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ABSTRACT

Objective: To examine the association between exacerbation frequency and mortality following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Design: Cohort study using medical databases.

Setting: Northern Denmark.

Participants: We identified all prevalent hospital-diagnosed COPD patients on January 1, 2005, who had at least one AECOPD during January 1, 2005 to December 31, 2009. We followed patients from the first AECOPD during this period until death, emigration, or December 31, 2009, whichever came first. We flagged all AECOPD events during follow-up and characterised each by the exacerbation frequency (0, 1, 2, or 3+) in the prior 12-month period.

Main outcomes and measures: Using Cox regression, we computed 0–30-day and 31–365-day age-, sex-, and comorbidity-adjusted mortality rate ratios (MRRs) with 95% confidence intervals entering exacerbation frequency as a time-varying exposure.

Results: We identified 16,647 eligible prevalent COPD patients, of whom 6,664 (40%) developed an AECOPD and were thus included in the study cohort. The 0–30-day MRRs were 0.97 (95% CI: 0.80, 1.18), 0.90 (95% CI: 0.70, 1.15), and 1.03 (95% CI: 0.81, 1.32) among AECOPD patients with 1, 2, and 3+ AECOPDs *vs.* no AECOPD within the last 12 months, respectively. The corresponding MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) for day 31-365.

Conclusions: Among AECOPD patients, one or more exacerbations in the previous year were not associated with 30-day mortality but were associated with an increased 31-365-day mortality.

Strengths and limitations of this study

- The universal healthcare system and complete follow-up of all residents reduces the risk of selection bias.
- The broad definitions included patients hospital-diagnosed COPD patients treated for AECOPD outside the hospital setting, but COPD patients treated in general practice exclusively were not included. Also, the use of a prevalent cohort may have resulted in a mix of patients at different stages in their clinical course of COPD.
- The study examined the association by preadmission therapy categorised based on GOLD treatment guidelines, which may have caused some misclassification of patients who were not treated accordingly.
- The study lacked information on lifestyle factors and clinical variables that would have been useful in classifying AECOPD.
- Excess non-COPD mortality may explain the association observed after 30 days of follow-up.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in pulmonary function due to airway inflammation in response to noxious particles and gases.[1,2] In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.[3] The 0-180-day and 181-day to 5-year standardized mortality rates in COPD patients were 389 per 1,000 person-years and 164 per 1,000 person-years, respectively,[3] making it one of the leading causes of death among the elderly.[4]

COPD is frequently complicated by acute exacerbations (AECOPD), defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication".[5] The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01 depending on disease severity[6] and history of frequent exacerbations.[7] The mortality for hospitalised AECOPD patients is high.[1,2] Several previous studies have examined the impact of AECOPD frequency on mortality following AECOPD overall showing that a history of AECOPD may be associated with worse prognosis. Comparison of these studies is, however, hampered by differences in the exposure windows used for assessing previous AECOPD hospitalisations, in the length of follow-up, and in the patient populations included.[8-17] Only one study examined if the association depended on preadmission therapy, but did not provide the results for the analysis except for an insignificant interaction term,[9] which limits the interpretation to statistical significance only. Finally, none of the studies included AECOPDs treated outside the hospital.

In order to address these limitations and fill this gap in the literature, we conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD using Danish registries with detailed hospital data and complete follow-up.

METHODS

Setting and data sources

We conducted this cohort study in northern Denmark, whose population numbers approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported healthcare plan guarantees universal medical care for all residents and partial reimbursement for prescribed medications.[18] Virtually all health services are recorded in various medical registries, of which the following formed the basis for this study. The Danish National Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room visits since 1995.[19] Each admission is described by one primary diagnosis and one or more secondary diagnoses classified according to the 8th revision of the *International Classification of Diseases* (ICD-8) through 1993 and the ICD–10 revision thereafter.[19]

Aarhus University Prescription Database records patient's personal identifier, the dispensing date, and the type and quantity of drug prescribed (according to the Anatomical Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at the pharmacy.[20]

Since 1968, the Danish Civil Registration System has recorded all Danish residents' administrative information and changes in vital status, such as date of death and emigration, with daily updates.[18] The registry assigns a unique personal identifier to all persons born in or immigrating to Denmark, which enables follow-up of patients and linkage of the various medical registries.[18]

All codes used for defining study variables in the current study can be found in the Supplementary File (eTable 1).

Study population

The population eligible for the study included all prevalent COPD patients on January 1, 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related diagnosis, as described previously[21] and defined in the Supplementary File. Patients younger than 40 years were excluded, given the low COPD prevalence in this patient group[22] and the potential for misclassifying asthma as COPD.

Among all eligible COPD patients, we then identified the study cohort as COPD patients who developed at least one AECOPD between January 1, 2005 and December 31, 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic prescription on the same day (to account for patients treated outside hospital), or (b) a primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge diagnosis of respiratory failure or acute respiratory infection with a secondary discharge diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of AECOPD cases were treated exclusively in the emergency department). Standard practice at Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also, COPD patients transferred to a specialized ward from the emergency room are coded as inpatient admissions and are therefore included in the study.

Using the Civil Registration System, we followed patients from the date of first exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until death, emigration, or December 31, 2009, whichever came first. To examine the effect of AECOPD frequency on mortality, we classified each AECOPD during follow-up according

to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the preceding 12 months. We then entered this value as a time-varying exposure in the analysis. Therefore, each time a patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and contribute person-time in several exposure groups depending on the rate of AECOPD. We adjudicated AECOPD events using a 30-day threshold following the prescription redemption or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not regarded as a new AECOPD.

Covariates

We used the DNRP to retrieve the hospital history for all study participants during the 5 years preceding the start of the study on January 1, 2005. We then ascertained the presence of the following diseases that are frequent among COPD patients and may affect mortality: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter, medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.

From the Prescription Database, we retrieved information on preadmission therapy and grouped patients based on the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (treatment groups A, B, C, D and an unclassified group).[5] The grouping was modified to avoid overlap between the groups, as defined in the Supplementary File (eTable 1). We also retrieved information on pharmacological treatment with systemic corticosteroids or theophylline within 12 months before study start, with antibiotics and/or

antivirals within three months before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment within the 12 months before study start and on lung volume reduction surgery between 1996 and study start.

Statistical analysis

We characterized the eligible population of COPD patients on January 1, 2005 by age, sex, comorbidities recorded in the 5 years before study start, as well as GOLD treatment group, pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the prior 12 months, and treatment with antibiotics and/or antivirals within the prior three months.

In the mortality analyses, we entered AECOPD frequency as a time-varying exposure and computed the number of deaths, person-time, and mortality rates in each exposure group. We then used Cox regression analysis to compute crude hazard ratios as a measure of mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with patients with no exacerbations in the preceding 12-month period. We then computed the MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis, we examined the effect of frequent severe exacerbations on mortality by including only severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed above). Both the present AECOPD and any exacerbations in the 12 months before had to be defined as severe. Finally, we stratified the results from the primary analysis and the results for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen therapy, lung volume reduction surgery, GOLD treatment group, and cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease).

Because AECOPD is an acute event, we expect the mortality rate to be greatest in the initial phase following and as the results of the event. We therefore separated the effect of AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all mortality rate calculations. We assessed the assumption of proportional hazards graphically using scaled Schoenfeld residuals and found it valid.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Agency. Danish legislation does not require ethical review board approval or informed consent from subjects in registry-based studies.

RESULTS

Descriptive data

We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age among eligible patients was 70 year and 53% were female. Comorbidities were frequent, especially cardiovascular disease, diabetes, osteoporosis, and asthma. The high proportion of patients had redeemed prescriptions for antibiotics within previous 3 months (31%) and for systemic steroids within previous 12 months (30%). The majority of patients received treatment recommended for GOLD group C. Among the 16,647 eligible COPD patients, 6,664 (40%) had at least one AECOPD during the subsequent five year and thus constituted the study population for our study.

Table 1. Characteristics of eligible prevalent COPD patients for the study on January 1, 2005

Characteristic	n	%
Total	16,647	100
Age at study start (years)		

40-50	1,198	7.2
50-60	2,764	17
60-70	4,522	27
70-80	5,422	33
80-90	2,492	15
90+	249	1.5
Sex		
Female	8,770	53
Male	7,877	47
Comorbidities (within previous 5 years)		
Myocardial infarction	795	4.8
Congestive heart failure	1,785	11
Peripheral vascular disease	922	5.5
Cerebrovascular disease	1,178	7.1
Peptic ulcer disease	627	3.8
Liver disease	176	1.1
Diabetes	1,134	6.8
Moderate to severe renal disease	287	1.7
Any malignancy except lung cancer	950	5.7
Alcoholism-related diseases	162	1.0
Atrial fibrillation/flutter	1,400	8.4
Medically diagnosed obesity	575	3.5
Hypertension	2,066	12
Osteoporosis	1,021	6.1
Lung cancer	186	1.1
Asthma	2,006	12
Obstructive sleep apnea	337	2.0
Rheumatoid arthritis	151	0.9
Depression	340	2.0
Treatments within previous 12 months		
Systemic steroids	4,993	30
Theophylline	1,164	7.0
Oxygen therapy	258	1.5
GOLD treatment group		
Unclassified	4,880	29
A	2,958	18
B	2,041	12
C	4,226	25
D	2,542	15
Infection within previous 3 months		
Prescription for antibiotics	5,103	31
Prescription for antivirals	55	0.3
Prescription for both antibiotics and antivirals	26	0.2

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definition of GOLD treatment groups.
*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)

Previous lung volume reduction surgery is not shown in the table because it was rare (close to 0%)

Mortality following AECOPD

The 30-day all-cause mortality rate following an AECOPD was 552, 485, 441, and 477 per 1,000 person-years for 0, 1, 2, and 3+ AECOPDs in the prior 12 months, respectively (Table 2). Compared with patients with no AECOPD in the prior 12 months, the mortality rate was increased but did not depend on the frequency of events. Thus, the MRR was 0.97 (0.80, 1.18) for 1 AECOPD, 0.90 (0.70, 1.15) for 2 AECOPDs, and 1.03 (0.81, 1.32) for 3+ AECOPDs in the prior 12 months (Table 2).

Table 2. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009.

Frequency of AECOPD in the 12 months prior to an AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	303	581	522 (466, 584)	(ref.)
1	164	338	485 (416, 565)	0.97 (0.80, 1.18)
2	79	179	441 (354, 550)	0.90 (0.70, 1.15)
3+	86	180	477 (386, 589)	1.03 (0.81, 1.32)
31 and up to 365 days				
0	933	5830	160 (150, 171)	(ref.)
1	359	1573	228 (206, 253)	1.47 (1.30, 1.66)
2	146	5205	281 (239, 331)	1.89 (1.59, 2.25)
3+	63	266	237 (185, 303)	1.59 (1.23, 2.05)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The absolute mortality rate decreased substantially after day 30 and was higher among patients with one or more AECOPDs in the 12 months preceding their AECOPD (Table 2).

Thus, the MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) among AECOPD patients who had experienced 1, 2, and 3+ AECOPDs compared with no AECOPD in the 12 months before the AECOPD event, respectively.

Severe AECOPDs (requiring hospitalisation) were associated with higher absolute mortality rates than AECOPDs overall, in particular for the 0–30-day period (Table 3). However, the relative impact of AECOPD frequency was similar to the overall results.

Table 3. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009. Only severe (hospitalised) AECOPDs included.

Frequency of severe AECOPD in the 12 months prior to a severe AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	283	301	939 (836, 1055)	(ref.)
1	109	114	954 (790, 1151)	1.07 (0.85-1.33)
2	52	46	1123 (855, 1473)	1.29 (0.96-1.75)
3+	32	36	893 (631, 1262)	1.09 (0.75-1.59)
31 and up to 365 days				
0	648	2974	218 (201, 235)	(ref.)
1	196	523	375 (326, 431)	1.75 (1.49, 2.06)
2	51	146	349 (265, 459)	1.67 (1.26, 2.23)
3+	22	59	371 (245, 564)	1.77 (1.15, 2.72)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The stratified main analyses showed that for the 31–365 day period, the MRRs were highest among those aged 50–59 years and those with oxygen therapy within 12 months before study start (Table 4). There was no substantial variation by GOLD treatment group. The stratified analysis considering severe AECOPDs only (Table 5) were similar to the stratification including all AECOPDs regardless of severity. However, the stratified analyses should be interpreted with the wide confidence intervals in mind.

Table 4. Adjusted hazard ratios* and 95% confidence intervals following AECOPD. Northern Denmark, 2005-2009.

			Frequency of AECOPD in the 12 months prior to an AECOPD		
			1	2	3+
0 to 30 days	**Overall**		0.97 (0.80, 1.18)	0.90 (0.70, 1.15)	1.03 (0.81, 1.32)
	Age	**40–49**	–	–	–
		50–59	1.74 (0.85, 3.59)	0.60 (0.17, 2.13)	2.89 (1.31, 6.36)
		60–69	1.00 (0.67, 1.50)	0.68 (0.39, 1.18)	1.10 (0.69, 1.77)
		70–79	0.98 (0.73, 1.30)	1.05 (0.73, 1.50)	1.10 (0.75, 1.60)
		80–89	0.70 (0.45, 1.08)	0.96 (0.56, 1.66)	0.61 (0.28, 1.34)
		90+	–	–	–
	Sex	**Female**	0.88 (0.67, 1.15)	0.90 (0.64, 1.26)	0.96 (0.67, 1.37)
		Male	1.06 (0.80, 1.39)	0.91 (0.63, 1.31)	1.14 (0.80, 1.62)
	Oxygen therapy within 12 months before study start	**Yes**	0.79 (0.27, 2.28)	0.24 (0.02, 2.45)	3.14 (0.27, 36.9)
		No	1.00 (0.82, 1.21)	0.96 (0.74, 1.23)	1.04 (0.81, 1.34)
	GOLD treatment group	**Unclassified**	1.60 (0.63, 4.04)	1.07 (0.11, 10.0)	2.62 (0.40, 17.3)
		A	1.12 (0.73, 1.73)	0.70 (0.36, 1.37)	1.38 (0.78, 2.44)
		B	0.69 (0.41, 1.17)	1.23 (0.67, 2.25)	0.93 (0.44, 2.00)
		C	1.01 (0.71, 1.45)	0.87 (0.54, 1.42)	1.24 (0.81, 1.91)
		D	1.05 (0.73, 1.50)	1.10 (0.71, 1.68)	0.90 (0.56, 1.43)
31 to 365 days	**Overall**		1.47 (1.30, 1.66)	1.89 (1.59, 2.25)	1.59 (1.23, 2.05)
	Age	**40–49**	0.69 (0.15, 3.27)	0.79 (0.08, 7.86)	1.68 (0.19, 14.6)
		50–59	2.13 (1.34, 3.41)	2.14 (1.07, 4.26)	3.43 (1.64, 7.15)
		60–69	1.28 (0.98, 1.67)	1.92 (1.37, 2.69)	1.16 (0.67, 2.01)
		70–79	1.62 (1.36, 1.94)	2.07 (1.61, 2.67)	1.56 (1.06, 2.29)
		80–89	1.35 (1.03, 1.77)	1.66 (1.05, 2.60)	2.12 (1.15, 3.93)
		90+	0.78 (0.19, 3.09)	8.42 (0.48, 147)	–
	Sex	**Female**	1.48 (1.24, 1.75)	2.02 (1.59, 2.55)	1.65 (1.15, 2.38)
		Male	1.47 (1.24, 1.76)	1.72 (1.32, 2.24)	1.48 (1.02, 2.14)

		Frequency of AECOPD in the 12 months prior to an AECOPD		
		1	2	3+
Oxygen therapy within 12 months before study start	**Yes**	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	No	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
GOLD treatment group	**Unclassified**	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	A	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	B	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	C	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	D	1.62 (1.29, 2.02)	1.52 (1.09, 2.13)	1.48 (0.95, 2.32)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.

*Adjusted for age (as a continuous variable), sex, and comorbidities.

Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

Table 5. Adjusted hazard ratios and 95% confidence intervals following severe AECOPD. Northern Denmark, 2005-2009. Only severe (hospitalised) AECOPDs included.

			Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
			1	2	3+
0 to 30 days	Overall		1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)
	Age	40–49	–	–	–
		50–59	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)
		60–69	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)
		70–79	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)
		80–89	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)
		90+	–	–	–
	Sex	Female	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)
		Male	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)
	Oxygen therapy within 12 months before study start	Yes	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
		No	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
	GOLD treatment group	Unclassified	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)
		A	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)
		B	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)
		C	1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)
		D	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)
31 to 365 days	Overall		1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)
	Age	40–49	–	–	–
		50–59	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)
		60–69	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)
		70–79	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)
		80–89	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)
		90+	–	–	–
	Sex	Female	1.62 (1.29, 2.03)	1.96 (1.37, 2.82)	2.28 (1.29, 4.04)

		Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
		1	2	3+
	Male	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)
Oxygen therapy within 12 months before study start	**Yes**	3.30 (1.16, 9.38)	1.50 (0.15-14.9)	–
	No	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
GOLD treatment group	**Unclassified**	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-295)
	A	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	B	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	C	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	D	1.90 (1.42, 2.56)	1.53 (0.91-2.57)	2.21 (1.14-4.29)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.

*Adjusted for age (as a continuous variable), sex, and comorbidities.

Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

DISCUSSION

In this large Danish cohort study, we found that the 31-365 day all-cause mortality rate following an AECOPD was higher among patients with at least one AECOPD in the preceding 12 months than among patients who did not have any recent AECOPD. All cause mortality did not vary substantially according to the actual number of AECOPDs within the preceding year and was not observed in excess within the first 30 days after the AECOPD after controlling for age, sex and comorbidities.

Strengths and limitations

The universal healthcare system and complete follow-up of all residents by the Danish Civil Registration System reduces the possibility of selection bias in our study. We aimed to reduce information bias by using broad definitions of COPD and AECOPD rather than more restrictive primary discharge diagnoses. A review of medical records has showed a PPV of 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.[23] However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on the same day to define AECOPDs outside hospital setting, we may have misclassified some patients who did not have AECOPD as AECOPD patients if the prescriptions were written as rescue packs for potential future events. Such misclassification would not affect the analysis restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may have resulted in misclassification of exposure status due to underreporting or misclassification of the number of AECOPDs. Previous data, however, show that the majority of patients recover within 30 days after AECOPD onset.[24]

Because we relied solely on registry data, we lacked information on lifestyle factors and clinical variables such as measurements of peak expiratory flow and arterial blood gases.

However, some of the clinical factors may be on the causal pathway linking AECOPD frequency and severity to high mortality, making adjustment inappropriate.[25] Nevertheless, such information would have been useful in classifying AECOPD. Instead, we categorised patients based on GOLD treatment groups using preadmission therapy. Although this classification relies on patients being treated according to current guidelines, we believe that it reflects the severity of COPD.

Finally, the generalizability of our results to the entire range of AECOPD cases may be affected by the fact that some COPD patients may be diagnosed in general practice, excluding them from registration in the DNRP.

Comparison with other studies

In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*[15] showed that the AECOPD mortality rate increased with each exacerbation, as compared with the mortality rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality peaked within the first week after admission. Similarly, other studies have found that a history of hospitalisation for AECOPD within 6 months,[14] 1 year,[8,9,12,16,17] and up to 7 years[10] before current AECOPD hospitalisation, within 2 years before inclusion period,[13] or admission with respiratory failure within 2 years before current admission,[11] increases AECOPD mortality in-hospital,[10,11,14] at 30 days[11] and at longer term (median 3.1 years)[12] following admission, and at 3 months,[8] 6 months,[9] 1 year,[9] 2 years,[9,17] and at longer-term mortality (3 or more years)[13,16] following discharge. Besides these differences in assessment of prior AECOPD hospitalisations and in follow-up periods, populations included also varied substantially (*e.g.*, inclusion of primarily men,[9,13,16] emergency room patients only,[12,14] and discharged patients only[8,13,16,17]).

Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in the previous year was less pronounced than in the study by Suissa *et al.*[15] and it did not increase further with increasing number of AECOPDs. There may be several potential explanations for this discrepancy. First, our study population included prevalent COPD patients at study start, which may have resulted in a mix of patients at different stages in their clinical course of COPD. Hence, by mixing patients that were experiencing their first AECOPD ever with patients that had previously experienced one or more AECOPDs, we may have obscured some of the effect of AECOPD frequency on mortality. Second, unmeasured severity of the AECOPD may have affected our results. We have previously shown that patients with no AECOPD in the year before an AECOPD are younger and have less comorbidity.[21] Even though these patients may have had more newly diagnosed, and thus less severe, COPD, it is possible that some of these patients have more severe AECOPDs because they postpone seeking medical attention due to unfamiliarity with the symptoms hereof. On the other hand, an older patient with higher comorbidity and a recent history of AECOPD may be more aware of the threatening situation and act more quickly, resulting in a lower mortality than expected in the acute phase. The situation may then reverse after day 30 when the relative impact of frequent exacerbations on severity of COPD, complication rate, and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the study population examined by Suissa *et al.*[15] included a higher proportion of men that was on average older than our study population. Thus, excess cardiovascular mortality in their population may partly explain the higher estimates observed in their study. Finally, because the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is possible that the relative effect of AECOPD history appeared less pronounced in the first period merely because of differences in the baseline rate. Such differences may also explain

the more pronounced associations observed for the younger patients in our subanalysis.

CONCLUSIONS

In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in the 12 months before exacerbation may serve as an indicator of a higher mortality rate during 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort of COPD patients or a higher baseline rate than in the 31-365-day period.

Contributors: All authors participated in designing the study. MBJ collected the data and carried out analyses. All authors participated in the discussion and interpretation of the results. SAJS organised the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Competing interests: XX and JMP are employed at AstraZeneca LP / MedImmune LLC. NAM was an employee of MedImmune, LLC at the time of the study. None of the other authors have received fees, honoraria, grants or consultancy fees related to the topic of this paper.

Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

Data sharing statement: No additional data are available.

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SUPPLEMENTARY FILE

Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

Journal: BMJ Open

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eTable 1: International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical (ATC) Classification System codes used in the study

Codes used for identifying COPD and AECOPD	
Simple and mucopurulent chronic bronchitis	ICD-10: J41
Chronic bronchitis	ICD-10: J42
Emphysema	ICD-10: J43
COPD	ICD-10: J44
Respiratory failure	ICD-10: J96.0 or J96.9
Acute respiratory infection	ICD-10: J00, J06, J10.1, J10.8, J11.1, J11.8, J20, J21, J22, B97.4
AECOPD	ICD-10: J44.1
Redeeming a glucocorticoid prescription and an antibiotic prescription on the same day	ATC codes: H02AB06/H02AB07 + J01
Comorbidities	
Myocardial infarction	ICD-10: I21, I22, I23
Congestive heart failure	ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease	ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease	ICD-10: I60-I69, G45, G46
Peptic ulcer disease	ICD-10: K22.1, K25-K28
Liver disease	ICD-10: B15.0, B16.0, B16.2, B18, B19.0, K70.0-K70.9, K71- K74, K76.0, K76.6, I85
Diabetes	ICD-10: E10.0-E10.9, E11.0-E11.9
Moderate to severe renal disease	ICD-10: 12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any malignancy (except lung cancer)	ICD-10: C00-C96 excl. C34
Alcoholism-related diseases	ICD-10: F10.7-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0
Atrial fibrillation/flutter	ICD-10: I48
Medically diagnosed obesity	ICD-10: E66

Lung cancer	ICD-10: C34
Asthma	ICD-10: J45
Hypertension	ICD-10: I10-I13
Osteoporosis	ICD-10: M80, M81
Rheumatoid arthritis	ICD-10: M05
Depression	ICD-10: F32-F33
Venous thromboembolism	ICD-10: I80.1-3; I26.0; I26.9
Obstructive sleep apnea	ICD-10: G47.32
Treatment modalities	
Systemic steroids	ATC codes: H02AB06 or H02AB07
Theophylline	ATC: R03DA
Antibiotics	ATC: J01
Antivirals	ATC: J05
Oxygen treatment	Treatment code: BGXA5
Lung volume reduction surgery	NOMESCO Classification of Surgical Procedures: KGDB30

GOLD treatment group*	**ATC code**	**Time-frame**
A	Short-acting beta$_2$-agonists (R03AC02-10; R03AC15-17) ***and/or***	Redeemed within 12 months before study start.
	Short-acting muscarinic antagonists (R03BB01, R03BB02) ***and/or***	Redeemed within 12 months before study start.
	Combination preparations of short-acting beta$_2$-agonists and short-acting muscarinic antagonists (R03AK03-04)	Redeemed within 12 months before study start.
B	Long-acting beta$_2$-agonists (R03AC excluding R03AC02-10 and R03AC15-17) ***or***	Redeemed within 12 months before study start.

	Long-acting muscarinic antagonists (R03BB04-06)	Redeemed within 12 months before study start.
C	Long-acting beta$_2$-agonists (R03AC excluding R03AC02-10 and R03AC15-17) and inhaled corticosteroids (R03BA) ***or***	Redeemed within 12 months before study start and within 30 days of each other
	Combination preparations with long-acting beta$_2$-agonists and inhaled corticosteroids (R03AK06-07) ***or***	Redeemed within 12 months before study start.
	Long-acting beta$_2$-agonists (R03AC excluding R03AC02-10 and R03AC15-17) and long-acting muscarinic antagonists (R03BB04-06) ***or***	Redeemed within 12 months before study start and within 30 days of each other
	Inhaled corticosteroids (R03AK06-07) and long-acting muscarinic antagonists (R03BB04-06)	Redeemed within 12 months before study start and within 30 days of each other
D	Long-acting beta$_2$-agonistst (R03AC excluding R03AC02-10 and R03AC15-17), inhaled corticosteroids (R03BA), and long-acting muscarinic antagonists (R03BB04-06) ***or***	Redeemed within 12 months before study start and within 30 days of each other
	Long-acting muscarinic antagonists (R03BB04-06) and combination preparations with Long-acting beta$_2$-agonists and inhaled corticosteroids (R03AK06-07)	Redeemed within 12 months before study start and within 30 days of each other
Non-treated	Remaining patients	

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD

*Groups are mutually exclusive.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Included in title and abstract]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Abstract, page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Introduction, page 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Introduction, page 4]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Introduction and Methods, pages 5-7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Methods, pages 5-7]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Methods, pages 5-7]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Methods, pages 5-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Setting and data sources, page 5]**
Bias	9	Describe any efforts to address potential sources of bias **[Study population about cohort and exposure defintion, page 6]**
Study size	10	Explain how the study size was arrived at **[Study population, page 6]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Statistical analysis, page 8: age]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Statistical analysis, pages 8-9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Statistical analysis, pages 8-9]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[Study population, page 7, first paragraph about follow-up]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Descriptive data, page 9 about eligible patients and study population]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[Not used]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Results, page 10 for eligible**

		patients, the time-varying analysis precludes a table on characteristics by exposure status]
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) Summarise follow-up time (eg, average and total amount) **[Person-years by subgroups Tables 2 and 3]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Results and Tables, pages 11-16]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Tables 2-5]**
		(*b*) Report category boundaries when continuous variables were categorized **[Quartiles presented in Table 1]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Tables 2-3 include mortality rates and ratios]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[Statistical analysis and results, pages 8-16]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[First paragraph of Discussion, page 17]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion, pages 17-19]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Comparison with other studies, page 19]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Final paragraph of Strengths and limitations, page 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Funding and Competing Interest, page 20]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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Keywords:	Cohort study, Registry study, Severe exacerbations, Time-varying exposure

Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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Keywords: Cohort study; registry study; severe exacerbations; time-varying exposure

Word count: 2,951

ABSTRACT

Objective: To examine the association between exacerbation frequency and mortality following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Design: Cohort study using medical databases.

Setting: Northern Denmark.

Participants: We identified all prevalent hospital-diagnosed COPD patients on January 1, 2005, who had at least one AECOPD during January 1, 2005 to December 31, 2009. We followed patients from the first AECOPD during this period until death, emigration, or December 31, 2009, whichever came first. We flagged all AECOPD events during follow-up and characterised each by the exacerbation frequency (0, 1, 2, or 3+) in the prior 12-month period.

Main outcomes and measures: Using Cox regression, we computed 0–30-day and 31–365-day age-, sex-, and comorbidity-adjusted mortality rate ratios (MRRs) with 95% confidence intervals entering exacerbation frequency as a time-varying exposure.

Results: We identified 16,647 eligible prevalent COPD patients, of whom 6,664 (40%) developed an AECOPD and were thus included in the study cohort. The 0–30-day MRRs were 0.97 (95% CI: 0.80, 1.18), 0.90 (95% CI: 0.70, 1.15), and 1.03 (95% CI: 0.81, 1.32) among AECOPD patients with 1, 2, and 3+ AECOPDs *vs.* no AECOPD within the last 12 months, respectively. The corresponding MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) for day 31-365.

Conclusions: Among AECOPD patients, one or more exacerbations in the previous year were not associated with 30-day mortality but were associated with an increased 31-365-day mortality.

Strengths and limitations of this study

- The universal healthcare system and complete follow-up of all residents reduces the risk of selection bias.
- The study examined the association according to COPD treatment at study start and found no substantial variation across treatment groups.
- The broad definitions included hospital-diagnosed COPD patients treated for AECOPD also outside the hospital setting, but COPD patients treated in general practice exclusively were not included. Also, the use of a prevalent cohort may have resulted in a mix of patients at different stages in their clinical course of COPD.
- The study lacked information on clinical variables that would have been useful in classifying AECOPD and elucidating the association.
- Excess non-COPD mortality may explain the association observed after 30 days of follow-up.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in pulmonary function due to airway inflammation in response to noxious particles and gases.[1,2] In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.[3] The 0-180-day and 181-day to 5-year standardised mortality rates in COPD patients were 389 per 1,000 person-years and 164 per 1,000 person-years, respectively,[3] making it one of the leading causes of death among the elderly.[4]

COPD is frequently complicated by acute exacerbations (AECOPD), defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication".[5] The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01, increasing with disease severity[6] and history of frequent exacerbations.[7] The mortality following AECOPD is high, especially in patients with severe COPD.[8] Thus, severity of disease is associated with both increased risk and mortality of AECOPD.[8] However, the relationship is complex because frequent exacerbations may themselves also result in decreased lung function and thereby increase mortality.[1,2,8,9] Indeed, several epidemiological studies have demonstrated an impact of AECOPD frequency on mortality following AECOPD overall showing that a history of AECOPD may be associated with worse prognosis. Comparison of these studies is, however, hampered by differences in the exposure windows used for assessing previous AECOPD hospitalisations, in the length of follow-up, and in the patient populations included.[10-19] Although current therapies for COPD may decrease the exacerbations frequency and mortality,[2,8] only one study examined if the association depended on preadmission therapy. However, authors did not provide the results for the analysis except for an insignificant interaction term,[11] which limits the interpretation to statistical significance only. Finally, none of the studies included AECOPDs treated outside the hospital.

We conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD. Specifically, we addressed the limitations of previous studies by including exacerbations treated in the hospital, outpatient clinics and in general practice, and by using Danish registries with detailed data on comorbidity, COPD treatment, and with complete follow-up.

METHODS

Setting and data sources

We conducted this cohort study in northern Denmark, whose population numbers approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported healthcare plan guarantees universal medical care for all residents and partial reimbursement for prescribed medications.[20] Virtually all health services are recorded in various medical registries, of which the following formed the basis for this study. The Danish National Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room visits since 1995.[21] Each admission is described by one primary diagnosis and one or more secondary diagnoses classified according to the 8th revision of the *International Classification of Diseases* (ICD-8) through 1993 and the ICD–10 revision thereafter.[21]

Aarhus University Prescription Database records patient's personal identifier, the dispensing date, and the type and quantity of drug prescribed (according to the Anatomical Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at the pharmacy.[22]

Since 1968, the Danish Civil Registration System has recorded all Danish residents' administrative information and changes in vital status, such as date of death and emigration, with daily updates.[20] The registry assigns a unique personal identifier to all persons born in or

immigrating to Denmark, which enables follow-up of patients and linkage of the various medical registries.[20]

All codes used for defining study variables in the current study can be found in the Supplementary File (eTable 1).

Study population

The population eligible for the study included all prevalent COPD patients on January 1, 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related diagnosis, as described previously[23] and defined in the Supplementary File. Patients younger than 40 years were excluded, given the low COPD prevalence in this patient group[24] and the potential for misclassifying asthma as COPD.

Among all eligible COPD patients, we then identified the study cohort as COPD patients who developed at least one AECOPD between January 1, 2005 and December 31, 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic prescription on the same day (to account for patients treated outside hospital), or (b) a primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge diagnosis of respiratory failure or acute respiratory infection with a secondary discharge diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of AECOPD cases were treated exclusively in the emergency department). Standard practice at Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also,

COPD patients transferred to a specialized ward from the emergency room are coded as inpatient admissions and are therefore included in the study.

Using the Civil Registration System, we followed patients from the date of first exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until death, emigration, or December 31, 2009, whichever came first. To examine the effect of AECOPD frequency on mortality, we classified each AECOPD during follow-up according to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months. We then entered this value as a time-varying exposure in the analysis. Therefore, each time a patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and contribute person-time in several exposure groups depending on the rate of AECOPD. We adjudicated AECOPD events using a 30-day threshold following the prescription redemption or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not regarded as a new AECOPD.

Covariates

We used the DNRP to retrieve the hospital history for all study participants during the 5 years preceding the start of the study on January 1, 2005. We then ascertained the presence of the following diseases that are frequent among COPD patients and may affect mortality: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter, medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.

From the Prescription Database, we retrieved information on COPD treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[5] we then grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta$_2$-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, as defined in the Supplementary File (eTable 1). We also retrieved information on pharmacological treatment with systemic corticosteroids or theophylline within 12 months before study start, with antibiotics and/or antivirals within three months before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment within the 12 months before study start and on lung volume reduction surgery between 1996 and study start.

Statistical analysis

We characterized the eligible population of COPD patients on January 1, 2005 by age, sex, comorbidities recorded in the 5 years before study start, as well as COPD treatment group, pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the prior 12 months, and treatment with antibiotics and/or antivirals within the prior three months.

In the mortality analyses, we entered AECOPD frequency as a time-varying exposure and computed the number of deaths, person-time, and mortality rates in each exposure group. We then used Cox regression analysis to compute crude hazard ratios as a measure of mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD

patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with patients with no exacerbations in the preceding 12-month period. We then computed the MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis, we examined the effect of frequent severe exacerbations on mortality by including only severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed above). Both the present AECOPD and any exacerbations in the 12 months before had to be defined as severe. Finally, we stratified the results from the primary analysis and the results for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen therapy, lung volume reduction surgery, COPD treatment group, and cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease).

Because AECOPD is an acute event, we expect the mortality rate to be greatest in the initial phase following and as the results of the event. We therefore separated the effect of AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all mortality rate calculations. We assessed the assumption of proportional hazards graphically using scaled Schoenfeld residuals and found it valid.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish legislation does not require ethical review board approval or informed consent from subjects in registry-based studies.

RESULTS

Descriptive data

We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age among eligible patients was 70 year and 53% were female. Comorbidities were frequent,

especially cardiovascular disease, diabetes, osteoporosis, and asthma. The high proportion of patients had redeemed prescriptions for antibiotics within previous 3 months (31%) and for systemic steroids within previous 12 months (30%). The majority of patients received double therapy. Among the 16,647 eligible COPD patients, 6,664 (40%) had at least one AECOPD during the subsequent five years and thus constituted the study population for our study.

Table 1. Characteristics of eligible prevalent COPD patients for the study on January 1, 2005

Characteristic	n	%
Total	16,647	100
Age at study start (years)		
40-50	1,198	7.2
50-60	2,764	17
60-70	4,522	27
70-80	5,422	33
80-90	2,492	15
90+	249	1.5
Sex		
Female	8,770	53
Male	7,877	47
Comorbidities (within previous 5 years)		
Myocardial infarction	795	4.8
Congestive heart failure	1,785	11
Peripheral vascular disease	922	5.5
Cerebrovascular disease	1,178	7.1
Peptic ulcer disease	627	3.8
Liver disease	176	1.1
Diabetes	1,134	6.8
Moderate to severe renal disease	287	1.7
Any malignancy except lung cancer	950	5.7
Alcoholism-related diseases	162	1.0
Atrial fibrillation/flutter	1,400	8.4
Medically diagnosed obesity	575	3.5
Hypertension	2,066	12
Osteoporosis	1,021	6.1
Lung cancer	186	1.1
Asthma	2,006	12
Obstructive sleep apnea	337	2.0
Rheumatoid arthritis	151	0.9
Depression	340	2.0
Treatments within previous 12 months		
Systemic steroids	4,993	30

Theophylline	1,164	7.0
Oxygen therapy	258	1.5
COPD treatment		
Non-treated/unclassified	4,880	29
Short-acting bronchodilators	2,958	18
Long-acting bronchodilator	2,041	12
Double therapy	4,226	25
Triple therapy	2,542	15
Infection within previous 3 months		
Prescription for antibiotics	5,103	31
Prescription for antivirals	55	0.3
Prescription for both antibiotics and antivirals	26	0.2

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definition of GOLD treatment groups.
*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)
Previous lung volume reduction surgery is not shown in the table because it was rare (close to 0%)

Mortality following AECOPD

The 30-day all-cause mortality rate following an AECOPD was 552, 485, 441, and 477 per 1,000 person-years for 0, 1, 2, and 3+ AECOPDs in the prior 12 months, respectively (Table 2). Compared with patients with no AECOPD in the prior 12 months, the mortality rate did not depend on the frequency of events. Thus, the MRR was 0.97 (95% CI: 0.80, 1.18) for 1 AECOPD, 0.90 (95% CI: 0.70, 1.15) for 2 AECOPDs, and 1.03 (95% CI: 0.81, 1.32) for 3+ AECOPDs in the prior 12 months (Table 2).

Table 2. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009.

Frequency of AECOPD in the 12 months prior to an AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	303	581	522 (466, 584)	(ref.)
1	164	338	485 (416, 565)	0.97 (0.80, 1.18)
2	79	179	441 (354, 550)	0.90 (0.70, 1.15)
3+	86	180	477 (386, 589)	1.03 (0.81, 1.32)

31 and up to 365 days				
0	933	5830	160 (150, 171)	(ref.)
1	359	1573	228 (206, 253)	1.47 (1.30, 1.66)
2	146	5205	281 (239, 331)	1.89 (1.59, 2.25)
3+	63	266	237 (185, 303)	1.59 (1.23, 2.05)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The absolute mortality rate decreased substantially after day 30 and was higher among patients with one or more AECOPDs in the 12 months preceding their AECOPD (Table 2). Thus, the MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) among AECOPD patients who had experienced 1, 2, and 3+ AECOPDs compared with no AECOPD in the 12 months before the AECOPD event, respectively.

Severe AECOPDs (requiring hospitalisation) were associated with higher absolute mortality rates than AECOPDs overall, in particular for the 0–30-day period (Table 3). However, the relative impact of AECOPD frequency was similar to the overall results.

Table 3. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009. Only severe (hospitalised) AECOPDs included.

Frequency of severe AECOPD in the 12 months prior to a severe AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	283	301	939 (836, 1055)	(ref.)
1	109	114	954 (790, 1151)	1.07 (0.85-1.33)
2	52	46	1123 (855, 1473)	1.29 (0.96-1.75)
3+	32	36	893 (631, 1262)	1.09 (0.75-1.59)
31 and up to 365 days				
0	648	2974	218 (201, 235)	(ref.)
1	196	523	375 (326, 431)	1.75 (1.49, 2.06)
2	51	146	349 (265, 459)	1.67 (1.26, 2.23)
3+	22	59	371 (245, 564)	1.77 (1.15, 2.72)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The stratified main analyses (eTable 2) showed that for the 31–365 day period, the MRRs were highest among those aged 50–59 years (MRR 2.13, 95% CI: 1.34, 3.41 for 1 AECOPD; MRR 2.14, 95% CI: 1.07, 4.26 for 2 AECOPDs; and MRR 3.43, 95% CI: 1.64, 7.15 for 3+ AECOPDs) and those with oxygen therapy within 12 months before study start ((MRR 3.61, 95% CI: 1.80, 7.27 for 1 AECOPD; MRR 4.87, 95% CI: 1.79, 13.2 for 2 AECOPDs; and MRR 4.22, 95% CI: 0.82, 21.7 for 3+ AECOPDs). There was no substantial variation by COPD treatment. The stratified analysis considering severe AECOPDs only (eTable 3) were similar to the stratification including all AECOPDs regardless of severity. However, the stratified analyses should be interpreted with the wide confidence intervals in mind.

DISCUSSION

In this large Danish cohort study, we found that the 31–365 day all-cause mortality rate following an AECOPD was higher among patients with at least one AECOPD in the preceding 12 months than among patients who did not have any recent AECOPD. All cause mortality did not vary substantially according to the actual number of AECOPDs within the preceding year and was not observed in excess within the first 30 days after the AECOPD after controlling for age, sex and comorbidities.

Strengths and limitations

The universal healthcare system and complete follow-up of all residents by the Danish Civil Registration System reduces the possibility of selection bias in our study. We aimed to reduce information bias by using broad definitions of COPD and AECOPD rather than more restrictive primary discharge diagnoses. A review of medical records has showed a PPV of 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also

primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.[25] However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on the same day to define AECOPDs outside hospital setting, we may have misclassified some patients who did not have AECOPD as AECOPD patients if the prescriptions were written as rescue packs for potential future events. Such misclassification would not affect the analysis restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may have resulted in misclassification of exposure status due to underreporting or misclassification of the number of AECOPDs. Previous data, however, show that the majority of patients recover within 30 days after AECOPD onset.[26]

Because we relied solely on registry data, we lacked information on lifestyle factors and clinical variables such as measurements of peak expiratory flow and arterial blood gases. However, some of the clinical factors may be on the causal pathway linking AECOPD frequency to high mortality,[1,2,8,9] making adjustment inappropriate.[27] Nevertheless, such information would have been useful in classifying AECOPD. Instead, we examined if the association depended on COPD therapy, which may be linked to underlying severity, and found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified, which may represent patients with poor adherence or possibly patients with mild COPD.

Finally, the generalizability of our results to the entire range of AECOPD cases may be affected by the fact that some COPD patients may be diagnosed in general practice, excluding them from registration in the DNRP.

Comparison with other studies

In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*[17] showed that the AECOPD mortality rate increased with each exacerbation, as compared with the mortality rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the

second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality peaked within the first week after admission. Similarly, other studies have found that a history of hospitalisation for AECOPD within 6 months,[16] 1 year,[10,11,14,18,19] and up to 7 years[12] before current AECOPD hospitalisation, within 2 years before inclusion period,[15] or admission with respiratory failure within 2 years before current admission,[13] increases AECOPD mortality in-hospital,[12,13,16] at 30 days[13] and at longer term (median 3.1 years)[14] following admission, and at 3 months,[10] 6 months,[11] 1 year,[11] 2 years,[11,19] and at longer-term mortality (3 or more years)[15,18] following discharge. Besides these differences in assessment of prior AECOPD hospitalisations and in follow-up periods, populations included also varied substantially (*e.g.*, inclusion of primarily men,[11,15,18] emergency room patients only,[14,16] and discharged patients only[10,15,18,19]).

Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in the previous year was less pronounced than in the study by Suissa *et al.*[17] and it did not increase further with increasing number of AECOPDs. There may be several potential explanations for this discrepancy. First, our study population included prevalent COPD patients at study start, which may have resulted in a mix of patients at different stages in their clinical course of COPD. Hence, by mixing patients that were experiencing their first AECOPD ever with patients that had previously experienced one or more AECOPDs, we may have obscured some of the effect of AECOPD frequency on mortality. Second, unmeasured severity of the AECOPD may have affected our results. We have previously shown that patients with no AECOPD in the year before an AECOPD are younger and have less comorbidity.[23] Even though these patients may have had more newly diagnosed, and thus less severe, COPD, it is possible that some of these patients have more severe AECOPDs because they postpone seeking medical attention due to unfamiliarity with the symptoms

hereof. On the other hand, an older patient with higher comorbidity and a recent history of AECOPD may be more aware of the threatening situation and act more quickly, resulting in a lower mortality than expected in the acute phase. The situation may then reverse after day 30 when the relative impact of frequent exacerbations on severity of COPD, complication rate, and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the study population examined by Suissa *et al.*[17] included a higher proportion of men that was on average older than our study population. Thus, excess cardiovascular mortality in their population may partly explain the higher estimates observed in their study. Finally, because the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is possible that the relative effect of AECOPD history appeared less pronounced in the first period merely because of differences in the baseline rate. Such differences may also explain the more pronounced associations observed for the younger patients in our subanalysis.

CONCLUSIONS

In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in the 12 months before exacerbation may serve as an indicator of a higher mortality rate during 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort of COPD patients or a higher baseline rate than in the 31-365-day period.

Contributors: SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in designing the study. MBJ collected the data and carried out analyses. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in the discussion and interpretation of the results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC critically revised the manuscript for intellectual content and

approved the final version. HTS is the guarantor.

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Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

Data sharing statement: No additional data are available.

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Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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ABSTRACT

Objective: To examine the association between exacerbation frequency and mortality following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Design: Cohort study using medical databases.

Setting: Northern Denmark.

Participants: We identified all prevalent hospital-diagnosed COPD patients on January 1, 2005, who had at least one AECOPD during January 1, 2005 to December 31, 2009. We followed patients from the first AECOPD during this period until death, emigration, or December 31, 2009, whichever came first. We flagged all AECOPD events during follow-up and characterised each by the exacerbation frequency (0, 1, 2, or 3+) in the prior 12-month period.

Main outcomes and measures: Using Cox regression, we computed 0–30-day and 31–365-day age-, sex-, and comorbidity-adjusted mortality rate ratios (MRRs) with 95% confidence intervals entering exacerbation frequency as a time-varying exposure.

Results: We identified 16,647 eligible prevalent COPD patients, of whom 6,664 (40%) developed an AECOPD and were thus included in the study cohort. The 0–30-day MRRs were 0.97 (95% CI: 0.80, 1.18), 0.90 (95% CI: 0.70, 1.15), and 1.03 (95% CI: 0.81, 1.32) among AECOPD patients with 1, 2, and 3+ AECOPDs *vs.* no AECOPD within the last 12 months, respectively. The corresponding MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) for day 31-365.

Conclusions: Among AECOPD patients, one or more exacerbations in the previous year were not associated with 30-day mortality but were associated with an increased 31-365-day mortality.

Strengths and limitations of this study

- The universal healthcare system and complete follow-up of all residents reduces the risk of selection bias.
- The study examined the association according to COPD treatment ~~before AECOPD~~at study start and found no substantial variation across treatment groups.
- The broad definitions included ~~patients~~ hospital-diagnosed COPD patients treated for AECOPD also outside the hospital setting, but COPD patients treated in general practice exclusively were not included. Also, the use of a prevalent cohort may have resulted in a mix of patients at different stages in their clinical course of COPD.
- ~~The study examined the association by preadmission therapy categorised based on GOLD treatment guidelines, which may have caused some misclassification of patients who were not treated accordingly.~~
- The study lacked information on ~~lifestyle factors and~~ clinical variables that would have been useful in classifying AECOPD and elucidating the association.
- Excess non-COPD mortality may explain the association observed after 30 days of follow-up.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in pulmonary function due to airway inflammation in response to noxious particles and gases.[1,2] In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.[3] The 0-180-day and 181-day to 5-year ~~standardized~~ standardised mortality rates in COPD patients were 389 per 1,000 person-years and 164 per 1,000 person-years, respectively,[3] making it one of the leading causes of death among the elderly.[4]

COPD is frequently complicated by acute exacerbations (AECOPD), defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication".[5] The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01, ~~depending on~~increasing with disease severity[6] and history of frequent exacerbations.[7] The mortality ~~for hospitalised~~following AECOPD ~~patients~~ is high, especially in patients with severe COPD.[8] Thus, severity of disease is associated with both increased risk and mortality of AECOPD.[8] However, the relationship is complex because frequent exacerbations may themselves also result in decreased lung function and thereby increase mortality.[1,2,8,9] Indeed, ~~Several~~ several ~~previous~~ epidemiological studies have ~~examined~~ demonstrated ~~the~~ an impact of AECOPD frequency on mortality following AECOPD overall showing that a history of AECOPD may be associated with worse prognosis. Comparison of these studies is, however, hampered by differences in the exposure windows used for assessing previous AECOPD hospitalisations, in the length of follow-up, and in the patient populations included.[10-19] Although current therapies for COPD may decrease the exacerbations frequency and mortality,[2,8] ~~O~~only one study examined if the association depended on preadmission therapy. However, authors ~~, but~~ did not provide the results for the analysis except for an insignificant interaction term,[11]

which limits the interpretation to statistical significance only. Finally, none of the studies included AECOPDs treated outside the hospital.

~~In order to address these limitations and fill this gap in the literature, w~~We conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD. Specifically, we addressed the limitations of previous studies by including exacerbations treated in the hospital, outpatient clinics and in general practice, and by using Danish registries with detailed data on comorbidity, COPD treatment, and with complete follow-up.~~using Danish registries with detailed hospital data and complete follow-up.~~

METHODS

Setting and data sources

We conducted this cohort study in northern Denmark, whose population numbers approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported healthcare plan guarantees universal medical care for all residents and partial reimbursement for prescribed medications.[20] Virtually all health services are recorded in various medical registries, of which the following formed the basis for this study. The Danish National Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room visits since 1995.[21] Each admission is described by one primary diagnosis and one or more secondary diagnoses classified according to the 8th revision of the *International Classification of Diseases* (ICD-8) through 1993 and the ICD–10 revision thereafter.[21]

Aarhus University Prescription Database records patient's personal identifier, the dispensing date, and the type and quantity of drug prescribed (according to the Anatomical Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at

the pharmacy.[22]

Since 1968, the Danish Civil Registration System has recorded all Danish residents' administrative information and changes in vital status, such as date of death and emigration, with daily updates.[20] The registry assigns a unique personal identifier to all persons born in or immigrating to Denmark, which enables follow-up of patients and linkage of the various medical registries.[20]

All codes used for defining study variables in the current study can be found in the Supplementary File (eTable 1).

Study population

The population eligible for the study included all prevalent COPD patients on January 1, 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related diagnosis, as described previously[23] and defined in the Supplementary File. Patients younger than 40 years were excluded, given the low COPD prevalence in this patient group[24] and the potential for misclassifying asthma as COPD.

Among all eligible COPD patients, we then identified the study cohort as COPD patients who developed at least one AECOPD between January 1, 2005 and December 31, 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic prescription on the same day (to account for patients treated outside hospital), or (b) a primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge diagnosis of respiratory failure or acute respiratory infection with a secondary discharge diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or

AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of AECOPD cases were treated exclusively in the emergency department). Standard practice at Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also, COPD patients transferred to a specialized ward from the emergency room are coded as inpatient admissions and are therefore included in the study.

Using the Civil Registration System, we followed patients from the date of first exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until death, emigration, or December 31, 2009, whichever came first. To examine the effect of AECOPD frequency on mortality, we classified each AECOPD during follow-up according to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the ~~preceding~~ prior 12 months. We then entered this value as a time-varying exposure in the analysis. Therefore, each time a patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and contribute person-time in several exposure groups depending on the rate of AECOPD. We adjudicated AECOPD events using a 30-day threshold following the prescription redemption or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not regarded as a new AECOPD.

Covariates

We used the DNRP to retrieve the hospital history for all study participants during the 5 years preceding the start of the study on January 1, 2005. We then ascertained the presence of the following diseases that are frequent among COPD patients and may affect mortality: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any

malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter, medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.

From the Prescription Database, we retrieved information on ~~preadmission~~ COPD ~~therapy~~treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[5] we then ~~and~~ grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta$_2$-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists~~based on the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (treatment groups A, B, C, D and an unclassified group).[5] The grouping was modified to avoid overlap between the group, s,~~ as defined in the Supplementary File (eTable 1). We also retrieved information on pharmacological treatment with systemic corticosteroids or theophylline within 12 months before study start, with antibiotics and/or antivirals within three months before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment within the 12 months before study start and on lung volume reduction surgery between 1996 and study start.

Statistical analysis

We characterized the eligible population of COPD patients on January 1, 2005 by age, sex, comorbidities recorded in the 5 years before study start, as well as COPD ~~GOLD~~ treatment group ~~group~~, pharmacological treatment with systemic steroids, theophylline, or oxygen

therapy within the prior 12 months, and treatment with antibiotics and/or antivirals within the prior three months.

In the mortality analyses, we entered AECOPD frequency as a time-varying exposure and computed the number of deaths, person-time, and mortality rates in each exposure group. We then used Cox regression analysis to compute crude hazard ratios as a measure of mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with patients with no exacerbations in the preceding 12-month period. We then computed the MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis, we examined the effect of frequent severe exacerbations on mortality by including only severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed above). Both the present AECOPD and any exacerbations in the 12 months before had to be defined as severe. Finally, we stratified the results from the primary analysis and the results for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen therapy, lung volume reduction surgery, COPD ~~GOLD~~ treatment group, and cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease).

Because AECOPD is an acute event, we expect the mortality rate to be greatest in the initial phase following and as the results of the event. We therefore separated the effect of AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all mortality rate calculations. We assessed the assumption of proportional hazards graphically using scaled Schoenfeld residuals and found it valid.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish

legislation does not require ethical review board approval or informed consent from subjects in registry-based studies.

RESULTS

Descriptive data

We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age among eligible patients was 70 year and 53% were female. Comorbidities were frequent, especially cardiovascular disease, diabetes, osteoporosis, and asthma. The high proportion of patients had redeemed prescriptions for antibiotics within previous 3 months (31%) and for systemic steroids within previous 12 months (30%). The majority of patients received double therapy~~treatment recommended for GOLD group C~~. Among the 16,647 eligible COPD patients, 6,664 (40%) had at least one AECOPD during the subsequent five years and thus constituted the study population for our study.

Table 1. Characteristics of eligible prevalent COPD patients for the study on January 1, 2005

Characteristic	n	%
Total	16,647	100
Age at study start (years)		
40-50	1,198	7.2
50-60	2,764	17
60-70	4,522	27
70-80	5,422	33
80-90	2,492	15
90+	249	1.5
Sex		
Female	8,770	53
Male	7,877	47
Comorbidities (within previous 5 years)		
Myocardial infarction	795	4.8
Congestive heart failure	1,785	11
Peripheral vascular disease	922	5.5
Cerebrovascular disease	1,178	7.1
Peptic ulcer disease	627	3.8
Liver disease	176	1.1

Diabetes	1,134	6.8
Moderate to severe renal disease	287	1.7
Any malignancy except lung cancer	950	5.7
Alcoholism-related diseases	162	1.0
Atrial fibrillation/flutter	1,400	8.4
Medically diagnosed obesity	575	3.5
Hypertension	2,066	12
Osteoporosis	1,021	6.1
Lung cancer	186	1.1
Asthma	2,006	12
Obstructive sleep apnea	337	2.0
Rheumatoid arthritis	151	0.9
Depression	340	2.0
Treatments within previous 12 months		
Systemic steroids	4,993	30
Theophylline	1,164	7.0
Oxygen therapy	258	1.5
~~**GOLD** **COPD** **treatment** **group**~~		
Non-treated/unclassified	4,880	29
Short-acting bronchodilators~~A~~	2,958	18
Long-acting bronchodilator~~B~~	2,041	12
Double therapy~~C~~	4,226	25
Triple therapy~~D~~	2,542	15
Infection within previous 3 months		
Prescription for antibiotics	5,103	31
Prescription for antivirals	55	0.3
Prescription for both antibiotics and antivirals	26	0.2

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definition of GOLD treatment groups.
*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)
Previous lung volume reduction surgery is not shown in the table because it was rare (close to 0%)

Mortality following AECOPD

The 30-day all-cause mortality rate following an AECOPD was 552, 485, 441, and 477 per 1,000 person-years for 0, 1, 2, and 3+ AECOPDs in the prior 12 months, respectively (Table 2). Compared with patients with no AECOPD in the prior 12 months, the mortality rate ~~was increased but~~ did not depend on the frequency of events. Thus, the MRR was 0.97 (95% CI: 0.80, 1.18) for 1 AECOPD, 0.90 (95% CI: 0.70, 1.15) for 2 AECOPDs, and 1.03 (95% CI:

0.81, 1.32) for 3+ AECOPDs in the prior 12 months (Table 2).

Table 2. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009.

Frequency of AECOPD in the 12 months prior to an AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	303	581	522 (466, 584)	(ref.)
1	164	338	485 (416, 565)	0.97 (0.80, 1.18)
2	79	179	441 (354, 550)	0.90 (0.70, 1.15)
3+	86	180	477 (386, 589)	1.03 (0.81, 1.32)
31 and up to 365 days				
0	933	5830	160 (150, 171)	(ref.)
1	359	1573	228 (206, 253)	1.47 (1.30, 1.66)
2	146	5205	281 (239, 331)	1.89 (1.59, 2.25)
3+	63	266	237 (185, 303)	1.59 (1.23, 2.05)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The absolute mortality rate decreased substantially after day 30 and was higher among patients with one or more AECOPDs in the 12 months preceding their AECOPD (Table 2). Thus, the MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) among AECOPD patients who had experienced 1, 2, and 3+ AECOPDs compared with no AECOPD in the 12 months before the AECOPD event, respectively.

Severe AECOPDs (requiring hospitalisation) were associated with higher absolute mortality rates than AECOPDs overall, in particular for the 0–30-day period (Table 3). However, the relative impact of AECOPD frequency was similar to the overall results.

Table 3. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009. Only severe (hospitalised) AECOPDs included.

Frequency of severe AECOPD in the 12 months prior to a severe AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*

0 to 30 days				
0	283	301	939 (836, 1055)	(ref.)
1	109	114	954 (790, 1151)	1.07 (0.85-1.33)
2	52	46	1123 (855, 1473)	1.29 (0.96-1.75)
3+	32	36	893 (631, 1262)	1.09 (0.75-1.59)
31 and up to 365 days				
0	648	2974	218 (201, 235)	(ref.)
1	196	523	375 (326, 431)	1.75 (1.49, 2.06)
2	51	146	349 (265, 459)	1.67 (1.26, 2.23)
3+	22	59	371 (245, 564)	1.77 (1.15, 2.72)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The stratified main analyses (eTable 2) showed that for the 31–365 day period, the MRRs were highest among those aged 50–59 years (MRR 2.13, 95% CI: 1.34, 3.41 for 1 AECOPD; MRR 2.14, 95% CI: 1.07, 4.26 for 2 AECOPDs; and MRR 3.43, 95% CI: 1.64, 7.15 for 3+ AECOPDs) and those with oxygen therapy within 12 months before study start ((MRR 3.61, 95% CI: 1.80, 7.27 for 1 AECOPD; MRR 4.87, 95% CI: 1.79, 13.2 for 2 AECOPDs; and MRR 4.22, 95% CI: 0.82, 21.7 for 3+ AECOPDs~~Table 4~~). There was no substantial variation by ~~GOLD~~ COPD treatment ~~group~~. The stratified analysis considering severe AECOPDs only (eTable ~~5~~3) were similar to the stratification including all AECOPDs regardless of severity. However, the stratified analyses should be interpreted with the wide confidence intervals in mind.

DISCUSSION

In this large Danish cohort study, we found that the 31–365 day all-cause mortality rate following an AECOPD was higher among patients with at least one AECOPD in the preceding 12 months than among patients who did not have any recent AECOPD. All cause mortality did not vary substantially according to the actual number of AECOPDs within the preceding year and was not observed in excess within the first 30 days after the AECOPD

after controlling for age, sex and comorbidities.

Strengths and limitations

The universal healthcare system and complete follow-up of all residents by the Danish Civil Registration System reduces the possibility of selection bias in our study. We aimed to reduce information bias by using broad definitions of COPD and AECOPD rather than more restrictive primary discharge diagnoses. A review of medical records has showed a PPV of 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.[25] However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on the same day to define AECOPDs outside hospital setting, we may have misclassified some patients who did not have AECOPD as AECOPD patients if the prescriptions were written as rescue packs for potential future events. Such misclassification would not affect the analysis restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may have resulted in misclassification of exposure status due to underreporting or misclassification of the number of AECOPDs. Previous data, however, show that the majority of patients recover within 30 days after AECOPD onset.[26]

Because we relied solely on registry data, we lacked information on lifestyle factors and clinical variables such as measurements of peak expiratory flow and arterial blood gases. However, some of the clinical factors may be on the causal pathway linking AECOPD frequency ~~and severity~~ to high mortality,[1,2,8,9] making adjustment inappropriate.[27] Nevertheless, such information would have been useful in classifying AECOPD. Instead, we examined if the association depended on COPD therapy, which may be linked to underlying severity, and found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified, which may represent patients with poor adherence or possibly patients

with mild COPD.~~categorised patients based on GOLD treatment groups using preadmission therapy. Although this classification relies on patients being treated according to current guidelines, we believe that it reflects the severity of COPD.~~

Finally, the generalizability of our results to the entire range of AECOPD cases may be affected by the fact that some COPD patients may be diagnosed in general practice, excluding them from registration in the DNRP.

Comparison with other studies

In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*[17] showed that the AECOPD mortality rate increased with each exacerbation, as compared with the mortality rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality peaked within the first week after admission. Similarly, other studies have found that a history of hospitalisation for AECOPD within 6 months,[16] 1 year,[10,11,14,18,19] and up to 7 years[12] before current AECOPD hospitalisation, within 2 years before inclusion period,[15] or admission with respiratory failure within 2 years before current admission,[13] increases AECOPD mortality in-hospital,[12,13,16] at 30 days[13] and at longer term (median 3.1 years)[14] following admission, and at 3 months,[10] 6 months,[11] 1 year,[11] 2 years,[11,19] and at longer-term mortality (3 or more years)[15,18] following discharge. Besides these differences in assessment of prior AECOPD hospitalisations and in follow-up periods, populations included also varied substantially (*e.g.*, inclusion of primarily men,[11,15,18] emergency room patients only,[14,16] and discharged patients only[10,15,18,19]).

Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in the previous year was less pronounced than in the study by Suissa *et al.*[17] and it did not

increase further with increasing number of AECOPDs. There may be several potential explanations for this discrepancy. First, our study population included prevalent COPD patients at study start, which may have resulted in a mix of patients at different stages in their clinical course of COPD. Hence, by mixing patients that were experiencing their first AECOPD ever with patients that had previously experienced one or more AECOPDs, we may have obscured some of the effect of AECOPD frequency on mortality. Second, unmeasured severity of the AECOPD may have affected our results. We have previously shown that patients with no AECOPD in the year before an AECOPD are younger and have less comorbidity.[23] Even though these patients may have had more newly diagnosed, and thus less severe, COPD, it is possible that some of these patients have more severe AECOPDs because they postpone seeking medical attention due to unfamiliarity with the symptoms hereof. On the other hand, an older patient with higher comorbidity and a recent history of AECOPD may be more aware of the threatening situation and act more quickly, resulting in a lower mortality than expected in the acute phase. The situation may then reverse after day 30 when the relative impact of frequent exacerbations on severity of COPD, complication rate, and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the study population examined by Suissa *et al.*[17] included a higher proportion of men that was on average older than our study population. Thus, excess cardiovascular mortality in their population may partly explain the higher estimates observed in their study. Finally, because the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is possible that the relative effect of AECOPD history appeared less pronounced in the first period merely because of differences in the baseline rate. Such differences may also explain the more pronounced associations observed for the younger patients in our subanalysis.

CONCLUSIONS

In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in the 12 months before exacerbation may serve as an indicator of a higher mortality rate during 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort of COPD patients or a higher baseline rate than in the 31-365-day period.

Contributors: SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC ~~All authors~~ participated in designing the study. MBJ collected the data and carried out analyses. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC ~~All authors~~ participated in the discussion and interpretation of the results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC ~~All authors~~ critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

Data sharing statement: No additional data are available.

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SUPPLEMENTARY FILE

Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

Journal: BMJ Open

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eTable 1: International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical (ATC) Classification System codes used in the study

Codes used for identifying COPD and AECOPD	
Simple and mucopurulent chronic bronchitis	ICD-10: J41
Chronic bronchitis	ICD-10: J42
Emphysema	ICD-10: J43
COPD	ICD-10: J44
Respiratory failure	ICD-10: J96.0 or J96.9
Acute respiratory infection	ICD-10: J00, J06, J10.1, J10.8, J11.1, J11.8, J20, J21, J22, B97.4
AECOPD	ICD-10: J44.1
Redeeming a glucocorticoid prescription and an antibiotic prescription on the same day	ATC codes: H02AB06/H02AB07 + J01
Comorbidities	
Myocardial infarction	ICD-10: I21, I22, I23
Congestive heart failure	ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease	ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease	ICD-10: I60-I69, G45, G46
Peptic ulcer disease	ICD-10: K22.1, K25-K28
Liver disease	ICD-10: B15.0, B16.0, B16.2, B18, B19.0, K70.0-K70.9, K71- K74, K76.0, K76.6, I85
Diabetes	ICD-10: E10.0-E10.9, E11.0-E11.9
Moderate to severe renal disease	ICD-10: 12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any malignancy (except lung cancer)	ICD-10: C00-C96 excl. C34
Alcoholism-related diseases	ICD-10: F10.7-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0
Atrial fibrillation/flutter	ICD-10: I48
Medically diagnosed obesity	ICD-10: E66

Lung cancer	ICD-10: C34
Asthma	ICD-10: J45
Hypertension	ICD-10: I10-I13
Osteoporosis	ICD-10: M80, M81
Rheumatoid arthritis	ICD-10: M05
Depression	ICD-10: F32-F33
Venous thromboembolism	ICD-10: I80.1-3; I26.0; I26.9
Obstructive sleep apnea	ICD-10: G47.32
Treatment modalities	
Systemic steroids	ATC codes: H02AB06 or H02AB07
Theophylline	ATC: R03DA
Antibiotics	ATC: J01
Antivirals	ATC: J05
Oxygen treatment	Treatment code: BGXA5
Lung volume reduction surgery	NOMESCO Classification of Surgical Procedures: KGDB30
COPD treatment in 12 months prior to study start*	**ATC code and time-frame**
Short-acting bronchodilators (beta$_2$-agonists **and/or** short-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC02-10, R03AC15-17, R03BB01, R03BB02, **and/or** R03AK03-04
Long-acting bronchodilators (beta$_2$-agonists **or** long-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC (excluding R03AC02-10 and R03AC15-17) **or** R03BB04-06
Double therapy with any possible combination of long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists	Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BA **or** Redeemed within 12 months before study start: R03AK06-07 **or** Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BB04-06 **or**

	Redeemed within 12 months before study start and within 30 days of each other: R03AK06-07 and R03BB04-06
Triple therapy with long-acting beta$_2$-agonists, inhaled corticosteroids, and long-acting muscarinic antagonists	Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BA and R03BB04-06 **or** Redeemed within 12 months before study start and within 30 days of each other: R03BB04-06 and R03AK06-07
Non-treated/unclassified	Remaining patients

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD
*Groups are mutually exclusive.

eTable 2: Adjusted hazard ratios* and 95% confidence intervals following AECOPD, northern Denmark, 2005-2009

			Frequency of AECOPD in the 12 months prior to an AECOPD		
			1	**2**	**3+**
0 to 30 days	**Overall**		0.97 (0.80, 1.18)	0.90 (0.70, 1.15)	1.03 (0.81, 1.32)
	Age	**40–49**	–	–	–
		50–59	1.74 (0.85, 3.59)	0.60 (0.17, 2.13)	2.89 (1.31, 6.36)
		60–69	1.00 (0.67, 1.50)	0.68 (0.39, 1.18)	1.10 (0.69, 1.77)
		70–79	0.98 (0.73, 1.30)	1.05 (0.73, 1.50)	1.10 (0.75, 1.60)
		80–89	0.70 (0.45, 1.08)	0.96 (0.56, 1.66)	0.61 (0.28, 1.34)
		90+	–	–	–
	Sex	**Female**	0.88 (0.67, 1.15)	0.90 (0.64, 1.26)	0.96 (0.67, 1.37)
		Male	1.06 (0.80, 1.39)	0.91 (0.63, 1.31)	1.14 (0.80, 1.62)
	Oxygen therapy within 12 months before study start	**Yes**	0.79 (0.27, 2.28)	0.24 (0.02, 2.45)	3.14 (0.27, 36.9)
		No	1.00 (0.82, 1.21)	0.96 (0.74, 1.23)	1.04 (0.81, 1.34)
	Baseline treatment	**Non-treated/unclassified**	1.60 (0.63, 4.04)	1.07 (0.11, 10.0)	2.62 (0.40, 17.3)
		Short-acting bronchodilators	1.12 (0.73, 1.73)	0.70 (0.36, 1.37)	1.38 (0.78, 2.44)
		Long-acting bronchodilator	0.69 (0.41, 1.17)	1.23 (0.67, 2.25)	0.93 (0.44, 2.00)
		Double therapy	1.01 (0.71, 1.45)	0.87 (0.54, 1.42)	1.24 (0.81, 1.91)
		Triple therapy	1.05 (0.73, 1.50)	1.10 (0.71, 1.68)	0.90 (0.56, 1.43)
31 to 365 days	**Overall**		1.47 (1.30, 1.66)	1.89 (1.59, 2.25)	1.59 (1.23, 2.05)
	Age	**40–49**	0.69 (0.15, 3.27)	0.79 (0.08, 7.86)	1.68 (0.19, 14.6)
		50–59	2.13 (1.34, 3.41)	2.14 (1.07, 4.26)	3.43 (1.64, 7.15)
		60–69	1.28 (0.98, 1.67)	1.92 (1.37, 2.69)	1.16 (0.67, 2.01)
		70–79	1.62 (1.36, 1.94)	2.07 (1.61, 2.67)	1.56 (1.06, 2.29)
		80–89	1.35 (1.03, 1.77)	1.66 (1.05, 2.60)	2.12 (1.15, 3.93)
		90+	0.78 (0.19, 3.09)	8.42 (0.48, 147)	–
	Sex	**Female**	1.48 (1.24, 1.75)	2.02 (1.59, 2.55)	1.65 (1.15, 2.38)
		Male	1.47 (1.24, 1.76)	1.72 (1.32, 2.24)	1.48 (1.02, 2.14)

		Frequency of AECOPD in the 12 months prior to an AECOPD		
		1	2	3+
Oxygen therapy within 12 months before study start	**Yes**	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	No	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
Baseline treatment	**Non-treated/unclassified**	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	Short-acting bronchodilators	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	Long-acting bronchodilator	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	Double therapy	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	Triple therapy	1.62 (1.29, 2.02)	1.52 (1.09, 2.13)	1.48 (0.95, 2.32)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.
*Adjusted for age (as a continuous variable), sex, and comorbidities.
Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

eTable 3: Adjusted hazard ratios and 95% confidence intervals following severe AECOPD, northern Denmark, 2005-2009, only severe (hospitalised) AECOPDs included

			Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
			1	2	3+
0 to 30 days	Overall		1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)
	Age	40–49	–	–	–
		50–59	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)
		60–69	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)
		70–79	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)
		80–89	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)
		90+	–	–	–
	Sex	Female	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)
		Male	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)
	Oxygen therapy within 12 months before study start	Yes	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
		No	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
	Baseline treatment	Non-treated/unclassified	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)
		Short-acting bronchodilators	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)
		Long-acting bronchodilator	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)
		Double therapy	1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)
		Triple therapy	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)
31 to 365 days	Overall		1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)
	Age	40–49	–	–	–
		50–59	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)
		60–69	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)
		70–79	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)
		80–89	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)
		90+	–	–	–
	Sex	Female	1.62 (1.29, 2.03)	1.96 (1.37, 2.82)	2.28 (1.29, 4.04)
		Male	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)
	Oxygen therapy within 12 months before study start	Yes	3.30 (1.16, 9.38)	1.50 (0.15-14.9)	–

		Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
		1	2	3+
Baseline treatment	**No**	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
	Non-treated/unclassified	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-295)
	Short-acting bronchodilators	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	Long-acting bronchodilator	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	Double therapy	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	Triple therapy	1.90 (1.42, 2.56)	1.53 (0.91-2.57)	2.21 (1.14-4.29)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.
*Adjusted for age (as a continuous variable), sex, and comorbidities.
Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Included in title and abstract]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Abstract, page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Introduction, page 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Introduction, page 4]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Introduction and Methods, pages 5-7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Methods, pages 5-7]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Methods, pages 5-7]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Methods, pages 5-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Setting and data sources, page 5]**
Bias	9	Describe any efforts to address potential sources of bias **[Study population about cohort and exposure defintion, page 6]**
Study size	10	Explain how the study size was arrived at **[Study population, page 6]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Statistical analysis, page 8: age]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Statistical analysis, pages 8-9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Statistical analysis, pages 8-9]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[Study population, page 7, first paragraph about follow-up]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Descriptive data, page 9 about eligible patients and study population]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[Not used]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Results, page 10 for eligible**

		patients, the time-varying analysis precludes a table on characteristics by exposure status]
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) Summarise follow-up time (eg, average and total amount) **[Person-years by subgroups Tables 2 and 3]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Results and Tables, pages 11-16]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Tables 2-5]**
		(*b*) Report category boundaries when continuous variables were categorized **[Quartiles presented in Table 1]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Tables 2-3 include mortality rates and ratios]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[Statistical analysis and results, pages 8-16]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[First paragraph of Discussion, page 17]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion, pages 17-19]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Comparison with other studies, page 19]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Final paragraph of Strengths and limitations, page 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Funding and Competing Interest, page 20]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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Keywords: Cohort study; registry study; severe exacerbations; time-varying exposure

Word count: 2,951

ABSTRACT

Objective: To examine the association between exacerbation frequency and mortality following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Design: Cohort study using medical databases.

Setting: Northern Denmark.

Participants: We identified all prevalent hospital-diagnosed COPD patients on January 1, 2005, who had at least one AECOPD during January 1, 2005 to December 31, 2009. We followed patients from the first AECOPD during this period until death, emigration, or December 31, 2009, whichever came first. We flagged all AECOPD events during follow-up and characterised each by the exacerbation frequency (0, 1, 2, or 3+) in the prior 12-month period.

Main outcomes and measures: Using Cox regression, we computed 0–30-day and 31–365-day age-, sex-, and comorbidity-adjusted mortality rate ratios (MRRs) with 95% confidence intervals entering exacerbation frequency as a time-varying exposure.

Results: We identified 16,647 eligible prevalent COPD patients, of whom 6,664 (40%) developed an AECOPD and were thus included in the study cohort. The 0–30-day MRRs were 0.97 (95% CI: 0.80, 1.18), 0.90 (95% CI: 0.70, 1.15), and 1.03 (95% CI: 0.81, 1.32) among AECOPD patients with 1, 2, and 3+ AECOPDs *vs.* no AECOPD within the last 12 months, respectively. The corresponding MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) for day 31-365.

Conclusions: Among AECOPD patients, one or more exacerbations in the previous year were not associated with 30-day mortality but were associated with an increased 31-365-day mortality.

Strengths and limitations of this study

- The universal healthcare system and complete follow-up of all residents reduces the risk of selection bias.
- The study examined the association according to COPD treatment at study start and found no substantial variation across treatment groups.
- The broad definitions included hospital-diagnosed COPD patients treated for AECOPD also outside the hospital setting, but COPD patients treated in general practice exclusively were not included. Also, the use of a prevalent cohort may have resulted in a mix of patients at different stages in their clinical course of COPD.
- The study lacked information on clinical variables that would have been useful in classifying AECOPD and elucidating the association.
- Excess non-COPD mortality may explain the association observed after 30 days of follow-up.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in pulmonary function due to airway inflammation in response to noxious particles and gases.[1,2] In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.[3] The 0-180-day and 181-day to 5-year standardised mortality rates in COPD patients were 389 per 1,000 person-years and 164 per 1,000 person-years, respectively,[3] making it one of the leading causes of death among the elderly.[4]

COPD is frequently complicated by acute exacerbations (AECOPD), defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication".[5] The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01.[6,7] Exacerbation frequency[6] and mortality[8] increases with increasing COPD severity. On the other hand, frequent AECOPDs may themselves result in decreased lung function and could thereby increase disease severity and AECOPD mortality.[1,2,8,9] Several epidemiological studies support this by demonstrating an impact of exacerbation history on mortality in patients admitted with AECOPD. Comparison of previous studies is, however, hampered by differences in the definitions of AECOPD frequency, in the length of follow-up, and in the patient populations included.[10-19] Furthermore, none of the studies included AECOPDs treated outside the hospital. Finally, only one of the studies examined if the association depended on preadmission therapy.[11] Unfortunately, authors provided only an insignificant interaction term for the analysis,[11] which limits the interpretation to statistical significance only.

We conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD. Specifically, we addressed the limitations of previous studies by including exacerbations treated in the hospital, outpatient clinics and in general

practice, and by using Danish registries with detailed data on comorbidity, COPD treatment, and with complete follow-up.

METHODS

Setting and data sources

We conducted this cohort study in northern Denmark, whose population numbers approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported healthcare plan guarantees universal medical care for all residents and partial reimbursement for prescribed medications.[20] Virtually all health services are recorded in various medical registries, of which the following formed the basis for this study. The Danish National Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room visits since 1995.[21] Each admission is described by one primary diagnosis and one or more secondary diagnoses classified according to the 8th revision of the *International Classification of Diseases* (ICD-8) through 1993 and the ICD–10 revision thereafter.[21]

Aarhus University Prescription Database records patient's personal identifier, the dispensing date, and the type and quantity of drug prescribed (according to the Anatomical Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at the pharmacy.[22]

Since 1968, the Danish Civil Registration System has recorded all Danish residents' administrative information and changes in vital status, such as date of death and emigration, with daily updates.[20] The registry assigns a unique personal identifier to all persons born in or immigrating to Denmark, which enables follow-up of patients and linkage of the various medical registries.[20]

All codes used for defining study variables in the current study can be found in the

Supplementary File (eTable 1).

Study population

The population eligible for the study included all prevalent COPD patients on January 1, 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related diagnosis, as described previously[23] and defined in the Supplementary File. Patients younger than 40 years were excluded, given the low COPD prevalence in this patient group[24] and the potential for misclassifying asthma as COPD.

Among all eligible COPD patients, we then identified the study cohort as COPD patients who developed at least one AECOPD between January 1, 2005 and December 31, 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic prescription on the same day (to account for patients treated outside hospital), or (b) a primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge diagnosis of respiratory failure or acute respiratory infection with a secondary discharge diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of AECOPD cases were treated exclusively in the emergency department). Standard practice at Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also, COPD patients transferred to a specialized ward from the emergency room are coded as inpatient admissions and are therefore included in the study.

Using the Civil Registration System, we followed patients from the date of first exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until

death, emigration, or December 31, 2009, whichever came first. To examine the effect of AECOPD frequency on mortality, we classified each AECOPD during follow-up according to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months. We then entered this value as a time-varying exposure in the analysis. Therefore, each time a patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and contribute person-time in several exposure groups depending on the rate of AECOPD. We adjudicated AECOPD events using a 30-day threshold following the prescription redemption or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not regarded as a new AECOPD.

Covariates

We used the DNRP to retrieve the hospital history for all study participants during the 5 years preceding the start of the study on January 1, 2005. We then ascertained the presence of the following diseases that are frequent among COPD patients and may affect mortality: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter, medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.

From the Prescription Database, we retrieved information on COPD treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[5] we then grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting

bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta$_2$-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, as defined in the Supplementary File (eTable 1). We also retrieved information on pharmacological treatment with systemic corticosteroids or theophylline within 12 months before study start, with antibiotics and/or antivirals within three months before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment within the 12 months before study start and on lung volume reduction surgery between 1996 and study start.

Statistical analysis

We characterized the eligible population of COPD patients on January 1, 2005 by age, sex, comorbidities recorded in the 5 years before study start, as well as COPD treatment group, pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the prior 12 months, and treatment with antibiotics and/or antivirals within the prior three months.

In the mortality analyses, we entered AECOPD frequency as a time-varying exposure and computed the number of deaths, person-time, and mortality rates in each exposure group. We then used Cox regression analysis to compute crude hazard ratios as a measure of mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with patients with no exacerbations in the preceding 12-month period. We then computed the MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis, we examined the effect of frequent severe exacerbations on mortality by including only

severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed above). Both the present AECOPD and any exacerbations in the 12 months before had to be defined as severe. Finally, we stratified the results from the primary analysis and the results for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen therapy, lung volume reduction surgery, COPD treatment group, and cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease).

Because AECOPD is an acute event, we expect the mortality rate to be greatest in the initial phase following and as the results of the event. We therefore separated the effect of AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all mortality rate calculations. We assessed the assumption of proportional hazards graphically using scaled Schoenfeld residuals and found it valid.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish legislation does not require ethical review board approval or informed consent from subjects in registry-based studies.

RESULTS

Descriptive data

We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age among eligible patients was 70 year and 53% were female. Comorbidities were frequent, especially cardiovascular disease, diabetes, osteoporosis, and asthma. The high proportion of patients had redeemed prescriptions for antibiotics within previous 3 months (31%) and for systemic steroids within previous 12 months (30%). The majority of patients received double therapy. Among the 16,647 eligible COPD patients, 6,664 (40%) had at least one AECOPD

during the subsequent five years and thus constituted the study population for our study.

Table 1. Characteristics of eligible prevalent COPD patients for the study on January 1, 2005

Characteristic	n	%
Total	16,647	100
Age at study start (years)		
40-50	1,198	7.2
50-60	2,764	17
60-70	4,522	27
70-80	5,422	33
80-90	2,492	15
90+	249	1.5
Sex		
Female	8,770	53
Male	7,877	47
Comorbidities (within previous 5 years)		
Myocardial infarction	795	4.8
Congestive heart failure	1,785	11
Peripheral vascular disease	922	5.5
Cerebrovascular disease	1,178	7.1
Peptic ulcer disease	627	3.8
Liver disease	176	1.1
Diabetes	1,134	6.8
Moderate to severe renal disease	287	1.7
Any malignancy except lung cancer	950	5.7
Alcoholism-related diseases	162	1.0
Atrial fibrillation/flutter	1,400	8.4
Medically diagnosed obesity	575	3.5
Hypertension	2,066	12
Osteoporosis	1,021	6.1
Lung cancer	186	1.1
Asthma	2,006	12
Obstructive sleep apnea	337	2.0
Rheumatoid arthritis	151	0.9
Depression	340	2.0
Treatments within previous 12 months		
Systemic steroids	4,993	30
Theophylline	1,164	7.0
Oxygen therapy	258	1.5
COPD treatment		
Non-treated/unclassified	4,880	29
Short-acting bronchodilators	2,958	18
Long-acting bronchodilator	2,041	12
Double therapy	4,226	25

Triple therapy	2,542	15
Infection within previous 3 months		
Prescription for antibiotics	5,103	31
Prescription for antivirals	55	0.3
Prescription for both antibiotics and antivirals	26	0.2

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definition of GOLD treatment groups.
*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)
Previous lung volume reduction surgery is not shown in the table because it was rare (close to 0%)

Mortality following AECOPD

The 30-day all-cause mortality rate following an AECOPD was 552, 485, 441, and 477 per 1,000 person-years for 0, 1, 2, and 3+ AECOPDs in the prior 12 months, respectively (Table 2). Compared with patients with no AECOPD in the prior 12 months, the mortality rate did not depend on the frequency of events. Thus, the MRR was 0.97 (95% CI: 0.80, 1.18) for 1 AECOPD, 0.90 (95% CI: 0.70, 1.15) for 2 AECOPDs, and 1.03 (95% CI: 0.81, 1.32) for 3+ AECOPDs in the prior 12 months (Table 2).

Table 2. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009.

Frequency of AECOPD in the 12 months prior to an AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	303	581	522 (466, 584)	(ref.)
1	164	338	485 (416, 565)	0.97 (0.80, 1.18)
2	79	179	441 (354, 550)	0.90 (0.70, 1.15)
3+	86	180	477 (386, 589)	1.03 (0.81, 1.32)
31 and up to 365 days				
0	933	5830	160 (150, 171)	(ref.)
1	359	1573	228 (206, 253)	1.47 (1.30, 1.66)
2	146	5205	281 (239, 331)	1.89 (1.59, 2.25)
3+	63	266	237 (185, 303)	1.59 (1.23, 2.05)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The absolute mortality rate decreased substantially after day 30 and was higher among patients with one or more AECOPDs in the 12 months preceding their AECOPD (Table 2). Thus, the MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) among AECOPD patients who had experienced 1, 2, and 3+ AECOPDs compared with no AECOPD in the 12 months before the AECOPD event, respectively.

Severe AECOPDs (requiring hospitalisation) were associated with higher absolute mortality rates than AECOPDs overall, in particular for the 0–30-day period (Table 3). However, the relative impact of AECOPD frequency was similar to the overall results.

Table 3. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009. Only severe (hospitalised) AECOPDs included.

Frequency of severe AECOPD in the 12 months prior to a severe AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	283	301	939 (836, 1055)	(ref.)
1	109	114	954 (790, 1151)	1.07 (0.85-1.33)
2	52	46	1123 (855, 1473)	1.29 (0.96-1.75)
3+	32	36	893 (631, 1262)	1.09 (0.75-1.59)
31 and up to 365 days				
0	648	2974	218 (201, 235)	(ref.)
1	196	523	375 (326, 431)	1.75 (1.49, 2.06)
2	51	146	349 (265, 459)	1.67 (1.26, 2.23)
3+	22	59	371 (245, 564)	1.77 (1.15, 2.72)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The stratified main analyses (eTable 2) showed that for the 31–365 day period, the MRRs were highest among those aged 50–59 years (MRR 2.13, 95% CI: 1.34, 3.41 for 1 AECOPD; MRR 2.14, 95% CI: 1.07, 4.26 for 2 AECOPDs; and MRR 3.43, 95% CI: 1.64, 7.15 for 3+ AECOPDs) and those with oxygen therapy within 12 months before study start

((MRR 3.61, 95% CI: 1.80, 7.27 for 1 AECOPD; MRR 4.87, 95% CI: 1.79, 13.2 for 2 AECOPDs; and MRR 4.22, 95% CI: 0.82, 21.7 for 3+ AECOPDs). There was no substantial variation by COPD treatment. The stratified analysis considering severe AECOPDs only (eTable 3) were similar to the stratification including all AECOPDs regardless of severity. However, the stratified analyses should be interpreted with the wide confidence intervals in mind.

DISCUSSION

In this large Danish cohort study, we found that the 31–365 day all-cause mortality rate following an AECOPD was higher among patients with at least one AECOPD in the preceding 12 months than among patients who did not have any recent AECOPD. All cause mortality did not vary substantially according to the actual number of AECOPDs within the preceding year and was not observed in excess within the first 30 days after the AECOPD after controlling for age, sex and comorbidities.

Strengths and limitations

The universal healthcare system and complete follow-up of all residents by the Danish Civil Registration System reduces the possibility of selection bias in our study. We aimed to reduce information bias by using broad definitions of COPD and AECOPD rather than more restrictive primary discharge diagnoses. A review of medical records has showed a PPV of 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.[25] However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on the same day to define AECOPDs outside hospital setting, we may have misclassified some patients who did not have AECOPD as AECOPD patients if the prescriptions were written as

rescue packs for potential future events. Such misclassification would not affect the analysis restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may have resulted in misclassification of exposure status due to underreporting or misclassification of the number of AECOPDs. Previous data, however, show that the majority of patients recover within 30 days after AECOPD onset.[26]

Because we relied solely on registry data, we lacked information on lifestyle factors and clinical variables such as measurements of peak expiratory flow and arterial blood gases. However, some of the clinical factors may be on the causal pathway linking AECOPD frequency to high mortality,[1,2,8,9] making adjustment inappropriate.[27] Nevertheless, such information would have been useful in classifying AECOPD. Instead, we examined if the association depended on COPD therapy, which may be linked to underlying severity, and found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified, which may represent patients with poor adherence or possibly patients with mild COPD.

Finally, the generalizability of our results to the entire range of AECOPD cases may be affected by the fact that some COPD patients may be diagnosed in general practice, excluding them from registration in the DNRP.

Comparison with other studies

In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*[17] showed that the AECOPD mortality rate increased with each exacerbation, as compared with the mortality rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality peaked within the first week after admission. Several other studies have also found an association between a history of AECOPD and mortality.[10-16,18,19] However, definitions of exposure have varied greatly, including a history of hospitalisation for AECOPD within 6

months,[16] 1 year,[10,11,14,18,19] and up to 7 years[12] before current AECOPD hospitalisation, within 2 years before inclusion period,[15] or admission with respiratory failure within 2 years before current admission.[13] Similarly, various definitions of AECOPD mortality were applied, including mortality in-hospital,[12,13,16] at 30 days[13] and at longer term (median 3.1 years)[14] following admission, and at 3 months,[10] 6 months,[11] 1 year,[11] 2 years,[11,19] and at longer-term mortality (3 or more years)[15,18] following discharge. Besides these differences in assessment of prior AECOPD hospitalisations and in follow-up periods, populations included also varied substantially (*e.g.*, inclusion of primarily men,[11,15,18] emergency room patients only,[14,16] and discharged patients only[10,15,18,19]).

Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in the previous year was less pronounced than in the study by Suissa *et al.*[17] and it did not increase further with increasing number of AECOPDs. There may be several potential explanations for this discrepancy. First, our study population included prevalent COPD patients at study start, which may have resulted in a mix of patients at different stages in their clinical course of COPD. Hence, by mixing patients that were experiencing their first AECOPD ever with patients that had previously experienced one or more AECOPDs, we may have obscured some of the effect of AECOPD frequency on mortality. Second, unmeasured severity of the AECOPD may have affected our results. We have previously shown that patients with no AECOPD in the year before an AECOPD are younger and have less comorbidity.[23] Even though these patients may have had more newly diagnosed, and thus less severe, COPD, it is possible that some of these patients have more severe AECOPDs because they postpone seeking medical attention due to unfamiliarity with the symptoms hereof. On the other hand, an older patient with higher comorbidity and a recent history of AECOPD may be more aware of the threatening situation and act more quickly, resulting in a

lower mortality than expected in the acute phase. The situation may then reverse after day 30 when the relative impact of frequent exacerbations on severity of COPD, complication rate, and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the study population examined by Suissa *et al.*[17] included a higher proportion of men that was on average older than our study population. Thus, excess cardiovascular mortality in their population may partly explain the higher estimates observed in their study. Finally, because the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is possible that the relative effect of AECOPD history appeared less pronounced in the first period merely because of differences in the baseline rate. Such differences may also explain the more pronounced associations observed for the younger patients in our subanalysis.

CONCLUSIONS

In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in the 12 months before exacerbation may serve as an indicator of a higher mortality rate during 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort of COPD patients or a higher baseline rate than in the 31-365-day period.

Contributors: SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in designing the study. MBJ collected the data and carried out analyses. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in the discussion and interpretation of the results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

Data sharing statement: No additional data are available.

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Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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ABSTRACT

Objective: To examine the association between exacerbation frequency and mortality following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Design: Cohort study using medical databases.

Setting: Northern Denmark.

Participants: We identified all prevalent hospital-diagnosed COPD patients on January 1, 2005, who had at least one AECOPD during January 1, 2005 to December 31, 2009. We followed patients from the first AECOPD during this period until death, emigration, or December 31, 2009, whichever came first. We flagged all AECOPD events during follow-up and characterised each by the exacerbation frequency (0, 1, 2, or 3+) in the prior 12-month period.

Main outcomes and measures: Using Cox regression, we computed 0–30-day and 31–365-day age-, sex-, and comorbidity-adjusted mortality rate ratios (MRRs) with 95% confidence intervals entering exacerbation frequency as a time-varying exposure.

Results: We identified 16,647 eligible prevalent COPD patients, of whom 6,664 (40%) developed an AECOPD and were thus included in the study cohort. The 0–30-day MRRs were 0.97 (95% CI: 0.80, 1.18), 0.90 (95% CI: 0.70, 1.15), and 1.03 (95% CI: 0.81, 1.32) among AECOPD patients with 1, 2, and 3+ AECOPDs *vs.* no AECOPD within the last 12 months, respectively. The corresponding MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) for day 31-365.

Conclusions: Among AECOPD patients, one or more exacerbations in the previous year were not associated with 30-day mortality but were associated with an increased 31-365-day mortality.

Strengths and limitations of this study

- The universal healthcare system and complete follow-up of all residents reduces the risk of selection bias.
- The study examined the association according to COPD treatment at study start and found no substantial variation across treatment groups.
- The broad definitions included hospital-diagnosed COPD patients treated for AECOPD also outside the hospital setting, but COPD patients treated in general practice exclusively were not included. Also, the use of a prevalent cohort may have resulted in a mix of patients at different stages in their clinical course of COPD.
- The study lacked information on clinical variables that would have been useful in classifying AECOPD and elucidating the association.
- Excess non-COPD mortality may explain the association observed after 30 days of follow-up.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in pulmonary function due to airway inflammation in response to noxious particles and gases.[1,2] In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.[3] The 0-180-day and 181-day to 5-year standardised mortality rates in COPD patients were 389 per 1,000 person-years and 164 per 1,000 person-years, respectively,[3] making it one of the leading causes of death among the elderly.[4]

COPD is frequently complicated by acute exacerbations (AECOPD), defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication".[5] The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01~~, increasing with disease severity[6], and history of frequent exacerbations.~~[7] Exacerbation frequency[6] and mortality~~The mortality following AECOPD is high, especially in patients with severe COPD.[8] Thus, severity of disease is associated with both increased risk and mortality of AECOPD.~~[8] increases with increasing COPD severity. ~~However~~On the other hand, ~~the relationship is complex because~~ frequent ~~exacerbations~~ AECOPDs may themselves ~~also~~ result in decreased lung function and could thereby increase disease severity and AECOPD mortality.[1,2,8,9] ~~Indeed, s~~Several epidemiological studies ~~have~~ support this by ~~demonstrated~~ demonstrating an impact of exacerbation history ~~AECOPD frequency~~ on mortality ~~following~~ in patients admitted with AECOPD~~ overall showing that a history of AECOPD may be associated with worse prognosis~~. Comparison of ~~these~~ previous studies is, however, hampered by differences in the definitions of AECOPD frequency~~the exposure windows used for assessing previous AECOPD hospitalisations~~, in the length of follow-up, and in the patient populations included.[10-19] Furthermore, none of the studies included AECOPDs treated outside the hospital. Finally, ~~Although current therapies for COPD may decrease the~~

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exacerbations frequency and mortality,[2,8] only one of the study studies examined if the association depended on preadmission therapy.[11] HoweverUnfortunately, authors did not provided only the results for the analysis except for an insignificant interaction term for the analysis,[11] which limits the interpretation to statistical significance only. Finally, none of the studies included AECOPDs treated outside the hospital.

We conducted a cohort study to examine how the exacerbation frequency impacts one-year mortality following an AECOPD. Specifically, we addressed the limitations of previous studies by including exacerbations treated in the hospital, outpatient clinics and in general practice, and by using Danish registries with detailed data on comorbidity, COPD treatment, and with complete follow-up.

METHODS

Setting and data sources

We conducted this cohort study in northern Denmark, whose population numbers approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported healthcare plan guarantees universal medical care for all residents and partial reimbursement for prescribed medications.[20] Virtually all health services are recorded in various medical registries, of which the following formed the basis for this study. The Danish National Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room visits since 1995.[21] Each admission is described by one primary diagnosis and one or more secondary diagnoses classified according to the 8th revision of the *International Classification of Diseases* (ICD-8) through 1993 and the ICD–10 revision thereafter.[21]

Aarhus University Prescription Database records patient's personal identifier, the dispensing date, and the type and quantity of drug prescribed (according to the Anatomical

Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at the pharmacy.[22]

Since 1968, the Danish Civil Registration System has recorded all Danish residents' administrative information and changes in vital status, such as date of death and emigration, with daily updates.[20] The registry assigns a unique personal identifier to all persons born in or immigrating to Denmark, which enables follow-up of patients and linkage of the various medical registries.[20]

All codes used for defining study variables in the current study can be found in the Supplementary File (eTable 1).

Study population

The population eligible for the study included all prevalent COPD patients on January 1, 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related diagnosis, as described previously[23] and defined in the Supplementary File. Patients younger than 40 years were excluded, given the low COPD prevalence in this patient group[24] and the potential for misclassifying asthma as COPD.

Among all eligible COPD patients, we then identified the study cohort as COPD patients who developed at least one AECOPD between January 1, 2005 and December 31, 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic prescription on the same day (to account for patients treated outside hospital), or (b) a primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge diagnosis of respiratory failure or acute respiratory infection with a secondary discharge

diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of AECOPD cases were treated exclusively in the emergency department). Standard practice at Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also, COPD patients transferred to a specialized ward from the emergency room are coded as inpatient admissions and are therefore included in the study.

Using the Civil Registration System, we followed patients from the date of first exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until death, emigration, or December 31, 2009, whichever came first. To examine the effect of AECOPD frequency on mortality, we classified each AECOPD during follow-up according to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months. We then entered this value as a time-varying exposure in the analysis. Therefore, each time a patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and contribute person-time in several exposure groups depending on the rate of AECOPD. We adjudicated AECOPD events using a 30-day threshold following the prescription redemption or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not regarded as a new AECOPD.

Covariates

We used the DNRP to retrieve the hospital history for all study participants during the 5 years preceding the start of the study on January 1, 2005. We then ascertained the presence of the following diseases that are frequent among COPD patients and may affect mortality: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular

disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter, medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.

From the Prescription Database, we retrieved information on COPD treatment within 12 months before study start. Following the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[5] we then grouped patients into the following five mutually exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta$_2$-agonists or long-acting muscarinic antagonists), (4) double therapy with any possible combination of long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5) triple therapy with long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, as defined in the Supplementary File (eTable 1). We also retrieved information on pharmacological treatment with systemic corticosteroids or theophylline within 12 months before study start, with antibiotics and/or antivirals within three months before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment within the 12 months before study start and on lung volume reduction surgery between 1996 and study start.

Statistical analysis

We characterized the eligible population of COPD patients on January 1, 2005 by age, sex, comorbidities recorded in the 5 years before study start, as well as COPD treatment group, pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the prior 12 months, and treatment with antibiotics and/or antivirals within the prior three months.

In the mortality analyses, we entered AECOPD frequency as a time-varying exposure and computed the number of deaths, person-time, and mortality rates in each exposure group. We then used Cox regression analysis to compute crude hazard ratios as a measure of mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with patients with no exacerbations in the preceding 12-month period. We then computed the MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis, we examined the effect of frequent severe exacerbations on mortality by including only severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed above). Both the present AECOPD and any exacerbations in the 12 months before had to be defined as severe. Finally, we stratified the results from the primary analysis and the results for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen therapy, lung volume reduction surgery, COPD treatment group, and cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease).

Because AECOPD is an acute event, we expect the mortality rate to be greatest in the initial phase following and as the results of the event. We therefore separated the effect of AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all mortality rate calculations. We assessed the assumption of proportional hazards graphically using scaled Schoenfeld residuals and found it valid.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish legislation does not require ethical review board approval or informed consent from subjects in registry-based studies.

RESULTS

Descriptive data

We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age among eligible patients was 70 year and 53% were female. Comorbidities were frequent, especially cardiovascular disease, diabetes, osteoporosis, and asthma. The high proportion of patients had redeemed prescriptions for antibiotics within previous 3 months (31%) and for systemic steroids within previous 12 months (30%). The majority of patients received double therapy. Among the 16,647 eligible COPD patients, 6,664 (40%) had at least one AECOPD during the subsequent five years and thus constituted the study population for our study.

Table 1. Characteristics of eligible prevalent COPD patients for the study on January 1, 2005

Characteristic	n	%
Total	16,647	100
Age at study start (years)		
40-50	1,198	7.2
50-60	2,764	17
60-70	4,522	27
70-80	5,422	33
80-90	2,492	15
90+	249	1.5
Sex		
Female	8,770	53
Male	7,877	47
Comorbidities (within previous 5 years)		
Myocardial infarction	795	4.8
Congestive heart failure	1,785	11
Peripheral vascular disease	922	5.5
Cerebrovascular disease	1,178	7.1
Peptic ulcer disease	627	3.8
Liver disease	176	1.1
Diabetes	1,134	6.8
Moderate to severe renal disease	287	1.7
Any malignancy except lung cancer	950	5.7
Alcoholism-related diseases	162	1.0
Atrial fibrillation/flutter	1,400	8.4
Medically diagnosed obesity	575	3.5
Hypertension	2,066	12

Osteoporosis	1,021	6.1
Lung cancer	186	1.1
Asthma	2,006	12
Obstructive sleep apnea	337	2.0
Rheumatoid arthritis	151	0.9
Depression	340	2.0
Treatments within previous 12 months		
Systemic steroids	4,993	30
Theophylline	1,164	7.0
Oxygen therapy	258	1.5
COPD treatment		
Non-treated/unclassified	4,880	29
Short-acting bronchodilators	2,958	18
Long-acting bronchodilator	2,041	12
Double therapy	4,226	25
Triple therapy	2,542	15
Infection within previous 3 months		
Prescription for antibiotics	5,103	31
Prescription for antivirals	55	0.3
Prescription for both antibiotics and antivirals	26	0.2

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definition of GOLD treatment groups.
*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)
Previous lung volume reduction surgery is not shown in the table because it was rare (close to 0%)

Mortality following AECOPD

The 30-day all-cause mortality rate following an AECOPD was 552, 485, 441, and 477 per 1,000 person-years for 0, 1, 2, and 3+ AECOPDs in the prior 12 months, respectively (Table 2). Compared with patients with no AECOPD in the prior 12 months, the mortality rate did not depend on the frequency of events. Thus, the MRR was 0.97 (95% CI: 0.80, 1.18) for 1 AECOPD, 0.90 (95% CI: 0.70, 1.15) for 2 AECOPDs, and 1.03 (95% CI: 0.81, 1.32) for 3+ AECOPDs in the prior 12 months (Table 2).

Table 2. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009.

Frequency of AECOPD	No.	Person-	Mortality rate	Hazard Ratio and

in the 12 months prior to an AECOPD	deaths	years	and 95% CI (per 1,000 person-years)	95% CI*
0 to 30 days				
0	303	581	522 (466, 584)	(ref.)
1	164	338	485 (416, 565)	0.97 (0.80, 1.18)
2	79	179	441 (354, 550)	0.90 (0.70, 1.15)
3+	86	180	477 (386, 589)	1.03 (0.81, 1.32)
31 and up to 365 days				
0	933	5830	160 (150, 171)	(ref.)
1	359	1573	228 (206, 253)	1.47 (1.30, 1.66)
2	146	5205	281 (239, 331)	1.89 (1.59, 2.25)
3+	63	266	237 (185, 303)	1.59 (1.23, 2.05)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The absolute mortality rate decreased substantially after day 30 and was higher among patients with one or more AECOPDs in the 12 months preceding their AECOPD (Table 2). Thus, the MRRs were 1.47 (95% CI: 1.30, 1.66), 1.89 (95% CI: 1.59, 2.25), and 1.59 (95% CI: 1.23, 2.05) among AECOPD patients who had experienced 1, 2, and 3+ AECOPDs compared with no AECOPD in the 12 months before the AECOPD event, respectively.

Severe AECOPDs (requiring hospitalisation) were associated with higher absolute mortality rates than AECOPDs overall, in particular for the 0–30-day period (Table 3). However, the relative impact of AECOPD frequency was similar to the overall results.

Table 3. Mortality following an AECOPD according to the number of exacerbations in the previous year. Northern Denmark, 2005–2009. Only severe (hospitalised) AECOPDs included.

Frequency of severe AECOPD in the 12 months prior to a severe AECOPD	No. deaths	Person-years	Mortality rate and 95% CI (per 1,000 person-years)	Hazard Ratio and 95% CI*
0 to 30 days				
0	283	301	939 (836, 1055)	(ref.)
1	109	114	954 (790, 1151)	1.07 (0.85-1.33)
2	52	46	1123 (855, 1473)	1.29 (0.96-1.75)
3+	32	36	893 (631, 1262)	1.09 (0.75-1.59)
31 and up to 365 days				

0	648	2974	218 (201, 235)	(ref.)
1	196	523	375 (326, 431)	1.75 (1.49, 2.06)
2	51	146	349 (265, 459)	1.67 (1.26, 2.23)
3+	22	59	371 (245, 564)	1.77 (1.15, 2.72)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of groups.
*Adjusted for age (as a continuous variable), sex, and comorbidities.

The stratified main analyses (eTable 2) showed that for the 31–365 day period, the MRRs were highest among those aged 50–59 years (MRR 2.13, 95% CI: 1.34, 3.41 for 1 AECOPD; MRR 2.14, 95% CI: 1.07, 4.26 for 2 AECOPDs; and MRR 3.43, 95% CI: 1.64, 7.15 for 3+ AECOPDs) and those with oxygen therapy within 12 months before study start ((MRR 3.61, 95% CI: 1.80, 7.27 for 1 AECOPD; MRR 4.87, 95% CI: 1.79, 13.2 for 2 AECOPDs; and MRR 4.22, 95% CI: 0.82, 21.7 for 3+ AECOPDs). There was no substantial variation by COPD treatment. The stratified analysis considering severe AECOPDs only (eTable 3) were similar to the stratification including all AECOPDs regardless of severity. However, the stratified analyses should be interpreted with the wide confidence intervals in mind.

DISCUSSION

In this large Danish cohort study, we found that the 31–365 day all-cause mortality rate following an AECOPD was higher among patients with at least one AECOPD in the preceding 12 months than among patients who did not have any recent AECOPD. All cause mortality did not vary substantially according to the actual number of AECOPDs within the preceding year and was not observed in excess within the first 30 days after the AECOPD after controlling for age, sex and comorbidities.

Strengths and limitations

The universal healthcare system and complete follow-up of all residents by the Danish Civil Registration System reduces the possibility of selection bias in our study. We aimed to reduce information bias by using broad definitions of COPD and AECOPD rather than more restrictive primary discharge diagnoses. A review of medical records has showed a PPV of 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.[25] However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on the same day to define AECOPDs outside hospital setting, we may have misclassified some patients who did not have AECOPD as AECOPD patients if the prescriptions were written as rescue packs for potential future events. Such misclassification would not affect the analysis restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may have resulted in misclassification of exposure status due to underreporting or misclassification of the number of AECOPDs. Previous data, however, show that the majority of patients recover within 30 days after AECOPD onset.[26]

Because we relied solely on registry data, we lacked information on lifestyle factors and clinical variables such as measurements of peak expiratory flow and arterial blood gases. However, some of the clinical factors may be on the causal pathway linking AECOPD frequency to high mortality,[1,2,8,9] making adjustment inappropriate.[27] Nevertheless, such information would have been useful in classifying AECOPD. Instead, we examined if the association depended on COPD therapy, which may be linked to underlying severity, and found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified, which may represent patients with poor adherence or possibly patients with mild COPD.

Finally, the generalizability of our results to the entire range of AECOPD cases may be affected by the fact that some COPD patients may be diagnosed in general practice, excluding them from registration in the DNRP.

Comparison with other studies

In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*[17] showed that the AECOPD mortality rate increased with each exacerbation, as compared with the mortality rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality peaked within the first week after admission. ~~Similarly~~Several ~~,~~ other studies have also found an association between a history of AECOPD and mortality.[10-16,18,19] However, ~~that~~ definitions of exposure have varied greatly, including a history of hospitalisation for AECOPD within 6 months,[16] 1 year,[10,11,14,18,19] and up to 7 years[12] before current AECOPD hospitalisation, within 2 years before inclusion period,[15] or admission with respiratory failure within 2 years before current admission.~~,~~[13] Similarly, various definitions of AECOPD mortality were applied, including~~increase~~ mortality ~~s AECOPD mortality~~ in-hospital,[12,13,16] at 30 days[13] and at longer term (median 3.1 years)[14] following admission, and at 3 months,[10] 6 months,[11] 1 year,[11] 2 years,[11,19] and at longer-term mortality (3 or more years)[15,18] following discharge. Besides these differences in assessment of prior AECOPD hospitalisations and in follow-up periods, populations included also varied substantially (*e.g.*, inclusion of primarily men,[11,15,18] emergency room patients only,[14,16] and discharged patients only[10,15,18,19]).

Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in the previous year was less pronounced than in the study by Suissa *et al.*[17] and it did not increase further with increasing number of AECOPDs. There may be several potential explanations for this discrepancy. First, our study population included prevalent COPD patients at study start, which may have resulted in a mix of patients at different stages in their clinical course of COPD. Hence, by mixing patients that were experiencing their first

AECOPD ever with patients that had previously experienced one or more AECOPDs, we may have obscured some of the effect of AECOPD frequency on mortality. Second, unmeasured severity of the AECOPD may have affected our results. We have previously shown that patients with no AECOPD in the year before an AECOPD are younger and have less comorbidity.[23] Even though these patients may have had more newly diagnosed, and thus less severe, COPD, it is possible that some of these patients have more severe AECOPDs because they postpone seeking medical attention due to unfamiliarity with the symptoms hereof. On the other hand, an older patient with higher comorbidity and a recent history of AECOPD may be more aware of the threatening situation and act more quickly, resulting in a lower mortality than expected in the acute phase. The situation may then reverse after day 30 when the relative impact of frequent exacerbations on severity of COPD, complication rate, and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the study population examined by Suissa *et al.*[17] included a higher proportion of men that was on average older than our study population. Thus, excess cardiovascular mortality in their population may partly explain the higher estimates observed in their study. Finally, because the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is possible that the relative effect of AECOPD history appeared less pronounced in the first period merely because of differences in the baseline rate. Such differences may also explain the more pronounced associations observed for the younger patients in our subanalysis.

CONCLUSIONS

In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in the 12 months before exacerbation may serve as an indicator of a higher mortality rate during 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort

of COPD patients or a higher baseline rate than in the 31-365-day period.

Contributors: SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in designing the study. MBJ collected the data and carried out analyses. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in the discussion and interpretation of the results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

Data sharing statement: No additional data are available.

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SUPPLEMENTARY FILE

Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

Journal: BMJ Open

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eTable 1: International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical (ATC) Classification System codes used in the study

Codes used for identifying COPD and AECOPD	
Simple and mucopurulent chronic bronchitis	ICD-10: J41
Chronic bronchitis	ICD-10: J42
Emphysema	ICD-10: J43
COPD	ICD-10: J44
Respiratory failure	ICD-10: J96.0 or J96.9
Acute respiratory infection	ICD-10: J00, J06, J10.1, J10.8, J11.1, J11.8, J20, J21, J22, B97.4
AECOPD	ICD-10: J44.1
Redeeming a glucocorticoid prescription and an antibiotic prescription on the same day	ATC codes: H02AB06/H02AB07 + J01
Comorbidities	
Myocardial infarction	ICD-10: I21, I22, I23
Congestive heart failure	ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease	ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease	ICD-10: I60-I69, G45, G46
Peptic ulcer disease	ICD-10: K22.1, K25-K28
Liver disease	ICD-10: B15.0, B16.0, B16.2, B18, B19.0, K70.0-K70.9, K71- K74, K76.0, K76.6, I85
Diabetes	ICD-10: E10.0-E10.9, E11.0-E11.9
Moderate to severe renal disease	ICD-10: 12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any malignancy (except lung cancer)	ICD-10: C00-C96 excl. C34
Alcoholism-related diseases	ICD-10: F10.7-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0
Atrial fibrillation/flutter	ICD-10: I48
Medically diagnosed obesity	ICD-10: E66

Lung cancer	ICD-10: C34
Asthma	ICD-10: J45
Hypertension	ICD-10: I10-I13
Osteoporosis	ICD-10: M80, M81
Rheumatoid arthritis	ICD-10: M05
Depression	ICD-10: F32-F33
Venous thromboembolism	ICD-10: I80.1-3; I26.0; I26.9
Obstructive sleep apnea	ICD-10: G47.32
Treatment modalities	
Systemic steroids	ATC codes: H02AB06 or H02AB07
Theophylline	ATC: R03DA
Antibiotics	ATC: J01
Antivirals	ATC: J05
Oxygen treatment	Treatment code: BGXA5
Lung volume reduction surgery	NOMESCO Classification of Surgical Procedures: KGDB30
COPD treatment in 12 months prior to study start*	**ATC code and time-frame**
Short-acting bronchodilators (beta$_2$-agonists **and/or** short-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC02-10, R03AC15-17, R03BB01, R03BB02, **and/or** R03AK03-04
Long-acting bronchodilators (beta$_2$-agonists **or** long-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC (excluding R03AC02-10 and R03AC15-17) **or** R03BB04-06
Double therapy with any possible combination of long-acting beta$_2$-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists	Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BA **or** Redeemed within 12 months before study start: R03AK06-07 **or** Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BB04-06 **or**

	Redeemed within 12 months before study start and within 30 days of each other: R03AK06-07 and R03BB04-06
Triple therapy with long-acting beta$_2$-agonists, inhaled corticosteroids, and long-acting muscarinic antagonists	Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BA and R03BB04-06 **or** Redeemed within 12 months before study start and within 30 days of each other: R03BB04-06 and R03AK06-07
Non-treated/unclassified	Remaining patients

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD
*Groups are mutually exclusive.

eTable 2: Adjusted hazard ratios* and 95% confidence intervals following AECOPD, northern Denmark, 2005-2009

			Frequency of AECOPD in the 12 months prior to an AECOPD		
			1	**2**	**3+**
0 to 30 days	**Overall**		0.97 (0.80, 1.18)	0.90 (0.70, 1.15)	1.03 (0.81, 1.32)
	Age	**40–49**	–	–	–
		50–59	1.74 (0.85, 3.59)	0.60 (0.17, 2.13)	2.89 (1.31, 6.36)
		60–69	1.00 (0.67, 1.50)	0.68 (0.39, 1.18)	1.10 (0.69, 1.77)
		70–79	0.98 (0.73, 1.30)	1.05 (0.73, 1.50)	1.10 (0.75, 1.60)
		80–89	0.70 (0.45, 1.08)	0.96 (0.56, 1.66)	0.61 (0.28, 1.34)
		90+	–	–	–
	Sex	**Female**	0.88 (0.67, 1.15)	0.90 (0.64, 1.26)	0.96 (0.67, 1.37)
		Male	1.06 (0.80, 1.39)	0.91 (0.63, 1.31)	1.14 (0.80, 1.62)
	Oxygen therapy within 12 months before study start	**Yes**	0.79 (0.27, 2.28)	0.24 (0.02, 2.45)	3.14 (0.27, 36.9)
		No	1.00 (0.82, 1.21)	0.96 (0.74, 1.23)	1.04 (0.81, 1.34)
	Baseline treatment	**Non-treated/unclassified**	1.60 (0.63, 4.04)	1.07 (0.11, 10.0)	2.62 (0.40, 17.3)
		Short-acting bronchodilators	1.12 (0.73, 1.73)	0.70 (0.36, 1.37)	1.38 (0.78, 2.44)
		Long-acting bronchodilator	0.69 (0.41, 1.17)	1.23 (0.67, 2.25)	0.93 (0.44, 2.00)
		Double therapy	1.01 (0.71, 1.45)	0.87 (0.54, 1.42)	1.24 (0.81, 1.91)
		Triple therapy	1.05 (0.73, 1.50)	1.10 (0.71, 1.68)	0.90 (0.56, 1.43)
31 to 365 days	**Overall**		1.47 (1.30, 1.66)	1.89 (1.59, 2.25)	1.59 (1.23, 2.05)
	Age	**40–49**	0.69 (0.15, 3.27)	0.79 (0.08, 7.86)	1.68 (0.19, 14.6)
		50–59	2.13 (1.34, 3.41)	2.14 (1.07, 4.26)	3.43 (1.64, 7.15)
		60–69	1.28 (0.98, 1.67)	1.92 (1.37, 2.69)	1.16 (0.67, 2.01)
		70–79	1.62 (1.36, 1.94)	2.07 (1.61, 2.67)	1.56 (1.06, 2.29)
		80–89	1.35 (1.03, 1.77)	1.66 (1.05, 2.60)	2.12 (1.15, 3.93)
		90+	0.78 (0.19, 3.09)	8.42 (0.48, 147)	–
	Sex	**Female**	1.48 (1.24, 1.75)	2.02 (1.59, 2.55)	1.65 (1.15, 2.38)
		Male	1.47 (1.24, 1.76)	1.72 (1.32, 2.24)	1.48 (1.02, 2.14)

		Frequency of AECOPD in the 12 months prior to an AECOPD		
		1	2	3+
Oxygen therapy within 12 months before study start	**Yes**	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	No	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
Baseline treatment	**Non-treated/unclassified**	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	Short-acting bronchodilators	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	Long-acting bronchodilator	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	Double therapy	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	Triple therapy	1.62 (1.29, 2.02)	1.52 (1.09, 2.13)	1.48 (0.95, 2.32)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.
*Adjusted for age (as a continuous variable), sex, and comorbidities.
Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

eTable 3: Adjusted hazard ratios and 95% confidence intervals following severe AECOPD, northern Denmark, 2005-2009, only severe (hospitalised) AECOPDs included

			Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
			1	2	3+
0 to 30 days	Overall		1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)
	Age	40–49	–	–	–
		50–59	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)
		60–69	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)
		70–79	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)
		80–89	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)
		90+	–	–	–
	Sex	Female	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)
		Male	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)
	Oxygen therapy within 12 months before study start	Yes	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
		No	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
	Baseline treatment	Non-treated/unclassified	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)
		Short-acting bronchodilators	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)
		Long-acting bronchodilator	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)
		Double therapy	1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)
		Triple therapy	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)
31 to 365 days	Overall		1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)
	Age	40–49	–	–	–
		50–59	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)
		60–69	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)
		70–79	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)
		80–89	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)
		90+	–	–	–
	Sex	Female	1.62 (1.29, 2.03)	1.96 (1.37, 2.82)	2.28 (1.29, 4.04)
		Male	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)
	Oxygen therapy within 12 months before study start	Yes	3.30 (1.16, 9.38)	1.50 (0.15-14.9)	–

		Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
		1	2	3+
Baseline treatment	**No**	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
	Non-treated/unclassified	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-295)
	Short-acting bronchodilators	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	Long-acting bronchodilator	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	Double therapy	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	Triple therapy	1.90 (1.42, 2.56)	1.53 (0.91-2.57)	2.21 (1.14-4.29)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.
*Adjusted for age (as a continuous variable), sex, and comorbidities.
Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Included in title and abstract]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Abstract, page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Introduction, page 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Introduction, page 4]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Introduction and Methods, pages 5-7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Methods, pages 5-7]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Methods, pages 5-7]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Methods, pages 5-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Setting and data sources, page 5]**
Bias	9	Describe any efforts to address potential sources of bias **[Study population about cohort and exposure defintion, page 6]**
Study size	10	Explain how the study size was arrived at **[Study population, page 6]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Statistical analysis, page 8: age]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Statistical analysis, pages 8-9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Statistical analysis, pages 8-9]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[Study population, page 7, first paragraph about follow-up]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Descriptive data, page 9 about eligible patients and study population]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[Not used]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Results, page 10 for eligible**

		patients, the time-varying analysis precludes a table on characteristics by exposure status]
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) Summarise follow-up time (eg, average and total amount) **[Person-years by subgroups Tables 2 and 3]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Results and Tables, pages 11-16]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Tables 2-5]**
		(*b*) Report category boundaries when continuous variables were categorized **[Quartiles presented in Table 1]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Tables 2-3 include mortality rates and ratios]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[Statistical analysis and results, pages 8-16]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[First paragraph of Discussion, page 17]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion, pages 17-19]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Comparison with other studies, page 19]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Final paragraph of Strengths and limitations, page 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Funding and Competing Interest, page 20]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.