

Impact of Lung Function and Exacerbations on Health-Related Quality of Life in COPD Patients Within One Year: Real-World Analysis Based on Claims Data

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Purpose: Real-world evidence on the impact of forced expiratory volume in one second (FEV₁) and exacerbations on health-related quality of life (HRQoL) in patients with chronic obstructive pulmonary disease (COPD) is sparse especially with regard to GOLD ABCD groups. This study investigates how changes in FEV₁ and exacerbations affect generic and disease-specific HRQoL in COPD patients over one year.

Methods: Using German claims data and survey data, we classified 3016 COPD patients and analyzed their health status by GOLD groups AB and CD. HRQoL was measured with the disease-specific COPD assessment test (CAT) and the visual analog scale (VAS) from the generic Euro-QoL 5D-5L. We applied change score models to assess associations between changes in FEV₁ (≥ 100 mL decrease/no change/ ≥ 100 mL increase) or the development of severe exacerbations with change in HRQoL.

Results: FEV₁ decrease was associated with a significant but not minimal important difference (MID) deterioration in disease-specific HRQoL (mean change [95% CI]: CAT +0.74 [0.15 to 1.33]), while no significant change was observed in the generic VAS. Experiencing at least one severe exacerbation also had a significant impact on CAT deterioration (+1.58 [0.52 to 2.64]), but again not on VAS. Here, GOLD groups AB showed not only a statistically but also a clinically relevant MID deterioration in CAT (+2.1 [0.88 to 3.32]). These particular patient groups were further characterized by a higher probability of being male, having a higher mMRC and Charlson index, and a lower probability of having higher FEV₁ or BMI values.

Conclusion: FEV₁ decline and the occurrence of ≥ 1 severe exacerbation are significantly associated with overall deterioration in disease-specific HRQoL. Preventing severe exacerbations particularly in patients without previous severe exacerbations (ABCD groups A and B) may help to stabilize the key patient-reported outcome HRQoL.

Keywords: COPD, health-related quality of life, longitudinal study, real-world evidence, forced expiratory volume in 1 second, exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious and usually progressive disease characterized by not fully reversible airflow obstruction and respiratory symptoms, such as breathlessness, cough, and sputum production.¹ In 2019, COPD was the third leading cause of death worldwide and claimed more than 3 million lives.² In the future, the burden of COPD is predicted to increase because of continued exposure to risk factors, such as smoking, and an aging population.³

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests characterizing COPD patients by airflow limitation and clinical presentation: first, GOLD grades I–IV, which are based on the lung function measure forced expiratory volume in one second (FEV₁); and second, ABCD groups that reflect a combination of exacerbation history and symptom burden. This highlights the importance of the FEV₁ and the exacerbation history as two markers of the disease.

Exacerbations can be attributed to patient-reported outcomes (PROMs).^{4,5} One of the most important PROMs is the patients' health-related quality of life (HRQoL). The HRQoL reflects the patient's perspective of their disease and is a key outcome in the German disease management programs (DMPs).⁶ Therefore, HRQoL measures are meaningful instruments, as they cover the subjective impact of the disease on daily life and the severity of symptoms.⁷

In COPD, HRQoL decreases with increasing severity of airflow limitation (GOLD I–IV^{8,9}) and also with higher symptom burden, and is thus worse in groups B and D.^{10,11} In COPD patients, FEV₁ usually shows a downward trajectory,^{12–14} which is steeper than the regular annual lung function decline in the healthy population (17.7–46.4 mL/year)¹⁵ especially in early disease stages.¹⁴ This decline in FEV₁ in COPD is associated with a decline in patients' HRQoL.^{16–18} On the other hand, exacerbations also negatively affect HRQoL.^{19–22} Nonetheless, the longitudinal association between these two clinical factors and HRQoL is not fully understood,^{23–25} especially with regard to GOLD ABCD groups. Although the relationship between clinical factors and HRQoL has often been analyzed for GOLD I–IV, there are few published reports regarding ABCD groups, even though classification by ABCD groups is more closely associated with HRQoL.¹⁰

Therefore, the aim of this study is to analyze the impact of changes in FEV₁ and severe exacerbations on generic and disease-specific HRQoL in COPD patients within one year with regard to ABCD groups, based on a large real-world dataset from a German statutory health insurance fund and survey data.

Methods

Data

Our real-world dataset combines pseudonymized health insurance claims data with survey data. The claims data

were provided by the AOK Bavaria, a regional statutory health insurance (SHI) fund with almost 4.5 million policyholders and a 40.5% share in this regional SHI market during conduct of the study.²⁶ We only included data from patients participating in the structured DMP for COPD. Incorporating DMP data made clinical factors such as, eg, FEV₁ or BMI, which are not documented routinely within claims data, available.

To obtain generic and disease-specific HRQoL information, a two-wave survey was conducted in 49662 DMP participants. Wave 1 took place in November 2017, with 14754 (29.7%) responders. Wave 2, conducted in November 2018, only addressed responders from wave 1 and yielded 9232 (62.6%) responders. Additionally, the survey addressed breathlessness measured by the modified British Medical Research Council (mMRC)²⁷ and socio-demographic data.

Disease Severity and HRQoL Assessment

Lung function was assessed as FEV₁ liters, because FEV₁ % predicted (FEV₁%pred.) values were not uniformly available for all patients on account of documentation issues (see limitations). Nonetheless, wherever possible, we additionally calculated GOLD grades I–IV based on FEV₁%pred. with reference values taken from the Global Lung Initiative¹ to perform a sensitivity analysis. FEV₁ values represent an annual average, whenever several measurements per patient were available within one year. Exacerbations were defined as moderate when COPD symptoms worsened and required a doctor's visit or as severe when symptoms worsened and required a hospital stay, both measured by the respective utilization documented in claims data.²⁸ We assessed disease severity by GOLD ABCD groups, starting from the least severe group A. The groups A–D reflect a combination of exacerbation history and COPD symptoms. More severe groups C and D are classified by ≥ 2 moderate or at least one severe exacerbation occurring. Symptoms can be assessed (among others) by COPD assessment test (CAT)²⁹ or by mMRC.²⁷ More severe groups B and D are classified by mMRC ≥ 2 . We decided to use the mMRC for classification, because we used CAT as an outcome measure and several literature sources suggested other cut-off points than the GOLD standard (≤ 10) to define ABCD groups using the CAT.^{30,31}

Further, we measured disease-specific HRQoL via CAT²⁹ and generic HRQoL via Euro-Qol 5D (EQ-5D-5L).^{32,33} The CAT is scaled from 40 to 0 and comprises eight dimensions

with six answer levels in each dimension (0 = best state to 5 = worst state). Thus, a CAT of 40 describes the worst possible HRQoL state and 0 the best possible HRQoL state. The eight CAT dimensions include disease assessments such as cough, sputum, sleep, and energy. The minimal clinically important difference for the CAT has been determined to be a minimum 2.0 point change.^{34,35} The decision for the CAT as disease-specific measure was made in line with the results of a proceeding pilot study. This pilot study unveiled that the CAT outperformed two other disease-specific questionnaires (St. George's Respiratory Questionnaire (SGRQ), Clinical COPD Questionnaire (CCQ)) regarding response rates, validly answered questions (eg, non-missing items), explanatory power, and ceiling/floor effects. Furthermore, given its shortness, the CAT was deemed more easily intelligible and hence applicable for a HRQoL self-reporting by COPD patients.³⁶

The EQ-5D-5L consists of two parts. First, a valuation section with five dimensions (mobility, self-care, activity, pain, anxiety/depression) and, second, the visual analog scale (VAS). The VAS is a scale on which patients can value their current health status between 0 (worst state) and 100 (best state). The EQ-5D-5L has been validated for use in COPD patients.³³ Several estimates exist for minimal clinically important difference for the VAS in COPD patients.^{33,37} A frequently used value for the minimal important difference (MID) is a 6.9 point change.³³ For our analysis, we used only the VAS because it was found to differentiate better between COPD grades than the EQ-5D index,⁹ as it is easily comprehensible for participants to display their generic HRQoL and we do not address resource allocation issues requiring population preferences.

Assessment of Covariates

All models included the following covariates: age, sex, exacerbation history, comorbidities (claims data based), smoking status, BMI, lung function (DMP data based), as well as education, breathlessness, and HRQoL baseline (survey data based). Reference categories were female, non-smokers, and basic education. Comorbidities were identified based on the Charlson index.³⁸ Further information about the index conditions can be found elsewhere.²⁸ Breathlessness was interrogated by mMRC scale, which indicates dyspnea on an ascending scale from 0 to 4.²⁷

Statistical Analysis

We calculated means and standard deviations (SD) for continuous variables or counts and percentages for categorical variables. For bivariate comparisons of baseline characteristics between HRQoL MID-Deterioration/No-MID-Deterioration groups within our study population, we used Chi-squares for nominal variables, Wilcoxon-Mann-Whitney-tests for ordinal variables, and *t*-tests for continuous variables. Based on claims data, we contrasted survey-responders and non-responders regarding main characteristics to detect a potential non-response bias.

We also evaluated linear change in HRQoL over one year for all 3016 patients in our study population based on *t*-tests. To investigate the association between clinical changes and changes in HRQoL, we used two different statistical approaches.

First, we applied generalized additive models (GAM) to evaluate the association between HRQoL and FEV₁. GAMs are non-parametric regression models that are able to portray non-linear relationships between a dependent variable (change in HRQoL) and an independent variable (change in FEV₁ liter) using a smoothing function while adjusting for covariates.³⁹ The variance inflation factor was below any meaningful threshold (<2) and thus did not indicate any multicollinearity issues.⁴⁰ Second, we ran change score models based on ordinary least squares (OLS) linear regression to evaluate the relationship between (1) clinical changes in FEV₁ or (2) the occurrence of severe exacerbations and change in HRQoL. We stratified the analyses by GOLD groups AB and CD because of the small number of patients in single groups.

In a first step, we regressed the HRQoL mean change between baseline and one-year follow-up on three categories of FEV₁ change (increase/decrease/no change). The categories were defined as a FEV₁ ≥ 100 mL increase, a FEV₁ ≥ 100 mL decrease, and no change (in between). This 100 mL change cut-off in FEV₁ is considered to represent the MID.⁴¹ As we assumed that the change in FEV₁ depends on the lung function's baseline,⁴¹ we included an interaction term to account for different relative milliliter declines, eg, lower decline values in more severe GOLD stages¹⁴ resulting from a lower initial FEV₁.

Subsequently, we regressed the change in severe exacerbation history on the HRQoL mean change. Therefore, we built a subgroup for patients without severe exacerbations in the year before wave 1 but at least one severe exacerbation between wave 1 and wave 2. Earlier exacerbation history preceding the year before wave 1 was not taken into account.

To characterize these patients at risk, we conducted a logistic regression with this particular subgroup as binary outcome.

Both GAMs and change score models were stratified by GOLD ABCD group and adjusted for age, sex, education, smoking status, moderate/severe exacerbations, Charlson Comorbidity index, BMI, FEV₁, mMRC, and HRQoL baseline.

To check the robustness of our results, we performed a sensitivity analysis for all models containing a core group. Our core group comprised only patients with plausible mMRC and GOLD combinations in wave 2. Therefore, patients with combinations of GOLD grade I and mMRC of 3 or 4 were excluded (N=65), as well as GOLD IV patients with a mMRC of 0 or 1 (N=25). This core group was built to rule out possible data issues resulting from a FEV₁ measure change in the DMP, which are discussed further in the limitations.

For all analyses, we used the SAS software (SAS Institute Inc., Cary, NC, USA, Version 9.4) and considered p-values <0.05 as statistically significant.

Results

Study Population

From 14754 initial participants, 9232 individuals took part in both waves; 3016 of these had complete information for FEV₁, Charlson index, mMRC, BMI, education status, and

HRQoL (VAS and CAT) and were thus included in the analysis. Reasons for exclusion are summarized in [Figure 1](#). The characteristics of responders and the study population can be seen in [Additional File 1](#). In general, responders presented a population at lower risk, with higher FEV₁, and less severe exacerbations.

[Table 1](#) shows the baseline characteristics of the entire study population and contrasts the participants with and without a MID-relevant deterioration in HRQoL. In the total sample, 59.8% were male, mean age was 68.9 years, and mean FEV₁ was 1.9 liters. Regarding HRQoL, mean VAS score was 58.6 (SD ±19.9) and mean CAT score was 19.2 (±7.7). Around one in four patients experienced at least one moderate and around one in twenty patients at least one severe exacerbation within the baseline year. Patients with a clinically relevant VAS deterioration were older, had worse lung function with higher breathlessness, and reported better HRQoL at baseline (p-values ranging between 0.03 and <0.0001). Patients with clinically relevant CAT deterioration had a lower burden of breathlessness and a better baseline HRQoL (p-values between 0.03 and <0.0001). Moreover, we found a moderate linear relationship between VAS and CAT (Pearson correlation −0.61; Spearman correlation −0.62).

Within the ABCD groups, the baseline distribution was 43.1% (A), 37.1% (B), 7.4% (C), 12.5% (D). Analysis group

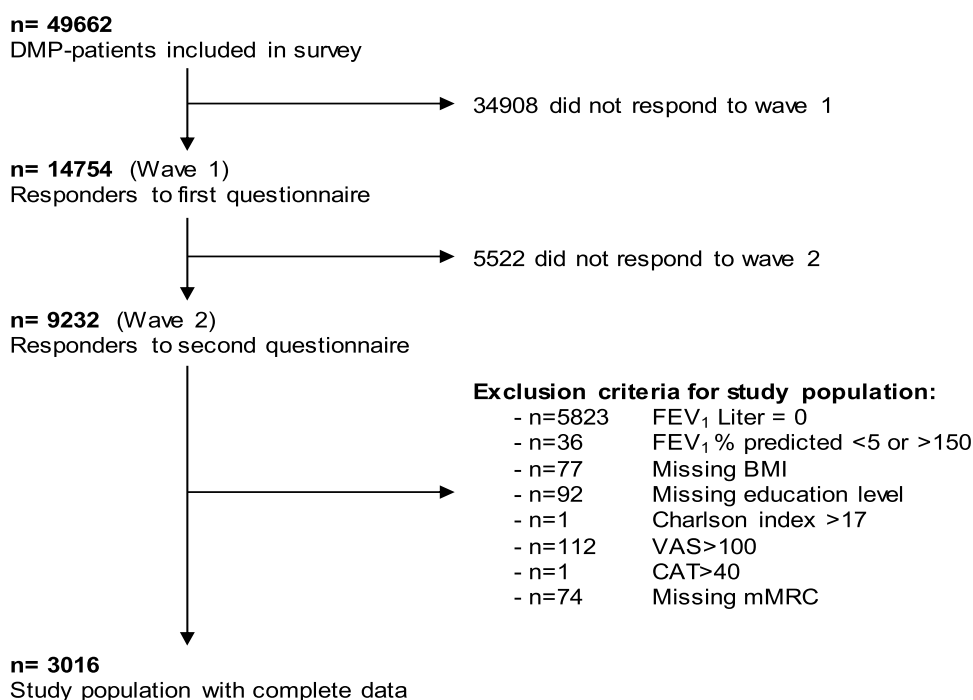


Figure 1 Overview of the study population.

Abbreviations: DMP, disease management program; FEV₁, forced expiratory volume in 1 second; BMI, body mass index; VAS, visual analog scale; CAT, COPD Assessment Test; mMRC, Modified Medical Research Council Questionnaire.

Table I Baseline Characteristics of Participants Who Experienced a Minimal Important Difference Deterioration in VAS (≥ -6.9) and CAT ($\geq +2$)

		Total Sample	No VAS MID-Deterioration	VAS MID-Deterioration		No CAT MID-Deterioration	CAT MID-Deterioration	
n		3016	2044	972	p-value	1759	1257	p-value
Male		1804 (59.81%)	1221 (59.74%)	583 (59.98%)	0.8985	1047 (59.52%)	757 (60.22%)	0.6989
Age, yrs. ^a		68.85 (± 9.49)	68.52 (± 9.53)	69.55 (± 9.36)	0.0051	68.72 (± 9.45)	69.04 (± 9.54)	0.3501
Smoking status ^a	Never smoker	1651 (54.74%)	1147 (56.12%)	504 (51.85%)	0.0850	981 (55.77%)	670 (53.3%)	0.1317
	Current smoker	1014 (33.62%)	664 (32.49%)	350 (36.01%)		566 (32.18%)	448 (35.64%)	
	Former smoker	351 (11.64%)	233 (11.4%)	118 (12.14%)		212 (12.05%)	139 (11.06%)	
Education ^a	Basic (9 yrs.)	2451 (81.27%)	1656 (81.02%)	795 (81.79%)	0.2022	1414 (80.39%)	1037 (82.5%)	0.1603
	Secondary (10 yrs.)	340 (11.27%)	233 (11.4%)	107 (11.01%)		216 (12.28%)	124 (9.86%)	
	Higher (12–13 yrs.)	83 (2.75%)	61 (2.98%)	22 (2.26%)		52 (2.96%)	31 (2.47%)	
	University	49 (1.62%)	38 (1.86%)	11 (1.13%)		29 (1.65%)	20 (1.59%)	
	None	93 (3.08%)	56 (2.74%)	37 (3.81%)		48 (2.73%)	45 (3.58%)	
BMI ^a		29.18 (± 6.02)	29.3 (± 6.07)	28.93 (± 5.92)	0.1144	29.25 (± 5.94)	29.08 (± 6.14)	0.4341
Exacerbations ^a	Moderate	0.84 (± 1.93)	0.8 (± 1.88)	0.92 (± 2.04)	0.1272	0.81 (± 1.91)	0.88 (± 1.97)	0.2897
	Severe	0.07 (± 0.39)	0.07 (± 0.38)	0.08 (± 0.4)		0.08 (± 0.45)	0.07 (± 0.29)	
FEV ₁ (Liter) ^a		1.88 (± 0.75)	1.91 (± 0.75)	1.83 (± 0.76)	0.0060	1.88 (± 0.74)	1.88 (± 0.76)	0.7869
Charlson index ^a		3.59 (± 2.69)	3.52 (± 2.67)	3.72 (± 2.73)	0.0567	3.57 (± 2.66)	3.61 (± 2.73)	0.6279
mMRC ^b		1.64 (± 0.99)	1.62 (± 0.99)	1.7 (± 0.99)	0.0343	1.69 (± 1)	1.58 (± 0.97)	0.0060
HRQoL: VAS baseline ^b		58.59 (± 19.94)	55.48 (± 20.43)	65.13 (± 17.14)	<0.0001	57.73 (± 20.04)	59.8 (± 19.75)	0.0048
HRQoL: CAT baseline ^b		19.2 (± 7.7)	19.08 (± 7.76)	19.47 (± 7.56)	0.1952	20.84 (± 7.46)	16.91 (± 7.45)	<0.0001
GOLD grade	I (FEV ₁ $\geq 80\%$)	412 (13.66%)	288 (14.09%)	124 (12.76%)	0.0012	233 (13.25%)	179 (14.24%)	0.5241
	II (FEV ₁ 50–79%)	1417 (46.98%)	992 (48.53%)	425 (43.72%)		827 (47.02%)	590 (46.94%)	
	III (FEV ₁ 30–49%)	940 (31.17%)	616 (30.14%)	324 (33.33%)		556 (31.61%)	384 (30.55%)	
	IV (FEV ₁ < 30%)	247 (8.19%)	148 (7.24%)	99 (10.19%)		143 (8.13%)	104 (8.27%)	
ABCD (mMRC)	A	1299 (43.07%)	911 (44.57%)	388 (39.92%)	0.0775	742 (42.18%)	557 (44.31%)	0.0312
	B	1118 (37.07%)	746 (36.5%)	372 (38.27%)		680 (38.66%)	438 (34.84%)	
	C	222 (7.36%)	146 (7.14%)	76 (7.82%)		113 (6.42%)	109 (8.67%)	
	D	377 (12.5%)	241 (11.79%)	136 (13.99%)		224 (12.73%)	153 (12.17%)	

Notes: Data are presented as mean (\pm SD) or n (%). Education is represented as three German school levels by years. P-values based on t-test, Chi-square-test and Wilcoxon–Mann–Whitney-test. Baseline data = Data previous 12 months before^a or from^b first questionnaire.

Abbreviations: Yrs, years; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; mMRC, Modified Medical Research Council Questionnaire; HRQoL, Health-related quality of life; VAS, visual analog scale; CAT, COPD assessment test.

AB comprised 2417 and group CD 599 patients. Overall, the largest proportion of COPD patients (12.9%) deteriorated in terms of symptom burden from AC to BD, of which 9.5% deteriorated from A to B ([Additional Files 2 and 3](#)).

Change in FEV₁, Exacerbations, and HRQoL

As visualized in [Table 2](#), FEV₁ and HRQoL decreased within one year. FEV₁ declined in the entire sample (significant) and in all ABCD groups (significant for group A only), except for group D, where a significant increase was observed. All these changes did not reach the established MID of 100mL.⁴¹

Regarding the occurrence of exacerbations, changes in the one-year observation period were small. We observed a statistically significant increase in moderate exacerbations in the total sample and all ABCD subgroups, except for a non-significant decrease in group C. Regarding severe exacerbations, there was an increase for the entire sample and groups A and B, although we observed a decrease for groups C and D. These changes were statistically significant for all subgroups except for group D. The biggest increase was found in group B (+0.22(moderate)/+0.08(severe)). An overview of the distribution of exacerbation frequency can be found in [Additional File 4](#).

Table 2 Change in FEV₁, Exacerbations and HRQoL for 3016 Patients Who Completed Both Questionnaires

		Baseline	1-Year	1-Year Change	1-Year % Change	p-value
FEV ₁ (Liter)	Total sample	1.88 (±0.75)	1.85 (±0.73)	−0.03	−1.7%	0.0005
	A	2.09 (±0.73)	2.01 (±0.69)	−0.08	−3.7%	<0.0001
	B	1.73 (±0.68)	1.72 (±0.69)	−0.01	−0.7%	0.4209
	C	2.01 (±0.79)	1.97 (±0.76)	−0.04	−2.2%	0.1149
	D	1.51 (±0.76)	1.58 (±0.8)	0.07	4.7%	0.0268
Moderate exacerbations	Total sample	0.84 (±1.93)	0.95 (±2.07)	0.11	13.0%	<0.0001
	A	0.08 (±0.27)	0.21 (±0.74)	0.13	154.7%	<0.0001
	B	0.08 (±0.27)	0.29 (±0.9)	0.22	278.2%	<0.0001
	C	4.23 (±2.43)	3.83 (±2.86)	−0.40	−9.4%	0.0099
	D	3.72 (±2.69)	3.76 (±3.07)	0.03	0.9%	0.7503
Severe exacerbations	Total sample	0.07 (±0.39)	0.1 (±0.46)	0.03	35.7%	0.0010
	A	0 (±0)	0.03 (±0.2)	0.03	/	<0.0001
	B	0 (±0)	0.08 (±0.36)	0.08	/	<0.0001
	C	0.2 (±0.64)	0.15 (±0.62)	−0.05	−26.7%	0.1803
	D	0.47 (±0.88)	0.37 (±0.92)	−0.10	−21.2%	0.0302
HRQoL: VAS	Total sample	58.59 (±19.94)	57.51 (±20.59)	−1.08	−1.8%	0.0006
	A	68.2 (±17.23)	66.94 (±17.94)	−1.25	−1.8%	0.0050
	B	50.24 (±17.54)	49.52 (±18.58)	−0.72	−1.4%	0.1802
	C	65.22 (±18.46)	63.9 (±19.11)	−1.32	−2.0%	0.2714
	D	46.37 (±18.66)	44.92 (±19.24)	−1.45	−3.1%	0.1388
HRQoL: CAT	Total sample	19.2 (±7.7)	19.75 (±7.9)	0.54	2.8%	<0.0001
	A	15.1 (±6.19)	15.93 (±6.86)	0.84	5.5%	<0.0001
	B	22.75 (±6.8)	22.99 (±7.1)	0.23	1.0%	0.1903
	C	15.88 (±7.03)	17.16 (±6.86)	1.28	8.1%	0.0008
	D	24.77 (±6.58)	24.78 (±7.03)	0.01	0.1%	0.9654

Note: Data are presented as mean (± SD) at baseline and follow-up.

Abbreviations: FEV₁, forced expiratory volume in 1 second; HRQoL, health-related quality of life; VAS, visual analog scale; CAT, COPD Assessment Test.

We also observed a significant overall deterioration in the disease-specific (CAT +0.54 units) and generic HRQoL (VAS −1.08 points). The changes were also statistically significant for groups A and B in VAS, and groups A and C in CAT. CAT change was mostly driven by a +1.28 point change in group C. Around one-third of the patients experienced a clinically relevant deterioration in VAS, and almost 42% in CAT (see [Figure 2](#)). Determinants of HRQoL deterioration can be seen in [Figure 3](#). A higher baseline HRQoL, age, mMRC, and having severe exacerbations significantly favored a MID deterioration in VAS, while being a never smoker and all education levels compared with the lowest level of education significantly prevented deterioration. For CAT, the results mirrored the findings regarding baseline HRQoL, never smokers, exacerbations, the mMRC, higher and secondary education level.

Impact of FEV₁ on HRQoL

Around 36% of DMP patients experienced a FEV₁ decrease, with group C having the highest (42%) and group D the lowest proportion of deterioration (29%) ([Table 3](#)).

We detected an approximately linear relationship between deterioration in VAS and FEV₁ (see [Figure 4](#)). The sensitivity analysis showed similar results ([Additional File 5](#)).

For the total sample, a one-year decrease in FEV₁ was associated with a significant deterioration in disease-specific HRQoL (mean change [95% CI]: CAT +0.74 [0.15 to 1.33]) (see [Figure 5](#)). At the same time, an increase in FEV₁ was also associated with a deterioration in CAT (+0.76 [0.16 to 1.37]), which thus highlights an overall downward trend in HRQoL in our study sample. This trend was also found in groups AB (CAT +1.05) but not in groups CD. Results for changes in VAS were neither

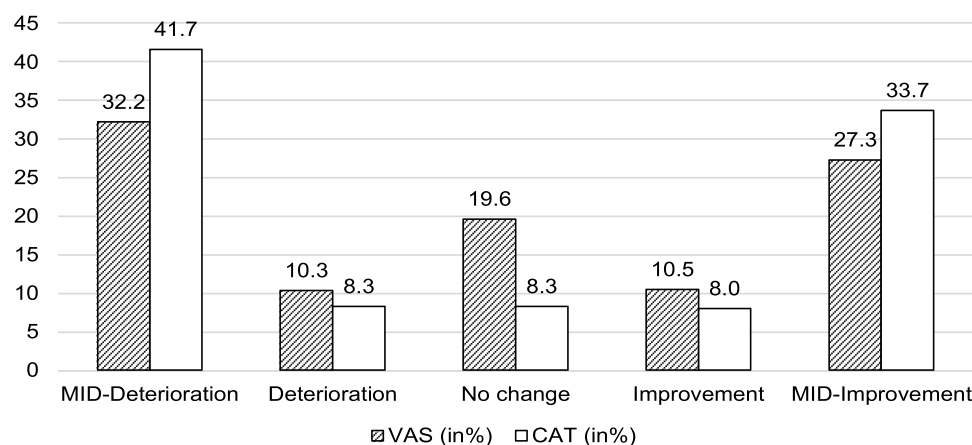


Figure 2 Proportion of HRQoL change with a Minimal Important Difference (MID).

Notes: MID-Deterioration in VAS ≥ -6.9 /MID-Improvement in VAS ≥ 6.9 . MID-Deterioration in CAT ≥ 2 /MID-Improvement in CAT ≥ -2 .

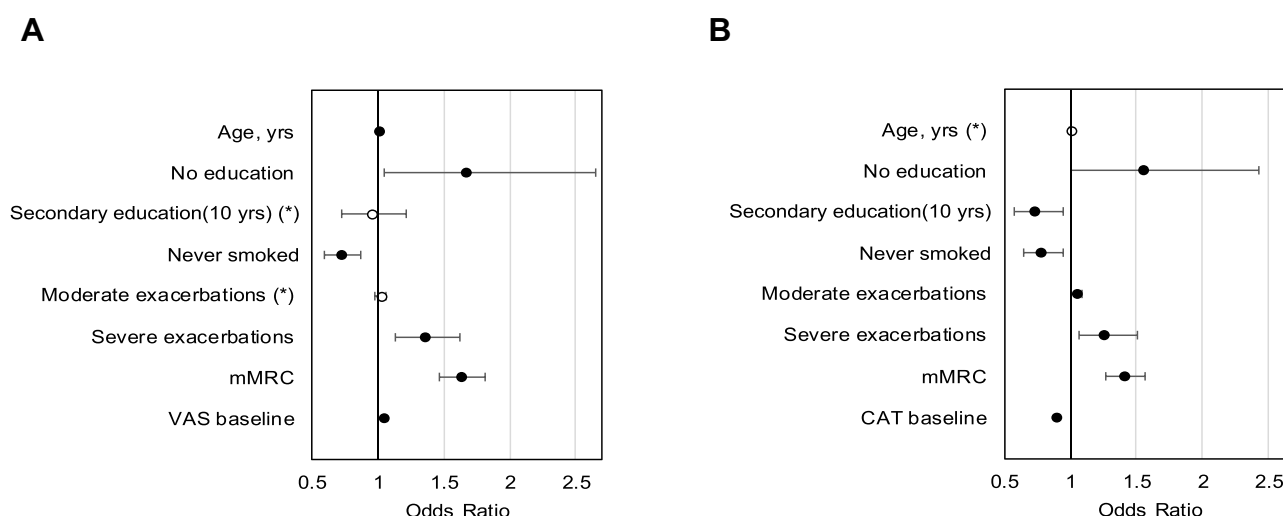


Figure 3 Determinants of a clinically relevant deterioration in generic HRQoL VAS (A) and disease-specific HRQoL CAT (B).

Note: *Not significant.

Abbreviations: mMRC, Modified Medical Research Council Questionnaire; VAS, visual analog scale; CAT, COPD Assessment Test.

significant nor clinically relevant. The sensitivity analysis validated these findings ([Additional File 6](#)).

Impact of Exacerbations on HRQoL

Focusing on patients without severe baseline exacerbations but newly occurring severe exacerbations in the observation period revealed a significant CAT deterioration (mean change [95% CI]: +1.58 [0.52 to 2.64]) that was also clinically relevant in groups AB (+2.1 [0.88 to 3.32]) (see [Figure 6](#)). Again, there were no significant results for the VAS model.

In group AB, being male, having a higher mMRC, and a higher Charlson index were linked to a higher probability

of experiencing severe exacerbations ([Additional File 7](#)). On the other hand, higher FEV₁ and BMI values reduced this probability.

The results for the change score models and logistic regression were robust in the sensitivity analysis ([Additional Files 8 and 9](#)).

Discussion

In this paper, we analyzed the association between a change in lung function or exacerbations and a one-year change in generic and disease-specific HRQoL in COPD patients stratified by GOLD ABCD groups. Overall, we found a small, statistically significant decrease in both

Table 3 Proportion of One-Year Changes in FEV₁

		Total	A	B	C	D
	n	3016	1299	1118	222	377
FEV ₁ change	Decrease	35.9%	39.2%	33.1%	42.3%	29.2%
	Stable	35.3%	33.4%	37.9%	32.9%	35.8%
	Increase	28.7%	27.4%	29.0%	24.8%	35.0%

Notes: Decrease: ≥ -100 mL of base value; Increase $\geq +100$ mL of base value.

Abbreviation: FEV₁, forced expiratory volume in 1 second.

HRQoL measures. For the generic VAS, almost one-third of patients deteriorated in a clinically relevant manner; for the disease-specific CAT, this proportion was 42%. In particular, patients in GOLD groups AB (no previous severe exacerbations) who developed at least one severe exacerbation in their follow-up showed a significant and clinically relevant deterioration in disease-specific HRQoL, which highlights a special need for prevention in this subgroup.

An overall deterioration in HRQoL at the population level is well known for other disease-specific and generic measures.^{16,42,43} In our sample, HRQoL was highest in group A, followed in descending order by groups C, B, and D. This signals a better health status in C over B, even though group C faces a higher exacerbation burden. This is in line with the literature.^{10,11} We observed the highest decrease rates in group C for disease-specific and in group D for generic HRQoL. The HRQoL deterioration within one year was significantly higher for patients with a more favorable baseline HRQoL, which supports the findings of Habraken et al.⁴⁴

Further, this overall deterioration was independent of the change direction in FEV₁ or severe exacerbations for the total sample, as the HRQoL decreased even with no severe exacerbation or with an increased lung function. This is contrary to the findings of Jones et al,¹⁹ who observed a slight increase in disease-specific HRQoL in absence of exacerbations or for a stable FEV₁ in a multinational, clinical trial population.

The portion of clinically relevant deteriorations at an individual patient level was higher in our population for the CAT (42%), whereas literature suggest a portion of only one-third for the similar disease-specific SGRQ.⁴⁵ Predictors for a MID deterioration in HRQoL for both VAS and CAT were found to be a higher HRQoL at baseline, greater breathlessness, and severe exacerbations, whereas being a never smoker decreased the probability of a clinically relevant deterioration. As on the other hand,

almost a third of our population presented a HRQoL improvement, more focus should be given to these different phenotypic cohorts in future research.

We are the first to analyze the HRQoL changes in VAS and CAT with regard to changes in FEV₁ or exacerbations, stratified by GOLD ABCD groups and based on a large claims dataset. Similar to Lutter et al,¹⁶ who evaluated the relationship of FEV₁ change and HRQoL change in GOLD groups I–IV within the German COSYCONET cohort, we did not find statistically significant changes in generic HRQoL for lung function declines.¹⁶ These authors used the SGRQ to measure disease-specific HRQoL, which limits direct comparability to only generic results. Nonetheless, we also found a statistically significant deterioration in disease-specific CAT for the total sample and groups AB, which did not exceed the MID. On the other hand, our findings diverge from the reference study, as they observed significant improvement in disease-specific and generic HRQoL for an increased FEV₁. Regarding disease-specific HRQoL, other studies using SGRQ confirm these results.^{17,46} In contrast, we detected a significant overall deterioration in HRQoL for our total sample and groups AB in CAT, even for an increased or stable FEV₁. This might indicate that FEV₁ change categories would be more appropriate with relative changes than absolute changes,^{47,48} but there is still no consensus yet about a %-MID.^{47,49} Mannino and Davis,¹³ for example, defined patients with an annual 3.5% change as rapid decliners. Thus, further research is needed, and our analysis should be reproduced when a consensus is reached on one relative MID, or even one MID per GOLD ABCD group.

Another aspect is that we observed small, non-significant HRQoL improvements over one year for groups CD, independent of lung function development. This can be attributed to relatively small group sizes leading to broad confidence limits, even though we combined both groups to counteract this issue (CD comprised 19.9% of the total sample).

For severe exacerbations, Nishimura et al⁵⁰ demonstrated a significant decline in disease-specific HRQoL (SGRQ) within 6 months, especially when they occur frequently (>1). Jones et al¹⁹ also analyzed the association of change in exacerbation rate on SGRQ over three years. Comparing our results with their placebo group, our results confirm that ≥ 1 severe exacerbations results in a significant HRQoL decrease, but we did not observe a HRQoL increase for having no severe exacerbations. This again mirrors our observation of an overall downward

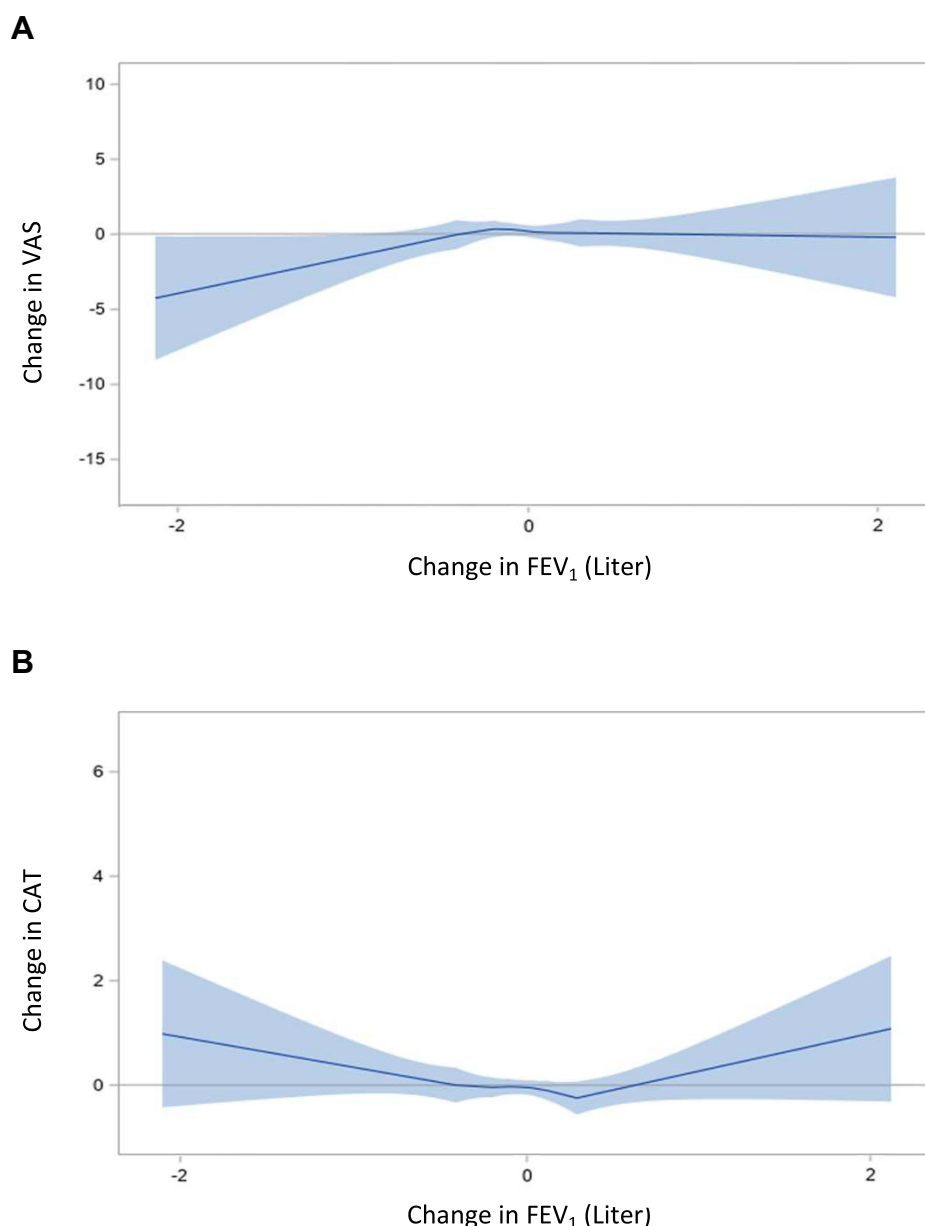


Figure 4 Impact of clinical indicators on HRQoL: Linear relationship between change in FEV₁ and VAS (**A**) and CAT (**B**).

Notes: The estimated smooth functions of the relationship between FEV₁ and HRQoL are represented by the solid curves. The shaded areas indicate the 95% confidence intervals. Generalized additive models were adjusted for age, sex, smoking status, education, BMI, number of moderate and severe exacerbation, FEV₁ liter change, Charlson Comorbidity index, mMRC, and VAS/CAT baseline.

trend in HRQoL in our study population. For our analysis, we did not measure the change in the absolute number of exacerbations, as no consistent MID exists for exacerbations.⁵¹ Therefore, we investigated the change from absence of severe exacerbation at baseline to presence of at least one severe exacerbation during the follow-up. Although we did not find significant changes in VAS, we found a markedly higher and statistically significant HRQoL deterioration in CAT in patients experiencing severe exacerbations. In subgroup GOLD AB, severe

exacerbations were associated not only with a significant but also with a clinically relevant deterioration in disease-specific HRQoL. Thus, our results highlight the importance of preventive measures, especially in patients who are in group AB without severe exacerbations in the previous year. For this subgroup, a MID reduction in disease-specific quality of life can be counteracted if one or more severe exacerbations can be prevented. Guo et al²¹ also recently stressed a need for effective prevention as exacerbations do have a sustainable and lasting impact on

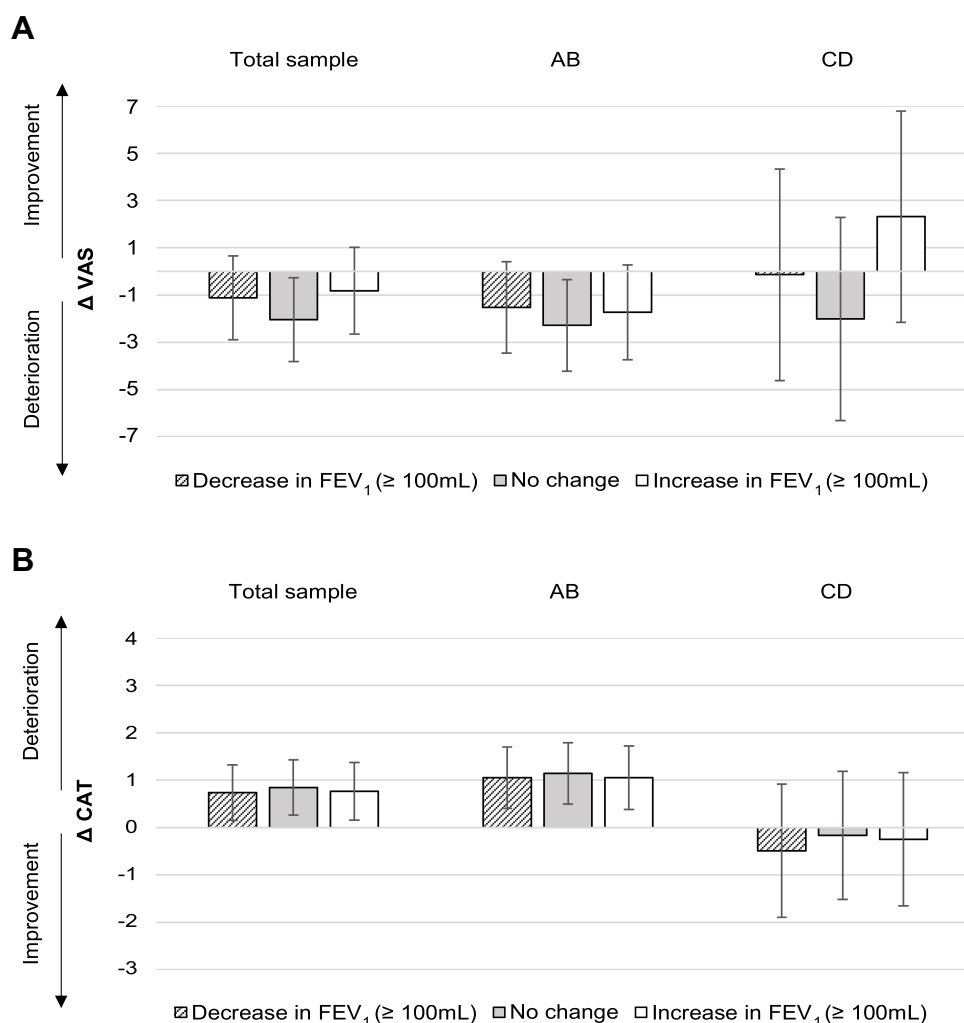


Figure 5 Change score model: impact of FEV₁ on HRQoL.

Notes: Absolute adjusted mean change in VAS (A) and CAT (B) after one year. ABCD groups at baseline. Error bars indicate 95% confidence intervals.

HRQoL. In the literature, lower mMRC, fewer exacerbations in history, and FEV₁ decrease were shown to affect exacerbation risk. For example, a FEV₁ lower than 50% results in a 2.6 higher risk of experiencing a severe exacerbation,⁵² whereas a 100-mL FEV₁ increase reduces exacerbation risk by 10%.⁵³ Countering this, exacerbations were also postulated to have a negative impact on FEV₁.²¹ All in all, the relationship between FEV₁ and exacerbations has been shown to be mostly consistent, but exceptions also exist⁵⁴ and, for example, not all exacerbations inevitably lead to a decline in FEV₁.⁵⁵ As exacerbations and FEV₁ appear to be connected, further research with a larger sample size could allow analysis of the combined interactional change in both clinical factors on HRQoL change.

For both clinical factors, methodological aspects can explain the different results in VAS and CAT models, as VAS only portrays the current and short-term overall health status, whereas the CAT is COPD specific and refers to the historic and current health status. Therefore, we agree with Lutter et al¹⁶ that disease-specific measures are more suitable to assess longitudinal HRQoL in COPD.

With regard to our study design, we need to address limitations, as our study population is exposed to selection bias. First, while our sample included data from an SHI fund with a large market share, we do not have information on COPD patients covered by respective DMPs by other SHI funds, nor on COPD patients not covered by respective DMPs. Second, all participants are voluntarily enrolled in the DMP, which implies that

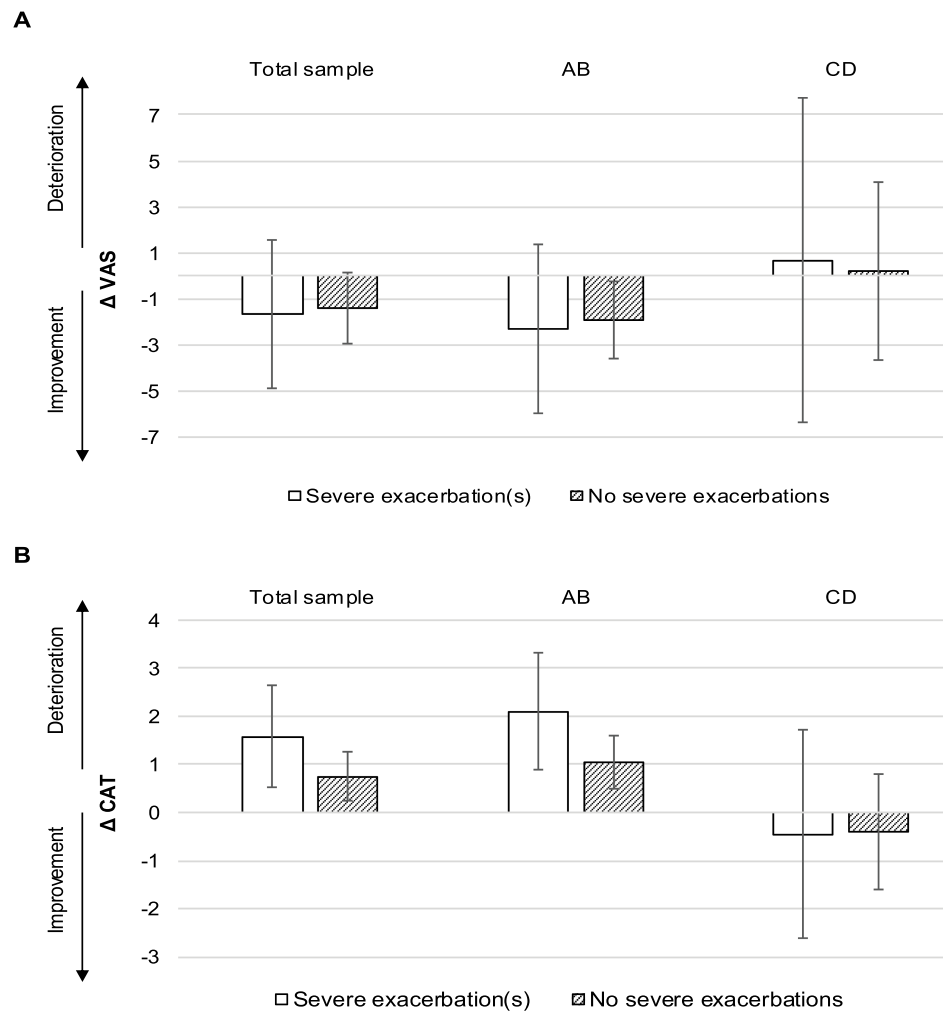


Figure 6 Change score model: impact of exacerbations on HRQoL.

Notes: Absolute adjusted mean change in VAS (**A**) and CAT (**B**) after one year. ABCD groups at baseline. Error bars indicate 95% confidence intervals.

“good risks” are more likely to participate and, non-responders were also shown to be at higher risk. Moreover, the DMP participation is associated with an increased quality of care, which could lead to a HRQoL gap between DMP and non-DMP settings.⁵⁶ This could result in an underestimated effect on HRQoL and more conservative results than in the whole patient population. Additionally, we only considered patients who did not die. Further, survey results were collected at varying, later times than events documented in claims data, and changes in patients’ health during that time cannot be excluded. Yet plausibility would suggest that patients are more likely to complete the self-administered questionnaire when they are in a more stable state, which tends to reduce this uncertainty.

Regarding our study population and generic HRQoL, we only included patients who had complete data from VAS, but we did not exclude patients with incomplete data in EQ-5D-5L dimensions, as the dimensions were not used in our models. By EQ-5D-5L dimension category, between 31 and 59 missing values occurred per category in the study sample, and an influence on VAS cannot be fully excluded.

Regression to the mean as a result of our repeated measurement of HRQoL, FEV₁, and exacerbations is a common issue.⁵⁷ To account for this, we adjusted all models for baseline values when analyzing changes in clinical factors and changes in HRQoL.

A further problem might be the shortness of our observation period, comprising only about one year, which might be too short to observe the influence of clinical

indicators on HRQoL. FEV₁ was found to have an important impact on HRQoL, particularly in the long term, and especially for severe exacerbations, an unequal rhythm over the years has been shown,⁵⁸ suggesting that just one year of observation may not be sufficient to catch the full effect. In addition, our clinical factors retrieved from claims data, such as FEV₁, are always from the time before the questionnaires that provided the HRQoL measurements. Nonetheless, this was considered negligible, as it was shown that small health changes often influence HRQoL only temporarily because patients tend to adapt to the impact of changes after a certain time.^{59,60} Further, we used an annual average of FEV₁ values, wherever possible, in an attempt to minimize bias caused by measurement variability.

A possible bias arose through a DMP request switch from liters to percent predicted values for FEV₁ within our study period. Several physicians reported values lower than 5 or higher than 120 for FEV₁%pred. in wave 2. We reconsidered these values as liter or milliliter values respectively. The remaining values were kept as predicted values, but different calculation methods for the FEV₁%pred. exist,⁶¹ and we cannot observe the calculation method used by practitioners. For this reason, we worked only with the liter values. We thus accounted for this bias by using only liter values for FEV₁ and conducting a sensitivity analysis, which showed robust overall results.

All patients were under their regular treatment, but treatment elements or interventions may have changed, eg, due to severe exacerbations resulting in treatment effects on HRQoL, which were not further considered in this study. Finally, generalizability is limited, because full data availability without any imputation reduced our original sample size considerably, and we analyzed only regional data from Germany.

Nonetheless, our study has some unique advantages, such as a large sample size and the combination of claims data and survey data, which is relatively rare and allowed us to build GOLD ABCD groups. GOLD ABCD groups were found to be more closely associated with disease-specific and generic HRQoL in COPD than GOLD I–IV.¹⁰ Second, we were thus able to investigate changes in disease-specific and generic HRQoL in relation to changes in lung function or exacerbations stratified by ABCD groups instead of GOLD I–IV. Also, the combination of EQ-5D and CAT has been shown to be a very useful measure to assess HRQoL in COPD.^{9,62} Compared with an expected

conservative response rate, we perceive our response rate of 29.7% in wave 1 and 62.6% in wave 2 to be good, and it is similar to comparable studies using postal questionnaires within the German DMPs, eg, 32% in DMP Asthma.⁶³

Conclusion

For the longitudinal impact of clinical changes on HRQoL in COPD patients within one year, we conclude that a decline in FEV₁ or the occurrence of at least one severe exacerbation is significantly associated with an overall deterioration in disease-specific HRQoL. In particular, patients in COPD groups AB need to be considered further: those experiencing a severe exacerbation within one year reported a clinically relevant deterioration in their disease-specific quality of life. To maintain or rather to improve HRQoL in COPD patients, our results underline the importance of optimal treatment.

Abbreviations

BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; COSYCONET, COPD and systemic consequences – comorbidities network; DMP, Disease management program; EQ-VAS, Euro-Qol visual analog scale; EQ-5D, Euro-Qol 5 dimensions questionnaire; FEV₁, Forced expiratory volume in 1 second; FEV₁%pred., FEV₁% predicted; GAM, Generalized additive model; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; HRQoL, Health-related quality of life; MID, Minimal important difference; MMRC, Modified British Medical Research Council questionnaire; PROM, Patient-reported outcome measure; SD, Standard deviation; SGRQ, Saint George's respiratory questionnaire; SHI, Statutory health insurance.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available according to the data protection concept approved by the responsible data security officials and the ethics committee.

Ethics Approval and Consent to Participate

The study complies with the Declaration of Helsinki and has been approved by the ethics committee of the Ludwig-Maximilians-University, Munich, Germany (vote no. 17-

358). All participants provided written informed consent at the time of inclusion in the disease management program.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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