 and 100 with higher values indicating worse HRQL. Its reliability, validity and responsiveness has been demonstrated in patients with COPD and a 4 units change is considered to indicate the minimal clinical important difference [22].

Assessment of covariates

Age, sex, education, and smoking status were assessed in standardized interviews complemented by self-administered questionnaires. Body mass index (BMI) was calculated based on measured height and weight. Information on 33 comorbid conditions was obtained by asking "Has a physician ever diagnosed one of the following diseases?". This information was summarised into a single count indicating the number of comorbidities (range 0–33) at each visit. This approach has been previously proven to be a sufficient proxy for total comorbidity burden [23]. Again based on self-reports the history of exacerbations was defined according to GOLD guidelines as no exacerbation, mild, moderate, or severe exacerbation. For each patient, only the most severe exacerbation that occurred in the 12 months preceding the respective study visit was coded. In this way, we attempted to minimize a potential recall bias especially with regard to an underestimation of lighter events. In case of missing values, we imputed the most frequent category or the mean value for continuous data. Considering all three visits and > 4500 observations, a total of only 25 values were imputed for the covariates.

Statistical analysis

Since loss of lung function and HRQL are both dependent on disease severity, patient characteristics including FEV$_1$ and measures of HRQL at baseline and all analyses are reported stratified by GOLD grade (1/2 vs. 3/4) [4, 24]. For 1182 patients with participation in the 3 year follow-up, change in FEV$_1$ and HRQL over 3 years was evaluated based on t-tests for paired data. To investigate the association between FEV$_1$ and HRQL over time, two statistical approaches were employed: change score analysis and hierarchical linear models. All models were adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history.

Change score analyses

First, using ordinary least squares linear regression models, we regressed the change in HRQL between baseline and 36 months follow-up on three categories of FEV$_1$ change and covariates to calculate mean changes in HRQL. The within-subject change in FEV$_1$ after 36 months was defined as either decrease in absolute FEV$_1$ ≥ 100 ml, increase in absolute FEV$_1$ ≥ 100 ml, and no change (in between). The 100 ml cut-off in FEV$_1$ was chosen in accordance with the previously published minimal important difference for COPD [25]. As we considered the change in FEV$_1$ to be dependent on baseline lung function, an interaction term to account for the relation between the FEV$_1$ change category and baseline FEV$_1$ was incorporated.

Second, generalized additive models (GAM) were conducted, to investigate the relationship between HRQL and a continuous measure of FEV$_1$. This nonparametric regression models the association between the dependent variable change in HRQL and

the independent variable change in FEV_1 using a smoothing function while adjusting for covariates. Further details have been published elsewhere [26].

Hierarchical linear model

We applied hierarchical linear models (HLM), which enable the inclusion of time-variant and time-invariant covariates and can be applied on datasets with missing variables at different time points (i.e. patient dropped out after second follow-up). These models were designed to provide information regarding mean population trends and individual change over time. Considering time points as time nested in individuals, the model divides the original independent variable into the mean over time (between-subject differences) and the deviation from the mean over time (within-subject change) [27]. In our specific case, the model distinguished between the cross-sectional between-subject and the longitudinal within-subject association of FEV_1 (included as a continuous variable with the unit 100 ml difference or change) and HRQL.

Sensitivity analysis

To account for selective dropout bias, we performed a sensitivity analysis including Inverse Probability Weights (IPW) in the change score- and hierarchical linear models. We first modelled the probability of follow-up based on baseline characteristics (demographics, disease characteristics and quality of life). Weights were then assigned to all patients, who were included in the present analysis, by calculating the inverse of the estimated probability of follow-up. Using this approach, patients, who were found to be similar to those who dropped out, were given greater weights resulting in a weighted population simulating a population without dropout.

All analyses were carried out using the SAS software (SAS Institute Inc., Cary, NC, USA, Version 9.4) package.

Results

Of the 2741 patients recruited into the COSYCONET cohort, 450 had to be excluded because of missing or non-obstructive spirometry at baseline. Of those entering the cohort ($n = 2291$), 1724 were seen at the second, and 1182 at third follow-up visit. Another 10 participants skipped the first follow-up, but were re-examined in the second follow-up and thus included for the present analysis, resulting in a sample size of $n = 1734$ at baseline.

Table 1 displays the baseline characteristics of the study sample, stratified by GOLD grade 1/2 versus 3/4. Patients with COPD GOLD 1/2 were found slightly older and reported a greater number of comorbidities.

The proportion of patients reporting at least one severe exacerbation in the 12 months before the baseline examination was greater for GOLD grade 3/4, as was the proportion of underweight patients. Similarly, mean baseline SGRQ total score and EQ VAS indicated worse HRQL for GOLD 3/4 compared to GOLD 1/2.

Change in FEV_1 and HRQL over three years

For 1182 COPD patients with participation at baseline and at the 36 months follow-up visit, mean change in FEV_1 and HRQL was calculated (Table 2). Baseline characteristics of this subpopulation are available in Additional file 1. For the 3 years time period, a 150 ml FEV_1 decrease was observed for all patients, while this decrease was 180 ml for those with GOLD 1/2 and 90 ml for those with GOLD 3/4 at baseline. Over the same period, we also observed a statistically significant deterioration in disease-specific HRQL (SGRQ total score + 1.3 units) on the population level. This overall change in SGRQ was fully driven by a + 4 units change in the activity component, which was present for both baseline GOLD strata. On an individual level, 73% of patients experienced a clinically relevant change in SGRQ after 3 years (40% deterioration, 33% improvement) (Additional file 1 Table A2).

Analysing the change of the generic EQ VAS in the same way, no significant change was observed on the population level. However, 66% of patients experienced a clinically relevant change in EQ VAS (34% deterioration, 32% improvement).

Relationship between FEV_1 and HRQL over time

Change score analysis

We then analysed all pairs of repeated FEV_1 and HRQL measurements stemming from 1173 patients who completed the follow-up after 36 months. Altogether, COPD patients with GOLD 1/2 at baseline contributed 695 pairs of observations, while those with GOLD 3/4 contributed 478 pairs. We observed a ≥ 100 ml FEV_1 decrease in 58% of the total sample, 28% were recorded as no change in FEV_1, and the remaining 13% experienced a ≥ 100 ml FEV_1 increase over the 3 years period (Table 3).

Figure 2 displays the adjusted mean change in SGRQ and EQ VAS as associated with FEV_1 change (decrease, no change, increase) for all participants and stratified by baseline GOLD grade of severity. Overall, a decrease in FEV_1 was associated with a deterioration in disease-specific and generic HRQL (mean change [95% CI] SGRQ + 3.20 [1.43 to 4.97], EQ VAS -1.05 [– 3.32 to 1.22]), although this was not significant for EQ VAS. On the other hand, we observed statistically significant improvement in generic and disease-specific HRQL for all patients with increased FEV_1 (SGRQ -3.81 [– 6.28 to –

Lutter *et al. BMC Pulmonary Medicine*   (2020) 20:148

Page 5 of 12

Table 1 Characteristics of the study population at baseline

		Total sample	GOLD 1/2	GOLD 3/4	
n		1734	943	791	*p*-value[1]
Male		1054 (60.8)	570 (60.5)	484 (61.2)	0.7523
Age, yrs		64.6 ± 8.2	65.5 ± 8.3	63.6 ± 8.0	<.0001
Age category	< 55	203 (11.7)	96 (10.2)	107 (13.5)	<.0001
	55–64	610 (35.2)	300 (31.8)	310 (39.2)	
	65–74	750 (43.3)	432 (45.8)	318 (40.2)	
	>= 75	171 (9.9)	115 (12.2)	56 (7.1)	
BMI category[2]	Normal	648 (37.4)	319 (33.8)	329 (41.6)	<.0001
	Overweight	642 (37.0)	366 (38.8)	276 (34.9)	
	Obese	392 (22.6)	242 (25.7)	150 (19.0)	
	Underweight	52 (3.0)	16 (1.7)	36 (4.6)	
FEV_1 (liters)		1.61 ± 0.64	2.00 ± 0.56	1.13 ± 0.33	<.0001
FEV_1% predicted		54.1 ± 18.4	69.6 ± 12.8	38.0 ± 8.2	<.0001
Education	Primary	939 (54.2)	480 (50.9)	459 (58.0)	0.0017
	Secondary	487 (28.1)	270 (28.6)	217 (27.4)	
	Higher	308 (17.8)	193 (20.5)	115 (14.5)	
Smoking status	Never smoker	124 (7.2)	73 (7.7)	51 (6.5)	<.0001
	Current smoker	403 (23.2)	258 (27.4)	145 (18.3)	
	Former smoker	1207 (69.6)	612 (64.9)	595 (75.2)	
Comorbidities	Mean number	3.8 (2.6)	3.9 ± 2.6	3.6 ± 2.5	0.0171
Exacerbation history[3]	none	806 (46.5)	519 (55.0)	287 (36.3)	<.0001
	mild	86 (5.0)	57 (6.0)	29 (3.7)	
	moderate	529 (30.5)	266 (28.2)	263 (33.3)	
	severe	313 (18.1)	101 (10.7)	212 (26.8)	
HRQL measures	SGRQ total score	41.6 ± 19.3	35.5 ± 18.5	48.8 ± 17.7	<.0001
	Activity component	56.2 ± 25.5	46.6 ± 24.3	67.6 ± 21.9	<.0001
	Symptoms component	54.4 ± 21.1	50.4 ± 21.6	59.1 ± 19.6	<.0001
	Impacts component	28.6 ± 19.8	23.8 ± 18.7	34.2 ± 19.4	<.0001
	EQ VAS	57.7 ± 19.6	62.9 ± 18.6	51.6 ± 19.0	<.0001

Data are presented as mean ± SD or n (%)
[1]*p*-values based on Chi-square-Tests and ANOVA
[2]BMI groups were defined as normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), obese (BMI ≥ 30), and underweight (BMI < 18.5)
[3]previous 12 months before examination
BMI Body mass index; *FEV₁* forced expiratory volume in 1 s; *HRQL* Health-related quality of life; *SGRQ* Saint George's Respiratory Questionnaire; *EQ VAS* Visual Analog Scale

1.34], EQ VAS + 5.38 [3.34 to 7.86]). Regarding the category no change in FEV_1, we found non-significant improvements in EQ VAS while the SGRQ remained unchanged. Both GOLD strata mirrored the results of the total sample. Our data indicated an approximately linear relationship between change in HRQL and FEV_1 (Fig. 3). However, the graph was found to be shifted to the left side of the x-axis meaning that a zero change in FEV_1 did not correspond to a zero change in HRQL but was associated with slight improvements in HRQL. Consequently, a clinical relevant deterioration in SGRQ was associated with a decrease in FEV_1 of more than − 600

ml, while an increase of more than 200 ml FEV_1 was associated with a clinical relevant improvement in SGRQ.

Hierarchical linear model

The results of the HLM analysis detailing the cross-sectional (between-subject) and longitudinal (within-subject) estimates for HRQL and FEV_1 are presented in Tables 4 and 5. Regarding the SGRQ total score (Table 4) and according to the cross-sectional estimate, higher FEV_1 was associated with better HRQL with 100 ml more (difference) FEV_1 corresponding to a mean improvement by − 1.42 units in SGRQ. Corresponding estimates for the

Table 2 Change in FEV$_1$ and HRQL for 1182 COPD patients who complete the 36-month follow-up

		Baseline	18-month	36-month	3 year change[1]	
FEV$_1$% predicted	Total sample [missing values]	56.1 (18.2) [–]	54.4 (18.5) [17]	53.0 (19.2) [9]	−3.0	<.0001
	GOLD 1/2	68.0 (12.8)	65.3 (14.7)	64.1 (15.5)	−3.9	<.0001
	GOLD 3/4	38.8 (8.1)	38.3 (9.8)	37.0 (11.0)	−1.8	<.0001
FEV$_1$ (liters)	Total sample	1.68 (0.65) [–]	1.60 (0.63) [17]	1.53 (0.64) [9]	−0.15	<.0001
	GOLD 1/2	2.02 (0.57)	1.90 (0.58)	1.84 (0.58)	−0.18	<.0001
	GOLD 3/4	1.17 (0.34)	1.14 (0.38)	1.08 (0.41)	−0.09	<.0001
SGRQ total score	Total sample	40.2 (19.1) [6]	39.7 (20.4) [22]	41.5 (20.4) [17]	1.3	0.0015
	GOLD 1/2	35.0 (18.3)	34.3 (19.3)	35.9 (19.6)	0.9	0.1201
	GOLD 3/4	47.9 (17.7)	47.9 (19.2)	49.8 (18.8)	1.9	0.0019
Activity component	Total sample	54.2 (25.3) [4]	54.8 (26.7) [17]	58.2 (26.9) [16]	4.0	<.0001
	GOLD 1/2	45.9 (24.1)	46.6 (26.0)	49.6 (26.1)	3.7	<.0001
	GOLD 3/4	66.2 (22.0)	67.1 (22.9)	71.0 (22.7)	4.8	<.0001
Symptoms component	Total sample	54.1 (21.3) [3]	52.2 (22.6) [18]	53.4 (22.0) [16]	− 0.7	0.2494
	GOLD 1/2	50.5 (21.6)	48.4 (22.4)	49.4 (22.5)	−1.1	0.1403
	GOLD 3/4	59.4 (19.7)	57.8 (21.6)	59.3 (19.8)	−0.1	0.9660
Impacts component	Total sample	27.2 (19.6) [3]	26.5 (20.3) [19]	27.5 (20.6) [15]	0.3	0.6627
	GOLD 1/2	23.2 (18.6)	22.1 (18.7)	23.0 (19.3)	−0.2	0.5685
	GOLD 3/4	33.1 (19.5)	33.1 (20.9)	34.0 (20.8)	0.9	0.1990
EQ VAS	Total sample	59.1 (19.4) [9]	59.9 (19.5) [22]	58.6 (19.5) [10]	−0.5	0.2830
	GOLD 1/2	63.5 (18.2)	64.1 (18.6)	62.4 (18.7)	−1.1	0.0899
	GOLD 3/4	52.7 (19.4)	53.7 (19.1)	52.9 (19.3)	0.2	0.8051

Data are presented as mean (SD), [number of missing values]
Patient numbers in each GOLD group: Total sample n = 1182; GOLD1/2 n = 702; GOLD 3/4 n = 480
[1]p-values based on paired t-test statistics

single GOLD strata were – 1.00 for GOLD 1/2, and – 1.57 for GOLD 3/4. Conversely, the longitudinal within-subject estimate indicated the effect of a 100 ml FEV$_1$ decrease within a patient. Overall, a 100 ml decrease in FEV$_1$ resulted in a deterioration in disease-specific HRQL, indicated as a 0.83 units change in SGRQ (p < 0.0001).

Regarding the three component scores of the SGRQ, we observe statistically significant longitudinal associations between a 100 ml decrease in FEV$_1$ and all domains (activity, symptoms, and impacts). The biggest impact of FEV$_1$ decrease was found on the activity domain, followed by the symptoms- and impacts components (data not shown).

Table 3 Change in FEV$_1$ over 36 months stratified by baseline GOLD grades

	Change in FEV$_1$		
	decrease ≥ 100 ml	no change	increase ≥ 100 ml
GOLD 1/2 (n = 695)	63,6%	24,6%	11,8%
GOLD 3/4 (n = 478)	50,4%	33,7%	15,9%
Total sample (n = 1173)	58,2%	28,3%	13,5%
Mean FEV$_1$ change	− 311 ml	−11 ml	269 ml
Responder[1] SGRQ	29,1%	35,5%	48,4%
Responder[1] VAS	26,5%	37,2%	43,9%

[1]Indicates the percentage of patients who experienced a clinically relevant improvement in HRQL
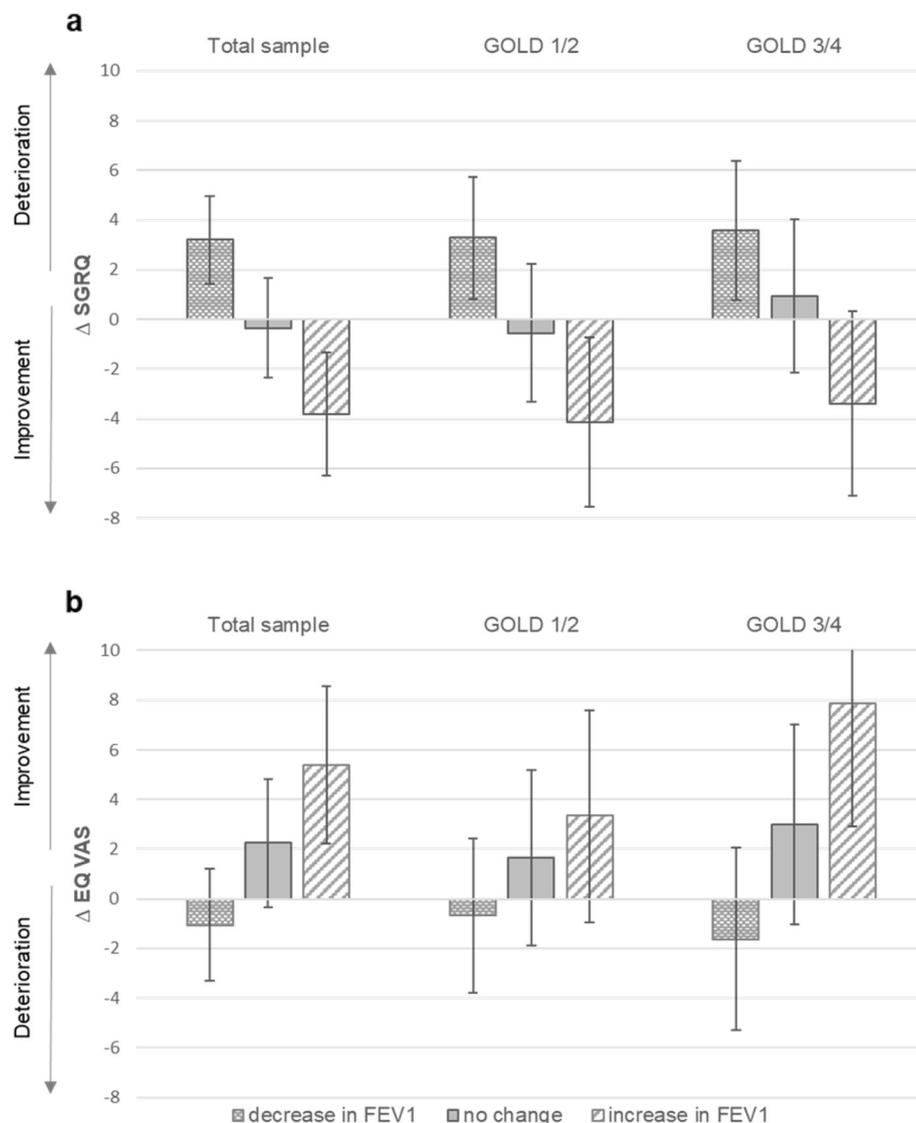
Fig. 2 Absolute adjusted mean change in SGRQ (a) and EQ VAS (b) after 36 months. Ordinary least square regression models were adjusted for age, sex, BMI, education, smoking status, number of comorbidities, exacerbation history, and FEV_1 change*baseline FEV_1. Error bars indicate 95% confidence intervals. Change categories in FEV_1 were defined as decrease in absolute $FEV_1 \geq 100$ ml, increase in absolute $FEV_1 \geq 100$ ml, and no change (in between) after 36 months

Regarding the generic EQ VAS (Table 5), we observed estimates of the same direction, but overall estimates were smaller regarding both the between- and within-subjects analysis in relation to a 100 ml FEV_1 difference or change, respectively.

Sensitivity analysis
The results of the sensitivity analysis are displayed in Additional file 2 (Change Score model) and Additional file 3 (HLM). Overall, the inclusion of IPW confirmed our results since all estimates and *p*-values were nearly identical. However, it also indicated a slight underestimation of the effect of change in FEV_1 on

HRQL particularly in patients with GOLD 3/4 at baseline when excluding dropouts. For example, in patients with baseline GOLD 3/4, the deterioration in SGRQ associated with decrease in FEV_1 was more pronounced when considering participants who dropped out through IPW (SGRQ mean change + 4.11 [1.37 to 6.84] including IPW vs. + 3.59 [0.79 to 6.38] without IPW (see Additional file 2).

Discussion
We analysed the change in HRQL over 3 years associated with change in FEV_1 and investigated both the cross-sectional and the longitudinal association of FEV_1
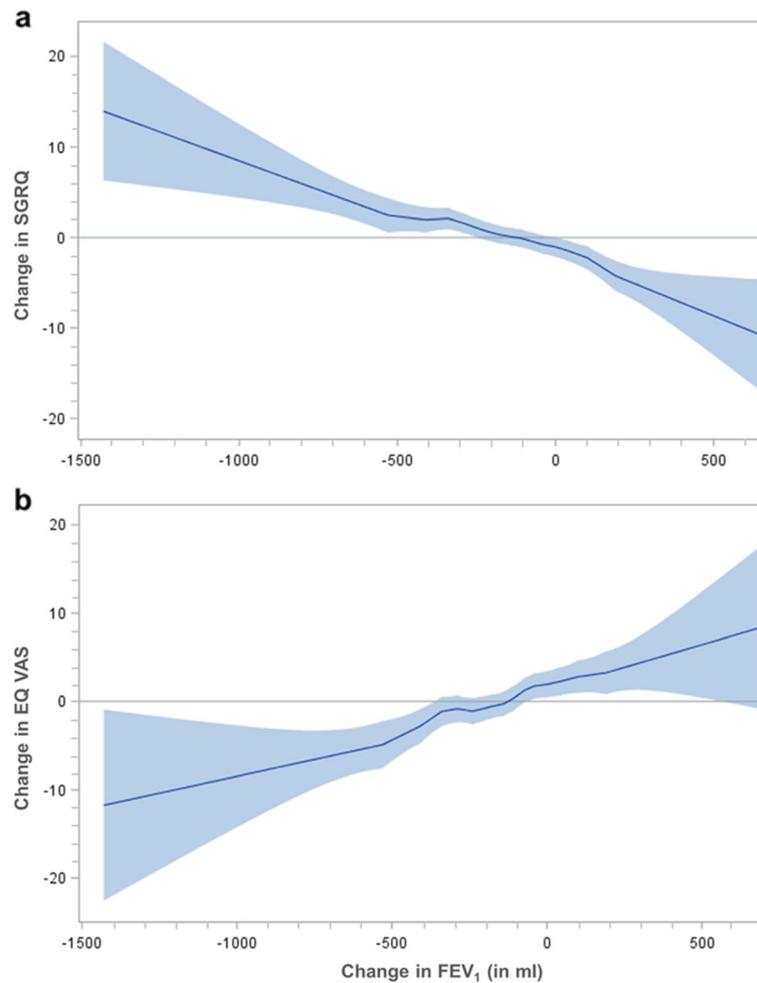
Fig. 3 Relationship between change in FEV$_1$ and SGRQ (a), EQ VAS (b). Generalized additive models were adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history. The solid curves represent the estimated smooth functions of the association between FEV$_1$ and HRQL. The shaded areas indicate 95% confidence intervals

and HRQL. On the population level, the overall decline in SGRQ total score was small but statistically significant and was completely driven by a significant deterioration of + 4 units in the activity domain. On the individual patient level, more than one-third of patients experienced a clinically relevant deterioration in SGRQ. We found a linear relationship between change in FEV$_1$ and change in HRQL meaning that decrease in FEV$_1$ was associated with a deterioration in HRQL whereas an increase in FEV$_1$ was similarly found associated with improved

Table 4 Cross-sectional and longitudinal estimates for the association between FEV$_1$ and disease-specific HRQL as measured with the SGRQ

Outcome: SGRQ	Total sample	GOLD 1/2	GOLD 3/4
	estimate [95% CI]	estimate [95% CI]	estimate [95% CI]
FEV$_1$ between-subjects	−1.42* [− 1.55 to − 1.29]	−1.00* [− 1.23 to −0.78]	−1.57* [− 1.95 to − 1.19]
FEV$_1$ within-subjects	0.83* [0.65 to 1.01]	0.86* [0.63 to 1.09]	0.92* [0.60 to 1.23]

*$p < 0.001$
Hierarchical linear models (HLM) adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history
Interpretation: Positive estimates indicate deterioration in HRQL. FEV$_1$ between-subjects: cross-sectional difference in HRQL per 100 ml difference in FEV$_1$ between subjects. FEV$_1$ within-subjects: longitudinal change in HRQL per 100 ml decrease in FEV$_1$ within subjects over time

Table 5 Cross-sectional and longitudinal estimates for the association between FEV_1 and generic HRQL as measured with the EQ VAS

Outcome: EQ VAS	Total sample	GOLD 1/2	GOLD 3/4
	estimate [95% CI]	*estimate [95% CI]*	*estimate [95% CI]*
FEV_1 between-subjects	1.08* [0.95 to 1.21]	0.71* [0.49 to 0.93]	1.20* [0.83 to 1.58]
FEV_1 within-subjects	−0.87* [− 1.13 to − 0.62]	−0.67* [− 0.98 to − 0.35]	−1.20* [− 1.64 to − 0.76]

*$p < 0.001$
Hierarchical linear models (HLM) adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history
Interpretation: Positive estimates indicate improvement in HRQL. FEV_1 between-subjects: cross-sectional difference in HRQL per 100 ml difference in FEV_1 between subjects. FEV_1 within-subjects: longitudinal change in HRQL per 100 ml decrease in FEV_1 within subjects over time

HRQL. Remarkably, a no change in FEV_1 was also associated with slight improvements in HRQL. We found a highly significant relation between a 100 ml within-subject FEV_1 decrease and generic and disease-specific HRQL, with the largest estimate for the activity domain of the SGRQ.

The overall decline in the disease-specific HRQL in COPD is in line with the literature [12, 28, 29]. Noteworthy enough, the decline was not steady over time, as we found small reductions in the SGRQ total score (i.e. improvement in HRQL) and symptoms component as well as in the EQ VAS for the first 18-months of follow-up, similar to what has been previously observed by Yoo and co-workers [30].

The deterioration in SGRQ was completely driven by the activity component. This aligns with Waschki et al. who reported a substantial decrease in physical activity over 3 years in a COPD cohort [31]. The finding, that the symptoms and impact component remained unchanged or even improved, would be compatible with the assumption that these factors can be managed through adequate medical or non-medical therapy [14]. Our data underline that maintenance of physical activity should play a much greater role in the treatment of COPD.

The mean changes in HRQL as related to the three FEV_1 change categories did not exceed the MCID. However, a mean deterioration in HRQL on the population level, which is significantly different from zero, indicates an important development, given that a relevant proportion of patients experienced a clinical relevant change in HRQL after 3 years. Furthermore, our results are in line with a systematic review by Westwood and co-workers, who summarized the information of 22 randomized controlled trials on the effects of long-acting bronchodilator therapy and analysed the relationship between increase in FEV_1 and patient-reported outcomes, including HRQL as measured using the SGRQ [13]. According to this analysis, a mean 2.5 units decrease in SGRQ total score (i.e. improvement) was estimated for a 100 ml increase in FEV_1.

Our results partly concur with Westwood et al., finding that even no change in FEV_1 is associated with improved HRQL. While the GAM indicated slight improvements in HRQL for a zero change in FEV_1, the stratified analysis confirmed this only for patients with baseline GOLD grades 1/2, but indicated a trend for deteriorations in SGRQ for the more severe grades GOLD 3/4. Westwood et al. discuss a potential Hawthorne effect – a phenomenon whereby patients modify their behaviour because of their active participation in science and their awareness of being observed [32]. However, in our study, this effect might be small because the intensity of supervision is rather low with more than a year between study visits. Adaptation processes or changes in treatment after recruitment into the cohort might rather play a role and additional research is needed to further explore this.

The observational Japanese COPD cohort HOK-KAIDO evaluated the relationship between FEV_1 decline and change in SGRQ and its component scores. Based on the degree of the annual decline in FEV_1, the cohort was split into three categories: rapid decliner (− 63 ± 2 ml/year), slow decliner (− 31 ± 1 ml/year) and sustainers (including improvements in FEV_1 (− 2 ± 1 ml/year)). The authors report deterioration in HRQL for the rapid decliners indicated by a change of 5 units of the SGRQ total score after 5 years, zero change for slow decliners and an improvement in HRQL (− 4 units SGRQ) for the sustainers [14]. Calculation of the change in SGRQ per 100 ml FEV_1 decrease based on the data given for the rapid decliner, results in a mean deterioration in HRQL by a 1.59 units change in SGRQ total score. The within-subject estimate of our HLM indicated a deterioration in HRQL of half the size (+ 0.83 units SGRQ per 100 ml FEV_1 decrease), which is not surprising, considering that our population was not stratified by categories of FEV_1 decline.

Both HRQL measures differentiated between GOLD strata at baseline and the longitudinal within-subject association between FEV_1 and HRQL showed a similar relationship. However, the overall change in EQ VAS after 3 years (− 0.5 units, n.s.) might have been too small to detect significant mean changes in EQ VAS as related to the FEV_1 change category decrease. Methodological

Lutter *et al. BMC Pulmonary Medicine*   (2020) 20:148

Page 10 of 12

aspects could explain part of the observed differences. Whereas the SGRQ covers history and current health status, the EQ VAS refers to the patients' current short-term health status, which might show more variation than a sort of averaging as implemented in the SGRQ. Moreover, the EQ VAS as a generic measure of HRQL includes aspects of the patients' life that are not related to his/her COPD all. We conclude that disease-specific instruments are more suitable for the longitudinal assessment of HRQL in patients with COPD.

Selective dropout of patients is an issue in long-term observational cohort studies. Regarding our data set of 2291 eligible patients recruited at baseline of the COSYCONET cohort study, 557 and 552 patients were not re-examined at the 18-month and 36-month follow-up visit, respectively. Of those 1109 patients, 153 (14%) died and 296 (27%) terminated their participation due to worsening of their health status. However, we do not think that dropout severely affected our findings and the sensitivity analysis including the IPW confirmed this hypothesis. One reason might be that our aim was to analyse the association of change in FEV_1 and HRQL and not to predict HRQL development. The latter would indeed be influenced by dropout as one would expect those with deteriorating COPD to also experience worse HRQL. Second, the hierarchical linear model also included patients who were available for only two examinations, therefore minimizing the number of patients not considered.

With regard to the observational and longitudinal design of our study, some limitations need to be addressed. First, regression to the mean might have occurred in the repeated measurement of lung function and HRQL values [33]. This bias seems, however, unlikely since we were interested in the association between the change in FEV_1 and the change in HRQL, which was independent from FEV_1 group assignment. Furthermore, longitudinal results were also confirmed by the HLMs, which are thought to be robust against a bias from regression to the mean. Second, our analyses do not allow drawing conclusions regarding treatment effects on lung function. All patients were under their usual therapy, but medication-specific variables were not considered in the models. This aspect might, however, be less important, as in general the treatment in the COSYCONET cohort is very intense and broad [34].

Conclusions

To conclude, our study provides estimates for both the cross-sectional and longitudinal association between FEV_1 and HRQL and these were highly statistically significant regarding both outcomes: disease-specific and generic HRQL. Overall, change in HRQL followed change in FEV_1, however, increases in FEV_1 were associated with greater HRQL gains than equal decreases in FEV_1 with HRQL losses. To monitor the progression of COPD from the patient's perspective, the disease-specific SGRQ was found superior to the generic EQ-VAS. As quality of life is an important aspect in patients' life, determining the course of the disease and therapeutic requirements, the findings suggest that optimal treatment of lung function and a minimization of its deterioration over time has an impact beyond the patients' functional status. Furthermore, deterioration of HRQL should induce timely re-examination of physical status and lung function and possibly reassessment of therapeutic regimes, particularly in patients with severe airflow obstruction.

Lutter *et al. BMC Pulmonary Medicine*   (2020) 20:148

Page 11 of 12

Therapieforschung GmbH); Virchow, J. Christian (Universitätsklinikum Rostock); Vogelmeier, Claus (Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg); Wagner, Ulrich (Klinik Löwenstein gGmbH); Welte, Tobias (Medizinische Hochschule Hannover); Wirtz, Hubert (Universitätsklinikum Leipzig).

Authors' contributions

JL and RH conceptualized the paper and performed the statistical analysis. JL, RJ, HS, LS, MS, and RH interpreted the data. JL and RH drafted the manuscript. RJ, SK, KK, HS, and CV were involved in the coordination and the data acquisition of the COSYCONET study. All authors took part in the discussion and critical revision of this manuscript. All authors read and approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

Availability of data and materials

Data may be obtained from a third party and are not publicly available. The full dataset supporting the conclusions of this article is available upon request and application from the Competence Network Asthma and COPD (ASCONET, http://www.asconet.net/html/cosyconet/projects).

Ethics approval and consent to participate

The COSYCONET study complies with the Declaration of Helsinki and Good Clinical Practice Guidelines and has been approved by the ethics committee of the medical faculty of the Philipps-Universität Marburg, the local ethics committees of the participating centers (a list of all participating study centers can be found here: http://www.asconet.net/html/cosyconet/studzent) and by the concerned data security authority (data security agency of the federal states of Hesse, Baden-Württemberg, Lower-Saxony, and Saarland). This approval covered the subsequent data analyses as performed here. All cohort participants gave their written informed consent.

Consent for publication

Not applicable.

Competing interests

CV reports grants and personal fees outside the submitted work from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Mundipharma, Novartis, and personal fees from Cipla, Berlin Chemie/ Menarini, CSL Behring, Teva, Bayer Schering Pharma AG, MSD, and Pfizer. All other authors declare no conflicts of interest.

Author details

[1]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, GmbH – German Research Center for Environmental Health, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany. [2]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Ziemssenstr. 1, 80336 Munich, Germany. [3]Department of Internal Medicine V, University of Munich (LMU), Comprehensive Pneumology Center, Member of the German Center for Lung Research, Ziemssenstr. 1, 80336 Munich, Germany. [4]Department of Pneumology, Paracelsus Medical University Salzburg, Universitätsklinikum Salzburg, Müllner Hauptstrasse 48, 5020 Salzburg, Austria. [5]Institute of Epidemiology, Helmholtz Zentrum München (GmbH) – German Research Center for Environmental Health, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany. [6]Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg, Member of the German Center for Lung Research (DZL), Baldingerstrasse, 35043 Marburg, Germany. [7]Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Ludwig-Maximilians-University Munich (LMU), Marchioninistr. 15, 81377 Munich, Germany.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, et al: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD executive summary. Eur Respir J 2017, 49.
2. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit Care Med. 2009;180:3–10.
3. Agustí A, Celli B. Natural history of COPD: gaps and opportunities. ERJ Open Res. 2017;3.
4. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Coxson HO, Crim C, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365:1184–92.
5. Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, Shimizu K, Betsuyaku T, Ito YM, Fuke S. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185:44–52.
6. Casanova C, de Torres JP, Aguirre-Jaíme A, Pinto-Plata V, Marin JM, Cordoba E, Baz R, Cote C, Celli BR. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med. 2011;184:1015–21.
7. Carone M, Antoniu S, Baiardi P, Digilio VS, Jones PW, Bertolotti G. Predictors of mortality in patients with COPD and chronic respiratory failure: the quality-of-life evaluation and survival study (QuESS): a three-year study. Copd. 2016;13:130–8.
8. Fan VS, Curtis JR, Tu SP, McDonell MB, Fihn SD. Using quality of life to predict hospitalization and mortality in patients with obstructive lung diseases. Chest. 2002;122:429–36.
9. Wilke S, Jones PW, Müllerova H, Vestbo J, Tal-Singer R, Franssen FM, Agusti A, Bakke P, Calverley PM, Coxson HO. One-year change in health status and subsequent outcomes in COPD. Thorax. 2015;70:420–5.
10. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M. Longitudinal deteriorations in patient reported outcomes in patients with COPD. Respir Med. 2007;101:146–53.
11. Jones PW, Donohue JF, Nedelman J, Pascoe S, Pinault G, Lassen C. Correlating changes in lung function with patient outcomes in chronic obstructive pulmonary disease: a pooled analysis. Respir Res. 2011;12:161.
12. Spencer S, Calverley PM, Sherwood Burge P, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163:122–8.
13. Westwood M, Bourbeau J, Jones PW, Cerulli A, Capkun-Niggli G, Worthy G. Relationship between FEV 1 change and patient-reported outcomes in randomised trials of inhaled bronchodilators for stable COPD: a systematic review. Respir Res. 2011;12:40.
14. Nagai K, Makita H, Suzuki M, Shimizu K, Konno S, Ito YM, Nishimura M. Differential changes in quality of life components over 5 years in chronic obstructive pulmonary disease patients. Int J Chronic Obstruct Pulmon Dis. 2015;10:745.
15. Karch A, Vogelmeier C, Welte T, Bals R, Kauczor H-U, Biederer J, Heinrich J, Schulz H, Gläser S, Holle R, et al. The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline. Respir Med. 2016;114:27–37.
16. Karl FM, Holle R, Bals R, Greulich T, Jorres RA, Karch A, Koch A, Karrasch S, Leidl R, Schulz H, et al. Costs and health-related quality of life in Alpha-1-antitrypsin deficient COPD patients. Respir Res. 2017;18:60.
17. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver B, Enright PL, Hankinson JL, Ip MS, Zheng J. Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations. Eur Respir J. 2012:erj00803–2012..
18. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. Am Rev Respir Dis. 1992;145:1321–7.

Lutter *et al. BMC Pulmonary Medicine*   (2020) 20:148

Page 12 of 12

19. 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;132:456–63.
20. Wacker ME, Jorres RA, Karch A, Wilke S, Heinrich J, Karrasch S, Koch A, Schulz H, Watz H, Leidl R, et al. Assessing health-related quality of life in COPD: comparing generic and disease-specific instruments with focus on comorbidities. BMC Pulm Med. 2016;16:70.
21. Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SS, Man WD: The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. Thorax 2016:thoraxjnl-2015-207782.
22. Jones PW. St. George's respiratory questionnaire: MCID. Copd. 2005;2:75–9.
23. Putcha N, Puhan MA, Drummond MB, Han MK, Regan EA, Hanania NA, Martinez CH, Foreman M, Bhatt SP, Make B, et al. A simplified score to quantify comorbidity in COPD. PLoS One. 2014;9:e114438.
24. Thomsen LH, Dirksen A, Shaker SB, Skovgaard LT, Dahlbäck M, Pedersen JH. Analysis of FEV1 decline in relatively healthy heavy smokers: implications of expressing changes in FEV1 in relative terms. COPD: J Chron Obstruct Pulmon Dis. 2014;11:96–104.
25. Donohue JF. Minimal clinically important differences in COPD lung function. COPD: J Chron Obstruct Pulmon Dis. 2005;2:111–24.
26. Hastie TJ: Generalized additive models. In Statistical models in S. Routledge; 2017: 249–307.
27. Hedeker D. An introduction to growth modeling. Sage Handb Quant Methodol Soc Sci. 2004:215–34.
28. Habraken JM, van der Wal WM, Ter Riet G, Weersink EJ, Toben F, Bindels PJ. Health-related quality of life and functional status in end-stage COPD: a longitudinal study. Eur Respir J. 2011;37:280–8.
29. Ferrari R, Tanni SE, Caram LM, Naves CR, Godoy I. Predictors of health status do not change over three-year periods and exacerbation makes difference in chronic obstructive pulmonary disease. Health Qual Life Outcomes. 2011; 9:112.
30. Yoo J, Kim Y, Kim S, Lee H, Park C, Oh E, Oh Y. Factors affecting the trajectory of health-related quality of life in COPD patients. Int J Tuberc Lung Dis. 2016;20:738–46.
31. Waschki B, Kirsten AM, Holz O, Mueller K-C, Schaper M, Sack A-L, Meyer T, Rabe KF, Magnussen H, Watz H. Disease progression and changes in physical activity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;192:295–306.
32. Calverley PM, Rennard SI. What have we learned from large drug treatment trials in COPD? Lancet. 2007;370:774–85.
33. Suissa S. Lung function decline in COPD trials: bias from regression to the mean. Eur Respir J. 2008;32:829-31.
34. Graf J, Jorres RA, Lucke T, Nowak D, Vogelmeier CF, Ficker JH. Medical treatment of COPD. Dtsch Arztebl Int. 2018;155:599–605.

Publisher's Note