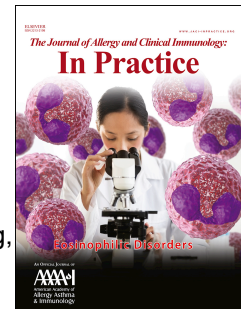


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Risk of re-hospitalization and death in patients hospitalized due to asthma

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Conflict of Interest

GT is employed by AstraZeneca.

FW is employed at Statisticon for which AstraZeneca is a client.

27 CJ has received payments for educational activities from AstraZeneca, Boehringer Ingelheim, Chiesi,
28 Novartis, and Teva, and has served on advisory boards arranged by AstraZeneca, Boehringer
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ABSTRACT

Background

Asthma is a heterogeneous inflammatory airway disease that continues to cause considerable morbidity across the world, with poor asthma control leading to hospitalizations.

Objective

The present study investigated the risk of re-hospitalization, mortality and the management of asthma patients that had been hospitalized due to an asthma exacerbation.

Methods

National Swedish health registries were linked for patients aged ≥ 6 years who were admitted to hospital due to asthma (index date) between 01/01/06 and 12/31/15. Exacerbations were defined as asthma-related hospitalization, emergency visits, or collection of oral steroids. Patients were followed for re-hospitalizations 12-months post index, health care resource utilization and treatment for 36-months, and mortality to study end. Regression models for time-to-event analyses were applied to assess risk factors for re-hospitalization and mortality.

Result

A total of 15,691 patients (mean age 51.5 years, 63% females) were included, of whom 1892 (12%) were re-hospitalized for asthma within 12-months. Re-hospitalized patients had a markedly increased risk of subsequent asthma related mortality (adjusted HR 2.80, 95% CI: 1.95 – 4.01) compared to those not re-hospitalized. Two thirds of the patients were not followed up by a hospital-

based specialist and 60% did not collect enough inhaled corticosteroids (ICS) doses to cover daily treatment the year post index.

Conclusion

In this study, more than one in ten patients were re-hospitalized due to asthma within 12 months, re-hospitalizations were associated with asthma related mortality. Few patients were seen by a hospital-based specialist and few used ICS continuously. Closer monitoring after hospitalization is needed.

Highlights box

What is already known about this topic? Asthma cause considerable morbidity across the world.

What does this article add to our knowledge? Re-hospitalizations occurred in more than one of ten asthma patients, few were seen by specialists and continuous ICS use was rare.

How does this study impact current management guidelines? Closer monitoring after asthma hospitalization is needed.

Key words

Asthma, exacerbation, re-hospitalization, pharmacological treatment, mortality, health care recourse utilization

List of abbreviation

ATC	Anatomical Therapeutic Chemical
CI	Confidence intervals
COPD	Chronic Obstructive Pulmonary Disease
HR	Hazard ratio
ICS	Inhaled corticosteroids
IQR	Interquartile range
IRR	Incident rate ratios
LABA	Long-acting β_2 -agonists
OCS	Oral corticosteroids
PY	Patient year
SABA	Short-acting β_2 -agonist
SD	Standard Deviation

INTRODUCTION

Asthma is a heterogeneous inflammatory airway disease that is estimated to affect 339 million people worldwide (1-3). The use of inhaled corticosteroids (ICS) transformed asthma care by significantly reducing severe exacerbations and asthma deaths (4). However, even though asthma is a rare cause of mortality (1), it continues to cause considerable morbidity across the world (5, 6). The persistently high levels of poor asthma control are a concern ((7, 8), as is the growing trend of overuse of short-acting bronchodilators (SABA) and its consequences (9, 10).

Asthma may be uncontrolled for several reasons, including persistent environmental exposures, comorbidities, ineffective treatment, poor adherence to pharmacological treatment or incorrect inhaler technique (11). Poor adherence to asthma medications has adverse effects on disease control and health care costs (12). Williams et al reported that 8% of the asthma patients never filled their ICS prescription (13).

There is a need for improved monitoring of asthma patients, especially during the period following a hospitalization due to asthma. The REALISE survey of 8000 adults with asthma in 11 European countries, including Sweden, showed that acute exacerbations were common and that 12% of the asthma patients had been hospitalized due to asthma during the previous year (14). Also, a recent study from Finland showed that the frequency of asthma follow-up contacts is insufficient, with only one of three asthma patients attending a planned visit each year (15), as recommended by guidelines (11). Whilst poor asthma control still leads to hospitalizations, few contemporary population-based studies have investigated the management, treatment patterns, and risk of re-hospitalization and mortality in asthma patients post discharge.

The aim of this study was to investigate the risk of re-hospitalization, mortality and the management of asthma patients that had been hospitalized because of an asthma exacerbation.

METHODS

Study design and data sources

This was a longitudinal nation-wide cohort study utilizing linked data from national Swedish health registries: (1) the National Patient Register covering all hospital admissions since 1987 and out-patient specialist visits since 2001; (2) the Prescribed Drug Registry, covering all collected outpatient drug prescriptions since July 2005 using Anatomical Therapeutic Chemical (ATC) codes; and (3) the Cause of Death Register (16-18). Individual patient data were linked by the Swedish National Board of Health and Welfare using each individual's unique personal identification number. The study protocol was approved by the Stockholm Regional Ethics Committee (registration number 2017/4:2).

Study population

The study population included all patients ≥ 6 years of age in Sweden who were admitted to hospital due to asthma (primary diagnoses ICD-10 code J45, J46.9) between 01/01/06 and 12/31/15 and had available data for a minimum of 365 days pre- and post-index. Index date was defined as the date of the first hospitalization during the time period, and the baseline period was the 12 months prior to index. Patients were followed for up to 10 years post index (Figure 1). Co-morbidities were retrieved from the National Patient Register using ICD-10 codes from up to 5 years prior to index date.

Outcomes and variables

Asthma exacerbations were defined as asthma-related hospitalization, hospital emergency visits because of asthma (primary diagnosis), or collection of oral steroids. Exacerbations occurring within a 14-day period were considered as one event.

Re-hospitalizations were defined as a hospitalization with a primary diagnosis of asthma during 12 months post index.

Outpatient visits in hospital-based specialist care was defined by a recorded primary asthma diagnosis (ICD-10 code J45 or J46). Comorbidities (cumulative prevalence, both primary and secondary diagnoses) were identified using ICD-10 codes. Medications were defined by ATC codes (ICS [R03BA], Short-acting β_2 -agonist [SABA] [R3AC02-03], long-acting β_2 -agonists [LABA] [R03AC12-13,17-18, R03CC12], oral corticosteroids [OCS] [H02AB]). ICS use included both monotherapy and fixed combinations. The mean daily ICS dose was defined as: low-dose, $\leq 400 \mu\text{g}$; medium-dose, 401–800 μg ; and high-dose, $> 800 \mu\text{g}$ (in budesonide equivalents). Patients were classified into different treatment severity steps based on their asthma-related drug use during the baseline period (details provided in Repository Text, Table E1). All cause and asthma related mortality was assessed post index date to 31/12/16.

Statistical analyses

Baseline characteristics were described as mean (standard deviation [SD]) for continuous variables and absolute and relative frequencies for categorical variables. Rate of hospitalisation was computed by number of events divided by number of person-years at risk. Confidence intervals (95% CI) for rates were derived by approximating the Poisson distribution by a normal distribution. Among patients followed for ≥ 12 months, risk factors for re-hospitalization was assessed by hazard ratios (HR) with 95% CI using Cox proportional hazard models. Index age, sex, treatment severity steps, baseline exacerbation frequency, comorbidity and hypertension were explored individually as well as in multivariable adjusted analyses. Risk of all-cause and asthma-specific mortality by post-index re-hospitalisations was assessed by hazard ratio (HR) with 95% CI using Cox proportional hazard models. Estimates adjusted for index age, sex, treatment severity steps, baseline exacerbation history, comorbidities and hypertension were calculated. The Fine-Gray competing risk model was applied to estimate cumulative risk of asthma-specific mortality adjusted for competing risk of non-asthma death. Predictors for asthma related outpatient hospital visits was assessed through incident rate ratios (IRR) with 95% CI derived from a negative binomial generalized regression model. Sensitivity

154 analyses representing both prevalent and incident asthma patients included during the year 2006
155 was performed. All statistical analyses were performed using R version 3.6.2 (R foundation for
156 Statistical Computing, Vienna, Austria, 2013).

RESULTS

A total of 15,691 patients (mean age 51.5 years, 63% females) with a hospitalization due to asthma during 2006-2015 were included in the study, of whom 42% had had an exacerbation, 65% had collected an ICS, and 174 patients were hospitalized due to asthma during the baseline year (Table 1). Further, 24% of the patients were on treatment severity step 1-2, 25% on step 3, and 29% on steps 4-5. The observation period was an average of 4.6 years (range 0-10 years) after baseline.

Asthma re-hospitalization and mortality

Overall, 1892 (12%) of the included patients were re-hospitalized for asthma during the first year of follow-up (mean age 57.2 years, 68% females). SABA and OCS were used by a greater proportion of the re-hospitalized compared to the non-re-hospitalized patients, 73% vs 59% and 57% vs 38%, respectively (Table 1).

Risk factors for asthma re-hospitalization were female sex, older age, presence of comorbidities, more severe treatment steps and baseline exacerbations (Table 2). When stratifying for age group (6-11, 12-17, and ≥ 18), we found no difference in risk factors for re-hospitalization. Patients who were re-hospitalized within one-year post index had a markedly increased risk of subsequent asthma related mortality (adjusted HR 2.80, 95% CI: 1.95– 4.01) as well as a small increase in all-cause mortality (1.16: 1.05 – 1.27), compared to those who were not re-hospitalized (Table 3, Figure 2 a + b). Median 35.4 interquartile range (IQR) number of days to re-hospitalization was 59 (10-177) days. Patients who were re-hospitalized had increased cumulative risk of asthma related mortality both after the first year of follow-up (0.99 [0.53-1.44] vs 0.15 [0.08-0.22]) and after eight years (3.61 [2.55-4.67] vs 0.93 [0.71-1.15]), adjusted for competing risk of death due to other causes.

179 Overall, 59 patients died due to asthma and 1118 due to other causes during a hospital admission.
180 Among them, 6 (10.2%) and 10 (0.8%) respectively, had asthma as the primary reason for
181 hospitalization.

Health Care Resource Utilization

Factors associated with having an asthma related outpatient hospital visit during the first year of follow-up were having more severe asthma (measured as baseline treatment severity steps and frequency of exacerbations), high comorbidity burden, male sex and younger age. Baseline factors associated with having a non-asthma related outpatient hospital visit were higher exacerbation frequency, high comorbidity burden, hypertension and increasing age, except for the oldest age group (Table 4). For patients with at least 3 years of follow-up (n=11,852), the proportion of patients seeing a hospital-based specialist due to asthma was 23.1% at baseline and increased to 35.7% during the first year post index, followed by a gradual decrease to 20.5% by the third year of follow-up. This pattern was different compared to visits due to other conditions than asthma, which was more stable over time. In addition, during follow-up years 1 – 3, 34.2%, 29.7% and 28.3% experienced an asthma exacerbation, respectively (Table E2).

Pharmacological treatments

The proportion of patients collecting a prescription of ICS increased from 65% at baseline to 86.2% the year post index hospitalization, followed by a decline to 71.4% at three years of follow-up (Table E2). In patients with at least 3 years of follow-up, more than half were no or low ICS users (0 - 1 ICS claim) during the baseline year. During the first year of follow-up, the proportion of patients with continuous ICS use (≥ 4 claims per year) increased from 24% to 41%, but decreased by year 3 to 31% (Figure 3). Compared to those with low ICS use, patients with continuous ICS use were older (mean age 59 vs 42), and had more exacerbations (181.8 [176.8-186.8] vs 37.7 [35.8-39.5] per 100 person years).

205 **Sensitivity analyses**

206 To explore the robustness and validity of our findings, a sensitivity analyses on patients with a
207 hospitalization during the year 2006 was performed. This represents a cross section of both
208 prevalent and incident asthma patients. Risk factors for re-hospitalization within 12 months post
209 index and risk of all cause and asthma-related mortality were similar in this population, compared to
210 the main population (Tables E3 – E6).

211

DISCUSSION

In this nationwide cohort including hospitalized asthma patients, we found that more than one out of ten were re-hospitalized due to asthma within a 12 months follow-up period. Re-hospitalization was associated with markedly increased risks of asthma related mortality and modestly increased all-cause mortality. Older age, presence of comorbidities and baseline exacerbation frequency were independent risk factors for re-hospitalization. Two thirds of the included asthma patients were not followed up by a hospital-based specialist the year after the index hospitalization, a proportion that increased to 80% after three years of follow-up. Sixty percent of the patients did not collect enough ICS doses to cover daily treatment the year after index.

Despite the availability of different treatment options, many asthma patients in Sweden, as well as in other countries, have low level of asthma control (19, 20) with impaired quality of life (21, 22), and the societal costs of asthma is high (23). In fact, 60% of the Swedish asthma patients are uncontrolled, a proportion that has not changed over the last 15 years (24). In our study, hospitalizations due to asthma occurred in all age groups and regardless of treatment severity step. This is in keeping with other reports on exacerbations also in patients with mild to moderate disease (14).

We found that 12% of the asthma patients were re-hospitalized and one third experienced exacerbations within the first year post the index hospitalization. One risk factor for re-hospitalizations was the presence of comorbidities. The association of comorbidities with frequent asthma exacerbations has previously been described in a Swedish population (25). In the USA (26) and in Australia (27), comorbidities have been shown to be independent risk factors for frequent

asthma exacerbations, poor asthma control, poor quality of life, and different features of severe asthma. Re-hospitalization were more common in older patients. Previous studies have found that elderly asthmatics have poorer asthma control and more impaired quality of life (22, 28), factors that can considerably impact on the likelihood of future asthma re-hospitalization and poor clinical outcomes of asthma in the future.

In addition, we found that re-hospitalizations were associated with asthma related mortality. Of note is that asthma mortality rates have been plateauing in many countries over the last two decades (6), whereas rates of hospitalizations has decreased (29-31). In line with our findings, results from a Taiwanese study show that a history of asthma re-hospitalization is one of the prominent risk factors for mortality (32). Very few of the patients in our study had a visit with an asthma specialist during the year post the index hospitalization. This has previously been described in a Swedish study, where only 1 in 5 patients with severe asthma had a visit in hospital based specialist care (25). Also, asthma patients with a higher burden of comorbidity in our study were less likely to have follow-up visits with an asthma specialist, and had increased risks of asthma re-hospitalization. Our data suggest that specialists should have an increased focus on asthma patients in risk groups, such as patients with comorbidities, exacerbations and older age.

In Sweden, medications for chronic diseases are normally prescribed for one year with four claims. A surprisingly high number of patients in our study were not using any inhaled steroids prior to the hospitalization and very few patients collected ICS doses enough to cover a daily treatment. This is in concordance with other studies, showing the ICS underuse and SABA overuse in asthma (9, 10, 14, 33).

One strength of the present study is the use of full-population, high quality health registries, including all patients in Sweden with a hospitalization during the study period. Use of nationwide

mandatory registry data ensured that selection bias and loss to follow-up was minimized. Sensitivity analyses to select the index case at random showed similar results as for the main population, which strengthen the robustness and validity of our data and increase the findings' generalizability.

A limitation of this study is that visits in primary care were not collected, which is why the potential post-discharge follow up by a primary care physician was not captured, as well as the report of comorbidities may be underestimated if managed fully in primary care. Data on some risk factors were not available such as smoking and body mass index as these are not usually captured in the registries used in the current study.

Conclusion

The present study demonstrates that more than one in ten asthma patients were re-hospitalized within 12 months after experiencing an asthma hospitalization. Re-hospitalizations are associated with all cause and asthma related mortality. Few patients were followed-up by a hospital-based specialist, one third had exacerbations during follow-up and the proportion of patients collecting ICS decreased over time. Our findings emphasize the need for closer monitoring after hospitalization to avoid re-hospitalizations in benefit of both patient and society.

DECLARATIONS**Ethics approval and consent to participate**

This study was performed in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practices, Good Pharmacoepidemiology Practice and the applicable legislation on non-interventional studies and/or observational Studies. The study was approved by the Stockholm regional ethics committee (registration number 2017/4:2). The linkage of registers data was approved and performed by the Swedish National Board of Health and Welfare. Patients do not need to give consent for use of public register data in Sweden.

Consent for publication

All authors read and approved the final manuscript. All authors gave consent to publish these data.

Availability of data and material

The dataset supporting the conclusions of this article can be available upon request.

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382 **FIGURES**

383 **Figure 1.** Study design

384

385 **Figure 2.** Cumulative incidence of all-cause mortality (top panel) and asthma-related mortality (lower
386 panel) among asthma patients with and without asthma re-hospitalization within 12 months after
387 index date. Asthma-specific mortality adjusted for competing risk of death due to other causes.

388

389 **Figure 3.** Proportion of study population collecting ICS during baseline period and follow-up years 1
390 to 3[#]

391 TABLES

Table 1. Baseline characteristics of study population

	All asthma n=15691	No re-hospitalization n=13799	Re-hospitalized n=1892
Females, n (%)	9938 (63.3)	8646 (62.7)	1292 (68.3)
Age			
Mean (SD)	51.5 (26.6)	50.7 (26.7)	57.2 (25.2)
Median (IQR)	56.0 (28.0-74.0)	55.0 (27.0-74.0)	62.0 (40.0-79.0)
Age categories, n (%)			
6-11	1859 (11.8)	1722 (12.5)	137 (7.2)
12-17	829 (5.3)	755 (5.5)	74 (3.9)
18-44	3198 (20.4)	2851 (20.7)	347 (18.3)
45-64	3663 (23.3)	3213 (23.3)	450 (23.8)
65-80	3419 (21.8)	2991 (21.7)	428 (22.6%)
>80	2723 (17.4)	2267 (16.4)	456 (24.1)
Treatment severity step, n (%)			
0	3469 (22.1)	3273 (23.7)	196 (10.4)
1	1799 (11.5)	1626 (11.8)	173 (9.1)
2	1896 (12.1)	1692 (12.3)	204 (10.8)
3	3932 (25.1)	3404 (24.7)	528 (27.9)
4	3062 (19.5)	2617 (19.0)	445 (23.5)
5	1533 (9.8)	1187 (8.6)	346 (18.3)
Any baseline exacerbation, n (%)	6573 (41.9)	5439 (39.4)	1134 (59.9)
Baseline exacerbation rate, per/100PY (95% CI)	103.9 (102.3-105.5)	93.4 (91.8-95.0)	180.6 (174.5-186.7)
Asthma medications, n (%)			
- ICS treatment	10180 (64.9)	8697 (63.0)	1483 (78.4)
- SABA	9525 (60.7)	8150 (59.1)	1375 (72.7)
- LABA	2339 (14.9)	1960 (14.2)	379 (20.0)
- OCS	6364 (40.6)	5279 (38.3)	1085 (57.3)
Co-morbidities, n (%)*			
- Chronic rhinitis	49 (0.3)	42 (0.3)	7 (0.4)
- Nasal polyps	198 (1.3)	168 (1.2)	30 (1.6)
- Acute lower respiratory infections	497 (3.2)	376 (2.7)	121 (6.4)
- Chronic bronchitis	135 (0.9)	111 (0.8)	24 (1.3)
- Pneumonia	868 (5.5)	686 (5.0)	182 (9.6)
- Hypertension	1711 (10.9%)	1418 (10.3%)	293 (15.5%)
Charlson Comorbidity Index, n (%)			
0	5817 (37.1)	5410 (39.2)	407 (21.5)
1	6314 (40.2)	5424 (39.3)	890 (47.0)
2	1645 (10.5)	1397 (10.1)	248 (13.1)
3+	1915 (12.2)	1568 (11.4)	347 (18.3)

Re-hospitalization defined as inpatient hospital visit with asthma (J45, J46.9) as primary diagnosis.

Treatment severity step 0 refers to patients without baseline asthma treatment.

*Comorbidities from secondary care only.

Table 2. Risk factors for re-hospitalization within 12 months post index

	Crude HR (95% CI)	Adjusted HR (95% CI)
Sex		
Male	1.00	1.00
Female	1.26 (1.15-1.39)	1.12 (1.02-1.24)
Index age		
6-17	1.00	1.00
18-44	1.42 (1.20-1.68)	1.23 (1.03-1.46)
45-64	1.61 (1.37-1.90)	1.15 (0.96-1.36)
65-80	1.64 (1.39-1.94)	1.05 (0.88-1.25)
>80	2.25 (1.91-2.64)	1.46 (1.21-1.75)
Charlson comorbidity index*		
0	1.00	1.00
1	2.09 (1.86-2.35)	1.59 (1.40-1.80)
2	2.24 (1.91-2.62)	1.54 (1.30-1.82)
3+	2.75 (2.38-3.17)	1.87 (1.59-2.19)
Any exacerbation during baseline		
No	1.00	1.00
Yes	2.17 (1.98-2.38)	1.51 (1.36-1.68)
Treatment severity step		
0	1.00	1.00
1	1.75 (1.42-2.14)	1.49 (1.21-1.83)
2	1.95 (1.60-2.37)	1.52 (1.25-1.86)
3	2.48 (2.10-2.92)	1.75 (1.47-2.08)
4	2.69 (2.28-3.19)	1.78 (1.49-2.14)
5	4.37 (3.67-5.21)	2.33 (1.90-2.85)
Hypertension		
No	1.00	1.00
Yes	1.54 (1.36-1.74)	1.14 (0.99-1.30)

Cox regression analyses of time to first re-hospitalization.

Only patients under observation 12 months after index event included.

Treatment severity step 0 refers to patients without baseline asthma treatment.

*Comorbidities from secondary care only.

Table 3. Risk of all cause and asthma-related mortality during follow-up by post-index re-hospitalization history

	Patients n	Events n	Crude HR (95% CI)	Adjusted HR (95% CI)
Overall death				
No re-hospitalization	13799	2400	1.00	1.00
Re-hospitalized	1892	531	1.67 (1.52-1.83)	1.16 (1.05-1.27)
Asthma-specific death				
No re-hospitalization	13799	84	1.00	1.00
Re-hospitalized	1892	50	4.49 (3.16-6.37)	2.80 (1.95-4.01)

Adjusted for index age, sex, baseline treatment severity step, baseline exacerbation history and baseline comorbidity index and history of hypertension. HRs estimated using Cox regression models.

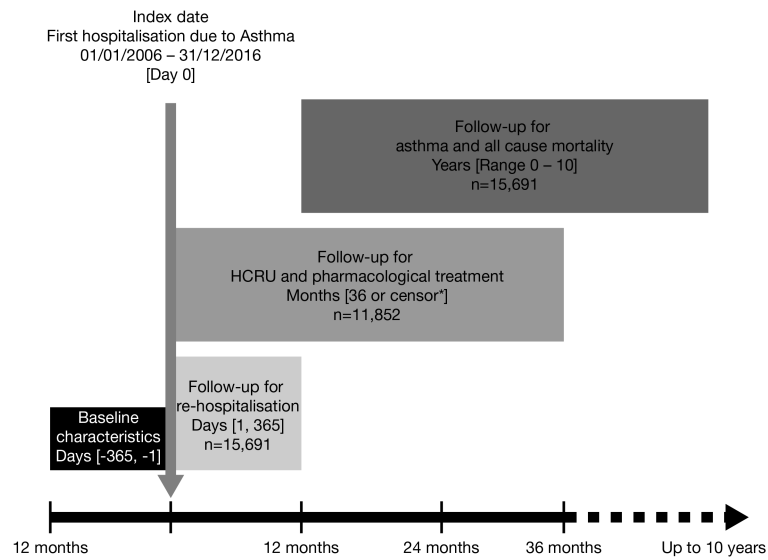
Table 4. Incident rate ratios (IRR) of asthma related and non-asthma related hospital visits during first year of follow-up

	Asthma related hospital visits		Non-asthma related hospital visits	
	IRR (95% CI)	P value	IRR (95% CI)	P value
Sex				
Male	1.00		1.00	
Female	0.94 (0.89-1.00)	0.044	1.02 (0.96-1.08)	0.540
Index age				
6-17	1.00		1.00	
18-44	0.47 (0.43-0.51)		1.29 (1.16-1.42)	
45-64	0.40 (0.37-0.44)		1.36 (1.23-1.50)	
65-80	0.23 (0.20-0.25)		1.25 (1.13-1.39)	
>80	0.13 (0.11-0.14)	<0.001	0.84 (0.75-0.94)	<0.001
Treatment severity step				
0	1.00		1.00	
1	1.14 (1.02-1.27)		0.93 (0.84-1.04)	
2	1.08 (0.97-1.21)		1.05 (0.94-1.17)	
3	1.32 (1.20-1.45)		1.12 (1.02-1.22)	
4	1.54 (1.39-1.70)		1.16 (1.05-1.28)	
5	1.84 (1.60-2.11)	<0.001	1.29 (1.12-1.49)	<0.001
Baseline exacerbation				
0	1.00		1.00	
1-2	1.64 (1.53-1.76)		1.31 (1.23-1.41)	
3+	2.57 (2.31-2.86)	<0.001	1.31 (1.17-1.47)	<0.001
Charlson Comorbidity Index*				
0	1.00		1.00	
1	1.42 (1.32-1.52)		1.50 (1.40-1.62)	
2	1.13 (1.00-1.27)		2.47 (2.23-2.74)	
3+	1.12 (1.00-1.26)	<0.001	3.51 (3.17-3.88)	<0.001
Hypertension				
No	1.00		1.00	
Yes	1.03 (0.93-1.15)		1.30 (1.18-1.42)	

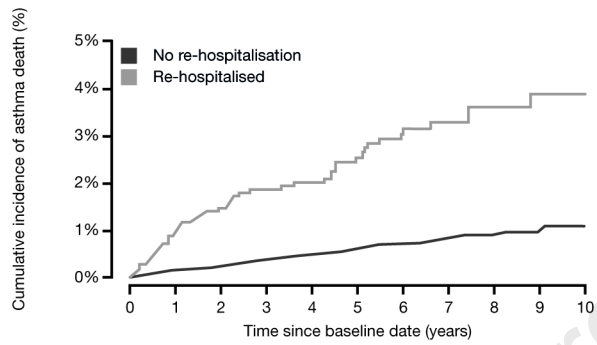
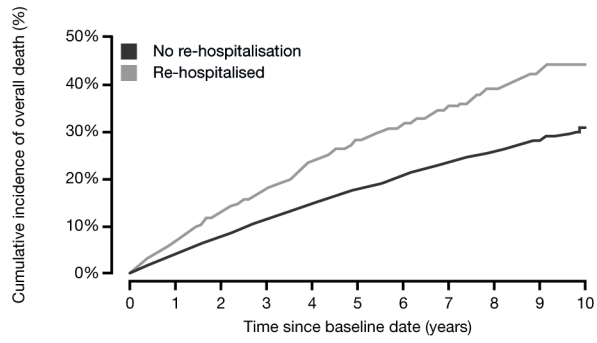
Negative binomial regression model

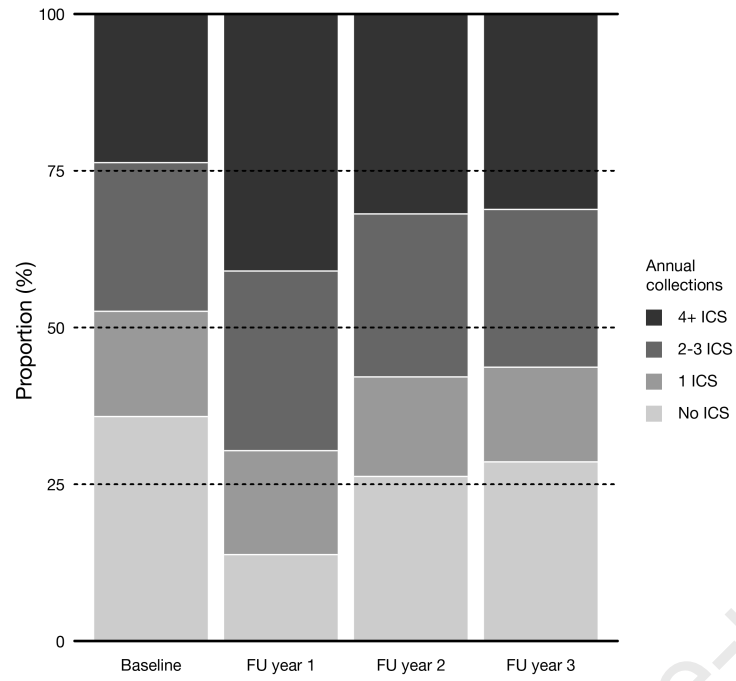
Treatment severity step 0 refers to patients without baseline asthma treatment.

*Comorbidities from secondary care only.



* Death, emigration or end of study Dec 31, 2016, which ever occurred first





Only patients with at least 3 years of follow-up included (n=11,852).