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Physical Activity and the Frequency of Acute Exacerbations in Patients with Chronic Obstructive Pulmonary Disease

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Abstract
Purpose Acute exacerbations (AE) in patients with COPD are associated with a decline in lung function, increased risk of hospitalization, and mortality. In this cross-sectional study we tested whether the level of objectively measured daily physical activity and exercise capacity are associated with the number of COPD exacerbations.
Methods In 210 patients with COPD (67 % men; mean (SD) age: 63 (8) years) enrolled in The Obstructive Pulmonary Disease Outcomes Cohort of Switzerland (TOPDOCS) physical activity (PA) (steps per day, physical activity level, (PAL)), exercise capacity (6-min walking distance, (6MWD)), comorbidities, lung function, and medication were assessed. Differences between COPD patients with frequent (≥2 year) and infrequent (0–1 year) exacerbations were assessed. Univariate and multivariate analyses were performed to investigate whether the level of objectively measured daily physical activity and exercise capacity are associated with the number of COPD exacerbations.
Results Patients with frequent AE had a significantly lower FEV_1 and 6MWD compared to patients with infrequent AE. In univariate analysis, the number of exacerbations was inversely associated with FEV_1, 6MWD, BMI, and smoking status while there was a positive association with RV/TLC and combined inhaled medication. However, there was no significant association with PAL and steps per day. In multivariate analysis, FEV_1 and the use of combined inhaled medication were independently associated with the number of AE, after correction for covariates.
Conclusions The findings of this study imply that FEV_1, independent of inhaled medication, is significantly associated with COPD exacerbations. Neither physical activity nor exercise capacity was independently associated with COPD exacerbations.

Keywords COPD · Acute exacerbations · Objective assessment of daily physical activity · Exercise capacity

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Introduction

Acute exacerbations (AE) of chronic obstructive pulmonary disease (COPD) constitute a substantial burden for COPD patients. Characterized by a worsening of symptoms that is beyond the normal day to day variation, AE may involve admission to hospital, and may lead to death [1]. The symptoms usually include increased dyspnea, cough, and sputum production [2]. In most COPD patients, AE become more frequent with progression of COPD. However, some COPD patients are prone to frequent AE, whereas other patients with COPD are spared from it [3]. The mechanisms underlying the variation of exacerbation frequency in COPD patients are currently unknown.

Findings from previous studies suggest associations between the frequency of AE and a decline in FEV_1 [3–8], worsening of health-related quality of life [3, 4, 9] and increased mortality [10–12]. Thus, AE are now accepted as an important outcome measure in COPD and it seems to be useful to identify those who are at risk for frequent AE in order to improve disease management and outcome.

The findings of previous studies suggested that an active lifestyle is an important factor in maintaining health in patients with COPD [13–15]. Dyspnea and other symptoms often contribute to an inactive lifestyle in COPD patients. Furthermore, inactivity leads to atrophy of the skeletal muscles with development of muscular weakness, which seems to increase the propensity of exertion to cause dyspnea [16]. Epidemiological studies suggest that physical activity (PA) plays an important part in the prevention of AE in patients with COPD [14, 17–19]. However, in these studies PA was assessed by patient's records and questionnaires only [14, 19], which is an important limitation as self-reported PA questionnaires rarely reflect the actual level of daily PA [20, 21]. A small cross-sectional study investigated an association between objectively measured PA and exacerbation frequency [22]. However, lung function was not considered as a confounder.

Thus, the objective of the present study was to investigate the effect of objectively assessed PA and exercise capacity on the number of COPD exacerbations adjusted for possible confounders.

Methods

Study Design and Subjects

This study was performed as part of the obstructive pulmonary disease outcomes cohort of Switzerland (TOPDOCS). TOPDOCS is an ongoing prospective, non-interventional cohort study including COPD patients from seven study centers in Switzerland. Patients were recruited during ambulatory visits in the pulmonary clinic or during hospital stay. The cohort includes male and female subjects, aged between 40 and 75 years, with mild to very severe COPD (GOLD stages I–IV).

Patients with mental or physical disability precluding informed consent were excluded from the study. Patients with an AE within the last 6 weeks were asked to take part in an exacerbation-free interval.

For the current cross-sectional study, 210 patients were included between October 2010 and October 2012 at the seven different study centers in Switzerland.

Ethics Statement

The study was conducted in accordance with the declaration of Helsinki of the World Medical Association, and has been registered at NCT01527773. Ethical committees of all participating centers approved the study (cantonal ethics committees of Zurich (leading center: KEK-ZH-NR: 2011-0106), ethics committee of canton St. Gallen, ethics committee of canton Thurgau, ethics committee of canton Basel, and ethics committee of canton Aargau). All subjects gave written informed consent to participate.

Demographics and Medication

Characteristics included age, gender, body mass index (BMI), smoking status, pack years of smoking (PY), MMRC (modified medical research council) dyspnea score, and comorbidities. A detailed patient history including an interview and review of medical records was undertaken regarding their use of medication and the presence of comorbidities. Adherence to described medications was monitored by patient interviews.

Assessment of Physical Activity and Exercise Capacity

The number of steps per day and the PA level (PAL) were assessed by a multisensory armband (SenseWear Pro^{TM}; Bodymedia Inc., Pittsburgh, PA, USA) which was worn on the upper left arm over the triceps muscle. PAL is an objective measure of daily PA and is defined as the total energy expenditure divided by the resting metabolic rate [23]. An inbuilt biaxial accelerometer records the number of steps per day [24].

Patient's data were recorded over a period of 7 consecutive days. The threshold for valid data from the multisensory armband was set at 4 days with a minimum of 22.5 h/day. In total, 178 patients had complete PA data. 22 of the 210 patients were excluded from the analysis due to technical reasons, and 10 patients were excluded because they wore the armband less than 4 days.

Exercise capacity was assessed by measuring the 6-min walking distance (6MWD) according to American thoracic

society (ATS) guidelines [25]. The patients did not practice the 6MWT before the actual study assessment.

Exacerbation Frequency

The patients were asked about the number of AE during the preceding year. AE was defined as an event which led to prescription of antibiotics and/or corticosteroids [26]. Patients with infrequent exacerbations were considered to have 0–1 AE per year, whereas patients with ≥2 AE per year were defined as frequent exacerbators [3]. In 141 patients, a follow-up visit one year after baseline examination was analyzed to verify the consistency of exacerbation frequency. Evaluation of exacerbation history followed the same standards as during the baseline examination.

Lung Function

All patients underwent standard pulmonary function testing according to ATS guidelines [27] to measure forced expiratory volume in one second (FEV_1), residual volume (RV), and total lung capacity (TLC).

Blood Analysis

Daytime arterial blood gas analysis was performed with an ABL 700 series blood gas analyzer (Radiometer Copenhagen) to measure partial oxygen pressure (PaO_2) and partial carbon dioxide pressure ($PaCO_2$).

Data Analysis and Statistics

All results are shown as median values and quartiles unless otherwise stated. Statistical analysis was performed with Statistica V6.0 (StatSoft, Tulsa, OK, USA) and STATA 12 (StataCorp, Texas, USA). Differences between COPD patients with frequent exacerbations and patients with infrequent exacerbations regarding PA, exercise capacity, respiratory variables, and medication were assessed by Wilcoxon rank-sum test, independent t test, and χ^2 tests. Univariate regression analysis was used to investigate associations between the number of AEs during the most recent year (dependent variable) and respiratory variables, PA (steps per day and PAL), exercise capacity (6MWD), as well as medications (independent variables). Furthermore, in those patients who had available follow-up visit data one year after the baseline examination univariate regression analysis was performed to investigate the association between PA (steps per day and PAL) and the number of AE occurring in the year after the baseline examination. Multivariate regression analysis included all variables with a p value of less than 0.1 in univariate analysis. A p value of <0.05 was considered to be statistically significant. Residual analysis was performed to check regression assumptions.

Results

Study Participants

Of the 277 patients assessed for eligibility 210 entered the study (Fig. 1). Patient characteristics are shown in Table 1. 15 Patients (7 %) were in GOLD stage I, 69 patients (33 %) in GOLD II, 74 patients (35 %) in GOLD III, and 52 patients (25 %) in GOLD stage IV. Considering the revised GOLD classification, 52 % of the infrequent exacerbators were in group GOLD D compared to 95 % of the frequent exacerbators. In total there were 236 exacerbations, 50 of them led to hospital admissions. In general, the level of daily PA was low (median PAL 1.4 (1.3/1.6)) with no influences of seasonality (median PAL spring/summer 1.4 (1.3/1.6) versus median PAL autumn/winter 1.4 (1.3/1.6), $p = 0.713$).

Comparison of Patients with Frequent and Infrequent Exacerbations

The comparison of patients with frequent and infrequent exacerbations is shown in Table 1. Patients with frequent AE had a significantly lower 6MWD, FEV_1, and a significantly higher RV/TLC compared to patients with infrequent exacerbations.

The distribution of steps per day, PAL, and 6MWD regarding frequent and infrequent exacerbators is shown in Fig. 2. As displayed in Fig. 2, only 6MWD differed significantly between infrequent and frequent exacerbators.

Univariate Regression Analysis Evaluating Determinants of Exacerbation Frequency

Exercise capacity assessed by the 6MWD-test was significantly inversely associated with the number of AE. The number of steps per day was borderline negatively associated with the number of AE. There was no statistically significant association between the number of AE and PAL (Table 2). In 141 patients who had a follow-up visit one year after the baseline examination the results of the univariate analysis remained unchanged.

Furthermore, the number of AE was inversely associated with BMI, smoking status, and FEV_1. RV/TLC as well as combined inhalation of steroids/long-acting beta-agonists/long-acting muscarinic-antagonists (LAMA + LABA + GC) showed a significant association (Table 3).

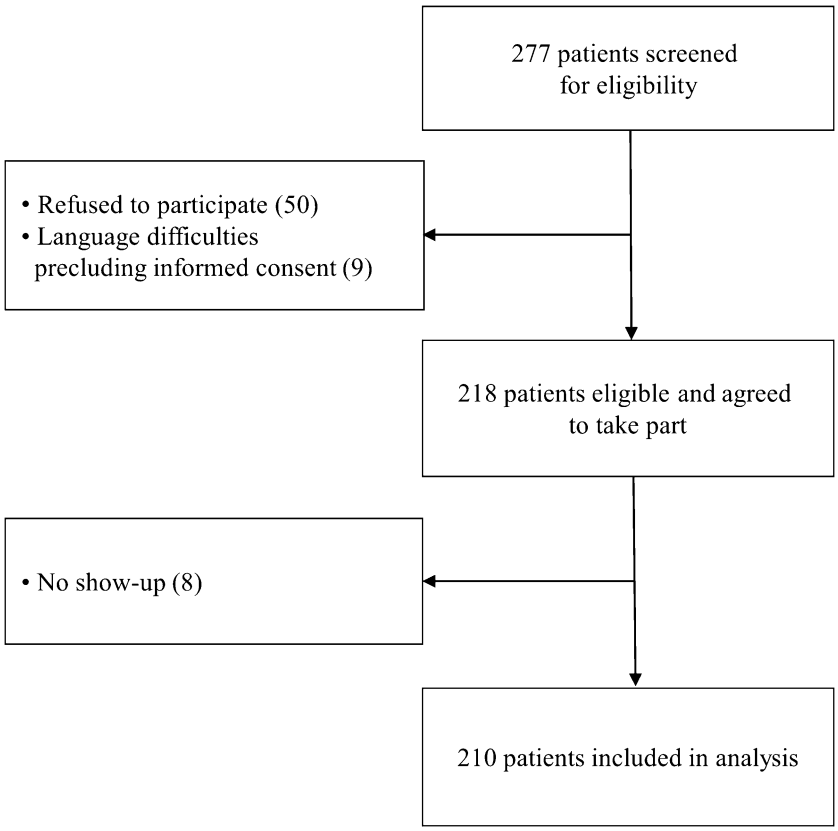

Fig. 1 Study flow

Multiple Regression Model of all Postulated Predictors

Table 3 shows the results of a multiple regression model including potential predictors with a univariate p value of <0.1. Because of an interrelationship between RV/TLC and FEV_1 ($r = -0.76$, $p < 0.001$), RV/TLC was removed from the model. 6MWD did not remain significantly associated with the number of AE after correction for BMI, smoking status, FEV_1, use of beta blockers, combined inhalation of LAMA + LABA + GC, and steps per day. In the final model, FEV_1 and combined inhalation of LAMA + LABA + GC were the only factor independently associated with the number of AE. In consideration of residual assumptions, the model was further validated after square root transformation and the results remained unchanged.

Discussion

This study investigated if objectively measured PA and exercise capacity have an independent effect on the number of AE in patients with COPD. The findings of this study imply that both PA and exercise capacity have no independent effect on the number of AE. Only the severity of airflow obstruction, measured by FEV_1, and the use of combined bronchodilators (LAMA + LABA + GC) were independently associated with AE in COPD patients.

There is preliminary evidence that a high level of PA is associated with a reduced risk of admission to hospital and mortality [14, 17, 19]. However, in these studies [14, 17, 19] PA was assessed by patient's records and questionnaires only. Garcia-Aymerich et al. [17] found that a relatively high level of PA, which was defined as ≥60 min walking/day, reduced the risk of admission to hospital due to an exacerbation by nearly 50 %. Furthermore, Garcia-Aymerich et al. [14] suggested that a level of PA equivalent to walking or cycling for 2 h/week or more is associated with a lower risk of admissions to hospital and mortality in COPD patients. Donaldson et al. [19] examined the patient's time spent outside their home in a longitudinal study including 147 COPD patients. Patients suffering from frequent exacerbations were more likely to become housebound, and patients with little outdoor activity had a greater risk of being hospitalized due to AE [19]. However, considerable differences between objective assessment and questionnaires have been reported. In general, questionnaires tend to overestimate PA when compared to objectively measured data [24, 28, 29].

Therefore, we considered two objectively assessed PA outcomes, steps per day and PAL measured during at least 4 days with a minimum of 22.5 h/day. Watz et al. [30]

Table 1 Comparison between patients with frequent and infrequent exacerbations

	All patients $N = 210$	Infrequent exacerbations $N = 152$	Frequent exacerbations $N = 58$	p value*
Characteristics				
Age, y	63 (57/68)	64 (58/69)	63 (57/68)	0.281
Male/female	139/71	104/48	35/23	0.269
BMI, kg/m^2	26.5 (22.4/28.9)	26.5 (22.5/30.0)	24.4 (21.6/27.6)	0.036
Current smokers, *N* (%)	51 (24)	42 (28)	9 (16)	0.067
Pack years of smoking, *N*	40 (25/60)	40 (27/60)	37 (24/52)	0.104
MMRC dyspnea score, *N*	1.9 (1.1)	1.7 (0.1)	2.4 (0.1)	<0.001
GOLD A	24 (11)	24 (16)	0 (0)	<0.001
GOLD B	43 (21)	42 (28)	1 (2)	<0.001
GOLD C	8 (4)	6 (4)	2 (3)	0.613
GOLD D	134 (64)	79 (52)	55 (95)	<0.001
Comorbidities				
Arterial hypertension, *N* (%)	100 (48)	77 (51)	23 (40)	0.154
CAD, *N* (%)	39 (19)	29 (19)	10 (17)	0.760
Diabetes, *N* (%)	25 (12)	21 (14)	4 (7)	0.166
Osteoporosis, *N* (%)	25 (12)	21 (14)	4 (7)	0.166
Respiratory variables				
FEV_1 post, % pred.	41.5 (30.0/63.0)	46.0 (32.0/65.5)	32.5 (25.0/45.0)	<0.001
RV/TLC, %	57.0 (47.5/65.0)	55.0 (45.5/63.0)	61.0 (52.0/68.0)	0.013
PaO_2, kPa	9.0 (8.1/10.0)	9.0 (8.0/10.0)	9.2 (8.1/10.1)	0.502
$PaCO_2$, kPa	5.1 (4.7/5.5)	5.1 (4.7/5.4)	5.0 (4.6/5.5)	0.650
Medication				
Antihypertensives, *N* (%)	101 (48)	77 (51)	24 (41)	0.229
Statins, *N* (%)	64 (30)	53 (35)	11 (19)	0.025
Beta blockers, *N* (%)	43 (20)	38 (25)	5 (9)	0.009
LABA, *N* (%)	3 (1)	3 (2)	0 (0)	<0.001
LABA + GC, *N* (%)	32 (15)	25 (16)	7 (12)	0.003
LAMA, *N* (%)	12 (6)	11 (7)	1 (2)	<0.001
LAMA + GC, *N* (%)	8 (4)	5 (3)	3 (5)	<0.001
LAMA + LABA, *N* (%)	28 (13)	18 (12)	9 (16)	<0.001
LAMA + LABA + GC, *N* (%)	119 (57)	72 (47)	47 (81)	<0.001
Acute Exacerbations				
Average number of AE per year	1 (0/2)	0 (0/1)	3 (2/3)	<0.001
Exercise capacity				
6-min walking distance, m	405 (135)	420.0 (131.9)	366.1 (134.5)	0.010
Physical activity				
Physical activity level	1.4 (1.3/1.6)	1.4 (1.3/1.6)	1.4 (1.3/1.6)	0.472
Steps per day, *N*	4,204 (2,394/6,575)	4,414 (2,478/7,022)	4,140 (2,377/5,290)	0.334

Values are median (quartiles) or mean (SD) unless otherwise stated

BMI body mass index, *MMRC* modified medical research council, *CAD* coronary artery disease, *FEV_1 Post* forced expiratory volume in one second after dilatation, *RV/TLC* residual volume to total lung capacity, *PaO_2* partial pressure for oxygen, *$PaCO_2$* partial pressure for carbon dioxide, *LABA* long-acting beta-agonist, *LAMA* long-acting muscarinic-antagonist, *GC* glucocorticoids

* p values for comparisons of infrequent versus frequent exacerbations

showed that a time frame of 2–3 days is sufficient to reliably assess PA in patients with severe COPD, whereas 5 days seem to be required in mild COPD. However, the association between PAL and the number of AE was not significant after correcting for covariates, neither was the association with steps per day. In contrast to our study, Waschki et al. [22] found in a study which included 134 COPD patients and 46 healthy controls significant associations between both, steps per day and PAL (dependent variables) and an exacerbation rate of >1 in the preceding

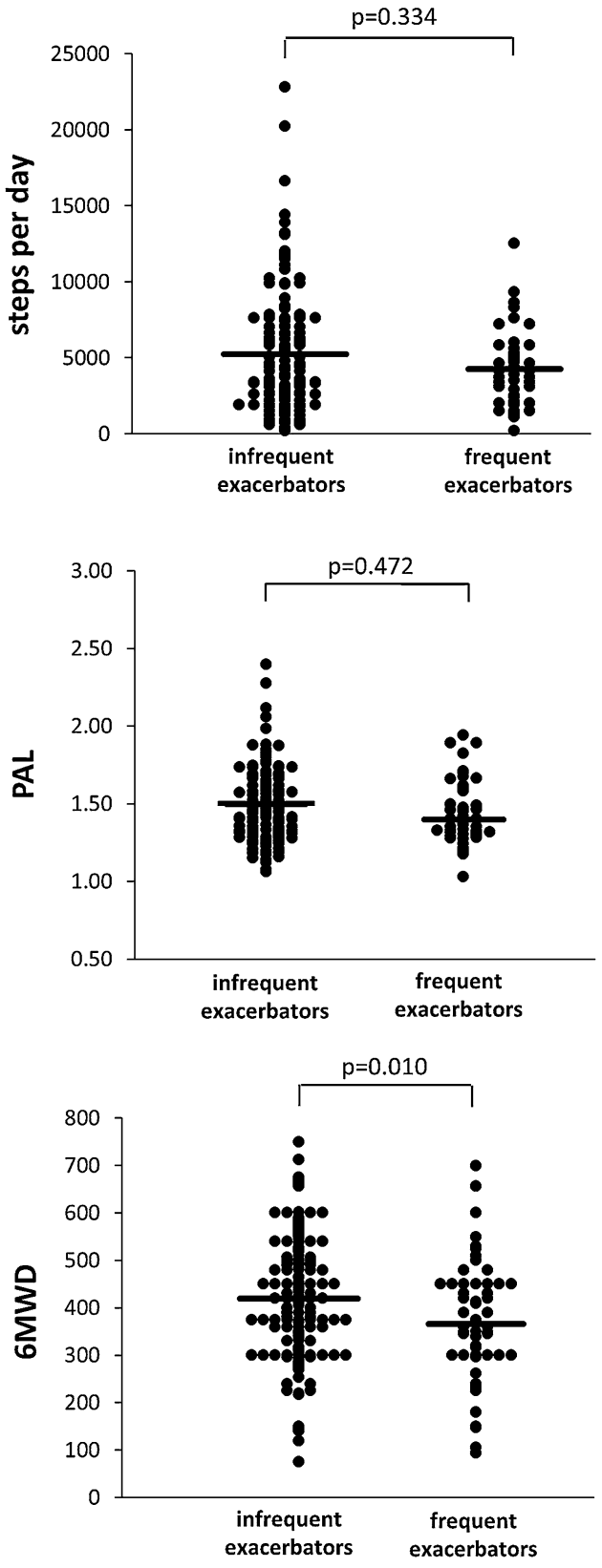

Fig. 2 The distribution of steps per day, PAL, and 6MWD in frequent and infrequent exacerbators is illustrated

Table 2 Univariate regression analysis evaluating the association between the number of acute exacerbations during the most recent year and patient characteristics

	B	95 % confidence interval	*p* value
Characteristics			
Age, y	0.00	−0.02/0.03	0.789
Male/female	−0.37	−0.80/0.06	0.095
BMI, kg/m^2	−0.04	−0.07/−0.01	0.015
Current smokers, *N*	−0.58	−1.05/−0.11	0.017
Pack years of smoking, *N*	−0.00	−0.01/0.00	0.474
Comorbidities			
Arterial hypertension, *N*	−0.10	−0.51/0.31	0.622
CAD, *N*	−0.15	−0.68/0.37	0.570
Diabetes, *N*	−0.50	−1.13/0.13	0.116
Depression, *N*	−0.05	−0.68/0.58	0.877
Respiratory variables			
FEV_1 post, % pred.	−0.03	−0.03/−0.02	<0.001
RV/TLC, %	0.03	0.02/0.05	<0.001
PaO_2, kPa	−0.03	−0.17/0.10	0.601
$PaCO_2$, kPa	−0.00	−0.30/0.30	0.988
Medication			
Antihypertensives, *N*	0.03	−0.38/0.44	0.891
Statins, *N*	−0.38	−0.82/0.06	0.092
Beta blockers, *N*	−0.45	−0.95/0.06	0.081
LABA, *N*	−1.14	−2.86/0.58	0.193
LABA + GC, I	−0.33	−0.90/0.24	0.254
LAMA, *N*	−0.66	−1.54/0.22	0.139
LAMA + GC, *N*	0.78	−0.29/1.85	0.150
LAMA + LABA, *N*	0.31	−0.29/0.91	0.310
LAMA + LABA + GC, *N*	0.99	0.60/1.39	<0.001
Exercise capacity			
6-min walking distance, m	−0.00	−0.00/−0.00	<0.001
Physical activity			
Physical activity level	−0.11	−0.98/0.76	0.808
Steps per day, *N*	−0.00	−0.00/0.00	0.060

BMI body mass index, *CAD* coronary artery disease, *FEV_1 Post* forced expiratory volume in one second after dilatation, *RV/TLC* residual volume to total lung capacity, *PaO_2* partial pressure for oxygen, *$PaCO_2$* partial pressure for carbon dioxide, *LABA* long-acting beta-agonist, *LAMA* long-acting muscarinic-antagonist, *GC* glucocorticoids

year. However, in the multivariate regression analyses, adjustment was only performed for age, gender, study site, and BMI > 30, but not for lung function parameters. Furthermore, the minimal clinical important difference of PAL is unknown, therefore, a formal power analysis would not be evidence based. However, if there was a consistent

Table 3 Multiple regression analysis evaluating the association between acute exacerbations during the most recent year and possible predictors

	B	95 % confidence interval	*p* value
BMI, kg/m^2	−0.02	−0.06/0.02	0.271
Current smokers, *N*	−0.15	−0.60/0.30	0.514
FEV_1 post, % pred.	−0.01	−0.03/−0.00	0.013
Beta blockers, *N*	−0.16	−0.61/0.28	0.470
LAMA + LABA + GC, *N*	0.43	0.01/0.85	0.047
6-min walking distance, m	−0.00	−0.00/0.00	0.160
Steps per day, *N*	0.00	−0.00/0.00	0.406

BMI body mass index, *FEV_1 Post* forced expiratory volume in one second after dilatation, *LABA* long-acting beta-agonist, *LAMA* long-acting muscarinic-antagonist, *GC* glucocorticoids

association between PA and exacerbation rate we would have expected to reproduce the findings of the considerably smaller study by Waschki et al. [22]. These contrasting findings may thus be explained by the fact that we also included FEV_1 as a covariate in the multivariate analysis. Another reason why our findings differ from those of Waschki et al. [22] may be that in their study COPD exacerbations were defined as exacerbations based on either the decision by a patient's primary clinician or by study personnel without any specific criteria that had to be met for the definition of an exacerbation.

Although we could demonstrate an association between the 6MWD and the number of AE in univariate regression analysis, this association did not remain significant after correction for covariates. However, when comparing frequent and infrequent exacerbators, there are previous studies which demonstrated significant differences between patients with frequent and infrequent exacerbations concerning the 6MWD [6, 31]. In a study including 205 patients with COPD, Cote et al. [6] found patients with frequent exacerbations to walk significantly less far (334 ± 117 m) compared to infrequent exacerbators (385 ± 116 m, $p = 0.006$) during the 6MWD. Furthermore, the findings of a small study including 60 patients with COPD suggest that AE are associated with reductions in functional exercise capacity measured by 6MWD [31]. These results confirm our findings that COPD patients with frequent AE had a significantly lower 6MWD compared to infrequent exacerbators (Table 2).

The different results on PA and exercise capacity may represent two different aspects of activity. While PA represents what people do during daily routine, exercise capacity represents what people could do [32].

We found an inverse relationship between the severity of airflow limitation and the frequency of AE. These results confirm the findings of previous studies [3–8]. Further, only the use of combined inhalation of LAMA + LABA + GC was also independently associated with exacerbation frequency. Our interpretation of this finding is that patients with more severe disease are more likely to receive combined inhaled medication. Since the efficacy of inhaled steroids on the prevention of AE is considerably low and a matter of current discussion [33] we think that the association between exacerbation frequency and disease severity predominates the potential preventive effect of GC on exacerbation.

The main limitation of our study is the cross-sectional design that does not allow establishing a causal relationship between PA and the number of AE. Further, due to the study design, we cannot determine whether PA influences exacerbation frequency or exacerbation frequency influences PA. Either a randomized controlled trial or a prospective cohort study would provide stronger evidence; in the latter case a temporal relationship as a possible element of causal interference may be determined. A further limitation of the study is that the lack of an independent association between PA and exacerbation frequency might also be due to insufficient power of the study. The use of formal exacerbation diary cards might have identified additional unreported exacerbations.

In conclusion, the findings of the current study underpin preliminary data that the severity of airflow obstruction, independent of inhaled medication, is significantly associated with the number of AE in COPD patients. The level of daily PA and exercise capacity seems to have no independent effect on the number of AEs in patients with COPD.

Conflict of interest There are no conflicts of interest.

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