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Hospitalization Rate and 30-day Mortality of Patients with Status Asthmaticus in Denmark

– A 16-year Nationwide Population-based Cohort Study

Research Year Report

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Denmark 2012

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PREFACE

I would like to express my sincere gratitude to Henrik Toft Sørensen for welcoming me to the Department of Clinical Epidemiology and teaching me the art of clinical epidemiology.

Thank you for investing resources in my education, for encouraging my continuing work, and for reminding us all of the importance of respecting spare time. From you, I have learned the process of writing, the dynamics of research, and that there are no limits for the creative mind.

I would also like to express my warmest thankfulness to Else Tønnesen, who welcomed and encouraged me, when I first started this journey of research. Your enthusiasm, engagement, and eagerness, as well as your social skills and humor, have truly been inspiring. You also introduced me to Henrik Toft Sørensen and Christian Fynbo Christiansen.

A special thank you to my primary guide during this year, Christian Fynbo Christiansen. Thank you for your advices and never ending answers, for your patience, flexibility, and always having your door (computer) open. You have put a great effort into my project and supported me whenever needed.

I have appreciated the highly competent and stimulating environment owe to all colleagues at the Department of Clinical Epidemiology. Especially Henrik Gammelager and Lene Rahr Wagner deserve an extra star. Also thank you to all coworkers at the Departments of Anesthesiology and Intensive Care Medicine for inspiring and pleasant meetings during the year.

Finally, thank you to my friends and family for the personal support and love you have given. This year has truly been enriching and full of experience, and you have all been a part of it.

Jennie M. C. Strid

LIST OF ABBREVIATIONS

CII	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPR	Civil Personal Registration Number
CRS	Civil Registration System
DNRP	Danish National Registry of Patients
ED	Emergency Department
ICD-10	International Classification of Diseases, 10 th revision
ICU	Intensive Care Unit
IQR	Interquartile Range
PY	Person-years
SA	Status Asthmaticus

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ABSTRACT

Study objective: To describe rates and 30-day mortality of first hospitalizations for status asthmaticus (SA) during 16 years, to examine the impact of gender, age and comorbidity, and to estimate the number of SA admissions to intensive care units (ICUs).

Methods: In this population-based cohort study, we identified all first-time SA hospitalizations in Denmark in 1996-2011 using medical registries. We characterized the cohort by gender, age, and comorbidity, calculated hospitalization rates per 1,000,000 person-years, and computed the proportion of ICU-admissions in 2005-2011. We estimated 30-day mortality risk standardized to the age-, gender-, and comorbidity composition in 2008-2011. In a sensitivity analysis, we assessed potential misclassification of acute exacerbation of chronic obstructive pulmonary disease (COPD) as SA by excluding patients registered with a concurrent/previous COPD diagnosis.

Results: Of the 5,001 SA hospitalizations identified, 50.5% were male, 40.3% < 15 years old, and 12.4% had comorbidity. Hospitalization rate increased from 48.0 (95% CI 45.1 to 51.1) per 1,000,000 person-years in 1996-1999 to 70.1 (95% CI 66.7 to 73.7) per 1,000,000 person-years in 2008-2011. Standardized 30-day mortality risk declined from 3.3% (95% CI 2.5% to 4.1%) in 1996-1999 to 1.5% (95% CI 0.9% to 2.1%) in 2008-2011. In 2005-2011, 10.1% of SA patients were admitted to ICUs. Hospitalization rates and mortality risk decreased by excluding 939 patients also registered with COPD, but overall temporal changes remained similar.

Conclusions: In 1996-2011, the SA hospitalization rate was less than 100 hospitalizations per 1,000,000 person-years, but increased. The 30-day mortality risk halved to below two percent.

INTRODUCTION

Status asthmaticus (SA) is the life-threatening medical emergency that occurs, when an acute exacerbation in asthma is refractory to initial standard treatment at the emergency department (ED).¹⁻³ SA involves a risk of respiratory failure and urgent intensive care may be needed.⁴

The prevalence of asthma has increased for decades and was recently described as the most common chronic disease among children.⁵⁻⁷ In 2007, WHO reported that 300 million people worldwide had asthma.⁸ The age- and sex standardized asthma prevalence in a state of Canada increased over a 15-year period to 13.3% in 2005, primarily due to increased incidence rates of asthma in children, while overall all-cause mortality declined.⁵ The prevalence of reported diagnosed asthma in younger adults has recently also increased in Denmark.⁹

The current knowledge about acute asthma and SA, including hospitalization rates, severity and prognosis, is ambiguous,^{3,4,6,10-18} and the understanding of overall incidence and mortality risk of SA hospitalizations in the population is complicated by previous studies being difficult to compare because of differences in design and setting. For example, we identified 17 studies on SA hospitalizations and prognosis that clearly were based on the definition of SA described above. Of these were six restricted to adult or pediatric study populations^{3,6,10,12,19,20} and four were based on only one or few hospitals or intensive care units (ICUs).^{3,13,14,20} Furthermore, eight studies included readmissions in their data,^{3,6,12,13,17,18,21} which may affect estimates of hospitalizations and prognosis due to the increased risk of further readmission and worsened prognosis.⁶ To provide more accurate estimates on hospitalization and prognosis of first-time SA, a large population-based longitudinal study is needed.

We therefore conducted this registry-based longitudinal cohort study, including all hospitals and all first-time hospitalizations of SA registered in Denmark, to analyze changes in

hospitalization rates and 30-day mortality risk of SA from 1996 through 2011, to examine the impact of gender, age, and comorbidity, and to assess the proportion of SA patients admitted to an ICU over the recent seven-year period.

METHODS

Study Design and Setting

We conducted this cohort study using population-based medical registries in Denmark. Based on the existence of the relevant registries and the implementation of the International Classification of Diseases, 10th revision (ICD-10), we defined the study period as 1 January 1996 to 31 December 2011. The Danish population (approximately 5.5 million inhabitants²²) has unfettered access to outpatient and inpatient medical care and partial reimbursement for prescribed medications through the tax-funded national health care system. We linked population databases to medical records at individual level using the unique Danish 10-digit identification number (CPR) assigned to all Danish citizens and residents by the Danish Civil Registration System (CRS) since 1 January 1968.²³ Data on ICU admissions have been routinely registered in the Danish National Registry of Patients (DNRP)²⁴ since 1 January 2005,²⁵ which enabled us to assess the proportion of patients admitted to an ICU during the last seven years of the study period.

Patients with Status Asthmaticus

We identified all residents with a first inpatient SA hospitalization occurring in Denmark from 1996 through 2011 by searching the DNRP. The DNRP was established in 1977 and contains information on patient contacts with Danish non-psychiatric hospitals, which all hospitals are required to transfer electronically to the registry. Since 1995, also data on

outpatient contacts and ED visits are registered in addition to the hospital stays. Records in the DNRP contain information on hospital and department codes, admission and discharge dates, discharge diagnoses (one primary diagnosis and up to 19 secondary diagnoses), major medical treatments, and surgical procedures. Diagnoses are coded according to the ICD-10 since 1994. Before 1994, the 8th revision was used.²⁴ The physician discharging the patient reviews the medical record and dictates a discharge summary, including diagnoses and relevant ICD codes. The codes are then entered into the hospital registry by a medical secretary and finally electronically transmitted to the National Board of Health. The recorded information has basically been the same since the establishment in 1977, but changes have taken place over time, which have to be considered when analyzing the data retrieved.

We used the ICD-10 code J46 to identify all patients registered with a primary or secondary diagnosis of *status asthmaticus*. In a sensitivity analyses, we assessed potential misclassification of acute exacerbation of chronic obstructive pulmonary disease (COPD) as SA, by identifying and excluding those of our study participants that were registered with a concurrent/previous COPD diagnosis (ICD-10 code J44). In another sensitivity analysis, we also identified all patients registered with a first SA diagnosis after only have visited the ED, but not been hospitalized.

Demographics and Mortality

We obtained data from the CRS on gender, age and death. The CRS is electronically updated daily and contains complete information for all Danish residents on gender, residence, vital status and date of birth, death and emigration.

We divided the SA patients into five age groups, categorized as “0-1 years”, “2-14 years”, “15-39 years”, “40-59 years”, and “ \geq 60 years”. We chose to analyze data separately for children aged 0-1 years, because of the uncertainty of diagnosing respiratory conditions in

young children.²⁶ Also, the age definitions were set as we aimed to analyze the impact of age on hospitalizations and mortality, and to increase comparability between our study and literature that does not include patients of all ages in the same analysis.

Comorbidity

We obtained information on comorbid conditions by searching the DNRP for any inpatient and outpatient hospital diagnoses for conditions included in the Charlson Comorbidity Index (CCI) recorded in a five years before SA or concurrent with the hospitalization for SA.²⁷ The CCI, a comorbidity scoring system adapted for hospital discharge data, includes 19 disease conditions (Appendix 1). Each condition is assigned a weight between one and six reflecting the prognostic impact, and the CCI score is computed as the sum of the weights. We defined severity of comorbidity as “comorbidity level”, with CCI values of 0 (low), 1-2 (medium), and ≥ 3 (high), based on the CCI scores (Appendix 1). We excluded chronic pulmonary diseases from the CCI, because these include the diagnostic codes for status asthmaticus and chronic obstructive pulmonary disease, which are used in the present study.

Validation of the *Status Asthmaticus* Registry Diagnosis

In order to validate the diagnosis of SA coded by physicians in the DNRP according to the ICD-10, we randomly selected three patients per calendar year from 1 January 1994 to 31 December 2009 from a subset of our cohort in North Jutland (approximate population 500,000²²) and retrieved their discharge summaries. Based on the definition of SA¹⁻³ and the amount of detailed data available in the discharge summaries, the diagnosis was confirmed when ≥ 2 of the following criteria were considered to be fulfilled: (1) presence of symptoms of asthma (for example dyspnea, wheezing, cough, chest tightness, and/or decreased peak flow); (2) the condition was refractory to standard initial treatment (inhalation

of bronchodilators and/or steroids) and further hospital care was required; (3) the condition was a medical emergency. A medical bachelor (JMCS) conducted the primary review and a medical doctor (HG) re-reviewed the discharge records in case of uncertainty. If disagreement occurred, a second medical doctor (CFC) assessed the particular question and the majority determined the outcome. We calculated the positive predictive value²⁸ including a 95% confidence interval (CI) of the SA registry diagnosis as the percentage proportion of our random sample with a confirmed registry diagnosis according to the algorithm above.

Statistical Analysis

We computed frequencies of first SA hospitalization for the Danish population and within categories of gender, age group, and comorbidity level. We also reported interquartile range (IQR) and median of age. The results are presented both for the study period as a whole and for four-year calendar periods (1996-1999, 2000-2003, 2004-2007, and 2008-2011). For the period 1 January 2005 to 31 December 2011, we also assessed the proportion of first-time SA patients that were admitted to an ICU.

We estimated annual rates of first hospitalization and 95% CIs for all patients and for different genders and age groups. The rates were calculated by dividing the number of first SA hospitalizations by total time at risk of disease among the population. The risk time defined using the estimated annual Danish population on 1 January of the year of interest,²² assuming that the number of individuals leaving respectively entering the Danish population was similar, and that each person was at risk for the entire calendar year and therefore contributed with one year each to the denominator. For gender and age groups, we used the corresponding portion of the population as the denominator. The resulting hospitalization rates are all reported per 1,000,000 person years (PY). To calculate mean hospitalization rate for the four-year calendar periods, the same algorithm was used but with the total number of

hospitalizations during the four years in question as nominator and the total population number for the corresponding years as denominator.

Patients were followed until death or up to 30 days after hospital admission, whichever came first. We computed 30-day mortality risk for all patients within each four-year calendar period. We used direct standardization²⁹ to calculate 30-day mortality risk, including 95% CIs, standardized to the gender, age group, and comorbidity (yes/no) distribution in the 2008-2011 period. We used presence/absence of comorbidity (CCI score of $\geq 1/0$, respectively) instead of comorbidity level in the standardization in order to increase the number of patients in the subgroups of the analysis.

We also conducted three sensitivity analyses. First, an acute exacerbation of COPD can be clinically difficult to distinguish from SA and may give rise to misclassification in the study.³⁰ To assess potential misclassification of an acute exacerbation in COPD as SA, we therefore identified and excluded all SA patients registered with a previous or concurrent COPD diagnosis in the DNRP, repeated all analyses, and analyzed potential changes in the results. Second, some SA patients are diagnosed during an ED visit without being further hospitalized. These may actually have SA and eventually die in the ED. We therefore also included all patients registered with a first SA diagnosis after an ED visit only and repeated the statistical analyses, focusing on changes in the proportion of SA diagnosis of SA over time and by age, specifically. Finally, we also examined the number of hospitalizations registered with SA as primary diagnosis by excluding all patients registered with SA as only as a secondary diagnosis. As for ED visits, we focused on changes in the proportion of registered SA diagnosis by age group.

All statistical analyses were performed using Stata Release 11 (StataCorp. LP, College Station, Texas, USA).

RESULTS

We identified 5,001 patients hospitalized with a first SA diagnosis in Denmark from 1996 through 2011. Of these, 50.5% were male, 40.3% < 15 years old, and 12.4% had any comorbidity (Table 1).

Hospitalizations

The total number of first-time SA hospitalizations in Denmark increased during the study period from 1,015 hospitalizations in 1996-1999 to 1,549 hospitalizations in 2008-2011 (Table 1). This trend was also demonstrated by the hospitalization rate of all SA patients during four-year calendar periods. The hospitalization rate was 48.0 (95% CI 45.1 to 51.1) per 1,000,000 PY in 1996-1999, 67.1 (95% CI 57.8 to 64.4) per 1,000,000 PY in 2004-2007, and 70.1 (95% CI 66.7 to 73.7) per 1,000,000 PY in 2008-2011. The annual hospitalization rate for all patients is illustrated as “Total” in Figure 1 and Figure 2, respectively.

The gender distribution of the cohort was similar during the study period, except for a higher hospitalization rate in 2004-2007 for males (67.6; 95% CI 62.7 to 72.7 per 1,000,000 PY) than for females (54.7; 95% CI 50.4 to 59.2 per 1,000,000 PY). (Table 1 and Figure 1).

The proportion of younger hospitalized SA patients increased during the study period: the proportion of the cohort aged < 40 years was 39.2% in 1996-1999 and peaked in 2004-2007 with 72.3% (Table 1). The median age declined from 51.4 years (IQR 23.1 years to 68.7 years) in the 1996-1999 period to 11.8 years (IQR 3.3 years to 43.7 years) and 17.2 years (IQR 5.6 years to 48.0 years) in the 2004-2007 and 2008-2011 period, respectively (Table 1) primarily because more children were hospitalized with an SA diagnosis in the late time periods (Figure 2). Primarily for < 2 year olds, did the proportion of SA hospitalizations decline during the end of the study period (12.0% in 2008-2011 compared with 17.8% in

2004-2007). This was also reflected in the median age of the cohort, which increased to 17.2 years (IQR 5.6 years to 48.0 years) in 2008-2011. Hospitalization rates for separate age groups are illustrated in Figure 2. During the whole 16-year period, there was a steady change in hospitalization rate of 2-14 year olds, which increased from 44.9 (95% CI 37.9 to 52.9) per 1,000,000 PY in 1996-1999 to 157.3 (95% CI 144.4 to 171.0) per 1,000,000 PY in 2008-2011. An increase in hospitalization rate was also observed for adults aged 15-39 years, for whom the rate was 27.3 (95% CI 25.6 to 33.5) per 1,000,000 PY in 1996-1999 compared with 47.8 (95% CI 42.8 to 53.3) per 1,000,000 PY in 2008-2011. A conspicuous peak in the hospitalization rate for < 2 year olds (452.8; 95% CI 396.8 to 514.6 per 1,000,000 PY) was observed in 2004-2007. In 1996-1999, the hospitalization rate for < 2 year olds was estimated to 91.1 (95% CI 67.6 to 120.1) per 1,000,000 PY. A sub analysis of the group revealed a majority of patients aged between one and two years old (68.5%). During the study period, the hospitalization rate for SA patients ≥ 60 years halved (96.0; 95% CI 86.8 to 105.9 per 1,000,000 PY in 1996-1999 compared with 38.7; 95% CI 33.2 to 44.9 per 1,000,000 PY in 2004-2007), while it was lower and kept more stable for SA patients aged 40-59 years than for the other age groups described (Figure 2).

In all four-year calendar periods, the majority of patients had no comorbidity of those included in the CCI (Table 1). The proportion of patients with comorbidity (≥ 1) declined from the start of the study period (18.1% in 1996-1999) to the end (10.7% in 2008-2011), which could be related to increased proportion of younger patients in the cohort over time.

From 1 January 2005 to 31 December 2011, 256 SA patients were admitted to an ICU, corresponding to 10.1% of all 2,524 first SA hospitalizations during these years.

Mortality

In total, 162 (3.2%) of the 5,001 SA patients were registered as not being alive 30 days after their respectively first hospitalization for SA (Table 1). The number of deaths decreased from 72 deaths (7.1%) in 1996-1999 to 23 deaths (1.5%) in 2008-2011. The standardized 30-day mortality risk after a first-time SA hospitalization declined during the 16-year period from 3.3% (95% CI 2.5% to 4.1%) in 1996-1999 to 1.5% (95% CI 0.9% to 2.1%) in 2008-2011 (Table 1).

Sensitivity Analyses

After exclusion of 939 (18.8%) SA patients registered with a previous and/or concurrent COPD diagnosis, 4,062 patients were included in the first sensitivity analysis (Appendix 2, Table 3). We observed a lower rate of first SA hospitalizations in all four-year calendar periods after the exclusion while temporal changes over time remained similar. Also the 30-day mortality risk decreased during the whole study period and the decrease was most pronounced in the 2008-2011 period with a 30-day mortality risk of 0.8% (95% CI 0.3% to 1.3%) compared with 1.5% (95% CI 0.9% to 2.1%) before the exclusion of patients with a COPD registry diagnosis. The median age of the cohort decreased from 27.7 years to 17.0 years, primarily because of decreased hospitalization rates of patients aged ≥ 40 years (Appendix 2, Figure 4). For example, the hospitalization rate of SA patients ≥ 60 years was 42.1 (95% CI 36.1 to 48.8) per 1,000,000 PY in 1996-1999 compared with 96.0 (95% CI 86.8 to 105.9 per 1,000,000 PY) in the main analysis. For patients aged 40-59 years, the hospitalization rate in 2000-20003 decreased from 37.6 (95% CI 32.9 to 42.9) per 1,000,000 PY to 25.9 (95% CI 22.0 to 30.3) per 1,000,000 PY. The exclusion of patients with a COPD registry diagnosis also resulted in a smaller proportion of patients with comorbidity (7.9% compared with 14.7% before) (Appendix 2, Table 3).

In the second sensitivity analysis, the inclusion of 1,312 patients registered with only an ED diagnosis of SA resulted in an increased number SA of registry diagnosis in all four-year calendar periods, but also changed the trend over time (Appendix 2, Table 4). Instead of an increased proportion of first-time SA hospitalizations during the study period from 1,015 (20.3%) hospitalizations in 1996-1999 in to 1,549 (31.0%) hospitalizations in 2008-2011, we observed a decline from 1996-1999 (1,686 [26.7%] hospitalizations) to 2000-2003 (1,497 [23.4%] hospitalizations), stabilization, and finally an increase in 2008-2011 (1,681 [26.6%] hospitalizations), as also seen in the main analysis. The median age of the cohort was higher in all four-year calendar periods, but changes in the age composition of the cohort was greatest during the first half of the study period due to a larger proportion of SA patients aged ≥ 60 years.

Finally, by excluding 860 (17.1%) patients registered only with a secondary diagnosis of SA in the registry, the median age of the cohort declined in all four-year calendar periods, however, no other pronounced changes in hospitalization trends or age composition of the cohort were observed (Appendix 2, Table 4).

Validation of the *Status Asthmaticus* Registry Diagnosis

Out of the random sample of 48 first hospitalizations from the region of Jutland between 1994 and 2009, 20 discharge records were reviewed by a second reviewer, and 12 of these were re-reviewed by a third reviewer because of disagreement between the first two reviewers. The SA diagnosis was confirmed in 42 hospitalizations, which corresponded to a positive predictive value of 87.5% (95% CI 74.7% to 95.3%).

LIMITATIONS

A weakness of this study is the potentially incomplete registration of SA in the DNRP, which could have led us to underestimate the hospitalization rate. However, the DNRP covers 99.4% of all discharge records³¹ and by including all hospitals within a homogenous tax-funded health care system, we increased the chance of potential SA patients to be registered in the DNRP and reduced the risk of introducing selection bias. Furthermore, data on follow-up were virtually complete.

Any uncertainty of the estimates related to the implementation of the ICD-10 in 1994 was limited by our choice of first starting the study in 1996. The potential proneness to changes in registration practices of the study was minimized owe to the use of the same revision of ICD throughout the study period. Also, in a sensitivity analysis, we examined potential changes in the number of SA registration diagnoses by including patients registered with only an ED visit for SA. The observed decline in additional SA registrations over time could possibly be explained by changed registration practices, but also that patients have improved their skills to detect and treat worsening of asthma, and increased use of general practitioner visits, telephone – and e-mail consultations, and outpatient clinics before asthma progresses to SA.³² Also, patients have access to emergent telephone consultations with general practitioners out of their working hours, and these consultations are not registered in the DNPR.

The clinical diagnostic process and registration practice of acute exacerbations in asthma can be difficult. Although a definition of status asthmaticus has been suggested,¹⁻³ there is a lack of consensus in previous studies that used different definitions including acute asthma, severe asthma, and admission as a result of asthma.^{3,4,10,13,17-19} Furthermore, in the ICD-10, no other code related to asthma than SA underlines the emergent character of the condition. Therefore clinicians could be prone to diagnose and register less serious asthmatic attacks as *status*

asthmaticus. However, the positive predictive value for the SA registry diagnosis in the DNRP was high and any uncertainty of the validation process due to limited information in the discharge records reflects the challenge in diagnosing acute respiratory diseases. In extension, we also assessed possible misclassification of acute exacerbation in COPD as SA and excluded patients registered with SA only as secondary diagnosis, respectively.

DISCUSSION

The present study is, to our awareness, the first nationwide study of patients of all ages with a first-time hospitalization for SA. We found that the SA hospitalization rate increased over a 16-year period while the associated 30-day mortality risk decreased, primarily explained by increased hospitalization rates of patients of a younger age and with less comorbidity. In Denmark, one out of ten hospitalized SA patients was admitted to an ICU.

Our finding of increasing first hospitalization rates, especially among children, is in line with the tripling in the rate of pediatric ICU admissions from 1992 and 2006 found by Hartman et al. in their pediatric study (28,309 participants) based on hospitalization and ICU data from the state of New Jersey, US.¹² However, the same investigators also observed a halving in the hospitalization rate for SA (1.98 per 1,000 children in 1992 and 0.93 per 1,000 children in 2006). Hartman et al.'s finding of an increased rate of ICU admissions was confirmed by Mannix et al,¹¹ whilst Han et al. observed a decreased number of severe asthma ICU admissions in 2000-2001 (0.8 admissions per month) compared with 1990-1991 (3.1 admissions per month).¹³ The study of Han et al. was though based on data from only one medical center (59 admissions) in New York, US, and included readmissions, which results in an overestimated incidence of hospitalizations. Furthermore, data on trends in severity are contradictory^{13,14} and Malmström et al. reported almost a three-fold increase in pediatric

hospital admissions as a result of asthma in five Finnish university hospitals between 1975 and 1995, but no change in ICU admissions.¹⁰ The results described are diverse and the studies – except the one of Mannix et al. – analyzed hospital admissions separately from ICU admissions, complicating direct comparison with our study. It can be discussed whether trends in ICU admissions versus hospitalizations for SA can be a marker for changes in disease severity, however, the SA hospitalization rates we observed among children from 1996 to 2011 were lower and more stable than those observed in the previous studies.

Other studies have reported differences in gender distribution among hospitalized SA patients and a relation between gender and age, suggesting that gender is a determinant for SA.^{14,33,34} The results of these studies have though been inconsistent and not supported by our study, as we observed a similar distribution of hospitalizations among females and males throughout our study period. Of our different sub analyses, age seemed to be the most important factor. Hospitalization rates were seen to increase among the young over time, which is in line with the general reports on rising prevalence of asthma among children.^{5,7}

The 30-day mortality we observed was low compared to other studies, which showed SA mortality ranging from 0.4% to 12% and even higher among patients who received mechanical ventilation.^{4,15-17,20} One possible explanation is that the present study focused on first-time hospitalizations and analyzed all hospitalizations and ICU admissions together as readmission increase the risk for further readmission and worsen prognosis. Also, as discussed before, the patients admitted to the ICU are supposedly in a worse condition than those patients not requiring intensive care, and therefore have a worse prognosis. The decrease in mortality risk observed over time in our study is consistent with the findings of Stow et al.,¹⁸ who reported a significant decline in annual mortality risk from acute severe asthma between 1997 (4.7%) and 2003 (1.1%), and Gershon et al.,⁵ who reported decreased overall all-cause mortality from asthma between 1996 and 2005.

Several potential mechanisms could have influenced the findings of this study: increased prevalence of asthma, modifications in treatment and management of asthma over time, and changed threshold for hospitalization. Different ways of living – both over time but also between different age groups – have been discussed as one underlying cause of changed asthma prevalence.⁹ Fluctuations in hospitalization rates for SA could also be related to viral infections, in children especially, that could provoke respiratory symptoms. Because of the difficult clinical diagnostic process, the patient could be considered to be in status asthmaticus hence registered with SA. Similarly, it is possible that some patients with an acute exacerbation in COPD are coded as status asthmaticus. Our sensitivity analysis of misclassification of COPD revealed a greater portion of older patients with a previous or concurrent COPD registry diagnosis than younger, however, no pronounced changes in time were observed. The fact that the inclusion of ED visits for SA and exclusion of patients with SA as a secondary diagnosis also affected the median age of the study population further reflects the difficulty in diagnosing acute exacerbations in pulmonary diseases. In this case, primarily the older population, which could be related the vulnerability among elderly for respiratory conditions. Furthermore, the intensive care of pediatric patients has been reorganized and during the last years, which have resulted in a centralization of pediatric ICUs and possibly an improved prognosis for these patients.³⁵ In extension, plausible changes in registration practices, over time, geographically, and/or related to pediatric/adult units that we are unaware of, could also have had an effect.

Future perspectives include examination of possible underlying mechanisms behind our findings. However, at this point in time, we have no access to such data. Neither do we have access to conduct studies on trends in severity of disease. As prevalence of asthma has increased, more individuals are at risk of developing status asthmaticus, and because of that reason our result of increased hospitalization rate of first-time SA is not surprising. However,

during the same time, we also observed an improved prognosis. This observation could be explained by less severe cases of SA, for example owe to patients seeking professional health care earlier in the progress of developing disease or because of enlarged access to health care. Another mechanism could be that patients of younger age have fewer comorbid conditions than older and have in general a greater chance of surviving an emergent condition. Finally, it is possible that the observed decrease in mortality risk associated to status asthmaticus is a result of improved knowledge, management and treatment for asthma and status asthmaticus over time.

CONCLUSIONS

We found that first-time hospitalization rate of status asthmaticus in Denmark was lower than 100 hospitalizations per 1,000,000 PY, but increased over a 16-year period. Meanwhile, the associated 30-day mortality risk halved to below two percentages. The observations were primarily related to increased hospitalization rates of younger patients with less comorbidity.

FUNDING

Aarhus University, Aarhus University Hospital, and the Department of Clinical Epidemiology, Aarhus, Denmark funded the present work.

ACKNOWLEDGEMENTS

We are grateful for the work of Martin Berg Johansen, who retrieved all data from the registries used and controlled the statistical analyses. We are also thankful to Elisabeth Kristoffersen, who retrieved the medical discharge records used in the validation study of the *status asthmaticus* registry diagnosis in the DNRP, and to Henrik Gammelager, who assisted in the conduction of validation study.

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TABLES AND FIGURES

Table 1. Characteristics of patients with first status asthmaticus hospitalization in Denmark, 1996-2011.

	All Years		Stratified by Calendar Period		
	1996-2011	1996-1999	2000-2003	2004-2007	2008-2011
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
All Patients	5,001 (100.0)	1,015 (100.0)	1,113 (100.0)	1,324 (100.0)	1,549 (100.0)
Gender					
Females	2,474 (49.5)	540 (53.2)	557 (50.0)	599 (45.2)	778 (50.2)
Males	2,527 (50.5)	475 (46.8)	556 (50.0)	725 (54.8)	771 (49.8)
Age (years)					
Age group					
0-1	534 (10.7)	50 (4.9)	63 (5.7)	235 (17.8)	186 (12.0)
2-14	1,481 (29.6)	145 (14.3)	301 (27.0)	485 (36.6)	550 (35.5)
15-39	1,018 (20.4)	203 (20.0)	248 (22.3)	237 (17.9)	330 (21.3)
40-59	866 (17.3)	218 (21.5)	225 (20.2)	189 (14.3)	234 (15.1)
≥60	1,102 (22.0)	399 (39.3)	276 (24.8)	178 (13.4)	249 (16.1)
Median (IQR)	27.7 (6.7, 56.6)	51.4 (23.1, 68.7)	35.2 (9.5, 60.0)	11.8 (3.3, 43.7)	17.2 (5.6, 48.0)
Comorbidity Level					
0	4,383 (87.6)	831 (81.9)	965 (86.7)	1,204 (90.9)	1,383 (89.3)
1-2	503 (10.1)	162 (16.0)	120 (10.8)	94 (7.1)	127 (8.2)
≥3	115 (2.3)	22 (2.2)	28 (2.5)	26 (2.0)	39 (2.5)
Sensitivity Analyses					
COPD excluded*	939 (18.8)	324 (31.9)	246 (22.1)	191 (14.4)	178 (11.5)
ED visits included*	1,312	671 (39.8)	366 (24.8)	143 (9.8)	132 (7.9)
Secondary SA registry diagnosis excluded*	860 (17.2)	191 (18.8)	233 (20.9)	219 (16.5)	217 (14.0)
30-day Mortality Risk					
No. deaths	162 (3.2)	72 (7.1)	38 (3.4)	29 (2.2)	23 (1.5)
Standardized mortality, %† (95% CI)		3.3 (2.5, 4.1)	2.3 (1.6, 3.0)	2.6 (1.7, 3.5)	1.5 (0.9, 2.1)

* The number excluded/included in the sensitivity analysis

† Standardized to the gender, age group, and comorbidity (yes/no) distribution in the 2008-2011 period.

Abbreviations: IQR, Interquartile Range; COPD, Chronic Obstructive Pulmonary Disease; ED, Emergency Department; SA, Status Asthmaticus; CI, Confidence Interval

Figure 1. First hospitalization rates of patients with status asthmaticus in Denmark 1996-2011, stratified by gender.

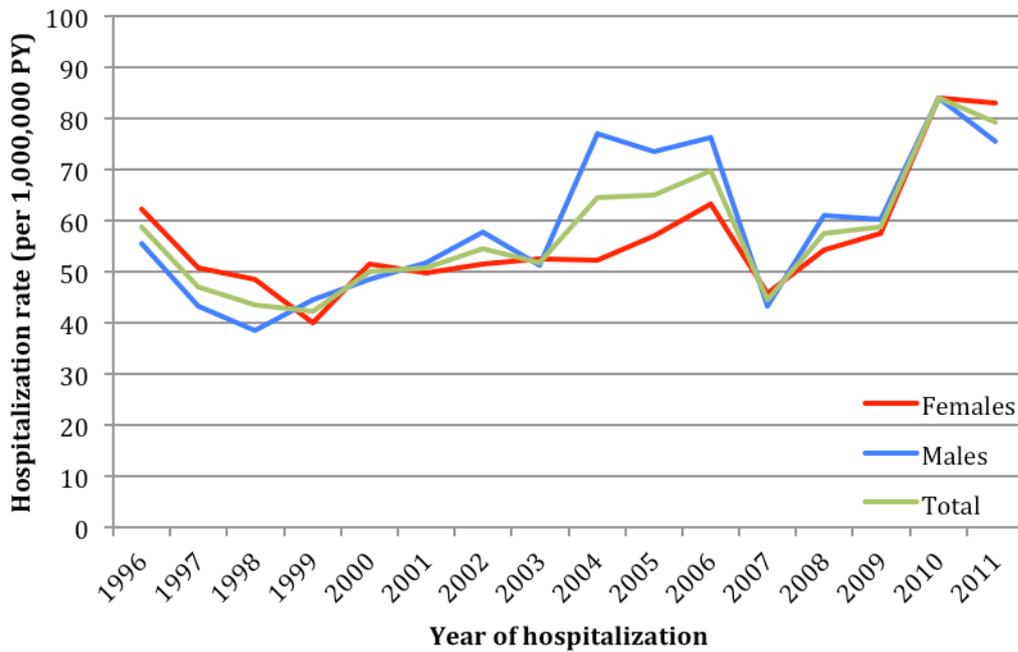
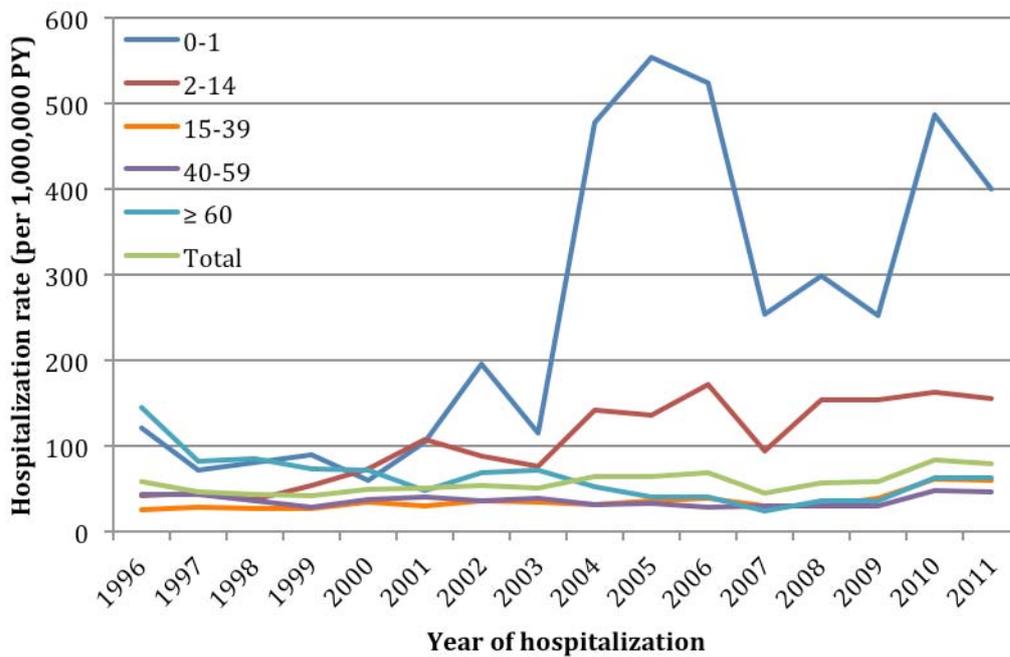


Figure 2. First hospitalization rates of patient with status asthmaticus in Denmark, 1996-2011, stratified by age group (years).



Appendices

APPENDIX 1: THE CHARLSON COMORBIDITY INDEX

The Charlson Comorbidity Index is a widely used comorbidity scoring system adapted for hospital discharge data. Nineteen different disease groups are included and each group is assigned one to six points depending on the strength of the relationship between the disease and the mortality during the following diseased (Table 2). A thorough validation study of the diagnoses included in the CCI revealed an overall positive prediction value of 98%.²⁷

Table 2. The Charlson Comorbidity Index

Charlson Comorbidity Index disease	ICD-10 Codes	Score
1 Myocardial infarction	I21; I22; I23	1
2 Congestive heart failure	I50; I11.0; I13.0; I13.2	1
3 Peripheral vascular disease	I70; I71; I72; I73; I74; I77	1
4 Cerebrovascular disease	I60-69; G45; G46	1
5 Dementia	F00-F03; F05.1; G30	1
6 Chronic pulmonary disease	J40-47; J60-67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7 Connective tissue disease	M06; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86	1
8 Ulcer disease	K22.1; K25-K28	1
9 Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
10 Diabetes Mellitus, Type 1 Diabetes Mellitus, Type 2	E10.0; E.10.1; E10.9 E11.0; E11.1; E11.9	1
11 Hemiplegia	G81; G82	2
12 Moderate/severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-19; Q61	2
13 Diabetes Mellitus, Type 1 and 2 with end organ damage	E10.2-E10.8 □ E11.2-E11.8	2
14 Any tumor	C00-C75	2
15 Leukemia	C91-C95	2
16 Lymphoma	C81-C85; C88; C90-C96	2
17 Moderate/severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18 Metastatic solid tumor	C76-C80	6
19 AIDS	B21-B24	6

Abbreviations: ICD, International Classification of Diseases, 10th revision; AIDS, Acquired Immune Deficiency Syndrome.

APPENDIX 2: SENSITIVITY ANALYSES – TABLES AND FIGURES

Table 3. Characteristics of patients with first status asthmaticus hospitalization in Denmark, 1996-2011. Patients with a previous/concurrent registry diagnosis of COPD excluded.

	All Years	Stratified by Calendar Period			
	1996-2011	1996-1999	2000-2003	2004-2007	2008-2011
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
All Patients	4062 (100.0)	691 (100.0)	867 (100.0)	1,133 (100.0)	1,371 (100.0)
Gender					
Females	1,947 (47.9)	352 (50.9)	418 (48.2)	498 (44.0)	679 (49.5)
Males	2,115 (52.1)	339 (49.1)	449 (51.8)	635 (56.1)	692 (50.5)
Age (years)					
Age group					
0-1	551 (12.8)	46 (6.7)	62 (7.2)	232 (20.5)	181 (13.2)
2-14	1,430 (35.2)	143 (20.7)	282 (32.5)	470 (41.5)	535 (39.0)
15-39	954 (23.5)	197 (28.5)	226 (26.1)	221 (19.5)	310 (22.6)
40-59	595 (14.7)	130 (18.8)	155 (17.9)	126 (11.1)	184 (13.4)
≥60	562 (13.8)	175 (25.3)	142 (16.4)	84 (7.4)	161 (11.7)
Median (IQR)	17.0 (5.3, 44.3)	34.8 (11.7, 60.2)	26.4 (7.9, 48.8)	9.5 (2.6, 32.5)	13.8 (4.9, 40.3)
Comorbidity Level					
0	3,742 (92.1)	614 (88.9)	791 (91.2)	1,069 (94.4)	1,268 (92.5)
1-2	271 (6.7)	72 (10.4)	60 (6.9)	53 (6.7)	86 (6.3)
≥3	49 (1.2)	5 (0.72)	16 (1.9)	11 (1.0)	17 (1.2)
30-day Mortality Risk					
No. deaths	82 (2.0)	32 (4.6)	22 (2.5)	17 (1.5)	11 (0.8)
Standardized mortality, % (95% CI)*		2.5 (1.7, 3.4)	1.8 (1.1, 2.5)	2.2 (1.2, 3.2)	0.8 (0.3, 1.3)

* Standardized to the gender, age group, and comorbidity (yes/no) distribution in the 2008-2011 period.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; IQR, Interquartile Range; CI, Confidence Interval.

Figure 3. First hospitalization rates of patients with status asthmaticus in Denmark, 1996-2011, stratified by gender. Patients with registry diagnosis of COPD excluded.

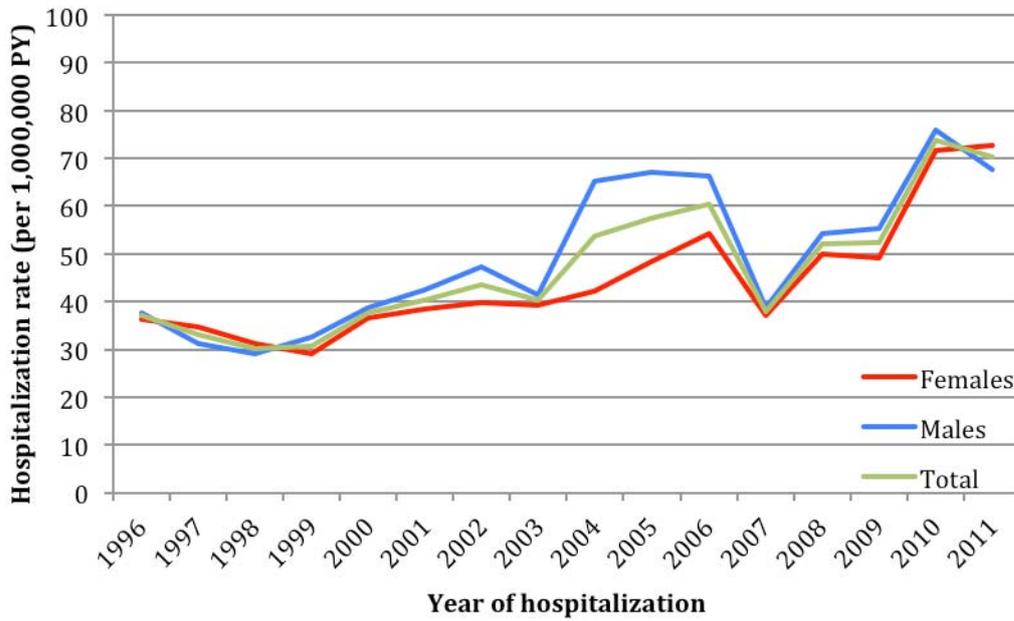


Figure 4. First hospitalization rates of patients with status asthmaticus in Denmark, 1996-2011, stratified by age group (years). Patients with registry diagnosis of COPD excluded.

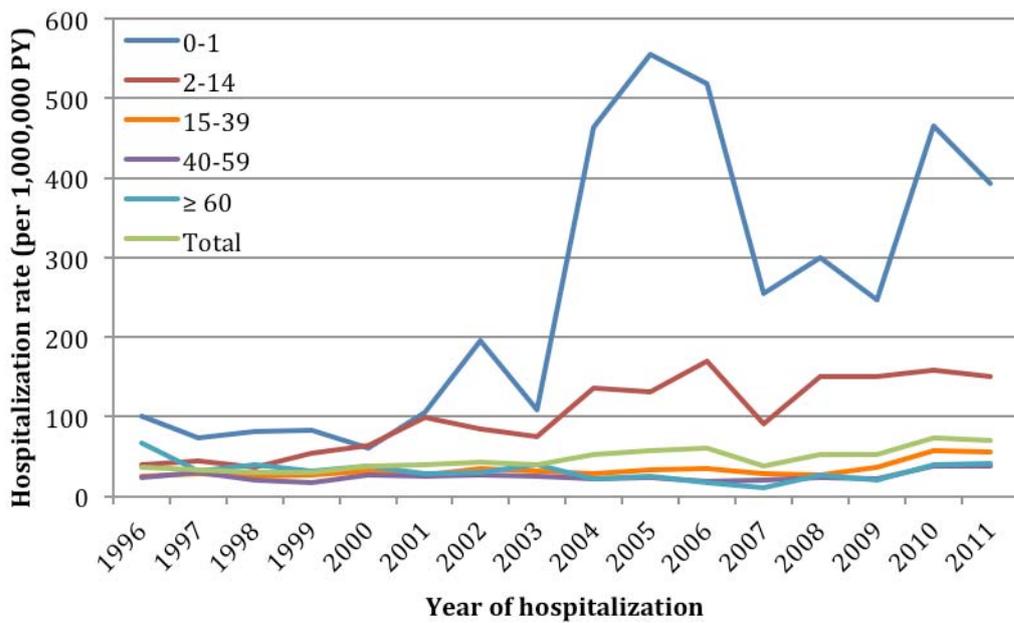


Table 4. Characteristics of patients with first status asthmaticus hospitalization in Denmark, 1996-2011, Patients registered with a) status asthmaticus during an “ED visit” included, and b) status asthmaticus as a “secondary diagnosis” excluded.

	All Years	Stratified by Calendar Periods			
	1996-2011	1996-1999	2000-2003	2004-2007	2008-2011
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
a) ED Visits Included					
All Patients	6,313 (100.0)	1,686 (100.0)	1,479 (100.0)	1,467 (100.0)	1,681 (100.0)
Age (years)					
Age groups					
0-1	572 (9.1)	71 (4.2)	72 (4.9)	238 (16.2)	191 (11.4)
2-14	1,569 (24.9)	175 (10.4)	333 (22.5)	496 (33.8)	565 (33.6)
15-39	1,264 (20.0)	307 (18.2)	306 (20.7)	278 (19.0)	373 (22.2)
40-59	1,145 (18.1)	358 (21.2)	302 (20.4)	220 (15.0)	265 (15.8)
≥60	1,763 (27.9)	775 (46.0)	466 (31.5)	235 (16.0)	287 (17.1)
Median (IQR)	35.5 (8.7, 62.4)	57.4 (29.0, 70.8)	42.2 (11.9, 64.6)	15.0 (3.9, 47.5)	19.7 (6.0, 49.5)
b) Secondary SA Registry Diagnosis Excluded					
All Patients	4,141 (100.0)	824 (100.0)	880 (100.0)	1,105 (100.0)	1,332 (100.0)
Age (years)					
Age groups					
0-1	479 (11.6)	42 (5.1)	59 (6.7)	212 (19.2)	166 (12.5)
2-14	1,372 (33.1)	132 (16.0)	269 (30.6)	454 (41.1)	517 (38.8)
15-39	883 (21.3)	180 (21.8)	220 (25.0)	201 (18.2)	282 (21.2)
40-59	682 (16.5)	181 (22.0)	171 (19.4)	135 (12.2)	195 (14.6)
≥60	725 (17.5)	289 (35.1)	161 (18.3)	103 (9.3)	172 (12.9)
Median (IQR)	21.7 (5.8, 51.0)	47.8 (20.0, 66.5)	29.4 (8.3, 53.0)	10.0 (2.9, 35.8)	14.2 (5.1, 43.1)

Abbreviations: ED, Emergency Department; IQR, Interquartile Range; SA, Status Asthmaticus.

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