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Early View

Original research article

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All-cause admissions following a first-ever exacerbation-related hospitalization in COPD

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Take home message

Non-respiratory events are the predominant cause of hospital admission in patients with COPD following their first-ever exacerbation-related hospitalization. These findings challenge the current global post-exacerbation management goals.

Abstract

Background: Hospital admissions are important contributors to the overall burden of chronic obstructive pulmonary disease (COPD). Understanding the patterns and causes of hospital admissions will help to identify targets for preventive interventions. This study aimed to determine the five-year all-cause hospital admission trajectories of patients with COPD following their first-ever exacerbation-related hospitalization.

Methods: Patients with COPD were identified from the Danish national registries. Patients experiencing their first-ever exacerbation-related hospitalization, defined as the index event, between 2000 and 2014 were included. All-cause hospital admissions were examined during a subsequent five-year follow-up period, and categorized using the International Classification of Diseases, 10th revision (ICD-10).

Results: In total, 82964 patients with COPD were included. The average age was 72 (SD 10) years and 48% was male. Comorbidities were present in 58%, and 65% of the patients collected inhalation medication ≤6 months prior to the index event. In total, 337066 all-cause hospital admissions were identified, resulting in a five-year admission rate of 82%. Most admissions were due to non-respiratory causes (59%), amongst which cardiac events were most common (19%).

Conclusion: Hospital admissions following a first exacerbation-related hospitalization are common, non-respiratory events constitute the majority of admissions. Besides the respiratory causes, treatment targeting the non-respiratory causes of hospital admission should be considered to effectively decrease the burden of hospitalization in COPD.

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Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) play a central role in the clinical course and disease-burden of the condition. Each event induces a decline in lung function, physical activity, mental health and overall quality of life which enhance the risk of further and substantially earlier AECOPD, as well as death (1, 2). Moreover, the degree of the disease severity contributes to the risk of AECOPD hospital admission. Indeed, the hospitalization rate increases from 11% to 54% in patients with incrementing airflow limitation from moderate to very severe COPD, respectively (3). The prognosis of hospitalized AECOPD is poor. In-hospital mortality rates of up to 10% (4), and two-year post-discharge mortality rates of 36% have been reported (5). Furthermore, patients hospitalized due to AECOPD are significantly predisposed to hospital readmission. Approximately one-third of patients is readmitted within 90 days (6). As such, exacerbation-related hospitalizations contribute to the majority of COPD-related healthcare costs (7).

Patients with COPD often suffer from multiple comorbidities (8). A recent systematic review and meta-analysis concluded that comorbidities were the most-commonly reported significant risk factor associated with 30- and 90-day all-cause hospital readmission following exacerbation-related hospitalization (9). Other major risk factors include prior exacerbations and hospitalizations, as well as prolonged length of hospital stay (9). Whilst comorbidities may play a role in the susceptibility to readmission following exacerbation-related hospitalization, AECOPD itself may also affect comorbidities. Exacerbation-related systemic manifestations, such as systemic inflammation, physical inactivity as well as pharmacological therapy with high-dose β_2 agonists may result in the onset and/or aggravation of metabolic and cardiovascular comorbidities, both during and after AECOPD (1, 10-12). Hence, whilst hospital readmissions for AECOPD are common, the causes of hospital admission following exacerbation-related hospitalization may well extend beyond the lungs (13).

To the best of our knowledge, the trajectories from first-ever exacerbation-related hospitalization to subsequent all-cause hospital admissions have not been studied to date. Therefore, the primary aim of this study is to explore the all-cause hospital admissions of patients with COPD in the first five years after their first exacerbation-related hospitalization. Secondary aims are to study the differences between the short- and long-term, and frequently and less-frequently admitted patients.

Methods

Study design and ethical approval

This Danish nationwide observational population-based study used a retrospective follow-up design. Retrospective registry research does not require ethical approval by Danish law. Access to the data was granted by the Capital Region of Denmark (approval number P-2019-

191). This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study setting

All 5.33 million (anno 2000) Danish citizens have a unique civil personal registration number (CPR) which is used as an identifier in the Danish registries. All citizens have access to free health care which is financed through the Danish taxpaying system. Medical doctors do not have financial incentives to admit patients within this system. The CPR number was used to identify individuals across multiple different Danish registries (14).

Data sources

Information on hospital admissions and preexisting comorbidities was gathered from the Danish National Patient Registry (DNPR) using the ICD-10 discharge diagnosis (14). The Danish National Prescription Registry was used to gather information on medication use collected in the 6 months prior to the index admission. The Danish Cause of Death Registry was used to gather the date of death. Finally, information on age, sex and educational level was gathered from The Statistics of Denmark Registry.

Study population

Patients with COPD admitted to any Danish hospital for their first-ever (i.e. lifetime) exacerbation-related hospitalization, also referred to as the index event, between January 1, 2000, and January 29, 2014, were included in the current study. Therefore, all first-time acute hospital episodes with a primary discharge diagnosis of COPD (J44), or a primary discharge diagnosis of acute respiratory failure (J96) or pneumonia (J13-J18) in combination with a secondary diagnosis of COPD were retrieved. These diagnostic criteria were previously validated with a predictive value ≥90% (15). Only admissions to a department with 24-hour surveillance (hereby excluding emergency room contacts not leading to admission) were recorded to enhance the comparability of the current cohort. As such, emergency room visits have been without prior visitation in Denmark for a greater part of the inclusion period. Therefore, visits without subsequent admission would include a number of moderate AECOPD. Furthermore, patients aged below 40 or above 90 years, and patients with chronic asthmatic bronchitis (J44.8B) or a (previous) diagnosis of asthma (J45) were excluded.

Outcomes and definitions

The primary outcome was all-cause hospital admission during a subsequent five-year follow-up period after the first exacerbation-related hospitalization. Mortality was explored during the same period. Admission causes were characterized according to their ICD-10 code: an overview is provided in online supplementary table 1. Specific diagnoses were characterized using the first subsequent digit. As such, respiratory related admissions were characterized

using the ICD-10 code J, whereas specific diagnoses such as acute infections of the upper respiratory tract would be denoted by J0-J06. The diagnostic codes H, L, O-Q and Z were combined in the 'other' cluster due to their low incidence. Short- and long-term outcomes were characterized by 30-day and five-year time-windows, respectively. Furthermore, frequently admitted patients were characterized by four or more admissions whereas less-frequently admitted patients were characterized by three or less admissions during follow-up.

Data collection

The following data was recorded from the index event: date of admission and discharge, discharge diagnosis and time until discharge. Time till first readmission was calculated based on the time between discharge from the index event and the admission date of the first admission. Likewise, time till death was calculated based on the time between discharge from the index event and the date of death.

Basic characteristics included age, sex, educational level according to the International Standard of Education (ISCED) (16): lower secondary education (0-2), upper secondary education (3), tertiary education or Bachelor's degree (5-6) and Master's or Doctoral degree (7-8). Please note that ISCED level 4 is not a part of the Danish education system. In addition, cohabitation status (i.e. living alone or together) and comorbidities ≤5 years prior to the index admission (using the Charlson Comorbidity Index [CCI](17)) were collected. Of note, the comorbidities anxiety, depression, and diabetes were defined using both the DNPR (for the corresponding ICD-10 codes) and the Danish National Prescription Registry for the corresponding medications (using the anatomic therapeutic chemic codes N05B, NO6A and A10, respectively). Furthermore, use of inhalation medication ≤6 months prior to the index admission was recorded as the following exclusive categories: short acting β2 agonist (SABA); long-acting muscarinic agonist (LAMA); long acting β2 agonist (LABA); inhaled corticosteroid (ICS); LAMA/LABA; ICS/LAMA; ICS/LABA; triple therapy (LAMA/LABA/ICS), and no treatment.

Statistical analysis

Continuous variables were presented using mean and standard deviation (SD) when normally distributed, otherwise using median and interquartile ranges (IQR). Categorical data was presented using absolute counts and relative percentages. Admission and mortality rates were displayed using two distinct methods. First, cumulative incidence plots of first-time all-cause hospital admission and mortality were created for the five-year follow-up period. The Aalen-Johanson estimator was used to account for competing risk of death in the all-cause admissions curve. Secondly, admission and mortality trajectories after the index event were displayed irrespective of time using Sankey diagrams. Furthermore, mean cumulative counts were displayed using the mean cumulative function (18). The 95%

confidence interval (CI) was constructed assuming Poisson distribution. The median admission rate per patient was simultaneously calculated as ([total admissions/days till death or end of follow-up period])/[365.25*5]). Corresponding IQR were created. Data management and analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 4.0.3).

Results

A total of 96335 patients with COPD experienced their first-ever exacerbation-related hospitalization during 2000-2014 in Denmark. After excluding patients aged below 40 or above 90 years, patients with chronic asthmatic bronchitis (J44.8B) or a (previous) diagnosis of asthma (J45), a total of 82964 patients were included (Figure 1). An overview of the characteristics of these patients at the index event is provided in table 1. Briefly, the average age of the population was 72 ± 10 years, and there was no sex predominance. The majority collected any inhalation medication in the six months prior to the index event (65.2%) and had at least one preexisting comorbidity (57.5%). Chronic heart failure, (complicated) diabetes and cerebrovascular disease were most prevalent.

[please insert figure 1 here]

Figure title: Fig 1. Flowchart of the study population

Table 1. Baseline characteristics of patients with COPD at their first exacerbation-related hospitalization

		Total (n= 82964)
Age	Years	72.2 ± 10.2
Sex	Male	39716 (47.9)
	Female	43248 (52.1)
Education[1]	Lower secondary education	45900 (61.0)
	Upper secondary education	22985 (30.6)
	Tertiary education or Bachelor degree	5246 (7.0)
	Master's or Doctoral degree	1083 (1.4)
Cohabitation status[2]	Living alone	39765 (53.8)
	Living together	34178 (46.2)
Inhalation medication	SABA	7160 (8.6)
	LAMA	4490 (5.4)
	LABA	2704 (3.3)
	ICS	8105 (9.8)
	LAMA and LABA	1120 (1.3)
	LAMA and ICS, or LABA and ICS	17031 (20.5)
	Triple therapy	13510 (16.3)
	Inhalation medication, total	54120 (65.2)
	No treatment	28844 (34.8)
Comorbidities	Chronic heart failure	13692 (16.5)
	(Complicated) Diabetes	10137 (12.2)
	Cerebrovascular disease	9059 (10.9)
	Peripheral vascular disease	8293 (10.0)
	Cancer	7886 (9.5)
	Myocardial infarction	6551 (7.9)
	Depression	4334 (5.2)
	Peptic ulcer disease	4264 (5.1)
	Rheumatic diseases	3459 (4.2)
	Chronic renal disease	2822 (3.4)
	Dementia	2342 (2.8)
	Anxiety	2310 (2.8)
	(Severe) Hepatic disease	1523 (1.8)
	Metastatic cancer	1102 (1.3)
	Hemiplegia	277 (0.3)
	AIDS	82 (0.1)
Comorbidities, total	0	35256 (42.5)
	1	20499 (24.7)
	2	12901 (15.6)
	≥3	14308 (17.2)
Characteristics index event		
Time until discharge	Days	4 [2, 8]

Total (%), mean ± SD and median [IQR] are presented. [1]n total=75214. [2]n total=73943. Abbreviations: ICS; inhaled corticosteroid, LABA; long-acting β2 agonist, LAMA; long-acting muscarinic antagonist, SABA; short-acting β2 agonist.

In total, 56.0% (95% CI 55.6-56.3) of patients had been admitted during the first 12 months after hospital discharge from the index event (Figure 2A). After five years of follow-up, 81.8% (95% CI 81.6-82.1) of patients had been admitted. Moreover, 5.5% (4554/82964) died during the index event. An additional 4029 patients died during the first 30 days post-discharge, resulting in a 30-day mortality rate of 10.4%. After five years of follow-up, 58.2% of patients had died (Figure 2B).

[please insert figure 2A and 2B here]

Figure title: Fig 2. A: Five-year cumulative incidence of experiencing a first all-cause hospital admission after hospital discharge from the index event. B: Five-year survival probability.

The cumulative average of the total number of hospital admissions during the first 30 days post-discharge was 0.27 (95% CI 0.27-0.28) per patient (Figure 3). A linear increase in the mean cumulative count was observed over time. After five years of follow-up, the mean cumulative number of hospital admission was 6.4 (95% CI 6.4-6.4), which corresponds to the median admission rate of 6 (IQR 2-14) per patient.

[please insert figure 3 here]

Figure title: Fig 3. Mean cumulative count of subsequent hospital admissions during the five-year follow-up.

Irrespective of time, 81.8% of patients (67882/82964) had experienced at least one subsequent hospital admission, 7.0% of patients (5821/82964) had not been admitted and 11.2% of patients (9261/82964) had died (Figure 4). Looking at the proportion of patients that had been admitted, non-respiratory admissions accounted for 57.2% (38852/67882) of the first hospital admission. Of these non-respiratory causes, cardiac-related events were most common (21.0% [8174/38852]). Respiratory causes accounted for 42.8% (29030/67882) of the first admission. Similar patterns were observed during subsequent admissions: non-respiratory causes remained the main cause of a second and third hospital admission.

[please insert figure 4 here]

Figure title: Fig 4. Sankey diagram displaying the diagnoses of the first three hospital admissions after the index event. Total number of patients (%) are presented.

A similar distribution of the main diagnostic clusters was observed during the first 30 days post-discharge compared to five years post-discharge after the index event (Table 2). Cardiac events remained the main non-respiratory cause of hospital admission over time (18.5% [36586/337066-139272]). The specific diagnoses of the two most common diagnostic clusters are shown in figure 5.

Table 2: Short-term (30-days post-discharge) versus long-term (five-years post-discharge) diagnoses of subsequent hospital admissions

	30-day	**5-year**
Total number of admissions	20894	337066
Respiratory	10194 (48.8)	139272 (41.3)
Cardiac	2419 (11.6)	36586 (10.9)
Other	1900 (9.1)	33149 (9.8)
Symptoms and signs not elsewhere classified	1406 (6.7)	25551 (7.6)
Cancer	963 (4.6)	16751 (5.0)
Digestive	854 (4.1)	18621 (5.5)
Trauma	648 (3.1)	16915 (5.0)
Infections	548 (2.6)	9180 (2.7)
Endocrine, nutritional, metabolic	544 (2.6)	8834 (2.6)
Genitourinary	530 (2.5)	10655 (3.2)
Musculoskeletal, connective tissue	262 (1.3)	8917 (2.6)
Mental, behavioral	209 (1.3)	3678 (1.1)
Hematologic, immunogenic	245 (1.2)	5674 (1.7)
Nervous system	172 (0.8)	3283 (1.0)

Total (%) are presented.

[please insert figure 5A and 5B here]

Figure title: Fig 5. Specific diagnoses of the two most common causes of hospital admission at the end of the five-year follow-up. Relative percentages of the total number of admissions are presented. A: Specific diagnoses of the 139272 respiratory-related admissions. B: Specific diagnoses of the 36586 cardiac-related admissions.

At the end of follow-up, 80.9% of all admissions occurred in a group of frequently admitted patients experiencing four or more hospital admissions. Differences in baseline characteristics were observed between the frequently and less-frequently admitted patients (Table 3). As such, the number of patients without preexisting comorbidities surviving follow-up was higher in the less-frequently admitted patients compared to the frequently admitted patients. Moreover, the average age was highest in the less-frequently admitted patients not surviving follow-up. In this view, regardless of the number of admissions, the patients not surviving follow-up were older, had more comorbidities and a longer hospital stay during the index event compared to the surviving patients.

Table 3. Baseline characteristics of the frequently (≥4 admissions) and less-frequently (≤3 admissions) admitted patients during the five-year follow-up period

		≤3 admissions		≥4 admissions		
		Alive (n=20200)	**Death (n=29937)**	**Alive (n=14466)**	**Death (n=18361)**	**Total (n=82964)**
Age	Years	67.5 ± 10.5	76.3 ± 8.7	68.7 ± 10.1	73.5 ± 9.1	72.2 ± 10.2
Sex	Male	8484 (42.0)	15173 (50.7)	6459 (44.6)	9600 (52.3)	39716 (47.9)
	Female	11716 (58.0)	14764 (49.3)	8007 (55.4)	8761 (47.7)	43248 (52.1)
Education[1]	Lower secondary education	11053 (58.0)	16520 (63.6)	8097 (59.6)	10230 (61.7)	45900 (61.0)
	Upper secondary education	6182 (32.4)	7376 (28.4)	4365 (32.1)	5062 (30.5)	22985 (30.6)
	Tertiary education or Bachelor degree	1540 (8.1)	1668 (6.4)	970 (7.1)	1068 (6.4)	5246 (7.0)
	Master's or Doctoral degree	295 (1.5)	397 (1.5)	162 (1.2)	229 (1.4)	1083 (1.4)
	n[1]	19070	25961	13594	16589	75214
Cohabitation status[2]	Living alone	9473 (47.0)	13305 (62.1)	7204 (49.8)	9783 (54.6)	39765 (53.8)
	Living together	10677 (53.0)	8111 (37.9)	7253 (50.2)	8137 (45.4)	34178 (46.2)
	n[2]	20150	21416	14457	17920	73943
Inhalation medication	SABA	2033 (10.1)	2363 (7.9)	1264 (8.7)	1500 (8.2)	7160 (8.6)
	LAMA	987 (4.9)	1746 (5.8)	722 (5.0)	1035 (5.6)	4490 (5.4)
	LABA	705 (3.5)	909 (3.0)	495 (3.4)	595 (3.2)	2704 (3.3)
	ICS	2306 (11.4)	2562 (8.6)	1511 (10.4)	1726 (9.4)	8105 (9.8)
	LAMA and LABA	231 (1.1)	382 (1.3)	216 (1.5)	291 (1.6)	1120 (1.3)
	LAMA and ICS, or LABA and ICS	4112 (20.4)	5705 (19.0)	3306 (22.8)	3908 (21.3)	17031 (20.5)
	Triple therapy	2582 (12.8)	4764 (15.9)	2510 (17.4)	3654 (19.9)	13510 (16.3)
	Inhalation medication, total	12956 (64.1)	18431 (61.6)	10024 (69.3)	12709 (69.2)	54120 (65.2)
	No treatment	7244 (35.9)	11506 (38.4)	4442 (30.7)	5652 (30.8)	28844 (34.8)
Comorbidities, total	0	12843 (63.6)	9597 (32.1)	6683 (46.2)	6133 (33.4)	35256 (42.5)
	1	4400 (21.8)	7594 (25.4)	3855 (26.6)	4650 (25.3)	20499 (24.7)
	2	1825 (9.0)	5675 (19.0)	2064 (14.3)	3337 (18.2)	12901 (15.6)
	≥3	1132 (5.6)	7071 (23.5)	1864 (12.9)	4241 (23.1)	14308 (17.2)
Characteristics index event						
Time until discharge	Days	3 [1, 7]	6 [2, 10]	4 [1, 7]	5 [2, 8]	4 [2, 8]

Time until death	Days		177 [20, 656]		969 [566, 1,379]	

Total (%), mean ± SD and median [IQR] are presented. [1,2] n is stated otherwise. Abbreviations: ICS; inhaled corticosteroid, LABA; long-acting β2 agonist, LAMA; long-acting muscarinic antagonist, SABA; short-acting β2 agonist.

Discussion

This study showed the five-year all-cause hospital admission trajectories of more than 80000 patients with COPD following their first-ever exacerbation-related hospitalization. The vast majority of patients had been admitted to the hospital for any cause five years after their first exacerbation-related hospitalization. Whilst the causes of hospital admission varied widely, more than half of the admissions were non-respiratory. Furthermore, more than half of the patients had died during follow-up. To the best of our knowledge, this is the first study to demonstrate the all-cause hospital admission trajectories of patients with COPD following their first-ever exacerbation-related hospitalization.

For many years it has been well established that after an exacerbation-related hospitalization patients with COPD will be admitted for a subsequent AECOPD (2, 4, 6). As such, the main goals in treating AECOPD are to minimize the negative impact of the current event and to prevent subsequent events (19). In this study we showed that, not surprisingly, respiratory admissions were most frequent. However, non-respiratory admissions accounted for the majority of subsequent admissions, both on the short- and long-term. Indeed, we demonstrated the patterns of incidence over time. Hence, it could be observed that admissions related to cancer, the digestive- and genitourinary tract became more incident over time. These findings hold important implications for clinical practice, challenging the current global post-AECOPD management goals.

The most common non-respiratory cause of hospital admission included cardiac events: ischaemic- and pulmonary heart diseases followed by myocarditis, cardiomyopathy and arrhythmias were most common. Indeed, cardiac diseases remain the leading cause of death worldwide (20). With an estimated prevalence ranging from 30% to 60%, COPD and cardiac diseases frequently co-occur (21, 22). This relationship is likely owned by shared risk factors such as smoking, low physical activity as well as persistent low-grade pulmonary and systemic inflammation (21). Additionally, cardiac related conditions are important differential diagnoses of AECOPD, underlining the challenges associated with the current AECOPD definition (19). Indeed, the question may arise to what extent the index AECOPD may have been affected by preexisting, or concurrent cardiovascular diseases, and whether such cardiovascular diseases were misclassified as AECOPD during the index admission. The current real-world data reflects the diagnostic difficulties clinicians are faced with. Nevertheless, it is unlikely that such single misclassifications have had an impact on the outcomes of the current study given its substantial cohort size. More so, we believe that these results are a true reflection of the impact of cardiac comorbidities on the need for hospitalization in patients with COPD.

Research has pointed out that comorbidities, previous AECOPD and hospitalizations as well as an increased length of hospital stay are major risk factors for all-cause hospital readmission following exacerbation-related hospitalization (9). In line with previous studies

(23), more than half of the patients in the current study had one or more preexisting comorbidity. One might question whether these comorbidities rather than the AECOPD per se were the major driver of the observed subsequent hospital admission(s). Yet, previous research in patients with COPD showed that AECOPD confer an increased risk of subsequent cardiovascular events, regardless of preexisting cardiac comorbidities (24). The current findings may therefore substantiate the previously identified increased risk of cardiovascular events following AECOPD.

Other non-respiratory causes of hospital admission included e.g. cancer, digestive- and genitourinary disorders. Close to one-third of the cancer-related admissions were driven by malignancies of the respiratory and intrathoracic organs. Indeed, patients with COPD are at high risk of lung cancer, irrespective of smoking status (25). However, digestive- and genitourinary related admissions are unreported in the current literature. Future studies are indicated to explore the mechanisms linking these types of admissions to AECOPD.

Respiratory-related admissions contributed to less than half of the observed admissions. The majority could be attributed to chronic lower respiratory diseases followed by acute respiratory infections. It is well recognized that a history of AECOPD predisposes patients to subsequent AECOPD (3), and that respiratory infections trigger these events (26). Indeed, the majority of the observed respiratory admissions was exacerbation-related.

Besides their cause, it is essential to understand the timing and rates of hospital admissions whilst striving to reduce their occurrence. The current study showed that most patients experienced their first hospital admission within the first year after hospital discharge from the index event. A linear increase in the cumulative average of the total number of admissions was observed over time. By the end of follow-up, the average number of admissions was six per patient. These findings underline the need for close monitoring, especially in the first year after AECOPD hospital discharge.

We noted an in-hospital mortality rate of 5.5% during the index event. This is in line with previously reported in-hospital mortality rates of first-ever hospitalized AECOPD (27, 28). Importantly, although mortality rates are heterogeneous across studies, similar in-hospital mortality rates were reported among patients with a (severe) AECOPD history (4). Moreover, the observed long-term mortality rates are in accordance with previous reports (29, 30), underlining the external validity of our findings. Thus, the prognosis of patients with COPD at their first exacerbation-related hospitalization may be as poor as during subsequent events, both during and after hospitalization.

A substantial part of the population had died after less than four subsequent admissions. We noted that, consistent with the general population (31), the worst prognosis (i.e. death) was not necessarily related to the number of admissions but rather to an older age, a higher

number of comorbidities and a longer duration of hospital stay during the index event. These findings highlight the need to incorporate these well recognized risk factors of mortality after exacerbation-related hospitalization in discharge planning (32). Moreover, over 30% of patients did not use inhalation medication prior to the index event. This group includes patients without a prior diagnosis of COPD, and non-adherent patients, indicating a need for earlier diagnosis and improved adherence. It may also represent a group of patients with mild disease, who have not received treatment for COPD. The likelihood of another respiratory admission may therefore be less likely, which could have contributed to the observed high number of non-respiratory admissions. However, our findings do underline that morbidity in COPD may not only be contributed to the disease itself.

Several strengths and limitations should be noted. A major strength of the current study was its unique national hospital dataset covering all first-time exacerbation-related hospitalizations in Denmark between 2000 and 2014. The substantial sample size and follow-up period allowed us to study the nationwide all-cause hospital admission trajectories following this index event. At the same time, the dataset presented important limitations. First, the dataset was administrative in nature and did not include information on certain clinical data (e.g. spirometry). The current definition used to characterize a (first) exacerbation-related hospitalization has been widely used in Danish registry research and was previously validated (i.e. >90% positive predictive value) (15). Yet, some inaccuracy is introduced which should be taken into consideration when interpreting the results. Furthermore, this study did not differentiate between less severe and very severe hospital admissions. To limit this bias, only admissions to a department with 24-hour surveillance were counted. Moreover, given that approximately 10% of patients had died after each hospital admission may indicate that these events were likely less severe. In this view, and whilst a control population was currently missing, the prognosis of more severe procedures is worse for patients with COPD than for patients without COPD (33).

Taken together, we showed that all-cause hospital admissions following a first exacerbation-related hospitalization are common and predominantly caused by non-respiratory events. Hence, besides the respiratory causes, treatment targeting the non-respiratory causes of hospital admission should be considered to effectively decrease the burden of hospitalization in COPD. Awareness amongst clinicians should be raised to proactively and comprehensively screen patients before hospital discharge, and to monitor patients accordingly post-discharge. The current findings show that particularly cardiac comorbidities should be monitored. This knowledge should be included in the patient's written action plans.

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Analyses were performed on the Statistics Denmark's secure database of registries, using pseudonymised data. Access to the extracted data, and/or the codes developed for this analysis, are possible upon reasonable request. Such queries may be directed towards the senior author.

Author contributions: K. Waeijen-Smit and P.A. Jacobsen contributed to the conception and design of this study, with substantial support from all coauthors. P.A. Jacobsen led the acquisition and analysis of the data with support from K. Waeijen-Smit. K. Waeijen-Smit and P.A. Jacobsen were responsible for the interpretation of the data, with substantial support from all coauthors. K. Waeijen-Smit drafted the work with support from P.A. Jacobsen. All coauthors provided criterial revisions for important intellectual content. All authors provided approval of the final version to be published, and take accountability for all aspects of the work.

Conflict of interest: S.O. Simons has received grants and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Chiesi outside the submitted work. F.M.E. Franssen has received grants and personal fees from AstraZeneca, Chiesi, Boehringer Ingelheim, Glaxosmithkline, Novartis and MSD outside the submitted work. M.A. Spruit has received grants and personal fees from the Netherlands Lung Foundation, Stichting Asthma Bestrijding, AstraZeneca, Boehringer Ingeheim, TEVA and CHIESI outside the submitted work. C.T. Pedersen has received grants from Bayer and Novo Nordisk outside the submitted work. All authors declare no conflicts of interest in relation to the present study.

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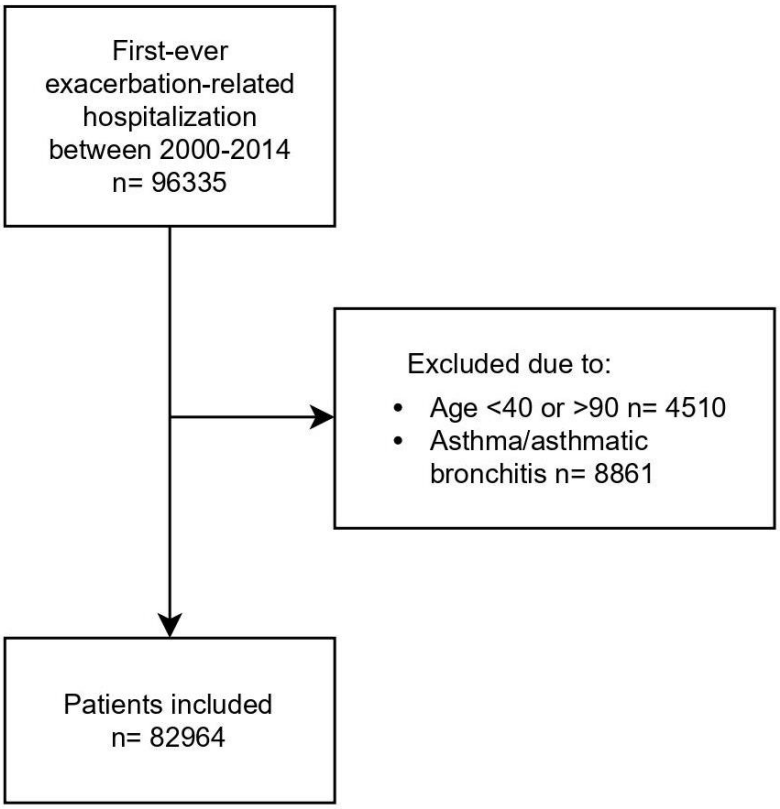

Figure 1. Flowchart of the study population

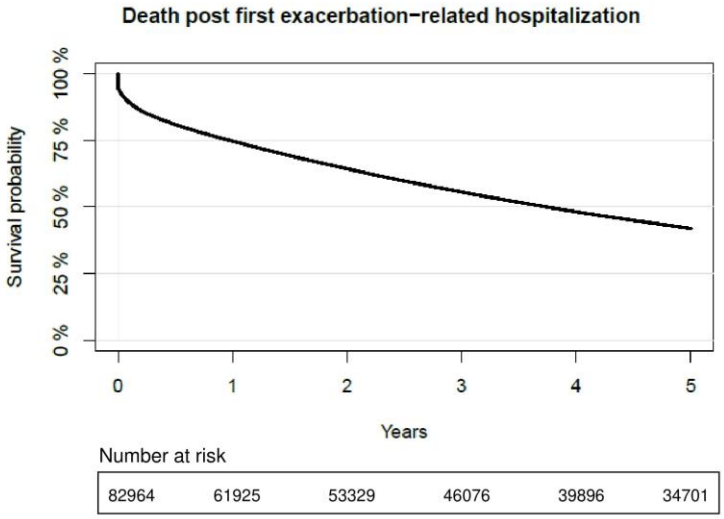

Figure 2A. Five-year cumulative incidence of experiencing a first all-cause hospital admission after hospital discharge from the index event.

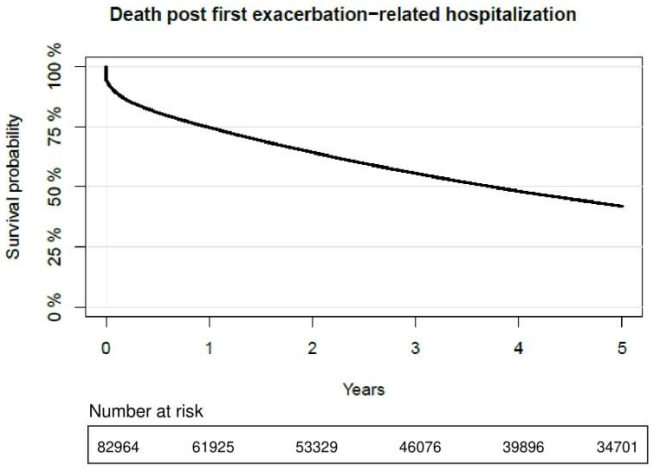

Figure 2B. Five-year survival probability.

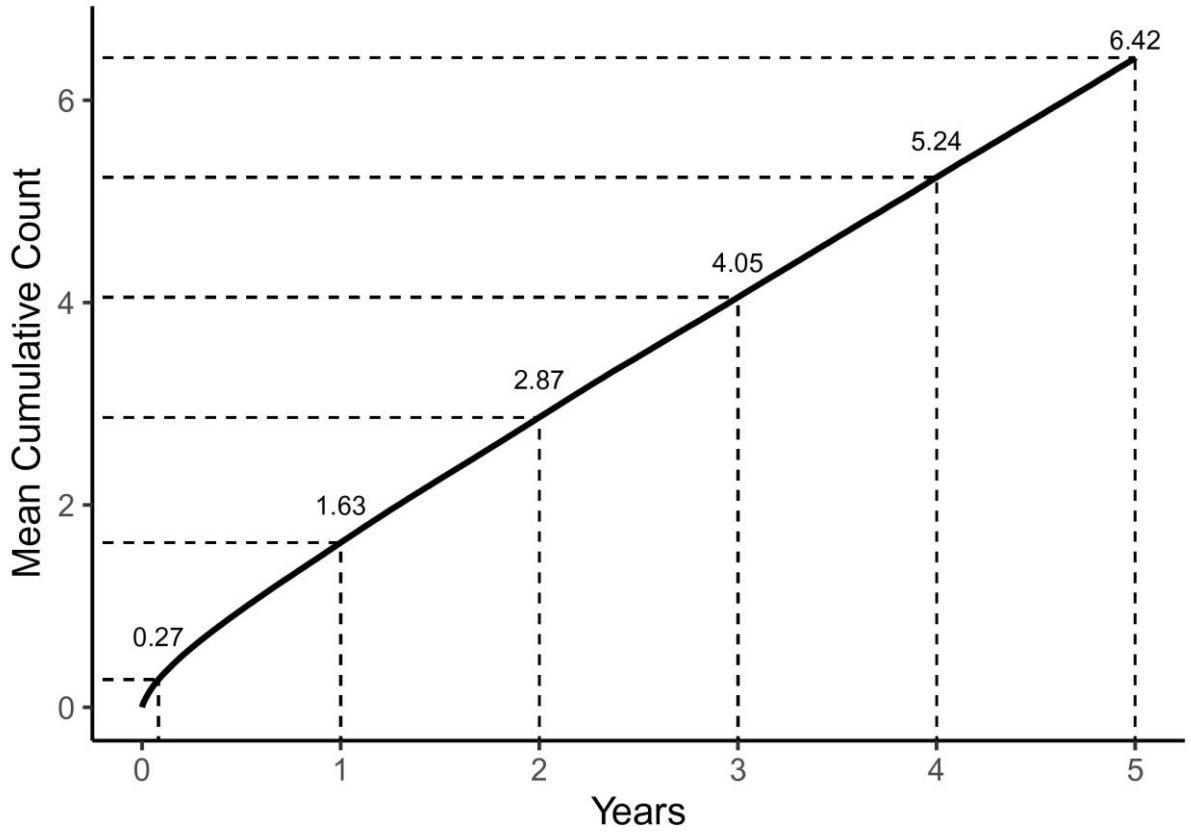
Mean Cumulative Count
Years
0
2
4
6
0
1
2
3
4
5
0.27
1.63
2.87
4.05
5.24
6.42

Figure 3

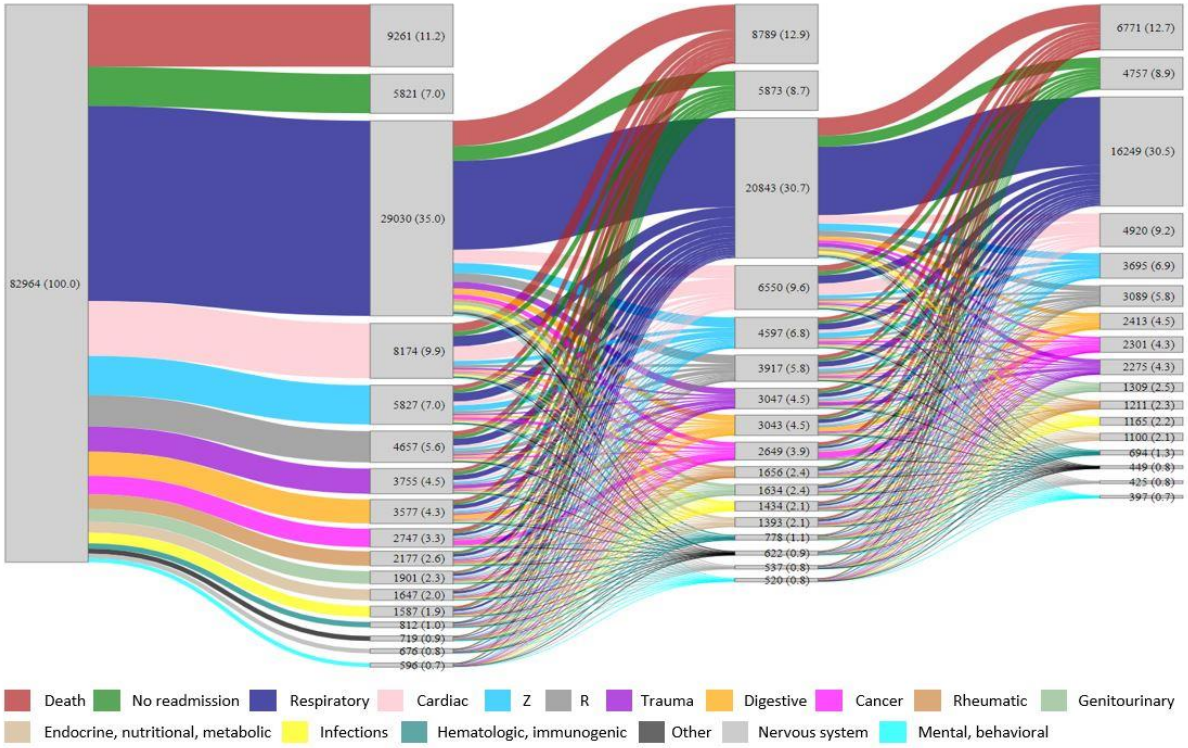

Figure 4. Sankey diagram displaying the diagnoses of the first three hospital admissions after the index event. Total number of patients (%) are presented.

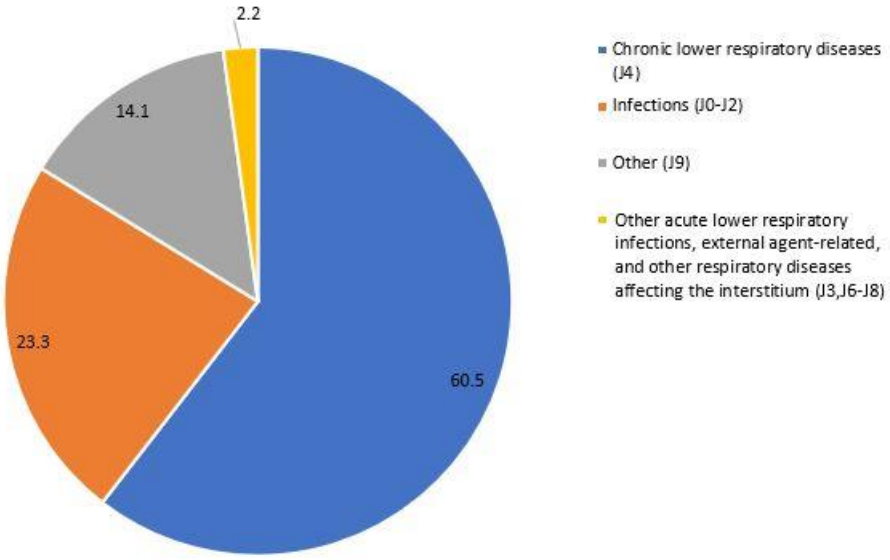

Figure 5A. Specific diagnoses of the 139272 respiratory-related admissions at the end of the five-year follow-up. Relative percentages of the total number of admissions are presented.

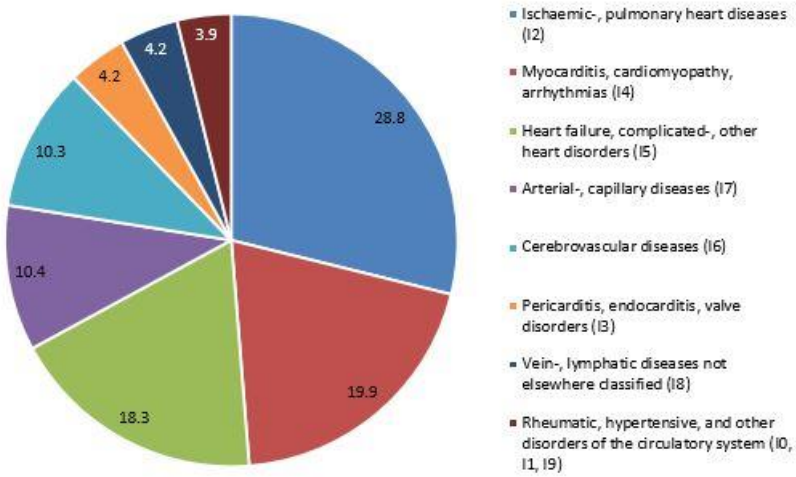

Figure 5B. Specific diagnoses of the 36586 cardiac-related admissions at the end of the five-year follow-up. Relative percentages of the total number of admissions are presented.

Online supplementary table 1. Diagnoses and corresponding ICD-10 codes used to characterize the causes of hospital admission following the index event

	ICD-10 code
Infections and parasitic diseases	A00-B99
Neoplasms	C00-D48
Hematologic, immunogenic diseases	D50-D89
Endocrine, nutritional, metabolic diseases	E00-E90
Mental and behavioral disorders	F00-F99
Diseases of the nervous system	G00-G99
Diseases of the eye and adnexa	H00-H59
Diseases of the ear and mastoid	H60-H95
Diseases of the circulatory system	I00-I99
Diseases of the respiratory system	J00-J99
Diseases of the digestive system	K00-K93
Diseases of the skin and subcutaneous tissue	L00-L99
Diseases of the musculoskeletal system and connective tissue	M00-M99
Diseases of the genitourinary system	N00-N99
Pregnancy, childbirth and the puerperium	O00-O99
Conditions originating in the perinatal period	P00-P96
Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	R00-R99
Trauma and accidents	S00-T98, X00-X99
Factors influencing health status and contact with health services	Z00-Z99