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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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## 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.<sup>1,2</sup>

In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.<sup>3</sup> 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,<sup>3</sup> making it one of the leading causes of death among the elderly.<sup>4</sup>

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”.<sup>5</sup> The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01 depending on disease severity<sup>6</sup> and history of frequent exacerbations.<sup>7</sup> The mortality for hospitalised AECOPD patients is high.<sup>1,2</sup> 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.<sup>8-17</sup> 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,<sup>9</sup> 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.<sup>18</sup> 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.<sup>19</sup> Each admission is described by one primary diagnosis and one or more secondary diagnoses classified according to the 8<sup>th</sup> revision of the *International Classification of Diseases* (ICD-8) through 1993 and the ICD-10 revision thereafter.<sup>19</sup>

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.<sup>20</sup>

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.<sup>18</sup> 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.<sup>18</sup>

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<sup>21</sup> and defined in the Supplementary File. Patients younger than 40 years were excluded, given the low COPD prevalence in this patient group<sup>22</sup> 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

1  
2  
3 to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the preceding 12 months. We then  
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5 entered this value as a time-varying exposure in the analysis. Therefore, each time a patient  
6  
7 had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months  
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9 before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+  
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11 AECOPDs). One patient could thus have multiple AECOPDs during follow-up and  
12  
13 contribute person-time in several exposure groups depending on the rate of AECOPD. We  
14  
15 adjudicated AECOPD events using a 30-day threshold following the prescription redemption  
16  
17 or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not  
18  
19 regarded as a new AECOPD.  
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### 24 25 **Covariates**

26  
27 We used the DNRP to retrieve the hospital history for all study participants during the 5 years  
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29 preceding the start of the study on January 1, 2005. We then ascertained the presence of the  
30  
31 following diseases that are frequent among COPD patients and may affect mortality:  
32  
33 myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular  
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35 disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any  
36  
37 malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter,  
38  
39 medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive  
40  
41 sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.  
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45 From the Prescription Database, we retrieved information on preadmission therapy and  
46  
47 grouped patients based on the latest Global Initiative for Chronic Obstructive Lung Disease  
48  
49 (GOLD) guidelines (treatment groups A, B, C, D and an unclassified group).<sup>5</sup> The grouping  
50  
51 was modified to avoid overlap between the groups, as defined in the Supplementary File  
52  
53 (eTable 1). We also retrieved information on pharmacological treatment with systemic  
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55 corticosteroids or theophylline within 12 months before study start, with antibiotics and/or  
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3 antivirals within three months before study start. Finally, we used the DNRP to identify  
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5 hospital codes for oxygen treatment within the 12 months before study start and on lung  
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7 volume reduction surgery between 1996 and study start.  
8  
9

### 10 11 **Statistical analysis**

12  
13 We characterized the eligible population of COPD patients on January 1, 2005 by age, sex,  
14  
15 comorbidities recorded in the 5 years before study start, as well as GOLD treatment group,  
16  
17 pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the  
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19 prior 12 months, and treatment with antibiotics and/or antivirals within the prior three  
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21 months.  
22  
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24  
25 In the mortality analyses, we entered AECOPD frequency as a time-varying exposure  
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27 and computed the number of deaths, person-time, and mortality rates in each exposure group.  
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29 We then used Cox regression analysis to compute crude hazard ratios as a measure of  
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31 mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD  
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33 patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with  
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35 patients with no exacerbations in the preceding 12-month period. We then computed the  
36  
37 MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis,  
38  
39 we examined the effect of frequent severe exacerbations on mortality by including only  
40  
41 severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed  
42  
43 above). Both the present AECOPD and any exacerbations in the 12 months before had to be  
44  
45 defined as severe. Finally, we stratified the results from the primary analysis and the results  
46  
47 for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen  
48  
49 therapy, lung volume reduction surgery, GOLD treatment group, and cardiovascular disease  
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51 (myocardial infarction, congestive heart failure, peripheral vascular disease, and  
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53 cerebrovascular disease).  
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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	%
<b>Total</b>	16,647	100
<b>Age at study start (years)</b>		

1			
2			
3	40-50	1,198	7.2
4	50-60	2,764	17
5	60-70	4,522	27
6	70-80	5,422	33
7	80-90	2,492	15
8	90+	249	1.5
9			
10	<b>Sex</b>		
11	Female	8,770	53
12	Male	7,877	47
13			
14	<b>Comorbidities (within previous 5 years)</b>		
15	Myocardial infarction	795	4.8
16	Congestive heart failure	1,785	11
17	Peripheral vascular disease	922	5.5
18	Cerebrovascular disease	1,178	7.1
19	Peptic ulcer disease	627	3.8
20	Liver disease	176	1.1
21	Diabetes	1,134	6.8
22	Moderate to severe renal disease	287	1.7
23	Any malignancy except lung cancer	950	5.7
24	Alcoholism-related diseases	162	1.0
25	Atrial fibrillation/flutter	1,400	8.4
26	Medically diagnosed obesity	575	3.5
27	Hypertension	2,066	12
28	Osteoporosis	1,021	6.1
29	Lung cancer	186	1.1
30	Asthma	2,006	12
31	Obstructive sleep apnea	337	2.0
32	Rheumatoid arthritis	151	0.9
33	Depression	340	2.0
34			
35	<b>Treatments within previous 12 months</b>		
36	Systemic steroids	4,993	30
37	Theophylline	1,164	7.0
38	Oxygen therapy	258	1.5
39			
40	<b>GOLD treatment group</b>		
41	Unclassified	4,880	29
42	A	2,958	18
43	B	2,041	12
44	C	4,226	25
45	D	2,542	15
46			
47	<b>Infection within previous 3 months</b>		
48	Prescription for antibiotics	5,103	31
49	Prescription for antivirals	55	0.3
50	Prescription for both antibiotics and antivirals	26	0.2
51			
52	COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See		
53	the text and Appendix for definition of GOLD treatment groups.		
54	*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)		
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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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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	<b>Overall</b>	0.97 (0.80, 1.18)	0.90 (0.70, 1.15)	1.03 (0.81, 1.32)	
	<b>Age</b>	<b>40–49</b>	–	–	–
		<b>50–59</b>	1.74 (0.85, 3.59)	0.60 (0.17, 2.13)	2.89 (1.31, 6.36)
		<b>60–69</b>	1.00 (0.67, 1.50)	0.68 (0.39, 1.18)	1.10 (0.69, 1.77)
		<b>70–79</b>	0.98 (0.73, 1.30)	1.05 (0.73, 1.50)	1.10 (0.75, 1.60)
		<b>80–89</b>	0.70 (0.45, 1.08)	0.96 (0.56, 1.66)	0.61 (0.28, 1.34)
		<b>90+</b>	–	–	–
	<b>Sex</b>	<b>Female</b>	0.88 (0.67, 1.15)	0.90 (0.64, 1.26)	0.96 (0.67, 1.37)
		<b>Male</b>	1.06 (0.80, 1.39)	0.91 (0.63, 1.31)	1.14 (0.80, 1.62)
	<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	0.79 (0.27, 2.28)	0.24 (0.02, 2.45)	3.14 (0.27, 36.9)
		<b>No</b>	1.00 (0.82, 1.21)	0.96 (0.74, 1.23)	1.04 (0.81, 1.34)
	<b>GOLD treatment group</b>	<b>Unclassified</b>	1.60 (0.63, 4.04)	1.07 (0.11, 10.0)	2.62 (0.40, 17.3)
		<b>A</b>	1.12 (0.73, 1.73)	0.70 (0.36, 1.37)	1.38 (0.78, 2.44)
		<b>B</b>	0.69 (0.41, 1.17)	1.23 (0.67, 2.25)	0.93 (0.44, 2.00)
<b>C</b>		1.01 (0.71, 1.45)	0.87 (0.54, 1.42)	1.24 (0.81, 1.91)	
<b>D</b>		1.05 (0.73, 1.50)	1.10 (0.71, 1.68)	0.90 (0.56, 1.43)	
31 to 365 days	<b>Overall</b>	1.47 (1.30, 1.66)	1.89 (1.59, 2.25)	1.59 (1.23, 2.05)	
	<b>Age</b>	<b>40–49</b>	0.69 (0.15, 3.27)	0.79 (0.08, 7.86)	1.68 (0.19, 14.6)
		<b>50–59</b>	2.13 (1.34, 3.41)	2.14 (1.07, 4.26)	3.43 (1.64, 7.15)
		<b>60–69</b>	1.28 (0.98, 1.67)	1.92 (1.37, 2.69)	1.16 (0.67, 2.01)
		<b>70–79</b>	1.62 (1.36, 1.94)	2.07 (1.61, 2.67)	1.56 (1.06, 2.29)
		<b>80–89</b>	1.35 (1.03, 1.77)	1.66 (1.05, 2.60)	2.12 (1.15, 3.93)
		<b>90+</b>	0.78 (0.19, 3.09)	8.42 (0.48, 147)	–
	<b>Sex</b>	<b>Female</b>	1.48 (1.24, 1.75)	2.02 (1.59, 2.55)	1.65 (1.15, 2.38)
		<b>Male</b>	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+
<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	<b>No</b>	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
<b>GOLD treatment group</b>	<b>Unclassified</b>	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	<b>A</b>	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	<b>B</b>	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	<b>C</b>	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	<b>D</b>	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+	
<b>0 to 30 days</b>	<b>Overall</b>	1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)	
	<b>Age</b>				
		<b>40–49</b>	–	–	–
		<b>50–59</b>	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)
		<b>60–69</b>	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)
		<b>70–79</b>	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)
		<b>80–89</b>	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)
		<b>90+</b>	–	–	–
		<b>Sex</b>			
		<b>Female</b>	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)
		<b>Male</b>	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)
		<b>Oxygen therapy within 12 months before study start</b>			
		<b>Yes</b>	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
		<b>No</b>	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
	<b>GOLD treatment group</b>				
	<b>Unclassified</b>	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)	
	<b>A</b>	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)	
	<b>B</b>	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)	
	<b>C</b>	1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)	
	<b>D</b>	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)	
<b>31 to 365 days</b>	<b>Overall</b>	1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)	
	<b>Age</b>				
		<b>40–49</b>	–	–	–
		<b>50–59</b>	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)
		<b>60–69</b>	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)
		<b>70–79</b>	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)
		<b>80–89</b>	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)
		<b>90+</b>	–	–	–
		<b>Sex</b>			
		<b>Female</b>	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+
	<b>Male</b>	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)
<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	3.30 (1.16, 9.38)	1.50 (0.15-14.9)	–
	<b>No</b>	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
<b>GOLD treatment group</b>	<b>Unclassified</b>	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-2.95)
	<b>A</b>	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	<b>B</b>	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	<b>C</b>	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	<b>D</b>	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.<sup>23</sup> 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.<sup>24</sup>

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.

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3 However, some of the clinical factors may be on the causal pathway linking AECOPD  
4 frequency and severity to high mortality, making adjustment inappropriate.<sup>25</sup> Nevertheless,  
5 such information would have been useful in classifying AECOPD. Instead, we categorised  
6 patients based on GOLD treatment groups using preadmission therapy. Although this  
7 classification relies on patients being treated according to current guidelines, we believe that  
8 it reflects the severity of COPD.  
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12 Finally, the generalizability of our results to the entire range of AECOPD cases may be  
13 affected by the fact that some COPD patients may be diagnosed in general practice,  
14 excluding them from registration in the DNRP.  
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### 25 **Comparison with other studies**

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27 In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*<sup>15</sup> showed that the  
28 AECOPD mortality rate increased with each exacerbation, as compared with the mortality  
29 rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the  
30 second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality  
31 peaked within the first week after admission. Similarly, other studies have found that a  
32 history of hospitalisation for AECOPD within 6 months,<sup>14</sup> 1 year,<sup>8,9,12,16,17</sup> and up to 7 years<sup>10</sup>  
33 before current AECOPD hospitalisation, within 2 years before inclusion period,<sup>13</sup> or  
34 admission with respiratory failure within 2 years before current admission,<sup>11</sup> increases  
35 AECOPD mortality in-hospital,<sup>10,11,14</sup> at 30 days<sup>11</sup> and at longer term (median 3.1 years)<sup>12</sup>  
36 following admission, and at 3 months,<sup>8</sup> 6 months,<sup>9</sup> 1 year,<sup>9</sup> 2 years,<sup>9,17</sup> and at longer-term  
37 mortality (3 or more years)<sup>13,16</sup> following discharge. Besides these differences in assessment  
38 of prior AECOPD hospitalisations and in follow-up periods, populations included also varied  
39 substantially (*e.g.*, inclusion of primarily men,<sup>9,13,16</sup> emergency room patients only,<sup>12,14</sup> and  
40 discharged patients only<sup>8,13,16,17</sup>).  
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3 Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days  
4 following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in  
5 the previous year was less pronounced than in the study by Suissa *et al.*<sup>15</sup> and it did not  
6 increase further with increasing number of AECOPDs. There may be several potential  
7 explanations for this discrepancy. First, our study population included prevalent COPD  
8 patients at study start, which may have resulted in a mix of patients at different stages in their  
9 clinical course of COPD. Hence, by mixing patients that were experiencing their first  
10 AECOPD ever with patients that had previously experienced one or more AECOPDs, we  
11 may have obscured some of the effect of AECOPD frequency on mortality. Second,  
12 unmeasured severity of the AECOPD may have affected our results. We have previously  
13 shown that patients with no AECOPD in the year before an AECOPD are younger and have  
14 less comorbidity.<sup>21</sup> Even though these patients may have had more newly diagnosed, and thus  
15 less severe, COPD, it is possible that some of these patients have more severe AECOPDs  
16 because they postpone seeking medical attention due to unfamiliarity with the symptoms  
17 hereof. On the other hand, an older patient with higher comorbidity and a recent history of  
18 AECOPD may be more aware of the threatening situation and act more quickly, resulting in a  
19 lower mortality than expected in the acute phase. The situation may then reverse after day 30  
20 when the relative impact of frequent exacerbations on severity of COPD, complication rate,  
21 and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the  
22 study population examined by Suissa *et al.*<sup>15</sup> included a higher proportion of men that was on  
23 average older than our study population. Thus, excess cardiovascular mortality in their  
24 population may partly explain the higher estimates observed in their study. Finally, because  
25 the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is  
26 possible that the relative effect of AECOPD history appeared less pronounced in the first  
27 period merely because of differences in the baseline rate. Such differences may also explain  
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3 the more pronounced associations observed for the younger patients in our subanalysis.  
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## 7 **CONCLUSIONS**

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10 In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in  
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12 the 12 months before exacerbation may serve as an indicator of a higher mortality rate during  
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14 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect  
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16 on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort  
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18 of COPD patients or a higher baseline rate than in the 31-365-day period.  
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23 **Contributors:** All authors participated in designing the study. MBJ collected the data and  
24  
25 carried out analyses. All authors participated in the discussion and interpretation of the  
26  
27 results. SAJS organised the writing and wrote the initial draft. All authors critically revised  
28  
29 the manuscript for intellectual content and approved the final version. HTS is the guarantor.  
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40  
41 NAM was an employee of MedImmune, LLC at the time of the study. None of the other  
42  
43 authors have received fees, honoraria, grants or consultancy fees related to the topic of this  
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45 paper.  
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48 **Ethics approval:** As this study did not involve any contact with patients or any intervention,  
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50 it was not necessary to obtain permission from the Danish Scientific Ethical Committee.  
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54 **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

**Authors:** Sigrun Alba Johannesdottir Schmidt,<sup>1</sup> Martin Berg Johansen,<sup>1</sup> Morten Olsen,<sup>1</sup> Xiao Xu,<sup>2</sup> Joseph M. Parker,<sup>3</sup> Nestor A. Molfino,<sup>4</sup> Timothy L. Lash,<sup>1,5</sup> Henrik Toft Sørensen,<sup>1</sup> Christian Fynbo Christiansen<sup>1</sup>

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

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**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

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**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

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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

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**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

<b>GOLD treatment group*</b>	<b>ATC code</b>	<b>Time-frame</b>
A	Short-acting beta <sub>2</sub> -agonists (R03AC02-10; R03AC15-17) <i>and/or</i>	Redeemed within 12 months before study start.
	Short-acting muscarinic antagonists (R03BB01, R03BB02) <i>and/or</i>	Redeemed within 12 months before study start.
	Combination preparations of short-acting beta <sub>2</sub> -agonists and short-acting muscarinic antagonists (R03AK03-04)	Redeemed within 12 months before study start.
B	Long-acting beta <sub>2</sub> -agonists (R03AC excluding R03AC02-10 and R03AC15-17) <i>or</i>	Redeemed within 12 months before study start.

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5		Redeemed within 12 months before study start.
6		(R03BB04-06)
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8	C	Redeemed within 12 months before study start and
9		within 30 days of each other
10		Long-acting beta <sub>2</sub> -agonists (R03AC
11		excluding R03AC02-10 and
12		R03AC15-17) and inhaled
13		corticosteroids (R03BA) <i>or</i>
14		Redeemed within 12 months before study start.
15		Combination preparations with long-
16		acting beta <sub>2</sub> -agonists and inhaled
17		corticosteroids (R03AK06-07) <i>or</i>
18		Redeemed within 12 months before study start and
19		within 30 days of each other
20		Long-acting beta <sub>2</sub> -agonists (R03AC
21		excluding R03AC02-10 and
22		R03AC15-17) and long-acting
23		muscarinic antagonists (R03BB04-
24		06) <i>or</i>
25		Redeemed within 12 months before study start and
26		within 30 days of each other
27		Inhaled corticosteroids (R03AK06-
28		07) and long-acting muscarinic
29		antagonists (R03BB04-06)
30	D	Redeemed within 12 months before study start and
31		within 30 days of each other
32		Long-acting beta <sub>2</sub> -agonistst (R03AC
33		excluding R03AC02-10 and
34		R03AC15-17), inhaled
35		corticosteroids (R03BA), and long-
36		acting muscarinic antagonists
37		(R03BB04-06) <i>or</i>
38		Redeemed within 12 months before study start and
39		within 30 days of each other
40		Long-acting muscarinic antagonists
41		(R03BB04-06) and combination
42		preparations with Long-acting beta <sub>2</sub> -
43		agonists and inhaled corticosteroids
44		(R03AK06-07)
45	Non-treated	Remaining patients

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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
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <b>[Included in title and abstract]</b> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <b>[Abstract, page 2]</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <b>[Introduction, page 4]</b>
Objectives	3	State specific objectives, including any prespecified hypotheses <b>[Introduction, page 4]</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper <b>[Introduction and Methods, pages 5-7]</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <b>[Methods, pages 5-7]</b>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>[Methods, pages 5-7]</b> (b) For matched studies, give matching criteria and number of exposed and unexposed <b>[N/A]</b>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <b>[Methods, pages 5-8]</b>
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 <b>[Setting and data sources, page 5]</b>
Bias	9	Describe any efforts to address potential sources of bias <b>[Study population about cohort and exposure definition, page 6]</b>
Study size	10	Explain how the study size was arrived at <b>[Study population, page 6]</b>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <b>[Statistical analysis, page 8: age]</b>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <b>[Statistical analysis, pages 8-9]</b> (b) Describe any methods used to examine subgroups and interactions <b>[Statistical analysis, pages 8-9]</b> (c) Explain how missing data were addressed <b>[N/A]</b> (d) If applicable, explain how loss to follow-up was addressed <b>[Study population, page 7, first paragraph about follow-up]</b> (e) Describe any sensitivity analyses <b>[N/A]</b>
<b>Results</b>		
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 <b>[Descriptive data, page 9 about eligible patients and study population]</b> (b) Give reasons for non-participation at each stage <b>[N/A]</b> (c) Consider use of a flow diagram <b>[Not used]</b>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <b>[Results, page 10 for eligible</b>

		<b>patients, the time-varying analysis precludes a table on characteristics by exposure status]</b>
		(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) <b>[Person-years by subgroups Tables 2 and 3]</b>
Outcome data	15*	Report numbers of outcome events or summary measures over time <b>[Results and Tables, pages 11-16]</b>
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 <b>[Tables 2-5]</b> (b) Report category boundaries when continuous variables were categorized <b>[Quartiles presented in Table 1]</b> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period <b>[Tables 2-3 include mortality rates and ratios]</b>
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses <b>[Statistical analysis and results, pages 8-16]</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <b>[First paragraph of Discussion, page 17]</b>
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 <b>[Discussion, pages 17-19]</b>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence <b>[Comparison with other studies, page 19]</b>
Generalisability	21	Discuss the generalisability (external validity) of the study results <b>[Final paragraph of Strengths and limitations, page 18]</b>
<b>Other information</b>		
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 <b>[Funding and Competing Interest, page 20]</b>

\*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

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3 **Title:** The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of  
4 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.<sup>1,2</sup>

In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.<sup>3</sup> 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,<sup>3</sup> making it one of the leading causes of death among the elderly.<sup>4</sup>

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”.<sup>5</sup> The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01, increasing with disease severity<sup>6</sup> and history of frequent exacerbations.<sup>7</sup> The mortality following AECOPD is high, especially in patients with severe COPD.<sup>8</sup> Thus, severity of disease is associated with both increased risk and mortality of AECOPD.<sup>8</sup> However, the relationship is complex because frequent exacerbations may themselves also result in decreased lung function and thereby increase mortality.<sup>1,2,8,9</sup> 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.<sup>10-19</sup> Although current therapies for COPD may decrease the exacerbations frequency and mortality,<sup>2,8</sup> 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,<sup>11</sup> which limits the interpretation to statistical significance only. Finally, none of the studies included AECOPDs treated outside the hospital.

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2  
3 We conducted a cohort study to examine how the exacerbation frequency impacts one-  
4 year mortality following an AECOPD. Specifically, we addressed the limitations of previous  
5 studies by including exacerbations treated in the hospital, outpatient clinics and in general  
6 practice, and by using Danish registries with detailed data on comorbidity, COPD treatment,  
7 and with complete follow-up.  
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## 13 14 15 16 **METHODS**

### 17 18 **Setting and data sources**

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20 We conducted this cohort study in northern Denmark, whose population numbers  
21 approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported  
22 healthcare plan guarantees universal medical care for all residents and partial reimbursement  
23 for prescribed medications.<sup>20</sup> Virtually all health services are recorded in various medical  
24 registries, of which the following formed the basis for this study. The Danish National  
25 Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-  
26 psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room  
27 visits since 1995.<sup>21</sup> Each admission is described by one primary diagnosis and one or more  
28 secondary diagnoses classified according to the 8<sup>th</sup> revision of the *International*  
29 *Classification of Diseases* (ICD-8) through 1993 and the ICD-10 revision thereafter.<sup>21</sup>  
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43 Aarhus University Prescription Database records patient's personal identifier, the  
44 dispensing date, and the type and quantity of drug prescribed (according to the Anatomical  
45 Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at  
46 the pharmacy.<sup>22</sup>  
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52 Since 1968, the Danish Civil Registration System has recorded all Danish residents'  
53 administrative information and changes in vital status, such as date of death and emigration,  
54 with daily updates.<sup>20</sup> The registry assigns a unique personal identifier to all persons born in or  
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3 immigrating to Denmark, which enables follow-up of patients and linkage of the various  
4  
5 medical registries.<sup>20</sup>  
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7 All codes used for defining study variables in the current study can be found in the  
8  
9 Supplementary File (eTable 1).  
10

### 11 12 13 14 **Study population**

15  
16 The population eligible for the study included all prevalent COPD patients on January 1,  
17  
18 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and  
19  
20 December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to  
21  
22 COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related  
23  
24 diagnosis, as described previously<sup>23</sup> and defined in the Supplementary File. Patients younger  
25  
26 than 40 years were excluded, given the low COPD prevalence in this patient group<sup>24</sup> and the  
27  
28 potential for misclassifying asthma as COPD.  
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31  
32 Among all eligible COPD patients, we then identified the study cohort as COPD  
33  
34 patients who developed at least one AECOPD between January 1, 2005 and December 31,  
35  
36 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute  
37  
38 exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic  
39  
40 prescription on the same day (to account for patients treated outside hospital), or (b) a  
41  
42 primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge  
43  
44 diagnosis of respiratory failure or acute respiratory infection with a secondary discharge  
45  
46 diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or  
47  
48 AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of  
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50 AECOPD cases were treated exclusively in the emergency department). Standard practice at  
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52 Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also,  
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3 COPD patients transferred to a specialized ward from the emergency room are coded as  
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5 inpatient admissions and are therefore included in the study.  
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8 Using the Civil Registration System, we followed patients from the date of first  
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10 exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until  
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12 death, emigration, or December 31, 2009, whichever came first. To examine the effect of  
13  
14 AECOPD frequency on mortality, we classified each AECOPD during follow-up according  
15  
16 to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months. We then  
17  
18 entered this value as a time-varying exposure in the analysis. Therefore, each time a patient  
19  
20 had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months  
21  
22 before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+  
23  
24 AECOPDs). One patient could thus have multiple AECOPDs during follow-up and  
25  
26 contribute person-time in several exposure groups depending on the rate of AECOPD. We  
27  
28 adjudicated AECOPD events using a 30-day threshold following the prescription redemption  
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30 or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not  
31  
32 regarded as a new AECOPD.  
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### 38 **Covariates**

39  
40 We used the DNRP to retrieve the hospital history for all study participants during the 5 years  
41  
42 preceding the start of the study on January 1, 2005. We then ascertained the presence of the  
43  
44 following diseases that are frequent among COPD patients and may affect mortality:  
45  
46 myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular  
47  
48 disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any  
49  
50 malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter,  
51  
52 medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive  
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54 sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.  
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3 From the Prescription Database, we retrieved information on COPD treatment within  
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5 12 months before study start. Following the latest Global Initiative for Chronic Obstructive  
6  
7 Lung Disease (GOLD) guidelines,<sup>5</sup> we then grouped patients into the following five mutually  
8  
9 exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting  
10  
11 bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta<sub>2</sub>-agonists or long-  
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13 acting muscarinic antagonists), (4) double therapy with any possible combination of long-  
14  
15 acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5)  
16  
17 triple therapy with long-acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or long-acting  
18  
19 muscarinic antagonists, as defined in the Supplementary File (eTable 1). We also retrieved  
20  
21 information on pharmacological treatment with systemic corticosteroids or theophylline  
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23 within 12 months before study start, with antibiotics and/or antivirals within three months  
24  
25 before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment  
26  
27 within the 12 months before study start and on lung volume reduction surgery between 1996  
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29 and study start.  
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### 36 **Statistical analysis**

37  
38 We characterized the eligible population of COPD patients on January 1, 2005 by age, sex,  
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40 comorbidities recorded in the 5 years before study start, as well as COPD treatment group,  
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42 pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the  
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44 prior 12 months, and treatment with antibiotics and/or antivirals within the prior three  
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46 months.  
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50 In the mortality analyses, we entered AECOPD frequency as a time-varying exposure  
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52 and computed the number of deaths, person-time, and mortality rates in each exposure group.  
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54 We then used Cox regression analysis to compute crude hazard ratios as a measure of  
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56 mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD  
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3 patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with  
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5 patients with no exacerbations in the preceding 12-month period. We then computed the  
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7 MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis,  
8  
9 we examined the effect of frequent severe exacerbations on mortality by including only  
10  
11 severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed  
12  
13 above). Both the present AECOPD and any exacerbations in the 12 months before had to be  
14  
15 defined as severe. Finally, we stratified the results from the primary analysis and the results  
16  
17 for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen  
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19 therapy, lung volume reduction surgery, COPD treatment group, and cardiovascular disease  
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21 (myocardial infarction, congestive heart failure, peripheral vascular disease, and  
22  
23 cerebrovascular disease).  
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27  
28 Because AECOPD is an acute event, we expect the mortality rate to be greatest in the  
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30 initial phase following and as the results of the event. We therefore separated the effect of  
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32 AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all  
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34 mortality rate calculations. We assessed the assumption of proportional hazards graphically  
35  
36 using scaled Schoenfeld residuals and found it valid.  
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39 All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study  
40  
41 was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish  
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43 legislation does not require ethical review board approval or informed consent from subjects  
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45 in registry-based studies.  
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## 49 50 **RESULTS**

### 51 52 **Descriptive data**

53  
54 We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age  
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56 among eligible patients was 70 year and 53% were female. Comorbidities were frequent,  
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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	%
<b>Total</b>	16,647	100
<b>Age at study start (years)</b>		
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
<b>Sex</b>		
Female	8,770	53
Male	7,877	47
<b>Comorbidities (within previous 5 years)</b>		
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
<b>Treatments within previous 12 months</b>		
Systemic steroids	4,993	30



Theophylline	1,164	7.0
Oxygen therapy	258	1.5
<b>COPD treatment</b>		
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
<b>Infection within previous 3 months</b>		
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*
<b>0 to 30 days</b>				
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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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.

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3 The stratified main analyses (eTable 2) showed that for the 31–365 day period, the  
4  
5 MRRs were highest among those aged 50–59 years (MRR 2.13, 95% CI: 1.34, 3.41 for 1  
6  
7 AECOPD; MRR 2.14, 95% CI: 1.07, 4.26 for 2 AECOPDs; and MRR 3.43, 95% CI: 1.64,  
8  
9 7.15 for 3+ AECOPDs) and those with oxygen therapy within 12 months before study start  
10  
11 ((MRR 3.61, 95% CI: 1.80, 7.27 for 1 AECOPD; MRR 4.87, 95% CI: 1.79, 13.2 for 2  
12  
13 AECOPDs; and MRR 4.22, 95% CI: 0.82, 21.7 for 3+ AECOPDs). There was no substantial  
14  
15 variation by COPD treatment. The stratified analysis considering severe AECOPDs only  
16  
17 (eTable 3) were similar to the stratification including all AECOPDs regardless of severity.  
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19 However, the stratified analyses should be interpreted with the wide confidence intervals in  
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21 mind.  
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## 27 **DISCUSSION**

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30 In this large Danish cohort study, we found that the 31–365 day all-cause mortality rate  
31  
32 following an AECOPD was higher among patients with at least one AECOPD in the  
33  
34 preceding 12 months than among patients who did not have any recent AECOPD. All cause  
35  
36 mortality did not vary substantially according to the actual number of AECOPDs within the  
37  
38 preceding year and was not observed in excess within the first 30 days after the AECOPD  
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40 after controlling for age, sex and comorbidities.  
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### 46 **Strengths and limitations**

47  
48 The universal healthcare system and complete follow-up of all residents by the Danish Civil  
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50 Registration System reduces the possibility of selection bias in our study. We aimed to reduce  
51  
52 information bias by using broad definitions of COPD and AECOPD rather than more  
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54 restrictive primary discharge diagnoses. A review of medical records has showed a PPV of  
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56 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also  
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3 primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.<sup>25</sup>  
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5 However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on  
6  
7 the same day to define AECOPDs outside hospital setting, we may have misclassified some  
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9 patients who did not have AECOPD as AECOPD patients if the prescriptions were written as  
10  
11 rescue packs for potential future events. Such misclassification would not affect the analysis  
12  
13 restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may  
14  
15 have resulted in misclassification of exposure status due to underreporting or  
16  
17 misclassification of the number of AECOPDs. Previous data, however, show that the  
18  
19 majority of patients recover within 30 days after AECOPD onset.<sup>26</sup>  
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22  
23 Because we relied solely on registry data, we lacked information on lifestyle factors and  
24  
25 clinical variables such as measurements of peak expiratory flow and arterial blood gases.  
26  
27 However, some of the clinical factors may be on the causal pathway linking AECOPD  
28  
29 frequency to high mortality,<sup>1,2,8,9</sup> making adjustment inappropriate.<sup>27</sup> Nevertheless, such  
30  
31 information would have been useful in classifying AECOPD. Instead, we examined if the  
32  
33 association depended on COPD therapy, which may be linked to underlying severity, and  
34  
35 found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified,  
36  
37 which may represent patients with poor adherence or possibly patients with mild COPD.  
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41 Finally, the generalizability of our results to the entire range of AECOPD cases may be  
42  
43 affected by the fact that some COPD patients may be diagnosed in general practice,  
44  
45 excluding them from registration in the DNRP.  
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### 48 49 **Comparison with other studies**

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51 In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*<sup>17</sup> showed that the  
52  
53 AECOPD mortality rate increased with each exacerbation, as compared with the mortality  
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55 rate following the first AECOPD. The adjusted MRR was 1.9 (95% CI: 1.8, 1.9) for the  
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3 second AECOPD increasing to 5.2 (95% CI: 4.9, 5.5) after the 10th or later events. Mortality  
4  
5 peaked within the first week after admission. Similarly, other studies have found that a  
6  
7 history of hospitalisation for AECOPD within 6 months,<sup>16</sup> 1 year,<sup>10,11,14,18,19</sup> and up to 7  
8  
9 years<sup>12</sup> before current AECOPD hospitalisation, within 2 years before inclusion period,<sup>15</sup> or  
10  
11 admission with respiratory failure within 2 years before current admission,<sup>13</sup> increases  
12  
13 AECOPD mortality in-hospital,<sup>12,13,16</sup> at 30 days<sup>13</sup> and at longer term (median 3.1 years)<sup>14</sup>  
14  
15 following admission, and at 3 months,<sup>10</sup> 6 months,<sup>11</sup> 1 year,<sup>11</sup> 2 years,<sup>11,19</sup> and at longer-term  
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17 mortality (3 or more years)<sup>15,18</sup> following discharge. Besides these differences in assessment  
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19 of prior AECOPD hospitalisations and in follow-up periods, populations included also varied  
20  
21 substantially (*e.g.*, inclusion of primarily men,<sup>11,15,18</sup> emergency room patients only,<sup>14,16</sup> and  
22  
23 discharged patients only<sup>10,15,18,19</sup>).

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27 Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days  
28  
29 following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in  
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31 the previous year was less pronounced than in the study by Suissa *et al.*<sup>17</sup> and it did not  
32  
33 increase further with increasing number of AECOPDs. There may be several potential  
34  
35 explanations for this discrepancy. First, our study population included prevalent COPD  
36  
37 patients at study start, which may have resulted in a mix of patients at different stages in their  
38  
39 clinical course of COPD. Hence, by mixing patients that were experiencing their first  
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41 AECOPD ever with patients that had previously experienced one or more AECOPDs, we  
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43 may have obscured some of the effect of AECOPD frequency on mortality. Second,  
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45 unmeasured severity of the AECOPD may have affected our results. We have previously  
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47 shown that patients with no AECOPD in the year before an AECOPD are younger and have  
48  
49 less comorbidity.<sup>23</sup> Even though these patients may have had more newly diagnosed, and thus  
50  
51 less severe, COPD, it is possible that some of these patients have more severe AECOPDs  
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53 because they postpone seeking medical attention due to unfamiliarity with the symptoms  
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3 hereof. On the other hand, an older patient with higher comorbidity and a recent history of  
4 AECOPD may be more aware of the threatening situation and act more quickly, resulting in a  
5 lower mortality than expected in the acute phase. The situation may then reverse after day 30  
6 when the relative impact of frequent exacerbations on severity of COPD, complication rate,  
7 and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the  
8 study population examined by Suissa *et al.*<sup>17</sup> included a higher proportion of men that was on  
9 average older than our study population. Thus, excess cardiovascular mortality in their  
10 population may partly explain the higher estimates observed in their study. Finally, because  
11 the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is  
12 possible that the relative effect of AECOPD history appeared less pronounced in the first  
13 period merely because of differences in the baseline rate. Such differences may also explain  
14 the more pronounced associations observed for the younger patients in our subanalysis.  
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## 32 CONCLUSIONS

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34 In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in  
35 the 12 months before exacerbation may serve as an indicator of a higher mortality rate during  
36 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect  
37 on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort  
38 of COPD patients or a higher baseline rate than in the 31-365-day period.  
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50 JMP, NAM, TLL, HTS, and CFC participated in the discussion and interpretation of the  
51 results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP,  
52 NAM, TLL, HTS, and CFC critically revised the manuscript for intellectual content and  
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3 approved the final version. HTS is the guarantor.  
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6

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9  
10

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14 paper.  
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20 **Ethics approval:** As this study did not involve any contact with patients or any intervention,  
21 it was not necessary to obtain permission from the Danish Scientific Ethical Committee.  
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27 **Data sharing statement:** No additional data are available.  
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3 **Title:** The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of  
4 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.<sup>1,2</sup>

In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.<sup>3</sup> 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,<sup>3</sup> making it one of the leading causes of death among the elderly.<sup>4</sup>

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”.<sup>5</sup> The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01, depending on increasing with disease severity<sup>6</sup> and history of frequent exacerbations.<sup>7</sup> The mortality ~~for hospitalised following~~ AECOPD ~~patients~~ is high, especially in patients with severe COPD.<sup>8</sup> Thus, severity of disease is associated with both increased risk and mortality of AECOPD.<sup>8</sup> However, the relationship is complex because frequent exacerbations may themselves also result in decreased lung function and thereby increase mortality.<sup>1,2,8,9</sup> ~~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.<sup>10-19</sup> Although current therapies for COPD may decrease the exacerbations frequency and mortality,<sup>2,8</sup> ~~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,<sup>11</sup>

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3 which limits the interpretation to statistical significance only. Finally, none of the studies  
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5 included AECOPDs treated outside the hospital.  
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7 ~~In order to address these limitations and fill this gap in the literature, w~~We conducted a  
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9 cohort study to examine how the exacerbation frequency impacts one-year mortality  
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11 following an AECOPD. ~~Specifically, we addressed the limitations of previous studies by~~  
12 ~~including exacerbations treated in the hospital, outpatient clinics and in general practice, and~~  
13 ~~by using Danish registries with detailed data on comorbidity, COPD treatment, and with~~  
14 ~~complete follow-up using Danish registries with detailed hospital data and complete follow-~~  
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## 22 23 24 25 **METHODS**

### 26 27 **Setting and data sources**

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29 We conducted this cohort study in northern Denmark, whose population numbers  
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31 approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported  
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33 healthcare plan guarantees universal medical care for all residents and partial reimbursement  
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35 for prescribed medications.<sup>20</sup> Virtually all health services are recorded in various medical  
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37 registries, of which the following formed the basis for this study. The Danish National  
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39 Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-  
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41 psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room  
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43 visits since 1995.<sup>21</sup> Each admission is described by one primary diagnosis and one or more  
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45 secondary diagnoses classified according to the 8<sup>th</sup> revision of the *International*  
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47 *Classification of Diseases* (ICD-8) through 1993 and the ICD-10 revision thereafter.<sup>21</sup>  
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52 Aarhus University Prescription Database records patient's personal identifier, the  
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54 dispensing date, and the type and quantity of drug prescribed (according to the Anatomical  
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56 Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at  
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3 the pharmacy.<sup>22</sup>  
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5 Since 1968, the Danish Civil Registration System has recorded all Danish residents'  
6 administrative information and changes in vital status, such as date of death and emigration,  
7 with daily updates.<sup>20</sup> The registry assigns a unique personal identifier to all persons born in or  
8 immigrating to Denmark, which enables follow-up of patients and linkage of the various  
9 medical registries.<sup>20</sup>  
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16 All codes used for defining study variables in the current study can be found in the  
17 Supplementary File (eTable 1).  
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### 23 **Study population**

24 The population eligible for the study included all prevalent COPD patients on January 1,  
25 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and  
26 December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to  
27 COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related  
28 diagnosis, as described previously<sup>23</sup> and defined in the Supplementary File. Patients younger  
29 than 40 years were excluded, given the low COPD prevalence in this patient group<sup>24</sup> and the  
30 potential for misclassifying asthma as COPD.  
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40 Among all eligible COPD patients, we then identified the study cohort as COPD  
41 patients who developed at least one AECOPD between January 1, 2005 and December 31,  
42 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute  
43 exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic  
44 prescription on the same day (to account for patients treated outside hospital), or (b) a  
45 primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge  
46 diagnosis of respiratory failure or acute respiratory infection with a secondary discharge  
47 diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or  
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3 AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of  
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5 AECOPD cases were treated exclusively in the emergency department). Standard practice at  
6  
7 Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also,  
8  
9 COPD patients transferred to a specialized ward from the emergency room are coded as  
10  
11 inpatient admissions and are therefore included in the study.  
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13

14 Using the Civil Registration System, we followed patients from the date of first  
15  
16 exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until  
17  
18 death, emigration, or December 31, 2009, whichever came first. To examine the effect of  
19  
20 AECOPD frequency on mortality, we classified each AECOPD during follow-up according  
21  
22 to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the ~~preceding-prior~~ 12 months. We  
23  
24 then entered this value as a time-varying exposure in the analysis. Therefore, each time a  
25  
26 patient had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12  
27  
28 months before the event and assigned the patient to the corresponding exposure group (0, 1,  
29  
30 2, or 3+ AECOPDs). One patient could thus have multiple AECOPDs during follow-up and  
31  
32 contribute person-time in several exposure groups depending on the rate of AECOPD. We  
33  
34 adjudicated AECOPD events using a 30-day threshold following the prescription redemption  
35  
36 or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not  
37  
38 regarded as a new AECOPD.  
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### 45 **Covariates**

46  
47 We used the DNRP to retrieve the hospital history for all study participants during the 5 years  
48  
49 preceding the start of the study on January 1, 2005. We then ascertained the presence of the  
50  
51 following diseases that are frequent among COPD patients and may affect mortality:  
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53 myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular  
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55 disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any  
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3 malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter,  
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5 medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive  
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7 sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.  
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10 From the Prescription Database, we retrieved information on ~~preadmission-COPD~~  
11 ~~therapy~~treatment within 12 months before study start. Following the latest Global Initiative  
12 for Chronic Obstructive Lung Disease (GOLD) guidelines,<sup>5</sup> we then~~and~~ grouped patients  
13 into the following five mutually exclusive groups of escalating treatment: (1) non-  
14 treated/unclassified, (2) short-acting bronchodilators, (3) monotherapy with a long-acting  
15 bronchodilator (beta<sub>2</sub>-agonists or long-acting muscarinic antagonists), (4) double therapy  
16 with any possible combination of long-acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or  
17 long-acting muscarinic antagonists, (5) triple therapy with long-acting beta<sub>2</sub>-agonists, inhaled  
18 corticosteroids, and/or long-acting muscarinic antagonists~~based on the latest Global Initiative~~  
19 ~~for Chronic Obstructive Lung Disease (GOLD) guidelines (treatment groups A, B, C, D and~~  
20 ~~an unclassified group)<sup>5</sup>. The grouping was modified to avoid overlap between the group\_s,~~ as  
21 defined in the Supplementary File (eTable 1). We also retrieved information on  
22  
23 pharmacological treatment with systemic corticosteroids or theophylline within 12 months  
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25 before study start, with antibiotics and/or antivirals within three months before study start.  
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27 Finally, we used the DNRP to identify hospital codes for oxygen treatment within the 12  
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29 months before study start and on lung volume reduction surgery between 1996 and study  
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31 start.  
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### 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 **Statistical analysis**

51 We characterized the eligible population of COPD patients on January 1, 2005 by age, sex,  
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53 comorbidities recorded in the 5 years before study start, as well as ~~COPD GOLD~~ treatment  
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55 ~~group~~group, pharmacological treatment with systemic steroids, theophylline, or oxygen  
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3 therapy within the prior 12 months, and treatment with antibiotics and/or antivirals within the  
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5 prior three months.  
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7 In the mortality analyses, we entered AECOPD frequency as a time-varying exposure  
8  
9 and computed the number of deaths, person-time, and mortality rates in each exposure group.  
10  
11 We then used Cox regression analysis to compute crude hazard ratios as a measure of  
12  
13 mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD  
14  
15 patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with  
16  
17 patients with no exacerbations in the preceding 12-month period. We then computed the  
18  
19 MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis,  
20  
21 we examined the effect of frequent severe exacerbations on mortality by including only  
22  
23 severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed  
24  
25 above). Both the present AECOPD and any exacerbations in the 12 months before had to be  
26  
27 defined as severe. Finally, we stratified the results from the primary analysis and the results  
28  
29 for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen  
30  
31 therapy, lung volume reduction surgery, COPD-GOLD treatment group, and cardiovascular  
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33 disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and  
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35 cerebrovascular disease).  
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40 Because AECOPD is an acute event, we expect the mortality rate to be greatest in the  
41  
42 initial phase following and as the results of the event. We therefore separated the effect of  
43  
44 AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all  
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46 mortality rate calculations. We assessed the assumption of proportional hazards graphically  
47  
48 using scaled Schoenfeld residuals and found it valid.  
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51 All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study  
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53 was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish  
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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	%
<b>Total</b>	16,647	100
<b>Age at study start (years)</b>		
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
<b>Sex</b>		
Female	8,770	53
Male	7,877	47
<b>Comorbidities (within previous 5 years)</b>		
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

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3	Diabetes	1,134	6.8
4	Moderate to severe renal disease	287	1.7
5	Any malignancy except lung cancer	950	5.7
6	Alcoholism-related diseases	162	1.0
7	Atrial fibrillation/flutter	1,400	8.4
8	Medically diagnosed obesity	575	3.5
9	Hypertension	2,066	12
10	Osteoporosis	1,021	6.1
11	Lung cancer	186	1.1
12	Asthma	2,006	12
13	Obstructive sleep apnea	337	2.0
14	Rheumatoid arthritis	151	0.9
15	Depression	340	2.0
16	<b>Treatments within previous 12 months</b>		
17	Systemic steroids	4,993	30
18	Theophylline	1,164	7.0
19	Oxygen therapy	258	1.5
20	<b><u>GOLD-COPD treatment group</u></b>		
21	<u>Non-treated/unclassified</u>	<u>4,880</u>	<u>29</u>
22	<u>Short-acting bronchodilators<sup>A</sup></u>	2,958	18
23	<u>Long-acting bronchodilator<sup>B</sup></u>	2,041	12
24	<u>Double therapy<sup>C</sup></u>	4,226	25
25	<u>Triple therapy<sup>D</sup></u>	2,542	15
26	<b>Infection within previous 3 months</b>		
27	Prescription for antibiotics	5,103	31
28	Prescription for antivirals	55	0.3
29	Prescription for both antibiotics and antivirals	26	0.2
30	COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definition of GOLD treatment groups.		
31	*Overall, the median age was 70 years (lower quartile 61 years; upper quartile 77 years)		
32	Previous lung volume reduction surgery is not shown in the table because it was rare (close to 0%)		
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### 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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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*
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<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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+ AECOPDsTable 4). There was no substantial variation by GOLD-COPD treatment-group. The stratified analysis considering severe AECOPDs only (eTable 53) 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

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3 after controlling for age, sex and comorbidities.  
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### 7 8 **Strengths and limitations**

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10 The universal healthcare system and complete follow-up of all residents by the Danish Civil  
11 Registration System reduces the possibility of selection bias in our study. We aimed to reduce  
12 information bias by using broad definitions of COPD and AECOPD rather than more  
13 restrictive primary discharge diagnoses. A review of medical records has showed a PPV of  
14 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also  
15 primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.<sup>25</sup>  
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17 However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on  
18 the same day to define AECOPDs outside hospital setting, we may have misclassified some  
19 patients who did not have AECOPD as AECOPD patients if the prescriptions were written as  
20 rescue packs for potential future events. Such misclassification would not affect the analysis  
21 restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may  
22 have resulted in misclassification of exposure status due to underreporting or  
23 misclassification of the number of AECOPDs. Previous data, however, show that the  
24 majority of patients recover within 30 days after AECOPD onset.<sup>26</sup>  
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41 Because we relied solely on registry data, we lacked information on lifestyle factors and  
42 clinical variables such as measurements of peak expiratory flow and arterial blood gases.

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45 However, some of the clinical factors may be on the causal pathway linking AECOPD  
46 frequency ~~and severity~~ to high mortality,<sup>1,2,8,9</sup> making adjustment inappropriate.<sup>27</sup>  
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49 Nevertheless, such information would have been useful in classifying AECOPD. Instead, we  
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52 examined if the association depended on COPD therapy, which may be linked to underlying  
53 severity, and found no evidence hereof. A total of 29% in the eligible cohort were non-  
54 treated/unclassified, which may represent patients with poor adherence or possibly patients  
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~~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.*<sup>17</sup> 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,<sup>16</sup> 1 year,<sup>10,11,14,18,19</sup> and up to 7 years<sup>12</sup> before current AECOPD hospitalisation, within 2 years before inclusion period,<sup>15</sup> or admission with respiratory failure within 2 years before current admission,<sup>13</sup> increases AECOPD mortality in-hospital,<sup>12,13,16</sup> at 30 days<sup>13</sup> and at longer term (median 3.1 years)<sup>14</sup> following admission, and at 3 months,<sup>10</sup> 6 months,<sup>11</sup> 1 year,<sup>11</sup> 2 years,<sup>11,19</sup> and at longer-term mortality (3 or more years)<sup>15,18</sup> 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,<sup>11,15,18</sup> emergency room patients only,<sup>14,16</sup> and discharged patients only<sup>10,15,18,19</sup>).

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.*<sup>17</sup> and it did not



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

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3 In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in  
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5 the 12 months before exacerbation may serve as an indicator of a higher mortality rate during  
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7 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect  
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9 on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort  
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11 of COPD patients or a higher baseline rate than in the 31-365-day period.  
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15  
16 **Contributors:** SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC ~~All authors~~  
17 participated in designing the study. MBJ collected the data and carried out analyses. SAJS,  
18  
19 MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC ~~All authors~~ participated in the discussion  
20  
21 and interpretation of the results. SAJS organised the writing and wrote the initial draft. SAJS,  
22  
23 MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC ~~All authors~~ critically revised the  
24  
25 manuscript for intellectual content and approved the final version. HTS is the guarantor.  
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31

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33 and a grant from MedImmune LLC.  
34  
35

36  
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38  
39 NAM was an employee of MedImmune, LLC at the time of the study. None of the other  
40  
41 authors have received fees, honoraria, grants or consultancy fees related to the topic of this  
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43 paper.  
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45 **Ethics approval:** As this study did not involve any contact with patients or any intervention,  
46  
47 it was not necessary to obtain permission from the Danish Scientific Ethical Committee.  
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51 **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

**Authors:** Sigrun Alba Johannesdottir Schmidt,<sup>1</sup> Martin Berg Johansen,<sup>1</sup> Morten Olsen,<sup>1</sup> Xiao Xu,<sup>2</sup> Joseph M. Parker,<sup>3</sup> Nestor A. Molfino,<sup>4</sup> Timothy L. Lash,<sup>1,5</sup> Henrik Toft Sørensen,<sup>1</sup> Christian Fynbo Christiansen<sup>1</sup>

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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: I12, 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*	<b>ATC code and time-frame</b>
Short-acting bronchodilators (beta <sub>2</sub> -agonists <b>and/or</b> short-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC02-10, R03AC15-17, R03BB01, R03BB02, <b>and/or</b> R03AK03-04
Long-acting bronchodilators (beta <sub>2</sub> -agonists <b>or</b> long-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC (excluding R03AC02-10 and R03AC15-17) <b>or</b> R03BB04-06
Double therapy with any possible combination of long-acting beta <sub>2</sub> -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 <b>or</b> Redeemed within 12 months before study start: R03AK06-07 <b>or</b> Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BB04-06 <b>or</b>

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8 Triple therapy with long-acting beta<sub>2</sub>-agonists,  
9 inhaled corticosteroids, and long-acting  
10 muscarinic antagonists  
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Redeemed within 12 months before study start and  
within 30 days of each other: R03AK06-07 and  
R03BB04-06

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

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18 Non-treated/unclassified

Remaining patients

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

20 \*Groups are mutually exclusive.  
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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+
<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	<b>No</b>	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
<b>Baseline treatment</b>	<b>Non-treated/unclassified</b>	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	<b>Short-acting bronchodilators</b>	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	<b>Long-acting bronchodilator</b>	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	<b>Double therapy</b>	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	<b>Triple therapy</b>	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

view only

**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+
<b>0 to 30 days</b>	<b>Overall</b>		1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)
	<b>Age</b>	<b>40–49</b>	–	–	–
		<b>50–59</b>	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)
		<b>60–69</b>	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)
		<b>70–79</b>	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)
		<b>80–89</b>	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)
		<b>90+</b>	–	–	–
	<b>Sex</b>	<b>Female</b>	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)
		<b>Male</b>	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)
	<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
		<b>No</b>	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
	<b>Baseline treatment</b>	<b>Non-treated/unclassified</b>	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)
		<b>Short-acting bronchodilators</b>	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)
		<b>Long-acting bronchodilator</b>	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)
<b>Double therapy</b>		1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)	
	<b>Triple therapy</b>	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)	
<b>31 to 365 days</b>	<b>Overall</b>		1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)
	<b>Age</b>	<b>40–49</b>	–	–	–
		<b>50–59</b>	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)
		<b>60–69</b>	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)
		<b>70–79</b>	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)
		<b>80–89</b>	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)
		<b>90+</b>	–	–	–
	<b>Sex</b>	<b>Female</b>	1.62 (1.29, 2.03)	1.96 (1.37, 2.82)	2.28 (1.29, 4.04)
		<b>Male</b>	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)
	<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	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+
<b>Baseline treatment</b>	<b>No</b>	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
	<b>Non-treated/unclassified</b>	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-2.95)
	<b>Short-acting bronchodilators</b>	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	<b>Long-acting bronchodilator</b>	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	<b>Double therapy</b>	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	<b>Triple therapy</b>	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
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <b>[Included in title and abstract]</b> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <b>[Abstract, page 2]</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <b>[Introduction, page 4]</b>
Objectives	3	State specific objectives, including any prespecified hypotheses <b>[Introduction, page 4]</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper <b>[Introduction and Methods, pages 5-7]</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <b>[Methods, pages 5-7]</b>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>[Methods, pages 5-7]</b> (b) For matched studies, give matching criteria and number of exposed and unexposed <b>[N/A]</b>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <b>[Methods, pages 5-8]</b>
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 <b>[Setting and data sources, page 5]</b>
Bias	9	Describe any efforts to address potential sources of bias <b>[Study population about cohort and exposure definition, page 6]</b>
Study size	10	Explain how the study size was arrived at <b>[Study population, page 6]</b>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <b>[Statistical analysis, page 8: age]</b>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <b>[Statistical analysis, pages 8-9]</b> (b) Describe any methods used to examine subgroups and interactions <b>[Statistical analysis, pages 8-9]</b> (c) Explain how missing data were addressed <b>[N/A]</b> (d) If applicable, explain how loss to follow-up was addressed <b>[Study population, page 7, first paragraph about follow-up]</b> (e) Describe any sensitivity analyses <b>[N/A]</b>
<b>Results</b>		
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 <b>[Descriptive data, page 9 about eligible patients and study population]</b> (b) Give reasons for non-participation at each stage <b>[N/A]</b> (c) Consider use of a flow diagram <b>[Not used]</b>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <b>[Results, page 10 for eligible</b>

		<b>patients, the time-varying analysis precludes a table on characteristics by exposure status]</b>
		(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) <b>[Person-years by subgroups Tables 2 and 3]</b>
Outcome data	15*	Report numbers of outcome events or summary measures over time <b>[Results and Tables, pages 11-16]</b>
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 <b>[Tables 2-5]</b> (b) Report category boundaries when continuous variables were categorized <b>[Quartiles presented in Table 1]</b> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period <b>[Tables 2-3 include mortality rates and ratios]</b>
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses <b>[Statistical analysis and results, pages 8-16]</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <b>[First paragraph of Discussion, page 17]</b>
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 <b>[Discussion, pages 17-19]</b>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence <b>[Comparison with other studies, page 19]</b>
Generalisability	21	Discuss the generalisability (external validity) of the study results <b>[Final paragraph of Strengths and limitations, page 18]</b>
<b>Other information</b>		
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 <b>[Funding and Competing Interest, page 20]</b>

\*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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Secondary Subject Heading:	Epidemiology, Respiratory medicine
Keywords:	Cohort study, Registry study, Severe exacerbations, Time-varying exposure

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3 **Title:** The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of  
4 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.<sup>1,2</sup>

In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.<sup>3</sup> 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,<sup>3</sup> making it one of the leading causes of death among the elderly.<sup>4</sup>

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”.<sup>5</sup> The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01.<sup>6,7</sup> Exacerbation frequency<sup>6</sup> and mortality<sup>8</sup> 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.<sup>1,2,8,9</sup> 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.<sup>10-19</sup> 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.<sup>11</sup> Unfortunately, authors provided only an insignificant interaction term for the analysis,<sup>11</sup> 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

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3 practice, and by using Danish registries with detailed data on comorbidity, COPD treatment,  
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5 and with complete follow-up.  
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## 8 9 10 **METHODS**

### 11 12 **Setting and data sources**

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14 We conducted this cohort study in northern Denmark, whose population numbers  
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16 approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported  
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18 healthcare plan guarantees universal medical care for all residents and partial reimbursement  
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20 for prescribed medications.<sup>20</sup> Virtually all health services are recorded in various medical  
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22 registries, of which the following formed the basis for this study. The Danish National  
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24 Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-  
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26 psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room  
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28 visits since 1995.<sup>21</sup> Each admission is described by one primary diagnosis and one or more  
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30 secondary diagnoses classified according to the 8<sup>th</sup> revision of the *International*  
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32 *Classification of Diseases* (ICD-8) through 1993 and the ICD-10 revision thereafter.<sup>21</sup>  
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37 Aarhus University Prescription Database records patient's personal identifier, the  
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39 dispensing date, and the type and quantity of drug prescribed (according to the Anatomical  
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41 Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at  
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43 the pharmacy.<sup>22</sup>  
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46 Since 1968, the Danish Civil Registration System has recorded all Danish residents'  
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48 administrative information and changes in vital status, such as date of death and emigration,  
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50 with daily updates.<sup>20</sup> The registry assigns a unique personal identifier to all persons born in or  
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52 immigrating to Denmark, which enables follow-up of patients and linkage of the various  
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54 medical registries.<sup>20</sup>  
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57 All codes used for defining study variables in the current study can be found in the  
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3 Supplementary File (eTable 1).  
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### 7 **Study population**

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10 The population eligible for the study included all prevalent COPD patients on January 1,  
11 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and  
12 December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to  
13 COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related  
14 diagnosis, as described previously<sup>23</sup> and defined in the Supplementary File. Patients younger  
15 than 40 years were excluded, given the low COPD prevalence in this patient group<sup>24</sup> and the  
16 potential for misclassifying asthma as COPD.  
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25 Among all eligible COPD patients, we then identified the study cohort as COPD  
26 patients who developed at least one AECOPD between January 1, 2005 and December 31,  
27 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute  
28 exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic  
29 prescription on the same day (to account for patients treated outside hospital), or (b) a  
30 primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge  
31 diagnosis of respiratory failure or acute respiratory infection with a secondary discharge  
32 diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or  
33 AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of  
34 AECOPD cases were treated exclusively in the emergency department). Standard practice at  
35 Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also,  
36 COPD patients transferred to a specialized ward from the emergency room are coded as  
37 inpatient admissions and are therefore included in the study.  
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54 Using the Civil Registration System, we followed patients from the date of first  
55 exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until  
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3 death, emigration, or December 31, 2009, whichever came first. To examine the effect of  
4 AECOPD frequency on mortality, we classified each AECOPD during follow-up according  
5 to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months. We then  
6 entered this value as a time-varying exposure in the analysis. Therefore, each time a patient  
7 had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months  
8 before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+  
9 AECOPDs). One patient could thus have multiple AECOPDs during follow-up and  
10 contribute person-time in several exposure groups depending on the rate of AECOPD. We  
11 adjudicated AECOPD events using a 30-day threshold following the prescription redemption  
12 or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not  
13 regarded as a new AECOPD.  
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### 30 **Covariates**

31 We used the DNRP to retrieve the hospital history for all study participants during the 5 years  
32 preceding the start of the study on January 1, 2005. We then ascertained the presence of the  
33 following diseases that are frequent among COPD patients and may affect mortality:  
34 myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular  
35 disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any  
36 malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter,  
37 medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive  
38 sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.  
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50 From the Prescription Database, we retrieved information on COPD treatment within  
51 12 months before study start. Following the latest Global Initiative for Chronic Obstructive  
52 Lung Disease (GOLD) guidelines,<sup>5</sup> we then grouped patients into the following five mutually  
53 exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting  
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3 bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta<sub>2</sub>-agonists or long-  
4 acting muscarinic antagonists), (4) double therapy with any possible combination of long-  
5 acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5)  
6  
7 triple therapy with long-acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or long-acting  
8 muscarinic antagonists, as defined in the Supplementary File (eTable 1). We also retrieved  
9 information on pharmacological treatment with systemic corticosteroids or theophylline  
10 within 12 months before study start, with antibiotics and/or antivirals within three months  
11 before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment  
12 within the 12 months before study start and on lung volume reduction surgery between 1996  
13 and study start.  
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### 25 26 27 **Statistical analysis**

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29 We characterized the eligible population of COPD patients on January 1, 2005 by age, sex,  
30 comorbidities recorded in the 5 years before study start, as well as COPD treatment group,  
31 pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the  
32 prior 12 months, and treatment with antibiotics and/or antivirals within the prior three  
33 months.  
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40 In the mortality analyses, we entered AECOPD frequency as a time-varying exposure  
41 and computed the number of deaths, person-time, and mortality rates in each exposure group.  
42 We then used Cox regression analysis to compute crude hazard ratios as a measure of  
43 mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD  
44 patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with  
45 patients with no exacerbations in the preceding 12-month period. We then computed the  
46 MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis,  
47 we examined the effect of frequent severe exacerbations on mortality by including only  
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3 severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed  
4 above). Both the present AECOPD and any exacerbations in the 12 months before had to be  
5 defined as severe. Finally, we stratified the results from the primary analysis and the results  
6 for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen  
7 therapy, lung volume reduction surgery, COPD treatment group, and cardiovascular disease  
8 (myocardial infarction, congestive heart failure, peripheral vascular disease, and  
9 cerebrovascular disease).

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

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

## 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **RESULTS**

### 42 43 44 **Descriptive data**

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46 We identified 16,647 COPD patients eligible for the study on January 1, 2005. Median age  
47 among eligible patients was 70 year and 53% were female. Comorbidities were frequent,  
48 especially cardiovascular disease, diabetes, osteoporosis, and asthma. The high proportion of  
49 patients had redeemed prescriptions for antibiotics within previous 3 months (31%) and for  
50 systemic steroids within previous 12 months (30%). The majority of patients received double  
51 therapy. Among the 16,647 eligible COPD patients, 6,664 (40%) had at least one AECOPD  
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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	%
<b>Total</b>	16,647	100
<b>Age at study start (years)</b>		
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
<b>Sex</b>		
Female	8,770	53
Male	7,877	47
<b>Comorbidities (within previous 5 years)</b>		
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
<b>Treatments within previous 12 months</b>		
Systemic steroids	4,993	30
Theophylline	1,164	7.0
Oxygen therapy	258	1.5
<b>COPD treatment</b>		
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
<b>Infection within previous 3 months</b>		
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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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

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

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

38 The universal healthcare system and complete follow-up of all residents by the Danish Civil  
39 Registration System reduces the possibility of selection bias in our study. We aimed to reduce  
40 information bias by using broad definitions of COPD and AECOPD rather than more  
41 restrictive primary discharge diagnoses. A review of medical records has showed a PPV of  
42 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also  
43 primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.<sup>25</sup>  
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45 However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on  
46 the same day to define AECOPDs outside hospital setting, we may have misclassified some  
47 patients who did not have AECOPD as AECOPD patients if the prescriptions were written as  
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3 rescue packs for potential future events. Such misclassification would not affect the analysis  
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5 restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may  
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7 have resulted in misclassification of exposure status due to underreporting or  
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9 misclassification of the number of AECOPDs. Previous data, however, show that the  
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11 majority of patients recover within 30 days after AECOPD onset.<sup>26</sup>  
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14 Because we relied solely on registry data, we lacked information on lifestyle factors and  
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16 clinical variables such as measurements of peak expiratory flow and arterial blood gases.  
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18 However, some of the clinical factors may be on the causal pathway linking AECOPD  
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20 frequency to high mortality,<sup>1,2,8,9</sup> making adjustment inappropriate.<sup>27</sup> Nevertheless, such  
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22 information would have been useful in classifying AECOPD. Instead, we examined if the  
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24 association depended on COPD therapy, which may be linked to underlying severity, and  
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26 found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified,  
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28 which may represent patients with poor adherence or possibly patients with mild COPD.  
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32 Finally, the generalizability of our results to the entire range of AECOPD cases may be  
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34 affected by the fact that some COPD patients may be diagnosed in general practice,  
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36 excluding them from registration in the DNRP.  
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#### 41 **Comparison with other studies**

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

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21  
22 Surprisingly, we found no relative effect of prior AECOPD on mortality within 0–30 days  
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24 following AECOPD. Also, the excess 31–365-day mortality associated with one AECOPD in  
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26 the previous year was less pronounced than in the study by Suissa *et al.*<sup>17</sup> and it did not  
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28 increase further with increasing number of AECOPDs. There may be several potential  
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30 explanations for this discrepancy. First, our study population included prevalent COPD  
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32 patients at study start, which may have resulted in a mix of patients at different stages in their  
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34 clinical course of COPD. Hence, by mixing patients that were experiencing their first  
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36 AECOPD ever with patients that had previously experienced one or more AECOPDs, we  
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38 may have obscured some of the effect of AECOPD frequency on mortality. Second,  
39  
40 unmeasured severity of the AECOPD may have affected our results. We have previously  
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42 shown that patients with no AECOPD in the year before an AECOPD are younger and have  
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44 less comorbidity.<sup>23</sup> Even though these patients may have had more newly diagnosed, and thus  
45  
46 less severe, COPD, it is possible that some of these patients have more severe AECOPDs  
47  
48 because they postpone seeking medical attention due to unfamiliarity with the symptoms  
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50 hereof. On the other hand, an older patient with higher comorbidity and a recent history of  
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52 AECOPD may be more aware of the threatening situation and act more quickly, resulting in a  
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3 lower mortality than expected in the acute phase. The situation may then reverse after day 30  
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5 when the relative impact of frequent exacerbations on severity of COPD, complication rate,  
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7 and relapse rate becomes clearer, as well as death from other causes than COPD. Third, the  
8  
9 study population examined by Suissa *et al.*<sup>17</sup> included a higher proportion of men that was on  
10  
11 average older than our study population. Thus, excess cardiovascular mortality in their  
12  
13 population may partly explain the higher estimates observed in their study. Finally, because  
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15 the absolute 30-day mortality rate was very high, but decreased substantially thereafter, it is  
16  
17 possible that the relative effect of AECOPD history appeared less pronounced in the first  
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19 period merely because of differences in the baseline rate. Such differences may also explain  
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21 the more pronounced associations observed for the younger patients in our subanalysis.  
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## 27 CONCLUSIONS

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30 In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in  
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32 the 12 months before exacerbation may serve as an indicator of a higher mortality rate during  
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34 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect  
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36 on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort  
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38 of COPD patients or a higher baseline rate than in the 31-365-day period.  
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44  
45 designing the study. MBJ collected the data and carried out analyses. SAJS, MBJ, MO, XX,  
46  
47 JMP, NAM, TLL, HTS, and CFC participated in the discussion and interpretation of the  
48  
49 results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP,  
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51 NAM, TLL, HTS, and CFC critically revised the manuscript for intellectual content and  
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53 approved the final version. HTS is the guarantor.  
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6

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9  
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12 paper.  
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16 **Ethics approval:** As this study did not involve any contact with patients or any intervention,  
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18 it was not necessary to obtain permission from the Danish Scientific Ethical Committee.  
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23 **Data sharing statement:** No additional data are available.  
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7 **Title:** The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of  
8 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.<sup>1,2</sup>

In Denmark, the standardised incidence rate of hospitalisation for COPD was 231 per 100,000 person-years in 2006.<sup>3</sup> 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,<sup>3</sup> making it one of the leading causes of death among the elderly.<sup>4</sup>

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”.<sup>5</sup> The annual number of exacerbations in COPD patients is estimated at between 0.82 and 2.01, ~~increasing with disease severity<sup>6</sup> and history of frequent exacerbations.<sup>7</sup> Exacerbation frequency<sup>6</sup> and mortality~~ The mortality following AECOPD is high, especially in patients with severe COPD.<sup>8</sup> Thus, severity of disease is associated with both increased risk and mortality of AECOPD.<sup>8</sup> 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.<sup>1,2,8,9</sup> Indeed, 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.<sup>10-19</sup> Furthermore, none of the studies included AECOPDs treated outside the hospital. Finally, Although current therapies for COPD may decrease the

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7 ~~exacerbations frequency and mortality,~~<sup>2,8</sup> only one ~~of the study studies~~ examined if the  
8 association depended on preadmission therapy.<sup>11</sup> ~~However~~ ~~Unfortunately~~, authors ~~did not~~  
9 provided ~~only the results for the analysis except for~~ an insignificant interaction term ~~for the~~  
10 ~~analysis~~,<sup>11</sup> which limits the interpretation to statistical significance only. ~~Finally, none of the~~  
11 ~~studies included AECOPDs treated outside the hospital.~~

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

### 29 **Setting and data sources**

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31 We conducted this cohort study in northern Denmark, whose population numbers  
32 approximately 1.8 million (30% of the Danish population). In Denmark, a tax-supported  
33 healthcare plan guarantees universal medical care for all residents and partial reimbursement  
34 for prescribed medications.<sup>20</sup> Virtually all health services are recorded in various medical  
35 registries, of which the following formed the basis for this study. The Danish National  
36 Registry of Patients (DNRP) has maintained records on all inpatient admissions to non-  
37 psychiatric hospitals since 1977, and on all outpatient specialist clinic and emergency room  
38 visits since 1995.<sup>21</sup> Each admission is described by one primary diagnosis and one or more  
39 secondary diagnoses classified according to the 8<sup>th</sup> revision of the *International*  
40 *Classification of Diseases* (ICD-8) through 1993 and the ICD-10 revision thereafter.<sup>21</sup>  
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51 Aarhus University Prescription Database records patient's personal identifier, the  
52 dispensing date, and the type and quantity of drug prescribed (according to the Anatomical  
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7 Therapeutic Chemical (ATC) Classification System) each time a prescription is redeemed at  
8 the pharmacy.<sup>22</sup>  
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10 Since 1968, the Danish Civil Registration System has recorded all Danish residents'  
11 administrative information and changes in vital status, such as date of death and emigration,  
12 with daily updates.<sup>20</sup> The registry assigns a unique personal identifier to all persons born in or  
13 immigrating to Denmark, which enables follow-up of patients and linkage of the various  
14 medical registries.<sup>20</sup>  
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20 All codes used for defining study variables in the current study can be found in the  
21 Supplementary File (eTable 1).  
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## 26 **Study population**

27 The population eligible for the study included all prevalent COPD patients on January 1,  
28 2005, who had a COPD diagnosis recorded in the DNRP between January 1, 1995 and  
29 December 31, 2004. We considered all primary inpatient and outpatient diagnosis related to  
30 COPD as well as all primary diagnoses of respiratory failure with a secondary COPD-related  
31 diagnosis, as described previously<sup>23</sup> and defined in the Supplementary File. Patients younger  
32 than 40 years were excluded, given the low COPD prevalence in this patient group<sup>24</sup> and the  
33 potential for misclassifying asthma as COPD.  
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41 Among all eligible COPD patients, we then identified the study cohort as COPD  
42 patients who developed at least one AECOPD between January 1, 2005 and December 31,  
43 2009. We used the DNRP and the Aarhus University Prescription Database to identify acute  
44 exacerbations as (a) a redemption of a systemic glucocorticoid prescription and an antibiotic  
45 prescription on the same day (to account for patients treated outside hospital), or (b) a  
46 primary hospital discharge diagnosis of AECOPD, or (c) a primary hospital discharge  
47 diagnosis of respiratory failure or acute respiratory infection with a secondary discharge  
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7 diagnosis of AECOPD. We did not include emergency room diagnoses of COPD or  
8 AECOPD in this study, as COPD is rarely treated in this setting in Denmark (only 1% of  
9 AECOPD cases were treated exclusively in the emergency department). Standard practice at  
10 Danish hospitals is to admit AECOPD patients directly to the acute admission unit. Also,  
11 COPD patients transferred to a specialized ward from the emergency room are coded as  
12 inpatient admissions and are therefore included in the study.  
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18 Using the Civil Registration System, we followed patients from the date of first  
19 exacerbation recorded between January 1, 2005 and December 31, 2009 and continued until  
20 death, emigration, or December 31, 2009, whichever came first. To examine the effect of  
21 AECOPD frequency on mortality, we classified each AECOPD during follow-up according  
22 to whether it was preceded by 0, 1, 2, or 3+ AECOPDs in the prior 12 months. We then  
23 entered this value as a time-varying exposure in the analysis. Therefore, each time a patient  
24 had an AECOPD during follow-up, we assessed the number of AECOPDs in the 12 months  
25 before the event and assigned the patient to the corresponding exposure group (0, 1, 2, or 3+  
26 AECOPDs). One patient could thus have multiple AECOPDs during follow-up and  
27 contribute person-time in several exposure groups depending on the rate of AECOPD. We  
28 adjudicated AECOPD events using a 30-day threshold following the prescription redemption  
29 or hospitalisation, *i.e.*, an AECOPD event within 30 days of a previous AECOPD was not  
30 regarded as a new AECOPD.  
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#### 45 **Covariates**

46 We used the DNRP to retrieve the hospital history for all study participants during the 5 years  
47 preceding the start of the study on January 1, 2005. We then ascertained the presence of the  
48 following diseases that are frequent among COPD patients and may affect mortality:  
49 myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular  
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7 disease, peptic ulcer disease, liver disease, diabetes, moderate to severe renal disease, any  
8 malignancy except lung cancer, alcoholism-related diseases, atrial fibrillation/flutter,  
9 medically diagnosed obesity, hypertension, osteoporosis, lung cancer, asthma, obstructive  
10 sleep apnoea, venous thromboembolism, rheumatoid arthritis, and depression.  
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14 From the Prescription Database, we retrieved information on COPD treatment within  
15 12 months before study start. Following the latest Global Initiative for Chronic Obstructive  
16 Lung Disease (GOLD) guidelines,<sup>5</sup> we then grouped patients into the following five mutually  
17 exclusive groups of escalating treatment: (1) non-treated/unclassified, (2) short-acting  
18 bronchodilators, (3) monotherapy with a long-acting bronchodilator (beta<sub>2</sub>-agonists or long-  
19 acting muscarinic antagonists), (4) double therapy with any possible combination of long-  
20 acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists, (5)  
21 triple therapy with long-acting beta<sub>2</sub>-agonists, inhaled corticosteroids, and/or long-acting  
22 muscarinic antagonists, as defined in the Supplementary File (eTable 1). We also retrieved  
23 information on pharmacological treatment with systemic corticosteroids or theophylline  
24 within 12 months before study start, with antibiotics and/or antivirals within three months  
25 before study start. Finally, we used the DNRP to identify hospital codes for oxygen treatment  
26 within the 12 months before study start and on lung volume reduction surgery between 1996  
27 and study start.  
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### 43 **Statistical analysis**

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45 We characterized the eligible population of COPD patients on January 1, 2005 by age, sex,  
46 comorbidities recorded in the 5 years before study start, as well as COPD treatment group,  
47 pharmacological treatment with systemic steroids, theophylline, or oxygen therapy within the  
48 prior 12 months, and treatment with antibiotics and/or antivirals within the prior three  
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7 In the mortality analyses, we entered AECOPD frequency as a time-varying exposure  
8 and computed the number of deaths, person-time, and mortality rates in each exposure group.  
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10 We then used Cox regression analysis to compute crude hazard ratios as a measure of  
11 mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) for AECOPD  
12 patients with 1, 2, or 3+ AECOPDs in the 12 months preceding an AECOPD, compared with  
13 patients with no exacerbations in the preceding 12-month period. We then computed the  
14 MRRs adjusted for sex, age (as a continuous variable), and comorbidities. In a subanalysis,  
15 we examined the effect of frequent severe exacerbations on mortality by including only  
16 severe AECOPDs, which were defined as inpatient admissions for AECOPD ([b] or [c] listed  
17 above). Both the present AECOPD and any exacerbations in the 12 months before had to be  
18 defined as severe. Finally, we stratified the results from the primary analysis and the results  
19 for severe AECOPD only by age group at study start, sex, and presence/absence of oxygen  
20 therapy, lung volume reduction surgery, COPD treatment group, and cardiovascular disease  
21 (myocardial infarction, congestive heart failure, peripheral vascular disease, and  
22 cerebrovascular disease).  
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35 Because AECOPD is an acute event, we expect the mortality rate to be greatest in the  
36 initial phase following and as the results of the event. We therefore separated the effect of  
37 AECOPD on mortality in the first 30 days versus day 31 to day 365 after the event in all  
38 mortality rate calculations. We assessed the assumption of proportional hazards graphically  
39 using scaled Schoenfeld residuals and found it valid.  
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45 All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The study  
46 was approved by the Danish Data Protection Agency (journal number 2013-41-1924). Danish  
47 legislation does not require ethical review board approval or informed consent from subjects  
48 in registry-based studies.  
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## 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	%
<b>Total</b>	16,647	100
<b>Age at study start (years)</b>		
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
<b>Sex</b>		
Female	8,770	53
Male	7,877	47
<b>Comorbidities (within previous 5 years)</b>		
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

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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
<b>Treatments within previous 12 months</b>		
Systemic steroids	4,993	30
Theophylline	1,164	7.0
Oxygen therapy	258	1.5
<b>COPD treatment</b>		
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
<b>Infection within previous 3 months</b>		
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
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in the 12 months prior to an AECOPD	deaths	years	and 95% CI (per 1,000 person-years)	95% CI*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				
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*
<b>0 to 30 days</b>				
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)
<b>31 and up to 365 days</b>				

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

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7 The universal healthcare system and complete follow-up of all residents by the Danish Civil  
8 Registration System reduces the possibility of selection bias in our study. We aimed to reduce  
9 information bias by using broad definitions of COPD and AECOPD rather than more  
10 restrictive primary discharge diagnoses. A review of medical records has showed a PPV of  
11 93% for primary COPD diagnoses in the DNRP and a PPV of 92% when including also  
12 primary diagnoses of respiratory failure or pneumonia with secondary COPD diagnosis.<sup>25</sup>  
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14 However, by using prescriptions for a systemic glucocorticoid and an antibiotic redeemed on  
15 the same day to define AECOPDs outside hospital setting, we may have misclassified some  
16 patients who did not have AECOPD as AECOPD patients if the prescriptions were written as  
17 rescue packs for potential future events. Such misclassification would not affect the analysis  
18 restricted to severe AECOPDs only. Also, our choice of an arbitrary duration of 30 days may  
19 have resulted in misclassification of exposure status due to underreporting or  
20 misclassification of the number of AECOPDs. Previous data, however, show that the  
21 majority of patients recover within 30 days after AECOPD onset.<sup>26</sup>  
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24 Because we relied solely on registry data, we lacked information on lifestyle factors and  
25 clinical variables such as measurements of peak expiratory flow and arterial blood gases.  
26 However, some of the clinical factors may be on the causal pathway linking AECOPD  
27 frequency to high mortality,<sup>1,2,8,9</sup> making adjustment inappropriate.<sup>27</sup> Nevertheless, such  
28 information would have been useful in classifying AECOPD. Instead, we examined if the  
29 association depended on COPD therapy, which may be linked to underlying severity, and  
30 found no evidence hereof. A total of 29% in the eligible cohort were non-treated/unclassified,  
31 which may represent patients with poor adherence or possibly patients with mild COPD.  
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34 Finally, the generalizability of our results to the entire range of AECOPD cases may be  
35 affected by the fact that some COPD patients may be diagnosed in general practice,  
36 excluding them from registration in the DNRP.  
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### Comparison with other studies

In a Canadian inception cohort of 73,106 COPD patients, Suissa *et al.*<sup>17</sup> 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.<sup>10-16,18,19</sup> ~~However, that definitions of exposure have varied greatly, including~~ a history of hospitalisation for AECOPD within 6 months,<sup>16</sup> 1 year,<sup>10,11,14,18,19</sup> and up to 7 years<sup>12</sup> before current AECOPD hospitalisation, within 2 years before inclusion period,<sup>15</sup> or admission with respiratory failure within 2 years before current admission.<sup>13</sup> ~~Similarly, various definitions of AECOPD mortality were applied, including increase mortality s AECOPD mortality~~ in-hospital,<sup>12,13,16</sup> at 30 days<sup>13</sup> and at longer term (median 3.1 years)<sup>14</sup> following admission, and at 3 months,<sup>10</sup> 6 months,<sup>11</sup> 1 year,<sup>11</sup> 2 years,<sup>11,19</sup> and at longer-term mortality (3 or more years)<sup>15,18</sup> 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,<sup>11,15,18</sup> emergency room patients only,<sup>14,16</sup> and discharged patients only<sup>10,15,18,19</sup>).

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.*<sup>17</sup> 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

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

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47 In this cohort of patients with AECOPD, we found that a history of at least one AECOPD in  
48 the 12 months before exacerbation may serve as an indicator of a higher mortality rate during  
49 31 to 365 days but not during the first 30 days following the AECOPD. The lack of an effect  
50 on 0-30-day mortality may be explained by study factors such as the use of prevalent cohort  
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7 of COPD patients or a higher baseline rate than in the 31-365-day period.  
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10 **Contributors:** SAJS, MBJ, MO, XX, JMP, NAM, TLL, HTS, and CFC participated in  
11 designing the study. MBJ collected the data and carried out analyses. SAJS, MBJ, MO, XX,  
12 JMP, NAM, TLL, HTS, and CFC participated in the discussion and interpretation of the  
13 results. SAJS organised the writing and wrote the initial draft. SAJS, MBJ, MO, XX, JMP,  
14 NAM, TLL, HTS, and CFC critically revised the manuscript for intellectual content and  
15 approved the final version. HTS is the guarantor.  
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29 NAM was an employee of MedImmune, LLC at the time of the study. None of the other  
30 authors have received fees, honoraria, grants or consultancy fees related to the topic of this  
31 paper.  
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35 **Ethics approval:** As this study did not involve any contact with patients or any intervention,  
36 it was not necessary to obtain permission from the Danish Scientific Ethical Committee.  
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41 **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: I12, 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*	<b>ATC code and time-frame</b>
Short-acting bronchodilators (beta <sub>2</sub> -agonists <b>and/or</b> short-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC02-10, R03AC15-17, R03BB01, R03BB02, <b>and/or</b> R03AK03-04
Long-acting bronchodilators (beta <sub>2</sub> -agonists <b>or</b> long-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC (excluding R03AC02-10 and R03AC15-17) <b>or</b> R03BB04-06
Double therapy with any possible combination of long-acting beta <sub>2</sub> -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 <b>or</b> Redeemed within 12 months before study start: R03AK06-07 <b>or</b> Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BB04-06 <b>or</b>



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8 Triple therapy with long-acting beta<sub>2</sub>-agonists,  
9 inhaled corticosteroids, and long-acting  
10 muscarinic antagonists  
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Redeemed within 12 months before study start and  
within 30 days of each other: R03AK06-07 and  
R03BB04-06

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

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18 Non-treated/unclassified

Remaining patients

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

20 \*Groups are mutually exclusive.  
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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+	
<b>0 to 30 days</b>	<b>Overall</b>		0.97 (0.80, 1.18)	0.90 (0.70, 1.15)	1.03 (0.81, 1.32)	
	<b>Age</b>	<b>40–49</b>	–	–	–	
		<b>50–59</b>	1.74 (0.85, 3.59)	0.60 (0.17, 2.13)	2.89 (1.31, 6.36)	
		<b>60–69</b>	1.00 (0.67, 1.50)	0.68 (0.39, 1.18)	1.10 (0.69, 1.77)	
		<b>70–79</b>	0.98 (0.73, 1.30)	1.05 (0.73, 1.50)	1.10 (0.75, 1.60)	
		<b>80–89</b>	0.70 (0.45, 1.08)	0.96 (0.56, 1.66)	0.61 (0.28, 1.34)	
		<b>90+</b>	–	–	–	
		<b>Sex</b>	<b>Female</b>	0.88 (0.67, 1.15)	0.90 (0.64, 1.26)	0.96 (0.67, 1.37)
			<b>Male</b>	1.06 (0.80, 1.39)	0.91 (0.63, 1.31)	1.14 (0.80, 1.62)
		<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	0.79 (0.27, 2.28)	0.24 (0.02, 2.45)	3.14 (0.27, 36.9)
			<b>No</b>	1.00 (0.82, 1.21)	0.96 (0.74, 1.23)	1.04 (0.81, 1.34)
		<b>Baseline treatment</b>	<b>Non-treated/unclassified</b>	1.60 (0.63, 4.04)	1.07 (0.11, 10.0)	2.62 (0.40, 17.3)
			<b>Short-acting bronchodilators</b>	1.12 (0.73, 1.73)	0.70 (0.36, 1.37)	1.38 (0.78, 2.44)
			<b>Long-acting bronchodilator</b>	0.69 (0.41, 1.17)	1.23 (0.67, 2.25)	0.93 (0.44, 2.00)
		<b>Double therapy</b>	1.01 (0.71, 1.45)	0.87 (0.54, 1.42)	1.24 (0.81, 1.91)	
		<b>Triple therapy</b>	1.05 (0.73, 1.50)	1.10 (0.71, 1.68)	0.90 (0.56, 1.43)	
<b>31 to 365 days</b>	<b>Overall</b>		1.47 (1.30, 1.66)	1.89 (1.59, 2.25)	1.59 (1.23, 2.05)	
	<b>Age</b>	<b>40–49</b>	0.69 (0.15, 3.27)	0.79 (0.08, 7.86)	1.68 (0.19, 14.6)	
		<b>50–59</b>	2.13 (1.34, 3.41)	2.14 (1.07, 4.26)	3.43 (1.64, 7.15)	
		<b>60–69</b>	1.28 (0.98, 1.67)	1.92 (1.37, 2.69)	1.16 (0.67, 2.01)	
		<b>70–79</b>	1.62 (1.36, 1.94)	2.07 (1.61, 2.67)	1.56 (1.06, 2.29)	
		<b>80–89</b>	1.35 (1.03, 1.77)	1.66 (1.05, 2.60)	2.12 (1.15, 3.93)	
		<b>90+</b>	0.78 (0.19, 3.09)	8.42 (0.48, 147)	–	
		<b>Sex</b>	<b>Female</b>	1.48 (1.24, 1.75)	2.02 (1.59, 2.55)	1.65 (1.15, 2.38)
			<b>Male</b>	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+
<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	<b>No</b>	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
<b>Baseline treatment</b>	<b>Non-treated/unclassified</b>	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	<b>Short-acting bronchodilators</b>	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	<b>Long-acting bronchodilator</b>	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	<b>Double therapy</b>	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	<b>Triple therapy</b>	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

view only

**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+
<b>0 to 30 days</b>	<b>Overall</b>		1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)
	<b>Age</b>	<b>40–49</b>	–	–	–
		<b>50–59</b>	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)
		<b>60–69</b>	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)
		<b>70–79</b>	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)
		<b>80–89</b>	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)
		<b>90+</b>	–	–	–
	<b>Sex</b>	<b>Female</b>	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)
		<b>Male</b>	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)
	<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
		<b>No</b>	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
	<b>Baseline treatment</b>	<b>Non-treated/unclassified</b>	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)
		<b>Short-acting bronchodilators</b>	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)
		<b>Long-acting bronchodilator</b>	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)
<b>Double therapy</b>		1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)	
	<b>Triple therapy</b>	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)	
<b>31 to 365 days</b>	<b>Overall</b>		1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)
	<b>Age</b>	<b>40–49</b>	–	–	–
		<b>50–59</b>	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)
		<b>60–69</b>	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)
		<b>70–79</b>	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)
		<b>80–89</b>	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)
		<b>90+</b>	–	–	–
	<b>Sex</b>	<b>Female</b>	1.62 (1.29, 2.03)	1.96 (1.37, 2.82)	2.28 (1.29, 4.04)
		<b>Male</b>	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)
	<b>Oxygen therapy within 12 months before study start</b>	<b>Yes</b>	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+
<b>Baseline treatment</b>	<b>No</b>	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
	<b>Non-treated/unclassified</b>	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-2.95)
	<b>Short-acting bronchodilators</b>	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	<b>Long-acting bronchodilator</b>	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	<b>Double therapy</b>	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	<b>Triple therapy</b>	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
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <b>[Included in title and abstract]</b> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <b>[Abstract, page 2]</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <b>[Introduction, page 4]</b>
Objectives	3	State specific objectives, including any prespecified hypotheses <b>[Introduction, page 4]</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper <b>[Introduction and Methods, pages 5-7]</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <b>[Methods, pages 5-7]</b>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>[Methods, pages 5-7]</b> (b) For matched studies, give matching criteria and number of exposed and unexposed <b>[N/A]</b>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <b>[Methods, pages 5-8]</b>
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 <b>[Setting and data sources, page 5]</b>
Bias	9	Describe any efforts to address potential sources of bias <b>[Study population about cohort and exposure definition, page 6]</b>
Study size	10	Explain how the study size was arrived at <b>[Study population, page 6]</b>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <b>[Statistical analysis, page 8: age]</b>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <b>[Statistical analysis, pages 8-9]</b> (b) Describe any methods used to examine subgroups and interactions <b>[Statistical analysis, pages 8-9]</b> (c) Explain how missing data were addressed <b>[N/A]</b> (d) If applicable, explain how loss to follow-up was addressed <b>[Study population, page 7, first paragraph about follow-up]</b> (e) Describe any sensitivity analyses <b>[N/A]</b>
<b>Results</b>		
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 <b>[Descriptive data, page 9 about eligible patients and study population]</b> (b) Give reasons for non-participation at each stage <b>[N/A]</b> (c) Consider use of a flow diagram <b>[Not used]</b>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <b>[Results, page 10 for eligible</b>

		<b>patients, the time-varying analysis precludes a table on characteristics by exposure status]</b>
		(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) <b>[Person-years by subgroups Tables 2 and 3]</b>
Outcome data	15*	Report numbers of outcome events or summary measures over time <b>[Results and Tables, pages 11-16]</b>
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 <b>[Tables 2-5]</b> (b) Report category boundaries when continuous variables were categorized <b>[Quartiles presented in Table 1]</b> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period <b>[Tables 2-3 include mortality rates and ratios]</b>
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses <b>[Statistical analysis and results, pages 8-16]</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <b>[First paragraph of Discussion, page 17]</b>
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 <b>[Discussion, pages 17-19]</b>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence <b>[Comparison with other studies, page 19]</b>
Generalisability	21	Discuss the generalisability (external validity) of the study results <b>[Final paragraph of Strengths and limitations, page 18]</b>
<b>Other information</b>		
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 <b>[Funding and Competing Interest, page 20]</b>

\*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>.