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Negative impacts of unreported COPD exacerbations on health-related quality of life at 1 year

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ABSTRACT: Unreported chronic obstructive pulmonary disease (COPD) exacerbations are common, but their intermediate-to-long-term impacts on health-related quality of life (HRQoL) are unknown. The aim of the present study was to examine the impact of unreported exacerbations on HRQoL at 1 yr.

A multicentric prospective cohort study in 491 COPD patients was conducted in China. HRQoL was measured using the St George's Respiratory Questionnaire (SGRQ). Other measurements included sociodemographic, clinical, psychosocial and treatment profiles. Patients were monitored monthly for 12 months to document exacerbations (at least one symptom worsening for $\geqslant$48 h). Patients were categorised into six groups: no exacerbation, one unreported exacerbation only, more than one unreported exacerbation only, one reported exacerbation only, more than one reported exacerbation only, and both unreported and reported exacerbations. Generalised estimating equations were used to estimate the adjusted associations between exacerbations and HRQoL change.

A total of 466 unreported and 410 reported exacerbations were recorded. Compared with patients with no exacerbations, the change in SGRQ total score was similar amongst patients with one unreported exacerbation (adjusted mean change 1.22 points (95% CI -4.05–6.48)), but significantly worse among patients with more than one unreported exacerbation (4.61 (95% CI 0.09–9.13)).

Development and evaluation of self-management programmes emphasising early recognition of exacerbations and consequent action appear to be warranted.

KEYWORDS: Chronic obstructive pulmonary disease, exacerbation, health-related quality of life, outcome evaluation, therapy, under-reporting

An exacerbation is the most important adverse event in the progression of chronic obstructive pulmonary disease (COPD). It is a common cause of death [1], hospital admission [1], increased healthcare costs [2] and diminished lung function [3]. A COPD exacerbation also has an immediate [4–6] and sustained [6–10] impact on health-related quality of life (HRQoL). HRQoL is an important outcome of clinical care in COPD patients. Clinicians and regulators recognise that measuring HRQoL is instrumental in making informed patient management and policy decisions [11, 12]. It is also well accepted that treatment effectiveness should be based on assessment of HRQoL rather than using spirometry alone [12].

Previous studies have shown that at least half of all COPD exacerbations identified by symptom worsening were not medically reported [5, 8], and, therefore, left untreated. Unreported exacerbations were shown to have similar characteristics to reported exacerbations in the East London cohort [8], but were found to be less severe in terms of the number of symptoms in the Canadian cohort [5]. These exacerbations are associated with symptom worsening [4, 5, 8], and may have important clinical consequences due to delaying or failing to seek treatment [4, 5, 13]. However, the impacts of unreported exacerbations on HRQoL have been examined only in the short term (3 months) [5]. This study showed that HRQoL declined among patients who had

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unreported exacerbations, as assessed by an increase (deterioration) in the St George's Respiratory Questionnaire (SGRQ) total score (median 3.4 points (interquartile range (IQR) -3.4–5.9); n=212). The median change was -2.3 (IQR -6.1–2.4; n=44) in patients who had no exacerbation and 4.3 (IQR -2.3–13.4; n=37) in those who had reported exacerbations [5]. This suggested that unreported exacerbations have a negative impact on HRQoL and may thus represent an unmet healthcare need. However, this study was based on univariate analyses involving neither a control group nor confounding adjustment. Moreover, the intermediate-to-long-term effects of unreported exacerbations on HRQoL have not been studied.

China has one of the largest COPD populations in the world, with a prevalence of 8.2% (mean 12.4%; females 5.1%) [14], and a huge population of >1.3 billion. It is responsible for a considerable part of the global burden of this disease. Despite being a major public health problem in China, very little information is available regarding this disease and its management in the Chinese population.

The main objective of the present study was to examine the impacts of unreported exacerbations on the change in HRQoL at 1 yr in patients with clinically stable COPD in China. It was hypothesised that patients with unreported exacerbations would show a worse HRQoL change at 1 yr compared to patients with no exacerbations.

METHODS

A prospective cohort study with a 12-month follow-up was carried out from August 2004 to June 2006 in the respiratory divisions of 10 general hospitals in Beijing, China. The study protocol was approved by the research ethics boards of the McGill University Health Centre (Montreal, QC, Canada) and all participating hospitals. Written informed consent was obtained from all participants.

Study population

In order to be eligible, patients were required to satisfy the following criteria [15]: 1) an age of ⩾30 yrs with physician-diagnosed COPD; 2) a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <0.7 and FEV_1 of <80% of the predicted value; 3) being at a clinically stable period of COPD (*i.e.* no fever, worsening of respiratory symptoms or related medication change) within 4 weeks prior to the baseline interview; 4) no primary diagnosis of asthma; 5) no previous lung volume reduction surgery, lung transplantation or pneumonectomy; and 6) an expected survival of ⩾6 months, as judged by site investigators on the basis of the patient's medical history. In each centre, 40–60 patients were recruited, at least a third of whom were female; 40% were at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II (FEV_1 of 50–79% pred), 40% were at stage III (FEV_1 of 30–49% pred) and 20% were at stage IV (FEV_1 of <30% pred).

Patient evaluation

Face-to-face interviews were administered at baseline and at the end of the study in order to assess patient characteristics and HRQoL. Both interviews were administered ⩾4 weeks after an exacerbation (*i.e.* during a clinically stable period). All interviewers were trained to administer the structured questionnaires in the same manner, and they were blinded to patients' HRQoL scores during the follow-up period.

COPD-specific HRQoL was measured using the reliable and valid SGRQ in Mandarin-Chinese [16]. It covers three domains: symptoms (respiratory symptoms), activity (physical activities that cause or are limited by breathlessness), and impact (social and psychological effects of the disease) [17]. A total score and three sub-scores are calculated, with higher scores indicating worse HRQoL [17].

Age, sex, education, employment, marital status, living alone, smoking history and body mass index (weight divided by height squared) were assessed at baseline. Clinical assessments included spirometric values [18], dyspnoea (the 5-grade UK Medical Research Council (MRC) dyspnoea scale) [19], daily productive cough and daily wheeze [20], 6-min walking distance (6MWD) [21], exacerbations and hospitalisations during the previous year and significant comorbid conditions. Psychosocial status was represented by anxiety and depression (hospital anxiety and depression scale (HADS)) [22], self-efficacy (COPD-specific self-efficacy scale) [23] and social support (Personal Resource Questionnaire 2000 (PRQ2000)) [24]. Treatment profiles were recorded, including long-acting bronchodilators, inhaled corticosteroids, oral mucolytics, vaccinations, long-term oxygen therapy (LTOT) and pulmonary rehabilitation. Full details of these measurements are provided elsewhere [15].

Exacerbations

All patients were monitored monthly by telephone in order to document the occurrence and characteristics of COPD exacerbations. At each contact, a structured questionnaire was administered to assess changes in respiratory symptoms and the occurrence of medical interventions during the past month. Patients were also encouraged to report to their attending physicians or nurses whenever they experienced symptom worsening. An exacerbation was defined as the worsening of at least one key symptom (increased sputum amount, changed sputum colour or purulence and increased dyspnoea) for ⩾48 h. An exacerbation was considered reported if it was brought to medical attention through scheduled or unscheduled doctor visits, emergency department visits or hospital admissions, and unreported if it was not medically reported but identified retrospectively using the monthly follow-up questionnaire. An exacerbation was considered treated if there was a change in at least one medication (*i.e.* antibiotics, corticosteroids and bronchodilators) for the symptom worsening. More details of the determination of exacerbations are provided elsewhere [15].

Statistical analyses

The main outcome of interest was the 1-yr change in SGRQ total score and sub-scores (*i.e.* the difference between the 1-yr and baseline assessment). Patients were categorised into six exclusive groups according to the combination of the frequency and reporting status of exacerbations: no exacerbation (reference group), one unreported exacerbation only, more than one unreported exacerbation only, one reported exacerbation only, more than one reported exacerbations only, and mixed unreported (at least one) and reported (at least one) exacerbations. Generalised estimating equations were used to

estimate the adjusted effects of exacerbations on the change in HRQoL, taking into account the potential hospital-level clustering effect by modelling the fixed effect and correlation structure separately. The adjusted effect estimates represented the differences between the mean change in HRQoL for patients who had different types of exacerbation and the mean change in HRQoL for patients who had no exacerbation. In order to estimate and control for the potential impact of exacerbations that occurred at the end of the study, patients who had experienced at least one exacerbation (regardless of reporting status) during the last 3 months were included in multivariate models. Similar analyses were repeated for patients who had experienced at least one exacerbation during the last 2 months. The interactions between exacerbation category (both unreported and reported exacerbations) and COPD severity (continuous percentage predicted FEV_1; FEV_1 of $\geqslant$30 *versus* <30% pred; GOLD stage II, III and IV; and dyspnoea grade $\geqslant$4 *versus* <4) were tested in multivariate models. Data analyses were performed using SAS® 9.1.2 (SAS Institute, Inc., Cary, NC, USA). The level of significance was set at $p<0.05$.

A priori subject matter causal knowledge was used to guide the confounder evaluation [25, 26]. Potential determinants of HRQoL were identified from a comprehensive literature review. Relevant studies were searched from PubMed, Embase and The Cochrane Library for the period 1980–2007, using the key words ''chronic obstructive pulmonary disease/COPD'', ''quality of life/HRQL'' and ''risk factor/determinant/predictor''. For the association under study, the causal relationships of each determinant with the outcome (HRQoL), exposure (COPD exacerbation) and other determinants were presented in directed acyclic graphs (DAGs) [25, 26]. The relevant confounders were identified using DAGs, and all identified confounders were adjusted for in multivariate analyses, except for those with low variability (*e.g.* <3% of subjects participated in pulmonary rehabilitation). The confounders adjusted for in the multivariate models were: baseline SGRQ scores, age, sex, marital status, current employment, education, current smoking, percentage predicted FEV_1, MRC dyspnoea score, 6MWD, daily productive cough, daily wheezing, depression (HADS depression score of $\geqslant$8 *versus* <8), anxiety (HADS anxiety score of $\geqslant$8 *versus* <8), self-efficacy score, social support score, significant comorbid conditions (yes *versus* no), and the use of long-acting bronchodilators (yes *versus* no), inhaled corticosteroid (yes *versus* no) and LTOT (yes *versus* no). Additional details of the DAG and the confounding evaluation are presented in supplement A of the online supplementary material.

Multiple imputation (Markov chain Monte Carlo method) [27, 28] was employed to impute the missing data. The 41 missing baseline 6MWDs (20 with contraindications for the walking test and 21 with unknown reasons) were imputed using all other baseline characteristics (sociodemographic, clinical, psychosocial and treatment profiles). The 41 missing SGRQ scores at the end of the study were imputed using both baseline characteristics and exacerbation characteristics (exacerbation rate and duration). The SAS PROC MI procedure was used to create multiple imputed data sets, and the SAS PROC MIANALYZE procedure was used to combine results following analyses. In order to examine the robustness of the results to the missing values, the multivariate analyses were conducted among 414 patients who had no missing data, 450 patients who completed the study (only imputing for the baseline 6MWD) and all 491 patients recruited into the study (imputing for both baseline 6MWD and 1-yr SGRQ score), respectively. The results were reported for the data set that provided the most conservative estimates of SGRQ total scores.

RESULTS

Study population

Of the 491 patients recruited, 41 (8%) did not complete the study due to death (n=16), severe comorbid conditions (n=1), withdrawal (n=9), being lost to follow-up (n=13), missing the SGRQ questionnaire at the 1-yr interview (n=1) and other reasons (n=1). The mean$\pm$SD follow-up time was 373$\pm$65 days. Table 1 shows that patients who were lost to follow-up were older, had shorter 6MWDs, and showed worse spirometric values, dyspnoea and SGRQ scores (activity, impact and total) at baseline than those who completed the study ($p<0.05$).

Exacerbations and hospitalisations

As shown in table 2, a total of 466 unreported exacerbations (mean 1.01 events·person-yr^{-1} (95% CI 0.92–1.09)) and 410 reported exacerbations (0.95 events·person-yr^{-1} (95% CI 0.87–1.04)) were recorded. When compared with reported exacerbations, unreported exacerbations showed a lower median number of key symptoms, a lower proportion of symptom worsening for each key symptom ($p<0.0001$), and a lower proportion of exacerbations with two (12.4 *versus* 19.7%; $p=0.0058$) and three key symptoms (4.3 *versus* 51.5%; $p<0.0001$). Conversely, more unreported exacerbations (83.3%) than reported exacerbations (28.8%) exhibited a single worsening symptom ($p<0.0001$). Most of the reported exacerbations (87.1%) were treated using antibiotics, corticosteroid and/or bronchodilators, and 19.9% of unreported exacerbations were also self-treated by patients using either medications remaining from previous prescriptions or certain available over-the-counter antibiotics. Stratified analyses by GOLD stages II, III and IV showed similar patterns (supplement B of online supplementary material). Among 450 exacerbations with at least one medication change (regardless of whether physician- or self-treated), 183 (40.7%) led to hospitalisation. Of all patients, 30% were admitted to hospital at least once due to an exacerbation during the study period (*i.e.*1 yr) (data not shown).

Baseline characteristics of patients by exacerbation category

Table 3 shows that patients with one unreported exacerbation showed similar baseline characteristics to patients with no exacerbation, except for a better percentage predicted FVC ($p<0.05$). Patients with more than one unreported exacerbation were more likely to be male and exhibited a higher FVC ($p<0.05$) than patients with no exacerbation. Patients with one reported exacerbation were older, had less cumulative smoking and reduced 6MWD, and were more likely to be on long-acting bronchodilators and mucolytic agents ($p<0.05$ or <0.01) compared with patients with no exacerbation. Patients with more than one reported exacerbations had less cumulative smoking and more hospital admissions in the past, and were

TABLE 1 Baseline characteristics of the study population

	Patients			p-value#
	All	Completing study	Lost to follow-up	
Subjects n	491	450	41	
Age yrs	65.7±10.7	65.2±10.6	70.7±10.1	0.002
Male sex	338 (68.8)	309 (68.7)	29 (70.7)	0.78
BMI kg·m^{-2}	23.9±4.2	24.0±4.2	23.0±4.0	0.15
Cumulative smoking pack-yrs	26.8±29.2	26.5±29.0	31.0±31.6	0.33
MRC dyspnoea grade ⩾4	123 (25.0)	103 (22.9)	20 (48.8)	0.001
6MWD¶ m	384.6±135.9	392.4±132.7	287.2±141.0	0.0002
Spirometry (post-BD)				
FEV1 L	1.16±0.47	1.18±0.47	0.96±0.36	0.005
FEV1 % pred	47.6±15.9	47.2±15.8	40.9±16.5	0.009
FVC L	2.35±0.80	2.37±0.79	2.07±0.79	0.02
FVC % pred	75.8±19.6	76.5±19.2	67.8±22.3	0.02
FEV1/FVC	0.49±0.10	0.49±0.10	0.47±0.10	0.10
GOLD stage (FEV1)				
II (50–79% pred)	211 (42.9)	199 (44.2)	12 (29.3)	0.02
III (30–49% pred)	204 (41.6)	188 (41.8)	16 (39.0)	
IV (<30% pred)	76 (15.5)	63 (14.0)	13 (31.7)	
SGRQ score				
Symptom	61.7±18.9	61.3±18.5	66.4±21.9	0.15
Activity	56.1±21.9	55.1±21.7	68.0±21.7	0.0007
Impact	35.7±22.3	35.2±22.1	42.3±23.7	0.07
Total	46.3±18.9	45.6±18.6	54.1±20.2	0.01

Data are presented as mean±SD or n (%), unless otherwise indicated. BMI: body mass index; MRC: UK Medical Research Council; 6MWD: 6-min walking distance; BD: bronchodilator; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SGRQ: St George's Respiratory Questionnaire. #: using unpaired two-tailed t-test for comparison of continuous variables (two means) and Chi-squared test for comparison of categorical variables (two proportions) between patients who completed the study and those lost to follow-up; ¶: analyses were conducted amongst patients who had complete baseline data for 6MWD.

more likely to be on long-acting bronchodilators and mucolytic agents ($p<0.05$ or $p<0.01$).

Change in HRQoL among all patients completing the study and by exacerbation category

On average, SGRQ scores had improved at the end of the study period (1 yr) among all patients who completed the study (n=450). The mean (95% CI) change in SGRQ total, activity, impact and symptom score were -3.40 (-4.88– -1.92), 0.09 (-1.62–1.81), -4.29 (-6.10– -2.48) and -6.87 (-8.73– -5.01), respectively. Table 4 shows that the improvement was predominant among patients with no exacerbation (n=167) and those with one unreported exacerbation only (n=30). SGRQ scores improved less in magnitude or deteriorated among patients in other exacerbation categories.

Adjusted effect of unreported and reported exacerbations on HRQoL at 1 yr

Multivariate analyses (table 5) showed that the 1-yr change in SGRQ total score was significantly worse in patients with more than one unreported exacerbation (adjusted β 4.61 (95% CI 0.09–9.13)) than in those with no exacerbation, after adjusting for known confounders. The greatest difference was observed for the activity domain (adjusted β 6.36 (95% CI 1.28–11.44)). These estimates were probably clinically significant as the point estimates were greater than the recommended clinically important difference (four points) [29] and the lower bounds of the 95% CIs were >0. Table 5 also shows that, compared to patients with no exacerbation, the 1-yr change in SGRQ total score was significantly worse among patients with one reported exacerbation (adjusted β 5.13 (95% CI 1.15–9.11)), patients with more than one reported exacerbation (adjusted β 12.33 (95% CI 7.72–16.95)) and patients with mixed unreported (⩾1) and reported (⩾1) exacerbations (adjusted β 8.22 (95% CI 4.46–11.98)). The greatest differences were observed for the symptom domains. Sensitivity analyses showed similar and even more significant estimates. For instance, the adjusted mean change in the SGRQ total score for more than one unreported exacerbation relative to no exacerbation was 4.69 (95% CI 0.13–9.25) among all 491 patients and 4.25 (95% CI 1.78–6.72) among 414 patients without any missing data. The interactions between exacerbations (both unreported and reported) and COPD severity were not significant ($p>0.1$ for all). The adjusted estimates were -1.93 (-6.18–2.32), -2.21 (-7.00–2.57), -2.49 (-7.72–2.73) and 0.23 (-4.82–5.29), respectively, for the association between the occurrence of exacerbations in the last 3 months and SGRQ total, activity, impact and symptom score. Similar results were observed for exacerbations in the last 2 months (unpublished data).

TABLE 2 Characteristics of unreported and reported exacerbations[#]

	Unreported	Reported
Exacerbations	466	410
Exacerbation rate events·person-yr^{-1}	1.01 (0.92–1.09)	0.95 (0.87–1.04)
Total number of key symptoms	1 (1–3)	3 (1–3)
Type of key symptoms		
Sputum amount	213 (45.7)	292 (71.2)[¶]
Sputum colour	72 (15.5)	268 (65.4)[¶]
Dyspnoea	279 (59.9)	353 (86.1)[¶]
One symptom	388 (83.3)	118 (28.8)[¶]
Two symptoms	58 (12.4)	81 (19.7)**
Three symptoms	20 (4.3)	211 (51.5)[¶]
Treatment of exacerbations		
Untreated exacerbations	373 (80.1)	53 (12.9)
Treated exacerbations	93 (19.9)	357 (87.1)

Data are presented as n, mean (95% CI) or n (%). Data for key symptoms are presented as median (range). [#]: among all 491 patients. **: $p<0.01$; [¶]: $p<0.0001$ using generalised estimating equations with each symptom as the dependent variable and the reporting status as the independent variable, and taking into account the potential individual-level clustering effect.

DISCUSSION

The present study shows that more than half of all exacerbations were not reported for medical attention in a population of COPD patients in China. More than one unreported exacerbations was associated with a significantly (both statistically and clinically) worse HRQoL change at 1 yr after adjusting for known confounders. Although this impact seems moderate in magnitude, it is far from negligible. It suggests that unreported exacerbations, despite being associated with less symptom worsening than reported exacerbations, may have an important intermediate-to-long-term impact on patients' physical activities (SGRQ activity domain). In addition, this study shows that the change in HRQoL at 1 yr was worse among patients with more frequent and reported exacerbations.

To our knowledge, this is the first prospective study to investigate the independent effect of unreported exacerbations on the change in HRQoL in the intermediate to long term. Previous studies have focused on the effect of exacerbations reported for medical attention [7, 9] or a combination of unreported and reported exacerbations [8]. One study [13] reported an association between worse HRQoL assessed at the beginning of the study and a higher proportion of untreated exacerbations during the follow-up period. However, this reverse temporal relationship precludes any causal inference regarding the effect of untreated exacerbations on the change in HRQoL. A recent Canadian cohort study [5] has shown that unreported exacerbations may have negative impacts on HRQoL in 3 months, and suggested that the health impact of this potential unmet healthcare need should be studied over the longer term. The present study, along with previous results, suggests a clinically important health impact of under-reporting of exacerbation in patients with COPD.

Selection bias is unlikely to be responsible for the significant association between more than one unreported exacerbation and change in HRQoL. Patients who were lost to follow-up had more severe COPD at baseline than those who completed the study. However, stratified analyses showed that the relation between unreported exacerbations and change in HRQoL was similar across different levels of disease severity. Therefore, there was no evidence that the association between unreported exacerbations and the change in HRQoL would be significantly different for patients who were lost to follow-up. Indeed, sensitivity analyses showed very similar and slightly more significant results among all 491 recruited patients.

The causal diagram approach [25, 26] was used for the comprehensive confounding evaluation. As discussed elsewhere [15], this approach is an alternative to other data-driven methods, such as stepwise regression and the change-in-estimation approach [30–32]. It allows for the consideration of inter-relationships between multiple covariates and explicitly models the causal assumptions between variables that were implied but obscured in most studies [25, 26]. Known confounders identified using causal diagrams were controlled for in the present study. As with any model, there can be no guarantee that the causal diagram is correct or that other models could not be put forward. However, this approach permits causal assumptions to be made explicit.

In order to avoid the acute effect of the last exacerbation on HRQoL measures, the SGRQ was administered $\geqslant$4 weeks after the last exacerbation. As a previous study [6] had shown that the effect of a single exacerbation may persist for months, the occurrence of exacerbations in the last 3 and 2 months, respectively, were further included in the multivariate models. There were no significant effects on the change in HRQoL after adjusting for the frequency and reporting status of exacerbations. This result suggests that a 1-month washout period appears to be appropriate to preclude the acute effect of recent exacerbations in therapeutic evaluations.

Based on the expected poor compliance to the patient-kept diary card approach [5, 8] in this relatively lesser-educated population (*i.e.* 35.5% primary school or no education), a monthly follow-up using a standardised questionnaire was employed in order to trace unreported exacerbations. As patients with COPD often under-recognise their symptom changes, a less strict criterion (*i.e.* at least one key symptom change) was used to capture as many unreported exacerbations as possible. The Canadian cohort study [5, 8], one of the two previous studies that investigated the under-reporting of COPD exacerbations, used a similar definition. The incidence rate of all exacerbations in the present study (1.95 events·person-yr^{-1}) [15] was lower than that observed using a diary card in the Canadian cohort (2.7 events·person-yr^{-1}) [5, 8]. This difference may be explained by the different inclusion criteria in these two studies. In order to be included in the Canadian cohort, patients needed to have a smoking history of $\geqslant$10 pack-yrs smoking and have had two exacerbations within the previous 3 yrs. In the present study, however, 27.3% of patients had never smoked and 16.5% of patients had had no exacerbation in the previous year. Conversely, it may indicate that patients who underwent monthly follow-up did not recall mild symptom worsening during the past month. Closer

TABLE 3 Baseline characteristics of patients by exacerbation group

	None	Unreported only		Reported only		Mixed#
		1	>1	1	>1	
Subjects n	167	30	45	70	46	92
Age yrs	64.8±11.4	63.0±10.8	63.5±10.8	68.6±8.9*	65.7±9.9	64.7±10.3
Male sex	110 (67.0)	21 (70.0)	37 (82.2)*	38 (54.3)	33 (71.7)	70 (73.6)
Cumulative smoking pack-yrs	29.1±34.9	25.6±20.4	20.1±23.8	21.7±24.1*	18.0±24.9*	29.1±27.2
MRC dyspnoea score ⩾4	29 (17.6)	7 (23.3)	7 (15.5)	19 (27.1)	11 (23.9)	30 (31.5)*
6MWD¶ m	398.7±139.3	369.7±85.6	437.2±130.7	348.6±119.2*	356.6±121.5	414.2±138.1
Spirometry (post-BD)						
FEV1 L	1.19±0.47	1.32±0.55	1.28±0.42	1.10±0.45	1.06±0.53	1.19±0.46
FEV1 % pred	48.3±15.1	53.7±18.4	48.1±14.6	49.6±16.1	44.3±15.5	47.5±16.0
FVC L	2.34±0.79	2.62±0.78	2.65±0.69*	2.13±0.79	2.20±0.83	2.47±0.77
FVC % pred	74.9±19.6	84.0±19.8*	78.0±17.5	75.0±20.9	74.9±16.7	78.2±18.6
FEV1/FVC	0.51±0.10	0.48±0.11	0.50±0.10	0.52±0.09	0.47±0.10	0.48±0.12*
Hospital admission for last exacerbation	66 (40.2)	9 (30.0)	23 (51.1)	33 (47.1)	28 (60.9)*	53 (55.7)*
Significant comorbid conditions ⩾1	23 (14.0)	6 (20.0)	6 (13.3)	12 (17.1)	7 (15.2)	19 (20.0)
Treatment profile						
LABD	62 (37.8)	13 (43.3)	17 (37.8)	42 (60.0)**	31 (67.4)**	46 (48.4)
ICS	50 (30.5)	9 (30.0)	8 (17.8)	26 (37.1)	17 (37.0)	32 (33.7)
Mucolytics	74 (45.1)	10 (33.3)	20 (44.4)	43 (61.4)*	32 (70.0)**	45 (47.3)
No medication+	47 (28.1)	10 (33.3)	15 (33.3)	15 (21.4)	4 (8.7)	25 (27.2)

Data are presented as mean±SD or n (%), unless otherwise indicated (n=450). MRC: UK Medical Research Council; 6MWD: 6-min walking distance; BD: bronchodilator; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; LABD: long-acting bronchodilator; ICS: inhaled corticosteroid. #: unreported (⩾1) and reported (⩾1); ¶: analyses were conducted amongst patients who had complete baseline data for 6MWD; +: no use of LABDs, ICSs or mucolytics. *: $p<0.05$; **: $p<0.01$ *versus* no exacerbations (reference) using unpaired two-tailed t-test for comparison of continuous variables (two means) and Chi-squared test for comparison of categorical variables (two proportions).

investigation revealed that, as compared to the Canadian cohort, the present study had a lower rate of unreported exacerbation (1.01 *versus* 1.9 events·person-yr^{-1}) and a higher rate of reported exacerbation (0.95 *versus* 0.8 events·person-yr^{-1}) [5, 8]. Indeed, patients in the present study were encouraged to report their symptom worsening to the research

TABLE 4 Change in health-related quality of life by exacerbation group at 1 yr

	None	Unreported only		Reported only		Mixed#
		1	>1	1	>1	
Subjects n	167	30	45	70	46	92
1-yr change in SGRQ score¶						
Symptom	-13.0±19.2	-16.2±18.0	-7.2±18.5	-2.1±18.5+	2.9±14.6+	-0.8±21.0+
Activity	-3.7±19.4	-4.4±18.8	1.1±17.2	2.2±17.2*	7.4±17.6**	2.8±17.1**
Impact	-6.6±20.6	-6.8±18.3	-1.5±17.2	-3.8±18.9	2.5±18.7**	-3.7±18.8
Total	-6.8±16.7	-7.7±13.1	-1.6±15.3	-1.7±15.0+	4.1±14.6+	-1.2±15.0**
1-yr change in SGRQ score of ⩾4¶						
Symptom	22 (13.4)	2 (6.7)	9 (20.0)	27 (38.6)+	26 (56.5)**	39 (41.0)+
Activity	47 (28.6)	7 (23.3)	19 (42.2)	27 (38.6)	28 (60.9)**	44 (46.3)**
Impact	38 (23.2)	6 (20.0)	14 (31.1)	19 (27.1)	20 (43.5)+	30 (31.6)
Total	32 (19.5)	3 (10.0)	13 (28.9)	21 (30.0)	23 (50.0)**	28 (29.5)*

Data are presented as mean±SD or n (%), unless otherwise indicated (n=450). SGRQ: St George's Respiratory Questionnaire. #: unreported (⩾1) and reported (⩾1); ¶: an increase in SGRQ score represents a deterioration in health-related quality of life and *vice versa*. *: $p<0.05$; **: $p<0.01$; +: $p<0.0001$ *versus* no exacerbations (reference) using unpaired two-tailed t-test for comparison of continuous variables (two means) and Chi-squared test for comparison of categorical variables (two proportions).

TABLE 5 Adjusted associations between unreported and reported exacerbations and the 1-yr change in St George's Respiratory Questionnaire (SGRQ) score among patients completing the study[#]

Exacerbations	Patients n	SGRQ domain β (95% CI)[¶]			
		Total	Activity	Impact	Symptom
None	167	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Unreported only					
1	30	1.22 (-4.05–6.48)	3.40 (-2.54–9.34)	1.30 (-5.16–7.76)	-3.38 (-9.65–2.88)
>1	45	4.61 (0.09–9.13)	6.36 (1.28–11.44)	3.17 (-2.37–8.71)	3.62 (-1.76–8.99)
Reported only					
1	70	5.13 (1.15–9.11)	3.99 (-0.50–8.48)	3.37 (-1.50–8.24)	11.73 (7.01–16.45)
>1	46	12.33 (7.72–16.95)	10.78 (5.57–16.00)	11.33 (5.67–16.99)	17.28 (11.80–22.77)
Mixed[+]	92	8.22 (4.46–11.98)	9.34 (5.11–13.57)	5.53 (0.92–10.14)	13.99 (9.51–18.46)

The estimated β represents the mean change in SGRQ score at 1 yr for patients with exacerbations compared with patients with no exacerbation. For instance, 4.61 means that the mean change in SGRQ total score at 1 yr is 4.61 points worse for patients with more than one unreported exacerbation than in those with no exacerbation. Other significant ($p<0.05$) estimates (adjusted β (95% CI)) in multivariate models are as follows. 1) In the model for the SGRQ total score: anxiety (hospital anxiety and depression scale (HADS) anxiety score of ⩾8 *versus* <8) (5.23 (0.05–10.42)); every 10-unit increase in self-efficacy score (0.74 (0.10–1.37)); current smoking (3.66 (0.28–7.04)); 50-m increase in 6-min walking distance (6MWD) (-0.70 (-1.32– -0.08)); every 1-grade increase in UK Medical Research Council (MRC) dyspnoea scale (1.63 (0.23–3.03)); and baseline SGRQ total score (-0.52 (-0.62– -0.42)). 2) In the model for the SGRQ activity score: depression (HADS depression score of ⩾8 *versus* <8) (4.69 (0.52–8.86)); self-efficacy (0.73 (0.01–1.45)); every 10% increase in percentage predicted forced expiratory volume in 1 s (FEV_1) (-1.43 (-2.38– -0.47)); current smoking (4.29 (0.46–8.12)); every 50-m increase in 6MWD (-0.87 (-1.56– -0.18)); dyspnoea (1.66 (0.05–3.28)); and baseline SGRQ activity score (-0.59 (-0.68– -0.50)). 3) In the model for the SGRQ impact score: anxiety (7.08 (0.67–13.49)); self-efficacy (1.10 (0.32–1.87)); dyspnoea (1.97 (0.30–3.64)); and baseline SGRQ impact score (-0.54 (-0.64– -0.44)). 4) In the model for the SGRQ symptom score: every 1-yr increase in age (-0.19 (-0.38– -0.01)); depression (4.64 (0.25–9.03)); dyspnoea (1.59 (0.01–1.38)); daily productive cough (4.26 (0.66–7.86)); and baseline SGRQ symptom score (-0.63 (-0.73– -0.53)). ref: reference. [#]: n=450; [¶]: adjusted for baseline SGRQ score, age, sex, marital status, current employment, education, current smoking, percentage predicted FEV_1, MRC dyspnoea grade, 6MWD, daily productive cough, daily wheezing, depression, anxiety, self-efficacy, social support, use of long-acting bronchodilators and inhaled corticosteroids, long-term oxygen therapy, significant comorbid conditions, and the occurrence of at least one exacerbation (regardless of reporting status) during the last 3 months of follow-up; [+]: unreported (⩾1) and reported (⩾1).

team. There was also a possibility that patients' awareness of the symptom change increased gradually during the study period, partly due to the monthly follow-up. Therefore, more reported exacerbations (*i.e.* reduced unreported exacerbations) might be observed than would be found in routine clinical settings. However, this is more likely to have led to underestimation of the negative impact of unreported exacerbations in current clinical care, although the impact of reported exacerbations might be exaggerated. In future research, applying different detection approaches in at least a sample of the study population would be helpful in directly evaluating the difference between these approaches.

Monthly follow-up showed that 87.1% of reported exacerbations were treated and 12.9% were not treated based upon clinicians' judgments. Conversely, 19.9% of unreported exacerbations were shown to be self-treated by patients. This self-treatment may be related to the use of medication remaining from a previous prescription and certain over-the-counter antibiotics available in China. The rate of hospital admission was relatively high in the present study, *i.e.* 40.7% of exacerbations with at least one medication change led to hospitalisation and 30.0% of patients were admitted to hospital at least once due to the exacerbation during the 1 yr. These observations suggest potential unmet health needs or less-than-optimal health resource utilisation in the management of COPD exacerbations.

The main limitation of the present study was that patients were only monitored for 1 yr and HRQoL was measured at only two time-points (on recruitment and at the end of the study) during the period of clinical stability. As a consequence, the fluctuation in HRQoL during the 1-yr follow-up period was unknown. A longer follow-up time and more frequent HRQoL measures would permit a more thorough investigation of the long-term impact of unreported exacerbations on the progression of HRQoL. Periodic measures of HRQoL during the period of clinical stability would also permit better use of the exacerbation and HRQoL data collected before loss to follow-up. The limited number of patients with one (n=30) and more than one (n=45) unreported exacerbation only is another concern. Multiple testing could be an issue, as several exacerbation groups were compared to the group with no exacerbations. It might increase the chance of incorrectly rejecting the null hypothesis.

On average, the SGRQ total, impact and symptom scores had improved significantly at the end of the study among patients who completed the follow-up. The overall improvement in HRQoL at 1 yr is not unexpected, as it has been a universal finding in the placebo arm of major intervention trials [33, 34] and in longitudinal observational studies [7]. Patients usually benefit from participation in clinical studies since this is associated with better decision-making with regard to therapy and patient care. The present study allowed for the standard treatments, such as bronchodilators and inhaled steroids,

based on clinical judgment, and for the treatments being optimised throughout the study. Although change in treatments was not recorded, it may partly explain the overall improvement in HRQoL. A closer investigation revealed that the improvement was predominant among patients who had had no exacerbation and those who had had one unreported exacerbation. However, the effect of having more than one unreported exacerbation was to reduce HRQoL improvement. This finding concurs with an observational study investigating the effect of reported exacerbations on the progression of HRQoL over 2 yrs [7].

In conclusion, unreported exacerbations, although associated with less symptom worsening than reported exacerbations, have a non-negligible negative impact on the change in HRQoL at 1 yr. The development of self-management programmes has been recommended [35], emphasising early recognition of exacerbation (symptom worsening) and consequent action. Intervention trials seem to be warranted for evaluation of the intermediate-to-long-term health benefit of these strategies. Given the large proportion of unreported exacerbations (associated with symptom change but usually not medication change) and their negative impact on patients' health over the intermediate to long term, the frequency of unreported exacerbations should also be monitored and evaluated as an important outcome in future intervention trials (or a part of the treatment benefit may be unrevealed). The intermediate-to-long-term HRQoL impacts of both unreported and reported exacerbations call for further investigations of modifiable risk factors for COPD exacerbations, as well as for interventional strategies that prevent the occurrence of COPD exacerbations.

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STATEMENT OF INTEREST

A statement of interest for J. Bourbeau can be found at www.erj.ersjournals.com/misc/statements.dtl

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