Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice–based Population with Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are important adverse events in the natural history of chronic obstructive pulmonary disease (COPD).

Objectives: To investigate the natural history of AECOPDs over 10 years of follow-up.

Methods: We identified 99,574 patients with COPD from January 1, 2004, to March 31, 2015, from the UK Clinical Practice Research Datalink. We defined moderate AECOPDs as those managed outside hospital and severe as those requiring hospitalization. During the baseline period (first year of follow-up), patients were grouped according to the number and severity of AECOPDs and then followed for a maximum of 10 years (mean, 4.9 yr). We investigated the effect of baseline AECOPD number and severity on risk of further events and death.

Measurements and Main Results: Around one-quarter of the patients with COPD did not exacerbate during follow-up. Compared with no AECOPDs in the baseline period,

AECOPD number predicted the future long-term rate of AECOPDs in a graduated fashion, ranging from hazard ratio (HR) of 1.71 (1.66–1.77) for one event to HR of 3.41 (3.27–3.56) for five or more events. Two or more moderate AECOPDs were also associated with an increased risk of death in a graduated fashion, ranging from HR of 1.10 (1.03–1.18) for two moderate AECOPDs to HR of 1.57 (1.45–1.70) for five or more moderate AECOPDs, compared with those with no AECOPDs at baseline. Severe AECOPDs were associated with an even higher risk of death (HR, 1.79; 1.65–1.94).

Conclusions: A large proportion of patients with COPD do not exacerbate over a maximum 10 years of follow-up. AECOPD frequency in a single year predicts long-term AECOPD rate. Increasing frequency and severity of AECOPDs is associated with risk of death and highlights the importance of preventing AECOPDs.

Keywords: epidemiology; cohort studies; case-control studies

Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are important events in the natural history of the disease. People who have frequent exacerbations (≥ 2 /yr) have higher mortality, worse quality of life, and faster FEV₁ decline than those with infrequent

exacerbations (0–1/yr) (1). Increasing exacerbation frequency is known to be a risk factor for future exacerbation events (2), and is thought to be a stable trait (2, 3), with exacerbations clustering in time (4). Previous work has shown that increased frequency of moderate AECOPDs is

associated with an increased risk of death in the year following an AECOPD (5) and that a hospitalization for AECOPD (i.e., severe AECOPD) is associated with an increased risk of death, with the risk of death increasing with increasing frequency of severe AECOPDs (6).

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At a Glance Commentary

Scientific Knowledge on the

Subject: People who have frequent exacerbations are known to have increased mortality compared with infrequent exacerbators, and severe exacerbations (requiring hospitalization) are associated with a higher risk of death than those managed in the community. However, the impact of multiple moderate exacerbations (those managed outside hospital) on the natural history of chronic obstructive pulmonary disease (COPD) is unknown. Recent evidence has suggested that there is substantial short-term variation in year-to-year acute exacerbations of COPD rates.

What This Study Adds to the

Field: We carried out a large study to investigate the natural history of COPD exacerbations with a follow-up of up to 10 years. Compared with previous studies, our study is larger in terms of patient numbers, has longer follow-up, and is generalizable to the real-life COPD population seen in clinical practice. We demonstrate that when taken as a cross-section of all patients with COPD, a substantial proportion do not seem to exacerbate; however, in our generalizable population, this proportion was half the previously estimated size. In addition, we also show that most patients do in fact exacerbate at least once following diagnosis of COPD, but once their COPD is established, many do not exacerbate again over the 10 years of follow-up (mean, 4.9 yr), suggesting phenotypic complexity among the COPD population. Although there is likely to be substantial year-to-year variation in exacerbation rates, because of our long follow-up, we were able to demonstrate that exacerbation frequency in a single year does predict long-term exacerbation rates in a graduated fashion. We also found a graduated increase in risk of mortality associated with moderate exacerbations (from 0–5 or more per year). However, no frequency of moderate exacerbations exceeded the mortality risk from a severe exacerbation.

Most published studies split patients with chronic obstructive pulmonary disease (COPD) into infrequent (0–1 events/yr) and frequent (≥ 2 events/yr) AECOPD categories because of the understanding of the importance of the frequent exacerbator phenotype. It is unclear, however, how a graduated increase in moderate AECOPD (managed outside hospital) events impacts the risk of death, and how the frequency of moderate events compares with hospitalized events in terms of risk of death. Furthermore, previous studies of the natural history and impact of AECOPD frequency and severity, have made use of more severe cohorts, or those treated in secondary care and with a relatively short follow-up of up to 3 years (3, 4, 6–8). Because most patients with COPD are cared for in primary care, it is unclear if previous work can be generalized.

Using a representative population-based cohort of linked primary care, hospitalization, and mortality data, we investigated the effect of frequency and severity of AECOPDs at baseline on the risk of death and future AECOPDs. We also aimed to determine if more distant AECOPDs have an effect on risk of death independent of the frequency of more recent events.

Some of the results of these studies have been previously reported in the form of an abstract (9).

Methods

Data Source and Study Population

We used data from the Clinical Practice Research Datalink (CPRD) linked with Hospital Episodes Statistics data and Office of National Statistics mortality database.

We used our previously validated algorithm to identify patients with COPD in the CPRD (10). Briefly, this consisted of patients aged older than 35, with a record for a validated diagnostic code for COPD, and a smoking history. We included all patients in the CPRD with COPD if they were eligible for linkage with Hospital Episodes Statistics, Office of National Statistics, and deprivation data (index of multiple deprivation [11]), and had at least 1 year between joining the database and censoring at death or moving outside the system. The Read codes used to identify COPD are presented in the online supplement (*see* Table E1 in the online supplement).

We used our previously validated algorithms to identify moderate (12) and severe (13) AECOPDs, and degree of airflow limitation (14). Further details on the data source and covariate and outcomes ascertainment are in the online supplement.

Statistical Analysis

Cohort study. This was an open cohort study using data from January 1, 2004, to March 31, 2015 (*see* Figures E1–E3). During the study period, patients were eligible to begin follow-up after both diagnosis with COPD and entry into the CPRD database. Patients who entered the CPRD database and who already had a diagnosis of COPD were labeled as having “established disease,” and those who developed COPD during their time in the CPRD database were labeled as “incident disease.”

The exposure categories were zero, one, two, three, four, and five or more moderate AECOPDs (and no severe AECOPDs); and one or more severe AECOPDs (and any number of moderate AECOPDs). Patients were categorized into these categories during their first year of available data post-COPD diagnosis, hereafter called the “baseline period.” Outcomes were then ascertained during follow-up period starting from the end of the baseline period, up to a maximum available follow-up of 10 years and 2 months.

Initially we described the rates of subsequent moderate and severe AECOPDs and time to first AECOPD by exposure category. We then used Cox proportional hazards models to investigate the effect of baseline AECOPD frequency and severity on time to first moderate AECOPD and severe AECOPD in separate analyses, adjusted for possible confounders. Covariates were identified in the period before study follow-up start. Depression, anxiety, gastroesophageal reflux disease, and asthma were ascertained in the baseline year only (*i.e.*, in the same year as AECOPD frequency categorization). All other comorbidities (myocardial infarction, stroke, heart failure, bronchiectasis, and lung cancer) were ascertained at any time before start of follow-up. Modified Medical Research Council (mMRC) score was ascertained in the baseline year, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade of airflow limitation (15) and body mass index were ascertained

using the closest measurement before start of follow-up. We then extended these models using the Andersen-Gill method to allow for repeat outcomes (AECOPDs) within person. Andersen-Gill models are an extension to Cox modeling, which allow for repeat events and preserve the ordering of events, and a robust sandwich covariance matrix for the estimates, which uses a jackknife estimate to provide robust SEs (16). We repeated each analysis stratified by timing of COPD diagnosis (established or incident COPD). We then investigated time to death by baseline AECOPD frequency and severity using Cox proportional hazards models.

To assess the impact of potential misclassification of AECOPD frequency in the first year, we also performed a sensitivity analysis that used the first 2 years of follow-up to classify patients according to AECOPD frequency and severity. In this analysis, we categorized those who had no AECOPDs in either of the first 2 years as having zero moderate AECOPDs, and then followed these patients up for up to 9 years.

Case-control study. We then conducted a nested case-control study for two of the outcomes (severe AECOPDs and death). Cases were matched to three control subjects based on age (year of birth) and general practitioner practice at the time of the event. We used incidence density sampling to mimic time to event analysis; this meant that control subjects could become future cases (17). Odds ratios produced by this method estimate the hazard ratio (HR). For the case-control studies, events were ascertained between March 2012 and March 2015 for risk of death, and from March 2014 to March 2015 for risk of severe AECOPDs. Covariates for the case-control study were ascertained at the start of the base cohort for the relevant case-control study.

The purpose of the case-control studies was to 1) account for the potential survivor bias in the cohort study where patients needed to survive for at least 1 year to be categorized, potentially impacting on patients with a severe AECOPD who are at high risk of death; 2) to account for the time-varying nature of the AECOPD exposure and changes over time in the effect of the exposure; and 3) to investigate the effect of recent versus distant AECOPDs on risk of future AECOPDs and death.

We investigated frequency and severity of AECOPDs in the previous 3 years

separately (i.e., for 0–12 mo before the event, 12–24 mo before the event, and for 24–36 mo before the event).

We used conditional logistic regression analysis, adjusting for the same confounders as the cohort study. We also additionally adjusted for number and severity of AECOPDs at other time points to assess whether more distant AECOPDs continue to influence the outcomes, conditional on more recent AECOPD frequency and severity.

Post Hoc Analysis

As a *post hoc* analysis, we investigated 1) the proportion of patients who switched AECOPD frequency (both between frequent and infrequent AECOPD status, and any and zero AECOPDs per year) by baseline AECOPD number and incident/established COPD, 2) the proportion of patients in each AECOPD frequency in both incident COPD groups and established COPD groups, and 3) whether receiving a prescription for a new inhaler was associated with switching from exacerbating in the baseline period to having no exacerbations in the first year of follow-up.

Analysis was conducted using Stata 14.2 MP.

Ethical Approval

The protocol for this research was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency Database Research (protocol number 17-013R) and the approved protocol was made available to the journal and reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from Independent Scientific Advisory Committee has been granted by a Health Research Authority Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

Results

In total, we included 99,574 patients who survived at least 1 year during follow-up (Figure E4). The characteristics of included patients are displayed in Table 1 (and detailed further in Table E2). The median age was 68 (interquartile range, 60–76), 52% were current smokers, 24% of patients had GOLD grade 1 airflow limitation, 44% had grade 2, 26% had grade 3, and 6%

had grade 4. In terms of frequency and severity of AECOPDs in the first year, 51.8% had no AECOPDs in the first year, 19.5% had one moderate AECOPD, 10.4% had two moderate AECOPDs, 5.7% had three moderate AECOPDs, 3.1% had four moderate AECOPDs, and 5.1% had five or more moderate AECOPDs; 4.3% had one or more severe AECOPDs. Greater AECOPD frequency was associated with female sex, older age, ex-smokers, higher mMRC score, more severe airflow limitation, previous myocardial infarction, stroke, heart failure, asthma, bronchiectasis, lung cancer, gastroesophageal reflux disease, depression, and anxiety (test for trend, all $P < 0.001$). Increasing AECOPD frequency was also associated with both underweight and overweight body mass index ($P < 0.001$).

A total of 38,178 (38.3%) patients had COPD diagnosed during the study (incident COPD), and 61,396 (61.7%) had COPD at the start of their follow-up (established COPD). Patients with incident disease were more likely to have experienced an exacerbation during the baseline year (53.1% in patients with incident disease, compared with 42.4% in the established disease group). In terms of other risk factors, patients in the incident disease group had better lung function and lower mMRC scores (Table E3).

Cohort Study

The mean follow-up was 4.9 years (SD, 3.2 yr). Over the follow-up, 26,987 patients (26.4%) did not have any AECOPDs in either the first year or during the follow-up period, meaning that only 47.7% of those with no AECOPDs in the first year exacerbated at all over follow-up (Figure E5). Kaplan-Meier curves stratified by established and incident COPD indicated that almost all patients with COPD with incident disease exacerbated at least once. This was also the case for those with established disease and at least one baseline exacerbation; however, only around one-quarter of those with established disease and no baseline exacerbations exacerbated over the follow-up (Figures 1 and 2). The rate of future and moderate and severe AECOPDs increased with increasing baseline frequency of AECOPDs in a graded fashion across all GOLD grades of airflow limitation (Table E4). Patients with COPD had an average of 1.3 AECOPDs per patient per year during the study period. From

Table 1. Baseline Study Characteristics

	Overall	Frequency and Severity of AECOPDs in Baseline Year						
		0 Moderate	1 Moderate	2 Moderate	3 Moderate	4 Moderate	5+ Moderate	1+ Severe
Patients, <i>n</i>	99,574	51,568	19,418	10,333	5,654	3,125	5,065	4,411
Age, mean (SD)	66.9 (11.5)	65.8 (11.7)	67.6 (11.2)	67.8 (11.1)	67.7 (11.0)	67.8 (11.1)	67.8 (11.0)	71.0 (10.8)
Sex								
Male	53,697 (53.9)	28,951 (56.1)	10,423 (53.7)	5,256 (50.9)	2,769 (49.0)	1,474 (47.2)	2,433 (48.0)	2,391 (54.2)
Female	45,877 (46.1)	22,617 (43.9)	8,995 (46.3)	5,077 (49.1)	2,885 (51.0)	1,651 (52.8)	2,632 (52.0)	2,020 (45.8)
Smoking status								
Ex-smoker	47,650 (47.9)	21,443 (41.6)	10,357 (53.3)	5,504 (53.3)	3,159 (55.9)	1,760 (56.3)	2,983 (58.9)	2,444 (55.4)
Current smoker	51,924 (52.2)	30,125 (58.4)	9,061 (46.7)	4,829 (46.7)	2,495 (44.1)	1,365 (43.7)	2,082 (41.1)	1,967 (44.6)
FEV ₁ , % predicted, mean (SD) (<i>n</i> = 48,075)	62.1 (21.9)	63.8 (21.7)	62.4 (21.7)	61.1 (21.8)	60.1 (21.9)	59.4 (22.1)	57.0 (22.5)	52.9 (22.3)
MRC score, mean (SD) (<i>n</i> = 35,284)	2.3 (1.0)	2.2 (1.0)	2.3 (1.0)	2.4 (1.0)	2.5 (1.0)	2.6 (1.0)	2.8 (1.1)	2.9 (1.1)
Myocardial infarction	7,516 (7.6)	3,429 (6.6)	1,491 (7.7)	873 (8.4)	491 (8.7)	284 (9.1)	427 (8.4)	521 (11.8)
Stroke	4,533 (4.6)	2,152 (4.2)	855 (4.4)	502 (4.9)	255 (4.5)	165 (5.3)	263 (5.2)	341 (7.7)
Heart failure	6,827 (6.9)	2,847 (5.5)	1,329 (6.8)	746 (7.2)	467 (8.3)	273 (8.7)	486 (9.6)	679 (15.4)
Lung cancer	1,200 (1.2)	398 (0.8)	248 (1.3)	166 (1.6)	109 (1.9)	63 (2.0)	103 (2.0)	113 (2.6)
Bronchiectasis	2,817 (2.8)	914 (1.8)	444 (2.3)	342 (3.3)	254 (4.5)	193 (6.2)	469 (9.3)	201 (4.6)
Asthma	32,818 (33.0)	14,755 (28.6)	6,607 (34.0)	3,978 (38.5)	2,327 (41.2)	1,295 (41.4)	2,280 (45.0)	1,576 (35.7)
GERD	4,091 (4.1)	879 (4.5)	488 (4.7)	294 (5.2)	192 (6.1)	314 (6.2)	213 (4.8)	879 (4.5)
Anxiety	5,694 (5.7)	1,085 (5.6)	667 (6.5)	423 (7.5)	229 (7.3)	472 (9.3)	329 (7.5)	1,085 (5.6)
Depression	6,265 (6.3)	2,943 (5.7)	1,164 (6.0)	745 (7.2)	412 (7.3)	254 (8.1)	435 (8.6)	312 (7.1)
BMI, mean (SD) (<i>n</i> = 92,628)	26.9 (6.0)	26.7 (5.8)	26.9 (5.9)	27.1 (6.1)	27.2 (6.4)	27.3 (6.3)	27.0 (6.7)	26.3 (6.5)
IMD decile, mean (SD)	5.9 (2.8)	5.9 (2.8)	5.8 (2.8)	6.0 (2.8)	6.0 (2.8)	6.0 (2.8)	6.0 (2.8)	6.1 (2.8)
Inhaled COPD therapy at baseline*								
LABA	12,669 (16.1)	5,295 (14.8)	2,484 (15.0)	1,599 (17.2)	948 (18.1)	573 (19.4)	968 (20.0)	802 (19.4)
LAMA	26,201 (33.2)	9,961 (27.8)	5,322 (32.1)	3,286 (35.3)	2,044 (39.1)	1,270 (42.9)	2,241 (46.3)	2,077 (50.2)
ICS	27,335 (34.7)	12,495 (34.9)	5,583 (33.7)	3,241 (34.9)	1,873 (35.8)	1,091 (36.9)	1,696 (35.0)	1,356 (32.8)
LABA-ICS	36,066 (45.7)	13,678 (38.2)	7,264 (43.8)	4,661 (50.1)	2,905 (55.5)	1,743 (58.9)	3,138 (64.8)	2,677 (64.7)
LABA-LAMA	41 (0.1)	22 (0.1)	8 (0.0)	6 (0.1)	2 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
SAMA	14,211 (18.0)	5,861 (16.4)	2,821 (17.0)	1,758 (18.9)	1,056 (20.2)	632 (21.4)	1,067 (22.0)	1,016 (24.6)
SABA	64,075 (81.2)	28,155 (78.6)	13,447 (81.1)	7,703 (82.8)	4,472 (85.5)	2,542 (85.9)	4,215 (87.0)	3,541 (85.6)
No inhaled treatment	20,709 (20.8)	15,747 (30.5)	2,844 (14.6)	1,035 (10.0)	421 (7.4)	167 (5.3)	222 (4.4)	273 (6.2)

Definition of abbreviations: AECOPDs = acute exacerbations of chronic obstructive pulmonary disease; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; IMD = index of multiple deprivation (socioeconomic status); LABA = long-acting β agonist; LAMA = long-acting muscarinic antagonist; MRC = Medical Research Council; SABA = short-acting β agonist; SAMA = short-acting muscarinic antagonist.

Data are shown as *n* (%) unless otherwise indicated.

*Not mutually exclusive groups.

those with no AECOPDs at baseline who survived over 10 years of follow-up (*n* = 5,623), 4,065 (72.3%) did not exacerbate at all.

When we performed our sensitivity analysis, which categorized patients over the first 2 years of follow-up. A total of 77,623 patients remained; of these 34,246 (44.1%) had no event in either year and 22,709 (29.3%) had no event during their entire follow-up.

Risk of moderate AECOPDs. In the analysis allowing for repeat moderate events, there was a graduated increase in the rate of moderate AECOPDs by increasing frequency of baseline moderate AECOPDs (Table 2). This pattern was maintained after adjustment

for potential confounders, with the relative risk of further moderate AECOPDs increasing from HR of 1.71 (95% confidence interval, 1.66–1.77) for those with one baseline moderate AECOPD to HR of 5.50 (5.32–5.68) for those with five or more baseline moderate AECOPDs, compared with those with no AECOPDs at baseline. The effect of baseline AECOPD frequency and severity on risk of future moderate AECOPDs were comparable between those with established and incident COPD and for time to first event analyses (Tables E5 and E6).

Risk of severe AECOPDs. Risk of future severe AECOPDs behaved in a similar way

to the risk of future moderate events (Table 2). There was again a graduated increase in the rate of severe AECOPDs with increasing number of baseline moderate AECOPDs, rising from 0.10 to 0.33 events per person-year for those without versus (0.32–0.35) five or more moderate AECOPDs. The rate of severe AECOPDs for those with one or more baseline severe AECOPDs was 0.51 per person year. This relationship corresponded with observed adjusted risk. Nevertheless, the presence of one or more baseline severe AECOPDs was associated with the highest risk of future severe AECOPDs (HR, 3.65; 3.53–3.78). The effect

Figure 1. Time to first acute exacerbation of chronic obstructive pulmonary disease (AECOPD) by baseline AECOPD frequency and severity, established patients with chronic obstructive pulmonary disease.

of baseline AECOPD frequency and severity on risk of future severe AECOPDs were comparable between those with established and incident COPD and for time to first event analyses (Tables E7 and E8).

Risk of death. Risk of death again gradually increased with increasing frequency of moderate baseline AECOPDs, and those who had one or more severe baseline AECOPDs had the highest risk of death with HR of 1.79 (95% confidence interval, 1.65–1.94) (Figure 3, Table 2).

Case-Control Study: Odds of Death

We identified 7,137 cases (deaths) and matched with three control subjects. Adjusted model considering 12 months

period before death showed an increasing frequency of moderate AECOPDs associated with higher risk of death up to over a doubling of risk of death for those with five or more moderate AECOPDs. Patients with only one moderate AECOPD were not in an increased risk as compared with those without AECOPDs (Table 2). Those who had a severe AECOPD in the previous 12 months had more than a 14 times increased risk of death compared with those who had no AECOPDs (odds ratio, 14.16; 95% confidence interval, 9.45–21.2). Using alternative time periods of 12–24 and 24–36 months, we observed similar results for moderate AECOPDs. However, the effect of severe AECOPDs in the 12–24 and 24–36 months previously was attenuated. After

Figure 2. Time to first AECOPD by baseline AECOPD frequency and severity, incident patients with chronic obstructive pulmonary disease. AECOPDs = acute exacerbations of chronic obstructive pulmonary disease.

adjusting for the frequency and severity of AECOPDs at other time points, only frequency and severity of AECOPDs in the previous 12 months remained associated with risk of death, with the exception of severe AECOPDs in the 12–24 months (Table E10). Results of the severe AECOPD case-control study are presented in Table E11.

Post Hoc Analysis

We found that 27.4% of patients without baseline AECOPDs exacerbated in the first year, 40% of patients with one or more baseline AECOPDs switched to none in the first year of follow-up, and 27% of patients with two or more AECOPDs switched to none in the first year of follow-up. Compared with those with established disease, patients with incident COPD were more likely to switch from having no exacerbations at baseline to having one or more in the first year of follow-up, and were more likely to switch from being an infrequent (0–1 AECOPDs/yr) to frequent exacerbator (≥ 2 AECOPDs/yr) (Table E12).

When comparing those with incident disease with a subset of those with established disease defined as less than 5-year duration, we found that the proportions of patients in each AECOPD frequency group were very similar between incident and established disease after Year 3 of follow-up (Figure E8).

We found that having a prescription for a new class of inhaled therapy was associated with switching from being an exacerbator in the baseline period to having no exacerbations in the first year of follow-up (full details in the online supplement).

Discussion

In our population-based study of patients with COPD with up to 10 years of follow-up (mean, 4.9 yr), we have identified a large subgroup of patients with COPD (26%) who do not exacerbate. Among those who did experience an exacerbation during the first baseline year, any AECOPDs, even moderate events, were associated with an increased risk of death. This risk increases in a graduated manner, meaning with every additional moderate AECOPD, there is a further increase in the risk of death. Furthermore, the risk of death associated with severe AECOPDs was higher than having any number of moderate AECOPDs that we

Table 2. Baseline Frequency and Severity of AECOPDs and Risk of Moderate AECOPDs, Severe AECOPDs, and Death

AECOPD Category	Adjusted HR (95% CI): Cohort Study			Adjusted OR (95% CI) for Risk of Death Associated with Earlier AECOPD Frequency and Severity: Case-Control Study		
	Future Moderate AECOPD (Repeat Events)	Future Severe AECOPD (Repeat Events)	Death	0–12 mo Prior	12–24 mo Prior	24–36 mo Prior
No AECOPDs	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1 Moderate	1.71 (1.66–1.77)	1.21 (1.14–1.27)	1.01 (0.93–1.11)	1.18 (0.83–1.67)	1.36 (1.02–1.83)	1.38 (1.02–1.87)
2 Moderate	2.35 (2.27–2.42)	1.61 (1.52–1.72)	1.10 (1.03–1.18)	1.80 (1.19–2.70)	1.56 (1.06–2.31)	1.54 (1.03–2.30)
3 Moderate	2.94 (2.83–3.05)	1.89 (1.76–2.03)	1.25 (1.15–1.36)	1.98 (1.13–3.49)	1.50 (0.95–2.37)	1.57 (0.99–2.51)
4 Moderate	3.41 (3.27–3.56)	2.14 (1.95–2.35)	1.32 (1.20–1.46)	1.00 (0.53–1.86)	2.23 (1.38–3.73)	1.45 (0.75–2.81)
5+ Moderate	5.50 (5.32–5.68)	2.92 (2.73–3.13)	1.57 (1.45–1.70)	2.33 (1.45–3.76)	2.50 (1.56–3.98)	2.80 (1.75–4.48)
1+ Severe	3.27 (3.13–3.41)	3.69 (3.44–3.94)	1.79 (1.65–1.94)	14.16 (9.45–21.20)	4.27 (2.78–6.55)	2.57 (1.61–4.13)

Definition of abbreviations: AECOPDs = acute exacerbations of chronic obstructive pulmonary disease; CI = confidence interval; HR = hazard ratio; OR = odds ratio.

All HRs and ORs are adjusted for age, sex, smoking status, body mass index, comorbidities, and FEV₁% predicted.

observed. We demonstrated that the risk of mortality associated with severe AECOPDs is time dependent with a peak relationship in the first 12 months after a severe AECOPD.

With regards to novelty, our study advances knowledge significantly in five areas 1) Although previous papers (e.g., Han and coworkers [18]) have shown that year to year there seems to be variation in AECOPD frequency, our results suggest a more long-term stability in rates when observed over up to 10 years of follow-up. 2) Unlike Han and colleagues (18), we demonstrate that most patients with COPD do in fact exacerbate at some point in their history, but a large proportion are likely to become nonexacerbators, suggesting the potential for successfully reducing the AECOPD rate to zero in a subgroup of patients with COPD who perhaps respond

particularly well to treatment. 3) We are the first to demonstrate a graded effect of AECOPD frequency moving from zero to five or more moderate events per year on long-term risk of death. 4) Uniquely, we were able to compare the risk of death between varying moderate AECOPD frequency and having one or more severe AECOPDs to demonstrate that no number of moderate AECOPDs ($\geq 5/\text{yr}$) is equivalent in risk to one or more severe AECOPDs per year. 5) Our case-control analysis indicated that after adjusting for previous AECOPD history, only recent AECOPD frequency is associated with increased risk of death. This finding suggests that the association between historic AECOPDs and risk of death may be mitigated by reduction of current AECOPD frequency (i.e., there is no long-

term impact of frequent AECOPDs if they can be brought under control).

Compared with Han and colleagues (18), our study is representative of the general COPD population because our study is based on routinely collected electronic health data from patients with a clinical diagnosis of COPD, rather than based on a physiologic definition (airflow obstruction among those with a smoking history) among a convenience sample. Compared with Han and colleagues (18), our study also benefitted from using observed rather than recalled exacerbation history as the exposure. We expect these differences in the populations might influence exacerbation patterns, and indeed we observed an average of 1.3 AECOPDs per year per patient, compared with 0.37 per year per patient in Han and colleagues' (18) study. This is likely reflected in our finding that around one-quarter of patients with COPD do not exacerbate over follow-up, compared with Han and coworkers' (18) finding that around one-half did not exacerbate. However, compared with Han and colleagues (18), we did find that a very similar proportion of patients switched from exacerbating to nonexacerbating and vice versa in between the baseline period and first year of follow-up. Although we found that a larger proportion of patients did not exacerbate among those who had a full 10 years of follow-up that in the overall study cohort, this subcohort will be selectively biased toward survivors who have fewer exacerbations. In patients with COPD, a follow-up longer than 2–3 years is related to relatively high mortality rates because of their advanced mean age,

Figure 3. Time to death by baseline AECOPD frequency and severity, all patients. AECOPDs = acute exacerbations of chronic obstructive pulmonary disease.

seriousness of their underlying condition, and other common morbidities (19).

In our cohort study, increasing frequency of moderate AECOPDs was associated with risk of death, although after adjustment for potential confounders this was only significant for those with two or more moderate AECOPDs per year. However, having one baseline moderate AECOPD was only associated with an increased risk of death in those patients with incident COPD, perhaps indicating a protective effect of treatment for those with established COPD. The higher relative risk of death associated with severe AECOPDs in the 1 year following COPD diagnosis (incident COPD subcohort) likely represents more severe disease in those patients with COPD who are hospitalized for their COPD early on in their disease course.

In our case-control study, we found that risk of death increases with increasing frequency of AECOPDs, again only for a frequency of two or more AECOPDs per year, and that the risk of death following severe AECOPD in the last year is 12 times that of those who did not exacerbate at all. In the fully adjusted analysis, the risk of death in the 12 months following severe AECOPD was more than 15 times that of those patients with COPD who did not have an AECOPD. Our findings suggest that the effect of more distant AECOPD frequency was mediated through higher propensity to have more recent AECOPDs, rather than a direct

effect of distant AECOPDs on risk of death.

The biggest strengths of our study were the representativeness of the cohort, the size, and the 10 years of follow-up data. Although there was likely to be a survival bias in the design of the cohort study, this was necessary so that the effect of moderate AECOPD frequency could be compared with the effect of severe AECOPD. In addition, we conducted a case-control study to investigate these effects with a design that did not have a survival bias. Our case-control study also allowed us to investigate the difference in effects of recent versus more distant AECOPDs. We also used validated definitions of COPD and AECOPD, which were found to have positive predictive values of more than 85% following case note review in previous validation studies (10, 12, 13).

Although we used validated definitions, there is still the potential for misclassification in electronic health care record studies. However, it is likely that any “missed” AECOPDs would be disproportionately distributed in those who have fairly frequent AECOPDs, and this is unlikely to influence our conclusions. We also recognize that other unmeasured confounders for the association between AECOPD frequency and severity, such as frailty, may not have been controlled for. In addition, a further weakness was that we could not assess the natural history and impact of “mild AECOPDs,” those events that might be managed at home. One other

potential weakness of our study is that some data were missing for covariates, notably FEV₁, mMRC score, and body mass index. Data were not missing for exposures or outcomes. Furthermore, our results did not change substantially on adjustment for potential confounders, and it is unlikely that missing data on these covariates would change our conclusions.

Conclusions

Our findings highlight the importance of collecting detailed and accurate information on AECOPD frequency and severity to consider the risk of future AECOPDs and death in terms of therapeutic management. In addition to already published data, we found that the risk of future adverse events in COPD neither starts nor stops with two or more moderate or severe events. Any moderate AECOPDs increased susceptibility of future moderate or severe AECOPDs and mortality among those with recent incident diagnosis. This increase in risk is stepwise with every additional moderate event leading to more future events. Taken with our finding that a large proportion of our established COPD subcohort did not exacerbate, this suggests that reduction in AECOPD frequency to zero is possible, perhaps for a subset of patients who respond particularly well to therapy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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