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Manuscript Draft

Manuscript Number: YRMED-D-19-00518R2

Title: Multinational cohort study of mortality in patients with asthma and severe asthma

Article Type: Research paper

Section/Category: Asthma and Allergy

Keywords: Asthma
Mortality
Epidemiology
Multidatabase
Cohort

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Abstract: Background: Data on the risk of death following an asthma exacerbation are scarce. With this multinational cohort study, we assessed all-cause mortality rates, mortality rates following an exacerbation, and patient characteristics associated with all-cause mortality in asthma.
Methods: Asthma patients aged ≥18 years and with ≥1 year of follow-up were identified in 5 European electronic databases from the Netherlands, Italy, UK, Denmark and Spain during the study period 1st January 2008 - 31st December 2013. Patients with asthma-COPD overlap were excluded. Severe asthma was defined as use of high dose ICS + use of a second controller. Severe asthma exacerbations were defined as emergency department visits, hospitalizations or systemic corticosteroid use, all for reason of asthma.
Results: The cohort consisted of 586,436 asthma patients of which 42,611 patients (7.3%) had severe asthma. The age and sex standardized all-cause mortality rates ranged between databases from 5.2 to 9.5/1,000 person-years (PY) in asthma, and between 11.3-14.8/1,000 PY in severe asthma. The all-cause mortality rate in the first week following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY. Mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. Higher age , male gender, comorbidity, smoking, and previous severe asthma exacerbations were associated with a higher risk of mortality.

Conclusion: All-cause mortality following a severe exacerbation is high, especially in the first month following the event. Smoking cessation, comorbidity-management and asthma-treatment focusing on the prevention of exacerbations might reduce associated mortality.

Cover Letter

Rotterdam, 24th February 2020

Dear Prof Lundbäck,

First of all, we want to thank you to provide us the chance to resubmit the revised manuscript entitled: *"Multinational cohort study of mortality in patients with asthma and severe asthma"*

Please find below our answers to the comments as raised after your review. Each comment was addressed point by point and corrections have been added to the manuscript. As requested, changes are tracked in the document but a clean version has been submitted as well.

As prof Brusselle has been heavily involved in the revision of this paper and because of his previous contribution to the paper (where he was acknowledged for), Prof Brusselle has now been added as co-author to the paper. A statement of Prof Brusselle agreeing to be added as co-author as well as his conflict of interest form has been uploaded. Please also be informed that all authors were asked whether they agreed on adding Prof Brusselle as co-author to the paper and no objections were received by the other co-authors.

We do hope that you will consider publishing this revised manuscript in Respiratory Medicine.

Yours Sincerely,

Katia Verhamme
Associate Professor of Use and analysis of observational data
Department of Medical Informatics; Erasmus MC, Rotterdam, The Netherlands

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Multinational cohort study of mortality ~~and related risk factors~~ in patients with asthma and severe asthma

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Keywords: asthma epidemiology, severe asthma, mortality, cohort studies~~, risk factors~~

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List of abbreviations

Term	Abbreviation
Asthma-COPD overlap	ACO
DK	Denmark
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance	ENCePP
Emergency department	ED
Gastro-oesophageal reflux disease	GERD
Global Initiative of asthma	GINA
Inhaled corticosteroids	ICS
IT	Italy
leukotriene modifier	LTRA
Long-acting β_2 agonists	LABA
NL	The Netherlands
Person-years	PY
Short-acting β_2 agonists	SABA
Short-acting muscarinic antagonist	SAMA
SP	Spain
UK	United Kingdom
World Health organisation	WHO

Declarations:

Acknowledgement: This work was carried out through the EU-ADR Alliance. The authors wish to acknowledge ~~Prof Guy Brusselle (UGhent) for his review of the paper and~~ Eva Molero and Natasha Yefimenko (Synapse Research Management Partners) for their contributions to managing the study protocol during the development of this manuscript.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Interest

Funding for this study was provided by GSK (PRJ2284) and ZonMw (ME and KV) (113201006).

Author's contribution

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. This work was carried out through the EU-ADR Alliance.

Conflicts of interest

FA, SC, and EB are GSK employees and own stocks/shares in GSK.

NB and RS were employees of GSK at the time this research was conducted and own stocks/shares in GSK.

GP, CG, KB have no conflicts to declare.

FL has received grants from Chiesi, GSK and Novartis.

DPA has received research grants from Amgen, Bioiberica and GSK and speaker/advisory fees from Amgen and Bioiberica, paid to his department.

KV has received grants from GSK and ZonMw.

MR, PR, MS and KV's institution has received unconditional research grants from Boehringer-Ingelheim, Novartis, Pfizer, Yamanouchi, Servier, and Johnson & Johnson, unrelated to the current manuscript; MR, PR, MS and KV's received an unconditional grant from GSK to conduct research on incidence and risk factors of asthma exacerbations as part of the GSK/EU-ADR alliance.

ES's institution (Aarhus University) has received a grant from the GSK/EU-ADR alliance related to this study.

GB has received fees for lectures and/or advisory boards of AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Sanofi and Teva.

ABSTRACT

Background: Data on the risk of death following an asthma exacerbation are scarce. With this multinational cohort ~~study~~study, we assessed all-cause mortality rates, mortality rates following an exacerbation, and patient characteristics associated with ~~risk factors for~~ all-cause mortality in asthma.

Methods: Asthma patients aged ≥18 years and with ≥1 year of follow-up were identified in 5 European electronic databases from the Netherlands, Italy, UK, Denmark and Spain during the study period 1st January 2008 – 31st December 2013. Patients with asthma-COPD overlap were excluded. Severe asthma was defined as use of high dose ICS + use of a second controller. Severe asthma exacerbations were defined as emergency department visits, hospitalizations or systemic corticosteroid use, all for reason of asthma.

Results: The cohort consisted of 586,436 asthma patients of which 42,611 patients (7.3%) had severe asthma. The age and sex standardized all-cause mortality rates ranged between databases from 5.2 to 9.5/1,000 person-years (PY) in asthma, and between 11.3-14.8/1,000 PY in severe asthma. The all-cause mortality rate in the first week following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY. Mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. ~~Risk factors for mortality were~~ Hhigher age ~~at asthma diagnosis~~, male gender, comorbidity, smoking, and previous severe asthma exacerbations were associated with mortality.

Conclusion: All-cause mortality following a severe exacerbation is high, especially in the first month following the event. Smoking cessation, comorbidity-management and

asthma-treatment focusing on the prevention of exacerbations might ~~are important to~~ reduce associated mortality ~~as these were independent risk factors of mortality~~.

Abstract word count: ~~250~~243

INTRODUCTION

Asthma is a highly prevalent and chronic respiratory condition affecting ~~235~~ 300-400 million people worldwide.[1, 2] Asthma is a major cause of disability, health resource utilization, and significantly reduces the patient's quality of life.[3] There is no cure for asthma, but it can generally be controlled through treatment as described by existing asthma management guidelines.[4] Real world surveys among asthmatic patients indicate that the incidence of exacerbations is much higher than observed in clinical trials.[5] Asthma exacerbations are associated with increased healthcare costs, reductions in health related quality of life, and increased mortality.[6] Although asthma-related mortality has decreased over the last decades, still on a global scale it is estimated that asthma accounts for about 250,000 deaths per year.[7, 8]

The Global Initiative of Asthma (GINA) published in 2004 mortality estimates of 5.2 per 100,000 asthma patients aged 5-34 years in the United States, with wide variations across Europe (e.g. 1.6 per 100,000 in Finland and 9.3 per 100,000 in Denmark).[9]

A more recent report based on data from the WHO mortality database using mortality data from 46 countries in the entire population of 5-34 years old (thus not necessarily diagnosed with asthma), report a reduction in asthma mortality rates from 0.44 deaths per 100,000 in 1993 to 0.19 deaths per 100,000 in 2006 with a stagnation in asthma mortality rates from 2006 on.[10]

Increasing age, lower socio-economic status, smoking status, low FEV_1 and poor asthma control have been associated with increased mortality.[11-14] Although there is a considerable amount of data on mortality rates in patients with asthma, data on all-cause mortality rates and mortality rates following asthma exacerbations is scarce.

In this study we aimed to estimate all-cause and asthma-related mortality, mortality rates following severe asthma exacerbations and ~~risk factors~~patient characteristics associated with ~~for~~ mortality in adult patients with asthma and severe asthma, using one protocol and harmonized methods with regard to data extraction and data analysis, across five different European countries.

METHODS

Design and setting

A retrospective cohort study was conducted using data from five European electronic health care databases: i) the Integrated Primary Care Information Project (IPCI) from the Netherlands, ii) the Health Search Database (HSD) from Italy, iii) Clinical Practice Research Datalink (CPRD) from the UK, iv) the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and v) the Aarhus University Prescription Database (Aarhus) from Denmark. Detailed descriptions of these databases have been published before [15-20] and are available in the online supplement. All databases comprise detailed information on drug prescriptions or dispensing, outpatient diagnoses and hospitalizations, comorbidity and measurement data (e.g. lab results, spirometry, BMI). Weaknesses and major differences of the registers ~~will be~~ are further ~~discussed~~commented on in the ~~D~~discussion section.

These databases contain information on mortality either through linkage with hospital data and death registries (Aarhus, SIDIAP and CPRD), via information from discharge letters (HSD and IPCI) or via information from death records as registered by the GP (CPRD, IPCI and SIDIAP). All participating databases comply with EU guidelines on the use of medical data for research and are registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database.[21]

Cohort definition

A cohort of patients with asthma was defined in each database. To enter the cohort, patients needed to be at least 18 years old, with a minimum of 1-year database history.

Asthma was defined as physician diagnosed asthma based on the presence of at least one asthma specific disease code (see online supplement) in combination with prescriptions/dispensing of asthma drugs within 3 months before or after an asthma disease code. Asthma drugs consisted of the following: inhaled corticosteroids (ICS), short-acting β_2 agonists (SABA), long-acting β_2 agonists (LABA), fixed combination of ICS+LABA, leukotriene modifier (LTRA), short-acting muscarinic antagonist (SAMA), fixed combination of SABA+SAMA, xanthines, and anti-IgE treatment. Information on drug use was retrieved by an ATC specific search from either the drug prescription or drug dispensing records. Based on the asthma index date (first date of an asthma disease code), patients were categorized into prevalent or incident asthma. Patients having both disease codes for asthma and disease codes for COPD, considered as patients with asthma-COPD overlap (ACO), were excluded from the analysis.

Within the cohort of patients with asthma, a sub-cohort of patients with severe asthma was identified. According to GINA guidelines, severe asthma was defined as asthma requiring treatment with high dose ICS plus a second controller (and/or systemic corticosteroids).[4, 22, 23] For each prescription of an ICS we were able to label this prescription as “use of high dose ICS” based on the dosing information and the strength and according to GINA guidelines [4]. Next, for each prescription of both ICS and controller therapy, the legend duration was derived from the information on strength, dosing and volume. Only those patients who fulfilled the criteria of high dose ICS plus a second controller therapy for a consecutive period of at least 120 days were included in the severe asthma cohort. The study period started on the first of January 2008 and ended on 31st December 2013.

Follow-up

For each patient, cohort follow-up started from the latest date of the following; start of study period, diagnosis of (severe) asthma, age of 18 years or after reaching a minimum of 365 days of database history. To account for immortal time bias, follow-up in the severe asthma cohort started on day 120 of consecutive use of high dose ICS with additional controller therapy.[24] Follow-up ended when leaving the database, death or end of the study period whichever came first.

For the analysis of mortality following severe asthma exacerbations, follow-up ran from the date of a severe asthma exacerbation until the end of the predefined time windows following the severe asthma exacerbation (7, 30, 90, 180 or 365 days), a next severe asthma exacerbation, end of study period, or death, whichever came first.

Severe asthma exacerbations

Severe asthma exacerbation was defined as any of the following: acute use of systemic corticosteroids, ED visit or hospitalisation for an asthma exacerbation.[25]

The indication of corticosteroid use was retrieved from the prescription/dispensing file or through an automated search on asthma or asthma exacerbation disease codes in a 7-day window before or after the prescription date. Continuous use of systemic corticosteroids, defined as consecutive use of 30 days or more, was not considered as a severe asthma exacerbation. If the time between 2 prescriptions of systemic corticosteroids was less than 2 weeks, this was considered as one single severe asthma exacerbation.

All cause and asthma-related mortality

In all databases, death and date of death are well documented but information on cause of death was only systematically available for IPCI and Aarhus (up to 2011). In SIDIAP, cause of death (i.e. asthma-related deaths) was only identifiable through hospital admissions data linkage, and therefore they only represent “in-hospital deaths". Where available, cause of death was classified into “asthma-related” or “non-asthma-related death”. Asthma-related death was defined as death with as main cause asthma and/or asthma exacerbation.

Covariates

We investigated the prevalence of the following comorbidities: atopy (allergic rhinitis, atopic eczema/dermatitis), chronic rhinosinusitis, nasal polyposis, gastro-oesophageal reflux disease (GERD), depression and anxiety, overweight and obesity, diabetes mellitus, cardio- and cerebrovascular diseases and cancer. Smoking status was classified as “current smoker”, “past smoker”, “non-smoker” or “smoking status unknown”. Comorbidities and smoking status were assessed at the start of follow up (using information in the entire period prior, even before start of study period). For each of the comorbidities of interest, diseases were mapped through the Unified Medical Language System (UMLS) generating a list of disease codes (see online supplement) which were verified by the databases prior to extraction.[26]

Analysis

Categorical data were presented in counts and proportions. For continuous data, the number of observations (n), mean, and standard deviation were presented.

The overall mortality rate was calculated by dividing the number of deaths by the respective number of person-years of follow-up. Mortality rates were calculated by ~~-~~age category (18-<35 years and subsequent 10-year age categories).

To account for differences in age and sex distribution between databases, direct standardization was applied using the largest population (CPRD) as reference population.[27]

Mortality rates were also calculated in predefined windows (7, 14, 30, 90, and 365 days) following the severe asthma exacerbation.

~~Risk factors~~Patient characteristics associated with mortality were assessed by means of univariate and multivariate Cox regression analys~~e~~is, including the following covariates: age at start of follow-up, sex, smoking status, comorbidity (cancer, cardiovascular and cerebrovascular disease, obesity (defined as a BMI of >=30) and diabetes mellitus), whether the patient had incident or prevalent asthma at start of follow-up and two time-dependent covariates; time since previous severe asthma exacerbation (classified in up to 30 days, 31 to 90 days, 91 to 365 days and more than 365 days) and asthma severity. At T=0 (start of follow-up), severity was either “yes” or “no”. From the time patients with non-severe asthma became severe, their severity was coded as “yes”.

Maximum follow-up in this analysis was restricted to 5 years. Pooled results for all hazard ratios were obtained using multivariate meta-analysis.[28]

As the duration of asthma disease might be an important risk factor of all-cause mortality, the analysis was repeated in patients with incident asthma only, i.e. without asthma diagnosis prior to study entry as the correct date of asthma onset was not always well documented in prevalent cases.

All analyses were done using the software package SAS version 9.2, SAS Institute Inc., Cary, NC.

RESULTS

Study population and baseline characteristics

The source population comprised 16,259,085 individuals with active follow-up during the study period of which 644,602 adult patients were diagnosed with asthma. As patients with ACO (n=58,166) were excluded, 586,436 patients remained of which 42,611 patients (7.3%) with severe asthma were identified. (Figure 1)

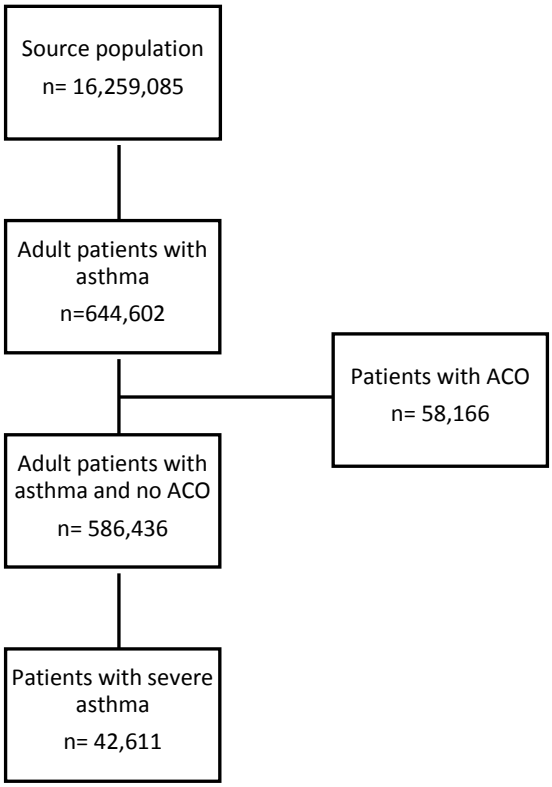

Figure 1: Patient flowchart
ACO= Asthma COPD overlap

The percentage of severe asthma was the highest in Aarhus (11.6%) and the lowest in SIDIAP (2.1%). Baseline characteristics of the asthma cohorts are further described in Table 1 and Table 2. Briefly, the mean age at start of follow up ranged between 45.2 -

48.3 years. In all databases, there was a preponderance of females (57.4-64.3% females) which remained when studying patients with severe asthma (59.3-69.9% females). The prevalence of atopy (consisting of atopic eczema and/or allergic rhinitis) ranged between 15.1-35.7% and did not increase in patients with severe asthma (11.5-37.8%). The prevalence of chronic rhinosinusitis and nasal polyposis ranged between 0.3%-9.9% and 0.5-2.8% ~~respectively, and~~respectively and increased in patients with severe asthma (0.9-14.1% and 1.0-6.8% respectively).

	IPCI (NL) (n,%)	AARHUS (DK) (n,%)	HSD (IT) (n,%)	CPRD (UK) (n,%)	SIDIAP (SP) (n,%)
Total	73,506 (100.0)	14,041 (100.0)	37,003 (100.0)	393,660 (100.0)	68,226 (100.0)
Incident asthma	16,265 (22.1)	4,083 (29.1)	15,842 (42.8)	77,884 (19.8)	42,086 (61.7)
Prevalent asthma	57,241 (77.9)	9,958 (70.9)	21,161 (57.2)	315,776 (80.2)	26,140 (38.3)
Female	44,394 (60.4)	8,172 (58.2)	21,959 (59.3)	226,026 (57.4)	43,857 (64.3)
Male	29,112 (39.6)	5,869 (41.8)	15,044 (40.7)	167,634 (42.6)	24,369 (35.7)
Age (mean,sd)	45.5 (16.9)	46.4 (17.6)	47.9 (18.0)	45.2 (18.4)	48.3 (18.9)
Smoking status*					
Current	10,899 (26.3)	112 (23.5)	5,227 (26.2)	84,449 (21.9)	12,992 (25.0)
Never	20,878 (50.4)	227 (47.6)	11,416 (57.2)	177,469 (45.9)	31,768 (61.1)
Past	9,616 (23.2)	138 (28.9)	3,328 (16.7)	124,512 (32.2)	7,236 (13.9)
Smoking status unknown	32,113 (43.7)	13564 (96.6)	17,032 (46.0)	7,230 (1.8)	16,230 (23.8)
Atopy	22,679 (30.9)	2,119 (15.1)	6,175 (16.7)	140,710 (35.7)	11,731 (17.2)
Chronic rhinosinusitis	2,235 (3.0)	42 (0.3)	628 (1.7)	38,980 (9.9)	398 (0.6)
Nasal polyposis	338 (0.5)	208 (1.5)	383 (1.0)	11,133 (2.8)	940 (1.4)
GERD	4,756 (6.5)	498 (3.5)	4,162 (11.3)	34,576 (8.8)	1,362 (2.0)
Diabetes mellitus	5,001 (6.8)	548 (3.9)	2,244 (6.1)	20,317 (5.2)	4,901 (7.2)
Obesity	19,358 (26.3)	1,281 (9.1)	7,436 (20.1)	231,604 (58.8)	34,265 (50.2)
Anxiety/Depression	9,440 (12.8)	336 (2.4)	7,144 (19.3)	108,229 (27.5)	15,910 (23.3)
Cardiovascular disease	3,265 (4.4)	839 (6.0)	577 (1.6)	17,844 (4.5)	1,095 (1.6)
Cerebrovascular disease	1,666 (2.3)	421 (3.0)	828 (2.2)	7,555 (1.9)	1,121 (1.6)
Cancer	3,870 (5.3)	590 (4.2)	731 (2.0)	13,418 (3.4)	2,467 (3.6)

Table 1: Baseline characteristics of total asthma cohorts

* Percentage of patients for whom smoking is available.

	IPCI (NL) (n,%)	AARHUS (DK) (n,%)	HSD (IT) (n,%)	CPRD (UK) (n,%)	SIDIAP (SP) (n,%)
Total	6,446 (100.0)	1,633 (100.0)	1,895 (100.0)	31,214 (100.0)	1,423 (100.0)
Incident asthma	443 (6.9)	205 (12.6)	91 (4.8)	1705 (5.5)	362 (25.4)
Prevalent asthma	6,003 (93.1)	1,428 (87.5)	1,804 (95.2)	29,509 (94.5)	1,061 (74.6)
Female	4,030 (62.5)	997 (61.1)	1,123 (59.3)	19,474 (62.4)	994 (69.9)
Male	2,416 (37.5)	636 (39.0)	772 (40.7)	11,740 (37.6)	429 (30.2)
Age (mean,sd)	50.8 (16.0)	53.2 (16.5)	55.0 (17.5)	55.8 (17.3)	66.3 (14.9)
Smoking status					
Current*	1,029 (23.3)	5 (13.9)	203 (19.8)	6,136 (19.7)	123 (10.1)
Never*	2,197 (49.7)	7 (19.4)	588 (57.3)	12,156 (39.0)	913 (74.8)
Past*	1193 (27.0)	24 (66.7)	235 (22.9)	12,871 (41.3)	184 (15.1)
Smoking status unknown	2,027 (31.5)	1,597 (97.8)	869 (45.9)	51 (0.2)	203 (14.3)
Atopy	2,084 (32.3)	223 (13.7)	282 (14.9)	11,808 (37.8)	163 (11.5)
Chronic rhinosinusitis	260 (4.0)	14 (0.9)	44 (2.3)	4,396 (14.1)	14 (1.0)
Nasal polyposis	62 (1.0)	50 (3.1)	77 (4.1)	1,924 (6.2)	43 (3.0)
GERD	564 (8.8)	66 (4)	279 (14.7)	4,712 (15.1)	58 (4.1)
Diabetes mellitus	669 (10.4)	75 (4.6)	161 (8.5)	3,082 (9.9)	229 (16.1)
Obesity	2,424 (37.6)	147 (9.0)	417 (22.0)	22,952 (73.5)	1,016 (71.4)
Anxiety/Depression	957 (14.9)	32 (2.0)	421 (22.2)	11,319 (36.3)	337 (23.7)
Cardiovascular disease	407 (6.3)	126 (7.7)	39 (2.1)	2,938 (9.4)	60 (4.2)
Cerebrovascular disease	175 (2.7)	74 (4.5)	52 (2.7)	1,242 (4.0)	50 (3.5)
Cancer	406 (6.3)	97 (5.9)	70 (3.7)	1,826 (5.9)	113 (7.9)

Table 2: Baseline characteristics of severe asthma cohorts

* Percentage of patients for whom smoking is available. NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Death and mortality rates

In total, 15,349 deaths were observed during follow-up. Characteristics of patients who died are further described in Online table 1. Asthma-related death was reported in 4.1% of deaths with known cause in Aarhus, 0.2% in IPCI, 4.1% in SIDIAP (hospital deaths only), and 2.0% in CPRD. However, it should be noted that cause of death was not reported in a substantial proportion of deaths in SIDIAP (58.6%) and CPRD (80.0%).

The overall age and sex standardized all-cause mortality rates were 5.2/1,000 PY (95% CI 4.9-5.5) in HSD, 5.5/1,000 PY (95% CI 5.1-5.8) in IPCI, 6.4/1,000 PY (95% CI 6.1-6.7) in SIDIAP, 6.5/1,000 PY (95% CI 6.4-6.6) in CPRD and 9.5/1,000 PY (95% CI 8.8-10.2) in Aarhus. These standardized all-cause mortality rates were higher in patients with severe asthma, ranging between 11.3-14.8/1,000 PY across databases. (Table 3)

	Asthma			Severe asthma		
	Overall MR	**Overall MR - Standardized**	**95% CI**	**Overall MR**	**Overall MR - Standardized**	**95% CI**
IPCI (NL)	4.9	5.5	5.1-5.8	7.3	11.3	9.2-13.7
AARHUS (DK)	9.2	9.5	8.8-10.2	12.2	14.6	11.8-17.9
HSD (IT)	6.0	5.2	4.9-5.5	11.9	11.6	9.2-13.9
CPRD (UK)	6.5	6.5	6.4-6.6	14.8	14.8	14.1-15.5
SIDIAP (SP)	8.8	6.4	6.1-6.7	25.3	13.0	10.5-20.6

Table 3: Crude and age & sex standardized mortality rate (distribution of CPRD as reference population) (Mortality Rates (MR) = number of deaths/per 1,000 PY)
NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

All-cause mortality rates increased with age both for the total asthma cohort and the severe asthma cohort (Online table 2). In order to compare our data to the WHO data on patients up to the age of 35, we defined an age category of patients 18-<35 years of age.[9] The all-cause mortality rate in asthma patients of this age group was the lowest in HSD (IT) namely 0.3/1,000 PY (95% CI 0.2-0.5) and highest in Aarhus (DK) namely 1.0/1,000 PY (95% CI 0.7-1.5).

The all-cause mortality rate in the first 7 days following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY across databases. All-cause mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. (Table 4)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI
ALL ASTHMA mortality following severe asthma exacerbation															
< 7 days	25.3	0.0%	0.0-0.1%	59.9	0.1%	0.1-0.2%	14.1	0.0%	0-0.1%	15.4	0.0%	0.0-0.0%	56.9	0.1%	0.1-0.1%
< 15 days	30.6	0.1%	0.1-0.2%	28.1	0.1%	0.1-0.2%	22.8	0.1%	0.1-0.1%	13.3	0.1%	0.0-0.1%	47.6	0.2%	0.2-0.2%
< 30 days	23.5	0.2%	0.1-0.3%	28.5	0.2%	0.1-0.4%	17.4	0.1%	0.1-0.2%	11.8	0.1%	0.1-0.1%	41.2	0.3%	0.3-0.4%
< 90 days	14.9	0.4%	0.3-0.5%	21.0	0.5%	0.4-0.7%	12.7	0.3%	0.2-0.4%	9.7	0.2%	0.2-0.3%	41.1	1.0%	0.9-1.1%
< 365 days	11.5	1.1%	1.0-1.4%	15.5	1.5%	1.2-1.9%	10.2	1.0%	0.9-1.2%	7.9	0.8%	0.7-0.9%	32.8	3.2%	3.0-3.5%
SEVERE ASTHMA mortality following severe asthma exacerbation															
< 7 days	61.4	0.1%	0.0-0.3%	80.6	0.2%	0.0-0.6%	0	0.0%	0.0-0.0%	18.0	0.0%	0.0-0.1%	28.4	0.1%	0.0-0.4%
< 15 days	57.8	0.2%	0.1-0.5%	37.8	0.2%	0.0-0.6%	26.5	0.1%	0.0-0.4%	14.1	0.1%	0.0-0.1%	26.7	0.1%	0.0-0.4%
< 30 days	33.4	0.3%	0.1-0.5%	28.8	0.2%	0.1-0.7%	26.9	0.2%	0.1-0.6%	19.5	0.2%	0.1-0.2%	27.1	0.2%	0.1-0.6%
< 90 days	15.3	0.4%	0.2-0.7%	24.4	0.6%	0.3-1.3%	17.8	0.4%	0.2-0.9%	16.7	0.4%	0.3-0.5%	53.8	1.3%	0.8-2.1%
< 365 days	11.1	1.1%	0.7-1.7%	17.8	1.8%	1.1-2.9%	15.1	1.5%	0.9-2.4%	13.1	1.3%	1.1-1.5%	56.8	5.5%	4.1-7.4%

Table 4: Mortality rate and cumulative incidence of mortality following severe asthma exacerbation

MR=mortality rate. CumInc=cumulative incidence. 95% CI= 95% confidence interval, NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

This was also observed in patients with severe asthma, except for SIDIAP, probably because of low numbers.

From the all-cause mortality ~~rates~~rates, the cumulative incidences of death were calculated (Table 4). Within seven days following a severe asthma exacerbation 0.0-0.1% of asthma patients died. Within one year following severe asthma exacerbation, 0.8-3.2% of asthma patients and 1.1-5.5% of severe asthma patients died.

~~Risk factors for~~Patient characteristics associated with mortality

~~Risk factors for all-cause mortality were studied in the cohort of patients with asthma.~~ In total 13,449 patients with asthma died during the first 5 years of follow up and the results of the univariate analysis of patient characteristics and mortality~~risk factors of mortality~~, adjusted for age at start follow-up, are documented in the Online table 3. In the multivariate analysis, age at start follow-up, male gender, previous severe exacerbations, smoking status, underlying comorbidity (history of cancer, cerebrovascular disease and history of diabetes) were associated with increased all-cause mortality in most databases. (Table 5)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)			Meta-analysis		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226			586,436		
Deaths in 5 years (n)	923			571			893			8,965			2,097			13,449		
Parameter	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age	1.10	1.09-1.11	<.0001	1.10	1.09-1.11	<.0001	1.11	1.11-1.12	<.0001	1.10	1.10-1.10	<.0001	1.12	1.11-1.12	<.0001	1.11	1.10-1.11	<.0001
Female gender	0.73	0.64-0.84	<.0001	0.93	0.78-1.10	0.3872	0.74	0.64-0.86	<.0001	0.81	0.78-0.85	<.0001	0.70	0.63-0.78	<.0001	0.78	0.70-0.86	<.0001
Previous severe asthma exacerbation																		
No previous exacerbations	1.00		<.0001	1.00		0.0465	1.00		0.0002	1.00		<.0001	1.00		<.0001			<.0001
30 days after exacerbation	1.67	0.96-2.89	.	1.97	1.19-3.26	.	2.25	1.48-3.43	.	1.95	1.56-2.44	.	2.69	2.23-3.25	.	2.10	1.72-2.55	
31-90 days after exacerbation	2.06	1.42-3.00	.	1.48	0.92-2.37	.	1.32	0.86-2.02	.	1.31	1.07-1.61	.	2.86	2.40-3.41	.	1.72	1.25-2.37	
91-365 days after exacerbation	1.47	1.13-1.92	.	0.98	0.70-1.39	.	1.39	1.08-1.77	.	1.10	0.98-1.25	.	2.18	1.91-2.50	.	1.37	1.04-1.81	
>365 days after exacerbation	1.42	1.09-1.85	0.0092	0.95	0.70-1.27	0.7114	0.98	0.78-1.25	0.8960	1.16	1.06-1.28	0.0021	1.41	1.22-1.64	<.0001	1.17	0.97-1.40	
Comorbidity																		
History of cancer	2.08	1.78-2.42	<.0001	1.81	1.46-2.25	<.0001	2.18	1.75-2.71	<.0001	2.06	1.95-2.18	<.0001	1.66	1.47-1.88	<.0001	1.95	1.75-2.16	<.0001
History of cardiovascular disease	1.03	0.87-1.22	0.7070	1.13	0.91-1.40	0.2818	1.13	0.85-1.49	0.4055	1.41	1.34-1.49	<.0001	1.62	1.39-1.89	<.0001	1.26	1.06-1.49	0.0097
History of cerebrovascular disease	1.38	1.13-1.68	0.0015	1.74	1.37-2.20	<.0001	1.44	1.17-1.78	0.0007	1.48	1.39-1.58	<.0001	1.64	1.42-1.90	<.0001	1.53	1.39-1.68	<.0001
History of diabetes mellitus	2.14	1.82-2.52	<.0001	1.57	1.21-2.05	0.0008	1.18	0.99-1.41	0.0693	1.70	1.61-1.80	<.0001	1.66	1.50-1.84	<.0001	1.61	1.33-1.95	<.0001
Obesity	0.70	0.59-0.82	<.0001	1.25	0.90-1.73	0.1857	1.52	1.31-1.78	<.0001	0.78	0.74-0.82	<.0001	0.69	0.63-0.76	<.0001	0.93	0.67-1.29	0.67
Prevalent asthma	1.11	0.93-1.31	0.2588	0.72	0.60-0.87	0.0008	0.98	0.85-1.13	0.7393	1.19	1.11-1.27	<.0001	0.96	0.88-1.05	0.3449	0.98	0.83-1.16	0.83
Severe asthma	1.05	0.86-1.28	0.6394	0.92	0.73-1.16	0.4800	1.21	0.96-1.52	0.1026	1.33	1.26-1.41	<.0001	0.98	0.81-1.20	0.8785	1.09	0.95-1.26	0.22
Smoking status																		
Smoking never	1.00		<.0001	1.00		0.5796	1.00		0.0198	1.00		<.0001	1.00		<.0001			<.0001
Smoking current	2.45	1.96-3.05	.	0.91	0.11-7.55	.	1.49	1.15-1.92	.	2.40	2.25-2.57	.	2.23	1.86-2.67	.	1.96	1.56-2.48	

Smoking past	1.45	1.17-1.79	.	0.36	0.07-1.80	.	1.16	0.94-1.43	.	1.10	1.05-1.16	.	1.13	0.95-1.34	.	1.13	0.97-1.32	
~~Smoking status~~Smoking status unknown	1.54	1.30-1.83	.	0.99	0.43-2.25	.	1.15	0.98-1.35	.	1.21	0.87-1.69	.	1.14	1.02-1.28	.	1.25	1.10-1.42	

Table 5: ~~Risk factors of mortality in asthma patients~~Patient characteristics and mortality (multivariate analysis)

NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Current smoking increased the risk of all-cause mortality with 50-150% in IPCI, HSD, CPRD and SIDIAP. This association was not observed for Aarhus (HR_{adj} 0.91, 95% CI 0.11-7.55) but it should be noted that the smoking status of patients in Aarhus was often unknown. (96.6% - table 1)

Hazard ratios for all-cause mortality in adults with asthma for the different periods after severe asthma exacerbation are shown both per database as well as the result of the meta-analysis of these results. (Figure 2) Compared to follow-up with no previous severe asthma exacerbation the pooled meta-analysis HR_{adj} of dying decreased from 2.10 (95% CI 1.72-2.55) in the first 30 days following a severe asthma exacerbation to 1.17 (95% CI 0.97-1.40) after one year. (Figure 2)

When the analysis was repeated in patients with incident asthma only (n=156,160, 2843 patients died) similar results with regard to risk estimates, but with wider 95% CI were obtained (online table 4).

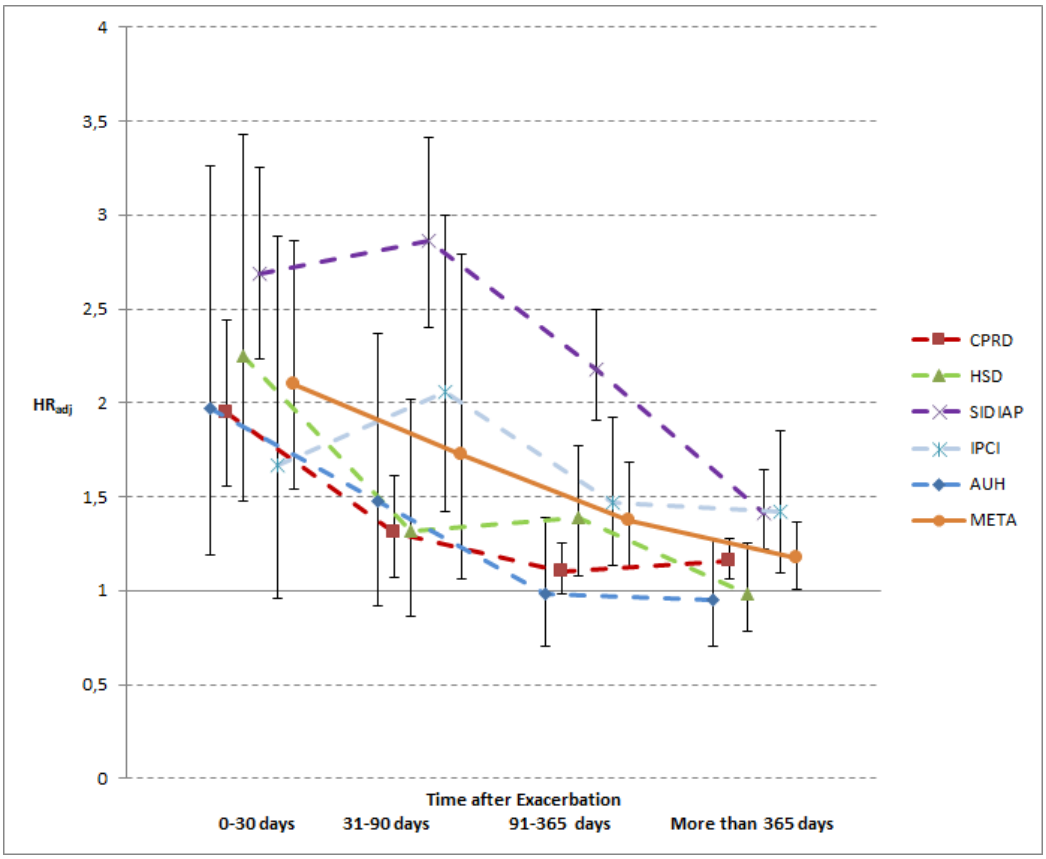

Figure 2: Hazard ratios of mortality in adult asthmatic patients for time periods after severe asthma exacerbation (0-30, 31-90, 91-365, >365 days after severe asthma exacerbation) compared to time before any exacerbation.

* adjusted for sex, age at start follow-up, asthma severity, history of cancer, history of cardiovascular disease, history of cerebrovascular disease, history of diabetes mellitus, history of obesity, incident or prevalent and smoking. ⊤⊥ represent 95% CI

DISCUSSION

In this study, we investigated all-cause mortality rates and all-cause mortality rates following a severe asthma exacerbation in five asthma cohorts from five European countries, using one protocol and harmonized methods for data extraction and data analysis.

The overall age and gender standardized all-cause mortality rate in patients with asthma ranged between 5.2-9.5/1,000 PY over ~~databases, and~~databases and doubled in patients with severe asthma (range 11.3 to 14.8/1,000 PY). The all-cause mortality rate in the first 7 days following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY across databases. All-cause mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. This was also observed in the meta-analysis on patient characteristics ~~f risk factors of mortality~~and mortality where the ~~risk of dying~~association with mortality was 2-fold higher in the month following a severe asthma exacerbation ~~compared to the risk of dying in patients~~using patients without a previous severe asthma exacerbation as a reference.

In a publication on WHO data considering all individuals and not only patients with asthma, the age standardised asthma-related mortality in people aged 5-34 years in the period 2008-2012, ranged between 0-0.17/100,000 people when considering Italy, the UK, Spain, the Netherlands and Denmark only.[10] As could be expected, these mortality rates are much lower than the overall mortality rates that we report for these respective countries and for comparable age categories (18-<35 years) (database range 0.3-1.0/1,000 PY) not only because the WHO data considered all individuals in the

denominator and not only individuals with asthma but more importantly because the WHO report only investigated asthma-related mortality.

Asthma-related-mortality is higher in the US based on findings from a recent publication exploring data from the Center for Disease Control and Prevention and reporting an overall asthma related mortality rate of 1.5/100,000 people during the study period 1999-2015.[29] In 2014, To et al. reported the results of a ten-year population study on asthma-related mortality and all-cause mortality using data from the health administrative database from Ontario, Canada. The age and sex ~~adjusted~~standardized, all-cause mortality in individuals with asthma declined from 9.9/1,000 PY in 1999 to 8.5/1,000 PY in 2009 which is comparable to the age and sex standardized mortality rate as reported for Aarhus (9.5/1,000 PY) but higher than the mortality rate as reported for the other databases (5.2-6.5/1,000 PY) .[30] A recent study on mortality rates in patients with chronic respiratory diseases in the UK, using CPRD data reported an age-standardized all-cause mortality rate of 8.6 per 1,000 person years. This is slightly higher than the standardized mortality rate that we reported namely 6.5 per 1,000 PY but Gayle et al. studied mortality using CPRD data between 2005-2015 whereas our study period was from 2008-2013.[31]

In 2006, Krishnan et al. published US data on mortality following hospital admission for asthma and reported an in-house mortality of 0.5%.[32] Similar results were recently described by Kaur et al. who reported that in the US, 1% of patients die in hospital following admission for severe asthma exacerbation.[33] In 2013, age-standardized mortality rates within 30 days following an admission for status asthmaticus in Denmark were published.[34] Between 2008-2011, the 30-day mortality rate was 1.5 % which is

higher than the 0.2% (95% CI 0.1-0.4%) that we reported for Denmark but in our definition of severe asthma exacerbation we did not limit to ED admission and/or hospitalisation only.

We studied ~~risk factors~~patient characteristics in association with ~~for~~ mortality in patients with asthma and in particular investigated the effect of ~~life style~~lifestyle factors (smoking), asthma severity, previous severe asthma exacerbations and underlying comorbidity. Underlying comorbidity, higher age, male gender and a previous severe asthma exacerbation were ~~risk factors of~~associated with mortality in most databases. In addition, current smoking was ~~a major risk factor~~associated with ~~–~~(HR_{adj} between 1.5-2.5) ~~for~~ mortality in all databases except Aarhus, stressing the relevance of smoking cessation in patients with asthma. Previous severe asthma exacerbation was also ~~an independent risk factor of~~ associated with mortality in all databases. This is in line with the study by Ali et al. who followed more than 1,000 Danish asthma patients over 25 years and reported a relative risk of dying of 2.9 in patients who had a history of acute hospital contacts for reason of asthma.[35] In a recent review article, hospitalization or emergency care visit for asthma in the past year was considered an important risk factor of asthma-related mortality.[36] The OLIN (Obstructive Lung Disease in Northern Sweden) study followed a cohort of asthma patients in Sweden up to 28 years and reported a cumulative mortality of 22.7%. Similar to our study, independent risk factors of mortality were age, male gender, current smoking, and underlying comorbidity.[37]

Our observational study has strengths and limitations. Major strengths are the fact that we included a large number of patients from different European databases that collect detailed information on drug exposure. However, our study has also several

weaknesses. Firstly, an important weakness is the fact that there are major differences between databases with respect to accurate information on important covariates such as ~~life style~~lifestyle factors (e.g. smoking)~~, drug exposure~~ obesity (BMI) and underlying comorbidity. Indeed, country-specific differences in the prevalence of comorbidities are more likely due to consequences of weaknesses in the registers (e.g. incomplete information) than due to real differences between countries. In several databases, the prevalence of comorbidities such as atopy, anxiety, depression, chronic rhinosinusitis and nasal polyposis are underestimates of the true prevalence of these comorbidities in patients with (severe) asthma due to incomplete data. ~~In addition, our results represent real life data hence increasing the external validity of our reported findings.~~

Secondly, ~~A~~as this is an observational study, using data from electronic health care databases, there is a potential risk of bias and/or confounding. ~~First,~~ As for all electronic health care databases, it should be noted that the primary aim of data collection is patient management and not research. This implies that only events that are deemed to be relevant to the patient's care are collected, and thus accurate information on concomitant diseases could be lacking. ~~However this also means that collected data are highly representative of actual practice conditions, and likely to minimise Hawthorne and similar effect/s.~~[38] ~~Second, F~~for those databases without linkage with hospital databases (HSD and IPCI), severe asthma exacerbations were retrieved either via disease specific codes in combination with codes for hospitalization or via review of the discharge letters. Underestimation of severe asthma exacerbations is likely for HSD where incidence rates of severe asthma exacerbations were indeed low.

In addition, underestimation of severe asthma exacerbations based on systemic steroid burst might as well have affected our results in case patients have a prescription or systemic steroids at home to be used in case of acute worsening of asthma.

For Aarhus and SIDIAP, dispensing data instead of prescription data were used, which reduced misclassification of exposure; however, dosing information was missing in these data sources. Therefore, dosing was estimated based on the strength per device and the window between prescriptions. This method is susceptible to misclassification of severe asthma, which was based on at least 120 consecutive days of use of high dose ICS. This might explain the relative low proportion of severe asthma patients in SIDIAP.

Because of large numbers, it was not possible to conduct a manual validation of asthma but asthma was based on the presence of an asthma disease code in combination with use of asthma drugs. To ensure good quality health care, GPs are trained and requested to enter disease codes in the patient's electronical medical record fitting the actual patient's diagnosis. Still potential misclassification of asthma cannot be excluded also as spirometry data was not considered as post bronchodilation FEV_1 is not well documented in all databases.

Comorbidity at study entry was assessed by searching for disease specific codes in the entire patient's medical history. Country specific differences in prevalence of comorbidities were observed with for instance lower prevalences of diseases primarily seen in primary care in Aarhus compared to the other databases and high prevalences of obesity in CPRD and SIDIAP. The Global burden of disease also reports lower rates of anxiety/depression in Denmark compared to the other participating database.[39] This

~~finding might in part also be explained by the fact that, in contrast to the other databases, Aarhus retrieves information on disease codes from hospital data (ambulatory care or hospitalized patients). This implies that comorbidities, which do not necessarily require secondary or tertiary care such as anxiety/depression and obesity might be underreported. The prevalence of obesity was much lower in IPCI, HSD and Aarhus compared to the prevalence as reported in SIDIAP and CPRD which might be explained by database specific differences in reporting of BMI. Overall we cannot exclude potential misclassification in case certain disease codes were omitted or in case of country-specific differences in coding for instance better coding of obesity as part of the Quality and Outcomes framework (QOF) criteria in the UK.~~[40]

A third weakness is the fact that the risk analyses between patient characteristics and mortality are based on incomplete information for instance with regard to smoking status and comorbidity, implicating that the results of the risk analyses must be taken with caution. Lastly, we have used the GINA definition of severe asthma, i.e. use of high dose ICS plus a second controller (most frequently a LABA). In contrast, the ERS/ATS definition of severe asthma is more stringent, since it requires that the diagnosis of asthma has been confirmed, comorbidities have been addressed and it distinguishes well-controlled from uncontrolled severe asthma [22]~~.~~ As a consequence, our estimate of the prevalence of severe asthma in primary care (7.3%) most probably overestimates the true prevalence of severe asthma.

The main outcome in this study was mortality, assessed either through direct linkage with death registries (CPRD, and Aarhus) or administrative data (SIDIAP), or via information as collected by the GP. Unfortunately, the cause of death was frequently

missing in particular in HSD (100%), CPRD (80%) and SIDIAP (60%) and the number of patients with known asthma-related death was low hampering the analysis of asthma-related mortality rates ~~and its associated risk factors~~. ~~The standardized all-cause mortality rates were similar between databases (except for Aarhus), suggesting that misclassification of the outcome is limited. The age standardized all-cause mortality rate for Aarhus was 9.5/1,000 PY whereas this ranged between 5.2-6.5/1,000 PY in the other databases. The higher mortality rates in Aarhus can be explained by the fact that Aarhus collects disease codes from hospital data (both outpatient and inpatient) only, implying that asthma patients in Aarhus all required secondary or tertiary care and probably had more severe asthma.~~ [41]

In conclusion, our data demonstrate that 1) mortality in patients with asthma, and especially severe asthma, is substantial and 2) is highest in the first month following a severe asthma exacerbation. Moreover, 3) ~~patient~~patient characteristics such as ~~s with~~ a history of severe asthma exacerbation, increasing age, smoking and underlying comorbidity were associated with ~~have an increased risk of~~ mortality but replication is needed as information on comorbidity and lifestyle factors is not completely captured within the databases. In addition to smoking cessation and management of comorbidities, asthma treatment focusing on the prevention of severe asthma exacerbations ~~is important as this~~ might reduce mortality.

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Online supplement

Online Table 1. Characteristics of asthma patients who died

	IPCI (NL) (n,%)		AARHUS (DK) (n,%)		HSD (IT) (n,%)		CPRD (UK) (n,%)		SIDIAP (SP) (n,%)	
	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma
	n=971	n=118	n=652	n=101	n=1,001	n=99	n=10,278	n=1,760	n=2,331	n=126
Cause of Death										
-Asthma-related*	2 (0.2)	2 (1.9)	17 (4.1)	2 (2.9)			42 (2.0)	21 (6.3)	40 (4.1)	2 (3.8)
- Other*	879 (99.8)	102 (98.1)	401 (95.9)	67 (97.1)			2,013 (98.0)	311 (93.7)	925 (95.9)	50 (96.2)
- Unknown	90 (9.3)	14 (11.9)	234 (35.9)	32 (31.7)	1,001 (100.0)	99 (100.0)	8,223 (80.0)	1,428 (81.1)	1,366 (58.6)	74 (58.7)
Gender										
- Female	595 (61.3)	68 (57.6)	403 (61.8)	58 (57.4)	592 (59.1)	53 (53.5)	6,172 (60.1)	1,122 (63.8)	1,721 (73.8)	83 (65.9)
- Male	376 (38.7)	50 (42.4)	249 (38.2)	43 (42.6)	409 (40.9)	46 (46.5)	4,106 (40.0)	638 (36.3)	610 (26.2)	43 (34.1)
Smoking status										
- Current*	157 (24.4)	22 (26.5)	38 (29.2)	5 (29.4)	91 (13.2)	10 (17.2)	1,434 (14.0)	194 (11.0)	163 (7.8)	3 (2.6)
- Never*	269 (41.8)	31 (37.4)	31 (23.9)	3 (17.7)	408 (59.1)	29 (50.0)	3,570 (34.8)	628 (35.7)	1,682 (80.6)	99 (85.3)
- Past*	218 (33.9)	30 (36.1)	61 (46.9)	9 (52.9)	191 (27.7)	19 (32.8)	5,263 (51.3)	937 (53.3)	241 (11.6)	14 (12.1)
- Smoking status unknown	327 (33.7)	35 (29.7)	522 (80.1)	84 (83.2)	311 (31.1)	41 (41.4)	11 (0.1)	1 (0.1)	245 (10.5)	10 (7.9)
Atopy	175 (18.0)	28 (23.7)	34 (5.2)	7 (6.9)	66 (6.6)	8 (8.1)	2,771 (27.0)	534 (30.3)	142 (6.1)	7 (5.6)
Chronic rhinosinusitis	21 (2.2)	3 (2.5)	2 (0.3)	1 (1.0)	15 (1.5)	1 (1.0)	1,328 (12.9)	270 (15.3)	8 (0.3)	1 (0.8)
Nasal polyposis	3 (0.3)	2 (1.7)	8 (1.2)	3 (3.0)	11 (1.1)	3 (3.0)	478 (4.7)	116 (6.6)	17 (0.7)	1 (0.8)
GERD	110 (11.3)	24 (20.3)	43 (6.6)	4 (4.0)	185 (18.5)	19 (19.2)	1,931 (18.8)	357 (20.3)	66 (2.8)	2 (1.6)
Diabetes mellitus	274 (28.2)	45 (38.1)	92 (14.1)	12 (11.9)	228 (22.8)	26 (26.3)	2,229 (21.7)	385 (21.9)	667 (28.6)	45 (35.7)
Obesity	355 (36.6)	51 (43.2)	112 (17.2)	15 (14.9)	472 (47.2)	44 (44.4)	7,326 (71.3)	1,291 (73.4)	1,628 (69.8)	95 (75.4)
Anxiety/Depression	160 (16.5)	23 (19.5)	90 (13.8)	13 (12.9)	338 (33.8)	31 (31.3)	3,590 (34.9)	648 (36.8)	706 (30.3)	31 (24.6)

	IPCI (NL) (n,%)		AARHUS (DK) (n,%)		HSD (IT) (n,%)		CPRD (UK) (n,%)		SIDIAP (SP) (n,%)	
	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma
	n=971	n=118	n=652	n=101	n=1,001	n=99	n=10,278	n=1,760	n=2,331	n=126
Cardiovascular disease	223 (23.0)	28 (23.7)	155 (23.8)	20 (19.8)	79 (7.9)	9 (9.1)	2,867 (27.9)	524 (29.8)	247 (10.6)	17 (13.5)
Cerebrovascular disease	191 (19.7)	20 (17.0)	133 (20.4)	21 (20.8)	168 (16.8)	14 (14.1)	1,698 (16.5)	284 (16.1)	306 (13.1)	15 (11.9)
Cancer	383 (39.4)	44 (37.3)	244 (37.4)	45 (44.6)	257 (25.7)	27 (27.3)	3,618 (35.2)	552 (31.4)	630 (27.0)	30 (23.8)

All characteristics measured at moment of death. * Percentage of patients for whom cause of death/smoking is available, NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Online Table 2. Number of persons, deaths and mortality rates (number of patients who died/1000 PY) by age category

	Asthma				Severe asthma			
	Number of persons (%)	**Number of deaths (%)**	**MR**	**95 %CI**	**Number of persons (%)**	**Number of deaths (%)**	**MR**	**95 %CI**
IPCI (NL)								
Overall	73,506	973	4.9	4.6-5.2	6,446	118	7.3	6.1-8.8
18-<35 yrs.	22,039 (30.0)	20 (2.0)	0.4	0.2-0.6	1,088 (16.9)	1 (0.8)	0.4	0.1-3.0
35-<45 yrs.	15,415 (21.0)	27 (2.8)	0.7	0.5-1.0	1,251 (19.4)	3 (2.5)	1.1	0.3-3.3
45-<55 yrs.	15,105 (20.5)	73 (7.5)	1.7	1.3-2.1	1,618 (25.1)	10 (8.5)	2.4	1.3-4.4
55-<65 yrs.	10,621 (14.4)	134 (13.8)	4.3	3.7-5.1	1,230 (19.1)	19 (16.1)	5.9	3.8-9.3
65-<75 yrs.	6,335 (8.6)	189 (19.4)	10.2	8.9-11.8	773 (12.0)	23 (19.5)	10.8	7.2-16.3
>=75 yrs.	3,991 (5.4)	530 (54.5)	44.9	41.2-48.9	486 (7.5)	62 (52.5)	48.3	37.7-62.0
AARHUS (DK)								
Overall	14,041	657	9.2	8.6-10.0	1,633	101	12.2	10.0-14.8
18-<35 yrs.	4,164 (29.7)	21 (3.2)	1	0.7-1.5	234 (14.3)	1(1.0)	0.8	0.1-5.9
35-<45 yrs.	2,704 (19.3)	19 (2.9)	1.5	0.9-2.3	254 (15.6)	1 (1.0)	1.0	0.1-7.0
45-<55 yrs.	2,586 (18.4)	60 (9.1)	4.6	3.5-5.9	344 (21.1)	10 (9.9)	6.0	3.2-11.1
55-<65 yrs.	2,271 (16.2)	78 (11.9)	7.0	5.6-8.7	402 (24.6)	13 (12.9)	6.3	3.7-10.9
65-<75 yrs.	1,421 (10.1)	120 (18.3)	14.9	12.4-17.8	242 (14.8)	17 (16.8)	11.7	7.3-18.8
>=75 yrs.	895 (6.4)	359 (54.6)	77.1	69.5-85.5	157 (9.6)	59 (58.4)	65.9	51.1-85.1
HSD (IT)								
Overall	37,003	1002	6.0	5.7-6.4	1,895	99	12.0	9.8-14.6
18-<35 yrs.	10,081 (27.2)	13 (1.3)	0.3	0.2-0.5	292 (15.4)	0 (0.0)	Nap	Nap
35-<45 yrs.	7,798 (21.1)	22 (2.2)	0.7	0.4-1.0	286 (15.1)	0 (0.0)	Nap	Nap
45-<55 yrs.	6,523 (17.6)	50 (5.0)	1.6	1.2-2.1	359 (18.9)	2 (2.0)	1.2	0.3-4.9
55-<65 yrs.	5,185 (14.0)	83 (8.3)	3.5	2.8-4.4	354 (18.7)	14 (14.1)	8.9	5.3-15.0
65-<75 yrs.	4,113 (11.1)	149 (14.9)	8.0	6.8-9.4	324 (17.1)	19 (19.2)	13.2	8.4-20.7
>=75 yrs.	3,303 (8.9)	685 (68.4)	45.6	42.3-49.1	280 (14.8)	64 (64.6)	46.5	36.4-59.4

	Asthma				Severe asthma			
	Number of persons (%)	**Number of deaths (%)**	**MR**	**95 %CI**	**Number of persons (%)**	**Number of deaths (%)**	**MR**	**95 %CI**
CPRD (UK)								
Overall	393,660	10,346	6.5	6.4-6.6	31,214	1.770	14.8	14.1-15.5
18-<35 yrs.	138,693 (35.2)	218 (2.1)	0.4	0.4-0.5	4,284 (13.7)	15 (0.8)	1.2	0.7-1.9
35-<45 yrs.	73,462 (18.7)	306 (3.0)	1.2	1.0-1.3	4,767 (15.3)	28 (1.6)	1.8	1.3-2.6
45-<55 yrs.	64,517 (16.4)	595 (5.8)	2.1	1.9-2.3	5,898 (18.9)	90 (5.1)	4.0	3.3-4.9
55-<65 yrs.	51,960 (13.2)	1,044 (10.1)	4.6	4.3-4.9	6,206 (19.9)	163 (9.2)	6.7	5.7-7.8
65-<75 yrs.	35,196 (8.9)	1,877 (18.1)	10.5	10.1-11.0	5,285 (16.9)	344 (19.4)	14.6	13.1-16.2
>=75 yrs.	29,832 (7.6)	6,306 (61.0)	43.7	42.7-44.8	4,774 (15.3)	1,130 (63.8)	54.6	51.5-57.8
SIDIAP (SP)								
Overall	68,226	2.347	8.8	8.4-9.2	1,423	126	25.3	21.3-30.2
18-<35 yrs.	20,811 (30.5)	33 (1.4)	0.4	0.3-0.6	48 (3.4)	0 (0.0)	Nap	Nap
35-<45 yrs.	13,506 (19.8)	53 (2.3)	1.0	0.7-1.3	109 (7.7)	0 (0.0)	Nap	Nap
45-<55 yrs.	9,519 (14.0)	84 (3.6)	2.1	1.7-2.6	158 (11.1)	2 (1.6)	3.9	1.0-15.7
55-<65 yrs.	8,747 (12.8)	123 (5.3)	3.7	3.1-4.4	277 (19.5)	3 (2.4)	3.3	1.1-10.1
65-<75 yrs.	7,914 (11.6)	297 (12.7)	9.5	8.5-10.6	372 (26.1)	18 (14.3)	14.4	9.1-22.9
>=75 yrs.	7,729 (11.3)	1,744 (74.7)	54.5	52.0-57.1	459 (32.3)	103 (81.7)	56.2	46.3-68.1

Yrs= Years, NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Online Table 3. Patient characteristics and mortality ~~Risk factors of mortality in asthma patients~~ (univariate analysis)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226		
Deaths in 5 years (n)	923			571			893			8,965			2,097		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age															
18-<25	1	Ref	<.0001	1	Ref	<.0001	1	Ref	<.0001	1	Ref	<.0001	1	Ref	<.0001
25-<35	1.19	0.50-2.82		2.09	0.74-5.93		2.07	0.56-7.63		1.87	1.42-2.44		1.26	0.61-2.61	
35-<45	2.25	1.08-4.69		3.32	1.27-8.69		3.92	1.17-13.11		3.51	2.75-4.46		2.41	1.22-4.77	
45-<55	5.74	2.88-11.42		7.24	2.89-18.18		11.27	3.52-36.10		7.24	5.75-9.10		5.64	2.92-10.89	
55-<65	14.59	7.44-28.59		12.65	5.12-31.28		22.95	7.25-72.62		15.49	12.39-19.36		10.41	5.48-19.79	
65-<75	33.18	16.99-64.77		29.48	12.02-72.32		63.79	20.37-199.7		36.49	29.27-45.49		31.04	16.56-58.20	
>=75	135.3	69.92-261.7		160.4	66.29-388.30		287.8	92.52-895.10		140.0	112.7-173.9		152.2	81.70-283.4	
Female gender	0.69	0.61-0.79	<.0001	0.93	0.78-1.10	0.4129	0.65	0.56-0.74	<.0001	0.76	0.73-0.79	<.0001	0.64	0.58-0.71	<.0001
Exacerbation history															
No previous exacerbations	1	Ref	<.0001	1	Ref	0.0286	1	Ref	0.0002	1	Ref	<.0001	1	Ref	<.0001
30 days after exacerbation	1.74	1.00-3.01		2.07	1.25-3.41		2.25	1.48-3.42		1.97	1.58-2.46		2.70	2.24-3.26	
31-90 days after exacerbation	2.14	1.48-3.11		1.53	0.95-2.46		1.32	0.86-2.01		1.29	1.05-1.59		2.79	2.34-3.33	
91-365 days after exacerbation	1.49	1.15-1.94		1.02	0.73-1.43		1.39	1.09-1.78		1.08	0.96-1.22		2.13	1.86-2.44	

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226		
Deaths in 5 years (n)	923			571			893			8,965			2,097		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
>365 days after exacerbation	1.45	1.12-1.88		1.02	0.76-1.37		0.98	0.77-1.24		1.14	1.04-1.25		1.39	1.20-1.61	
Comorbidity															
History of cancer	2.12	1.82-2.47	<.0001	1.80	1.45-2.23	<.0001	2.56	2.07-3.17	<.0001	2.07	1.96-2.18	<.0001	1.75	1.55-1.98	<.0001
History of cardiovascular disease	1.21	1.02-1.43	0.0260	1.26	1.01-1.56	0.0376	1.28	0.97-1.69	0.0807	1.56	1.49-1.64	<.0001	1.76	1.51-2.05	<.0001
History of cerebrovascular disease	1.48	1.21-1.80	0.0001	1.85	1.46-2.33	<.0001	1.46	1.19-1.80	0.0004	1.65	1.54-1.76	<.0001	1.73	1.50-2.01	<.0001
History of diabetes mellitus	1.69	1.46-1.97	<.0001	1.74	1.34-2.25	<.0001	1.22	1.02-1.45	0.0274	1.75	1.66-1.84	<.0001	1.57	1.42-1.73	<.0001
Obesity	0.82	0.72-0.95	0.0059	1.43	1.05-1.96	0.0243	1.50	1.30-1.73	<.0001	0.86	0.83-0.90	<.0001	0.72	0.66-0.79	<.0001
Prevalent asthma	1.03	0.87-1.22	0.7324	0.72	0.60-0.86	0.0003	0.93	0.81-1.06	0.2813	1.18	1.10-1.26	<.0001	0.92	0.85-1.01	0.0767
Severe asthma	1.12	0.92-1.36	0.2714	0.91	0.73-1.14	0.4257	1.27	1.01-1.58	0.0376	1.38	1.31-1.46	<.0001	1.05	0.86-1.27	0.6406
Smoking status															
Smoking never	Ref		<.0001	Ref		0.7725	Ref		<.0001	Ref		<.0001	Ref		<.0001
Smoking current	2.55	2.05-3.16		1.00	0.12-8.33		1.55	1.20-1.99		2.54	2.38-2.71		2.58	2.16-3.08	
Smoking past	1.54	1.25-1.90		0.47	0.09-2.31		1.46	1.20-1.77		1.20	1.15-1.26		1.39	1.18-1.62	

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226		
Deaths in 5 years (n)	923			571			893			8,965			2,097		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
~~Smoking status~~Smoking status unknown	1.56	1.33-1.84		0.72	0.32-1.63		1.04	0.89-1.21		1.36	0.97-1.89		1.25	1.12-1.39	

Adjusted for age at start of follow-up (except for univariate analysis of age categories), NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Online Table 4. Patient characteristics and mortality ~~Risk factors of mortality in~~ incident asthma patients only (Multivariate analysis)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)			Meta-analysis		
Incident asthma patients (n)	16,265			4,083			15,842			77,884			42,086					
Deaths in 5 years (n)	165			176			375			1,047			1,080					
Parameter	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age at asthma diagnosis	1.12	1.10-1.13	<.0001	1.11	1.09-1.12	<.0001	1.11	1.10-1.13	<.0001	1.10	1.09-1.10	<.0001	1.12	1.11-1.12	<.0001	1.11	1.10-1.12	<.0001
Female gender	0.68	0.49-0.95	0.0224	0.82	0.60-1.12	0.2173	0.70	0.56-0.88	0.0020	0.91	0.80-1.03	0.1371	0.71	0.61-0.82	<.0001	0.76	0.66-0.87	<.0001
Previous severe asthma exacerbation																		
No previous exacerbations	1.00		0.0380	1.00		0.7366	1.00		0.1709	1.00		0.0005	1.00		<.0001			0.0001
30 days after exacerbation	1.89	0.57-6.21	.	1.51	0.68-3.36	.	1.42	0.69-2.92	.	1.78	1.01-3.14	.	2.56	1.95-3.37	.	1.82	1.34-2.46	
31-90 days after exacerbation	2.52	1.21-5.22	.	0.67	0.24-1.84	.	1.33	0.74-2.36	.	1.20	0.74-1.97	.	2.81	2.20-3.59	.	1.61	1.05-2.47	
91-365 days after exacerbation	1.50	0.89-2.52	.	1.10	0.66-1.83	.	1.45	1.04-2.03	.	1.39	1.09-1.77	.	1.91	1.58-2.32	.	1.48	1.22-1.79	
>365 days after exacerbation	1.48	0.91-2.42	0.1150	0.90	0.53-1.52	0.6918	1.10	0.80-1.50	0.5567	1.37	1.13-1.66	0.0015	1.49	1.21-1.82	0.0001	1.28	1.08-1.51	
Comorbidity																		
History of cancer	1.64	1.13-2.37	0.0085	1.48	0.97-2.25	0.0667	2.09	1.50-2.93	<.0001	2.04	1.74-2.40	<.0001	1.58	1.34-1.87	<.0001	1.79	1.54-2.08	<.0001
History of cardiovascular disease	0.89	0.60-1.32	0.5771	1.17	0.81-1.69	0.4074	1.40	0.96-2.03	0.0788	1.49	1.28-1.73	<.0001	1.51	1.21-1.87	0.0002	1.28	1.05-1.57	0.0161
History of cerebrovascular disease	0.84	0.49-1.43	0.5102	1.38	0.89-2.13	0.1531	1.47	1.09-1.98	0.0106	1.71	1.42-2.06	<.0001	1.82	1.50-2.20	<.0001	1.44	1.13-1.83	0.003
History of diabetes mellitus	1.75	1.18-2.60	0.0055	1.69	1.08-2.63	0.0209	1.27	0.98-1.65	0.0695	1.79	1.53-2.09	<.0001	1.62	1.41-1.86	<.0001	1.60	1.37-1.86	<.0001
Obesity	0.81	0.55-1.18	0.2664	1.00	0.59-1.69	0.9936	1.82	1.45-2.29	<.0001	0.75	0.65-0.85	<.0001	0.66	0.58-0.76	<.0001	0.95	0.65-1.38	0.782
Severe asthma	0.56	0.27-1.14	0.1102	0.77	0.43-1.39	0.3839	1.02	0.56-1.86	0.9577	1.26	1.02-1.55	0.0285	0.98	0.72-1.33	0.8952	0.91	0.67-1.22	0.5162
Smoking status																		
Smoking never	1.00		0.0627	1.00		0.5618	1.00		0.0259	1.00		<.0001	1.00		<.0001			<.0001
Smoking current	2.02	1.19-3.43	.	0.98	0.12-8.23	.	1.58	1.09-2.28	.	2.62	2.18-3.14	.	2.30	1.81-2.91	.	2.07	1.66-2.59	

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)			Meta-analysis		
Incident asthma patients (n)	16,265			4,083			15,842			77,884			42,086					
Deaths in 5 years (n)	165			176			375			1,047			1,080					
Parameter	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Smoking past	1.11	0.70-1.77	.	0.39	0.08-1.96	.	0.93	0.66-1.30	.	1.04	0.90-1.19	.	1.11	0.89-1.39	.	1.02	0.90-1.16	
~~Smoking status~~Smoking status unknown	1.32	0.89-1.98	.	1.09	0.47-2.54	.	1.26	0.98-1.63	.	1.51	0.48-4.73	.	1.14	0.97-1.36	.	1.30	1.12-1.50	

NL= Netherlands, DK= Denmark, IT=Italy, UK= United Kingdom, SP= Spain

Online supplement: Description of databases

The **Integrated Primary Care Information** (IPCI) database is a Dutch database containing the complete medical record of more than 1.5 million patients provided by more than 450 GPs geographically spread over the Netherlands. [15] In the Netherlands, all citizens are registered with a GP practice which acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care. The International Classification of Primary Care (ICPC) is the coding system but diagnoses and complaints can also be entered as free text. Prescription data contain information on product name, quantity prescribed, dosage regimens, strength, indication and ATC codes.

The **Health Search Database** (HSD). is a longitudinal observational database that is representative of the Italian general population. HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.5 million patients) located throughout Italy. The database includes information on age, gender, patient and GP identification, which is linked to prescription information, clinical events and diagnoses and date of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision. Drug names are coded according to the ATC classification. [17, 18]

Clinical Practice Research Datalink (CPRD) is a large validated computerized database of anonymized longitudinal medical records for primary care. Data comprise approximately 12 million patients with around 5.4 million of these being currently alive and registered from 680 primary care practices spread throughout the UK. The database contains the entire anonymized electronic medical record of each patient, including medical codes associated with consultations and referrals, details of all drugs prescribed, ~~life style~~lifestyle factors and laboratory tests. [19]. Information on hospitalization is collected through linkage HES and information on mortality is retrieved through linkage with the Office of National Statistics (ONS) Mortality data.

The **Aarhus University Prescription Database** comprises clinical and prescription data from the Central Denmark Region and the North Denmark Region. It covers a total of 1.2 million inhabitants and is representative of the population of Denmark [16]. Data are available on demographics, ~~life style~~lifestyle factors, dispensing data, hospitalizations and procedures. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data are linked to the national registry [38] of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures to the Central Registration system [39] that records information on mortality and to the Danish Registry of Cause of death. [20]

The **SIDIAP** (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria) **Database** comprises the electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices. The SIDIAP data comprises the clinical and referral events (coded by ICD-10), demography information, prescription and dispensing, specialist referrals, ~~life style~~lifestyle factors, laboratory test results, and hospital admissions and their major outcomes. [40]

Online supplement: Disease codes

Asthma

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for asthma

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493*	H33*..	R96
Asthma confirmed			1O2..00	
Extrinsic asthma with asthma attack			663d.00 663m.00	
Asthma severity			663V*	
Number of asthma exacerbations in past year			663y.00	
Emergency admission. asthma			8H2P.00	
Status asthmaticus	J46			
Induced asthma			173A.00	
Asthma trigger			173c.00 173d.00 178*.00	
Asthma accident and emergency attendance since last visit			663m.00	
Emergency asthma admission since last appointment			663d.00	
Asthma and exercise			663e.00 663e000 663e100 663f.00 663w.00 663x.00	
Asthma currently dormant			663h.00	
Asthma currently active			663j.00	
Asthma treatment compliance satisfactory			663n.00	
Asthma treatment compliance unsatisfactory			663p.00	
Asthma disturbing sleep Asthma causing night waking Asthma disturbs sleep weekly Asthma disturbs sleep frequently Asthma not disturbing sleep Asthma never disturbs sleep Asthma night-time symptoms Asthma causes night time symptoms Asthma causes symptoms most nights Asthma never causes night symptoms			663N.00 663N000 663N100 663N200 663O.00 663O000 66YP.00 66Yq.00 66Yr.00 66Ys.00	
Asthma limits activities			663P*	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma daytime symptoms			663q.00	
Asthma not limiting activities			663Q.00	
Asthma causes night symptoms 1 to 2 times per month			663r.00	
Asthma never causes daytime symptoms			663s.00	
Asthma causes daytime symptoms 1 to 2 times per month			663t.00	
Asthma causes daytime symptoms 1 to 2 times per week			663u.00	
Asthma causes daytime symptoms			663v.00	
Asthma prophylactic medication used			663W.00	
Asthma medication review			8B3j.00	
Absent from work or school due to asthma			66YC.00	
Number days absent from school due to asthma in past 6 months			66Yu.00	
Health education - asthma			679J.*	
Asthma control			8793.00 8794.00 8795.00 8796.00 8797.00 8798.00	
Asthma quality indicators			9hA*.00	

*means all codes falling under this category

Asthma exacerbation

Definition of severe asthma exacerbation

Asthma exacerbation was defined as the use of acute systemic corticosteroids, ED visit, or hospitalisation for reasons of asthma exacerbation. To identify patients with a severe asthma exacerbation defined as ED visit or hospitalisation for reasons of asthma, an automated search was done on codes specific for severe asthma exacerbation. In addition, the medical file was searched for asthma specific disease codes (thus not only asthma exacerbation codes) in combination with codes for hospitalisation. Hospitalization was retrieved either via linkage with hospital admission/discharge database (Aarhus. CPRD (➔ HES)).combination of disease codes with information from hospital referral (HSD. SIDIAP and IPCI) and discharge letters (SIDIAP and IPCI) or combination of disease codes with source codes (hospital discharge letters) (CPRD ➔ for those patients where we did not have HES).

The following disease codes also did fit the criteria of asthma exacerbation:

Terms	ICD10	ICD9CM	Read Codes	ICPC
Emergency admission. asthma			8H2P.00	

Status asthmaticus	J46 J45.22 J45.32 J45.42 J45.52 J45.902	493.01 493.11 493.21 493.91	H33z000
Severe asthma attack			H33z011
Asthma accident and emergency attendance since last visit			663m.00
Emergency asthma admission since last appointment			663d.00

Atopy

Atopy is defined as any of the following: atopic dermatitis/eczema or allergic rhinitis.
The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for atopy.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atopy				
Atopic dermatitis/eczema	L20*	691*	M111.00 M112.00 M113.00 M114.00 M11z.00	S87
Allergic rhinitis	J30* (excluding J30.0)	477*	H17* H120.11	R97
Asthma with allergic rhinitis (nasal congestion)	J45.909			
Other allergic rhinitis			Hyu2100 Hyu2000	
Allergic eczema			M114.00	

*means all codes falling under this category

Chronic rhinosinusitis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for chronic rhinosinusitis.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic rhinitis			H120*	
Chronic allergic sinusitis			H 13..11	R75.02
Allergic sinusitis			H17..00	
Other chronic sinusitis			Hyu2200	
Chronic sinusitis, unspecified	J32.9	473.9		
Chronic sinusitis			H13*	

Allergic rhinosinusitis			H17..12	

*means all codes falling under this category

COPD

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for COPD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease	J44			R95
Chronic airway obstruction		496.*		
Obstructive chronic bronchitis		491.2*	H312z00	
Chronic obstructive lung disease			H3...00	
Chronic obstructive airways disease			H3...11	
			H3z..00	
Other specified chronic obstructive pulmonary disease	J44.8		Hyu31	
			H3z..11	
Chronic obstruct pulmonary dis with acute lower respiratory infection			H3y0.00	
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1		H3y1.00	
Mild chronic obstructive pulmonary disease			H36..00	
Moderate chronic obstructive pulmonary disease			H37..00	
Severe chronic obstructive pulmonary disease			H38..00	
Very severe chronic obstructive pulmonary disease			H39..00	
End stage chronic obstructive airways disease			H3A..00	
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0		H3y0.00	
COPD exacerbation			66Yd.00	
			66Ye.00	
			66Yf.00	
			8H2R.00	
			H3y1.00	
			H312200	
Multiple COPD emergency hospitalisations			66Yi.00	

*means all codes falling under this category

Gastroesophageal reflux disease

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for GERD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Gastroesophageal reflux disease	K21*	530.81		
Reflux esophagitis			J101100	
Acid reflux			J101111	
Gastroesophageal reflux with esophagitis	K21.0	530.81	J101112	
Gastroesophageal reflux without esophagitis	K21.9	530.81	J101112	

Esophageal reflux with esophagitis		530.11	J101113	D84.03
Esophageal reflux without (mention) of esophagitis			J10y400	D84.02
Esophageal reflux	K21.9		J10y411	
Gastroesophageal reflux	K21.9		J10y412	
Acid reflux	K21.9	530.81	J10y413	
Peptic esophagitis			J101114	
Regurgitant oesophagitis			J101115	
Gastric reflux			1957.00	

*means all codes falling under this category

Nasal Polyposis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for nasal polyps.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Nasal Polyps	J33*	471*	H11*	R99.02
Nasal polyp present			2D33.00	
Nasal polypectomy			7406000	
			7402900	
			7402911	
			7406700	
			7416F00	

*means all codes falling under this category

Depression and anxiety

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for depression.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Depression			E2B*.00	P76
			E112*	
Major depressive disorder, recurrent	F33*	296.3*	E113*	
Major depressive disorder, single	F32*	296.2*	E112*	
Depressive episode			Eu32*	
Recurrent episode of depressive reaction			Eu33*	
Depressive disorder, nos		311*	Eu3y111 Eu34112	
Chronic depressive personality disorder		301.12	E2112000	
Post schizophrenic depression			Eu20400	
History of depression			1465.00	
History of manic depressive disorder			146D.00	
Other and unspecified manic depressive disorder			E11y.00 E11y.000 E11y.200	
Psychotic reactive depression			E130.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Agitated depression			E135.00	
Mild anxiety depression			Eu41211	

*means all codes falling under this category --- Post-natal depression not included

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for anxiety.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Phobic anxiety disorders	F40*	300*	E202.12	P74
Other anxiety disorders	F41*			
Anxiety states			E200*	
Organic anxiety disorder			Eu05400	
Phobic anxiety disorders			Eu40*	
Other anxiety disorders			Eu41*	

*means all codes falling under this category

Overweight and obesity

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for obesity.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Overweight and Obesity bmi>30	E66*	278.0*	C38*	T83
Adipositas				T82
Body mass index (BMI > 40.0-44.9)	Z68.4*	278.01	22K7.00	
Body mass index (BMI 45.0-49.9)	Z68.42			
Body mass index (BMI >30)		V85.3*	22K5.00	
Body mass index (85^{th}<95^{th} percentile)	Z68.53	V85.53		
Body mass index (=>95^{th} percentile)	Z68.54	V85.54		
Other obesity			Cyu7*	

*means all codes falling under this category

In addition, BMI was retrieved from the measurement table in all databases.
Cut-off values for obesity or overweight were as following:

	Adults (>19)
Obese	BMI>=30
Overweight	BMI between 25 and 29.9

Angina pectoris

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for angina pectoris.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina pectoris	I20*	413*	G33*	K74

Other acute and subacture ischaemic heart disease	I24*		G31***00	
Atherosclerotic heart disease of native coronary artery with angina pectoris	I25.11 I25.7*			
Ischemic heart disease		411*	G3...00 G3...13	
Dressler's syndrome			G310.11 G31y.00 G34..00 G3y..00 G3z..00 G340*	
Other forms of angina pectoris			Gyu3000	
Other forms of ischemic heart disease			Gyu3.00	
Intermediate coronary syndrome				K76.01
H/O angina pectoris			14A5. 14AJ.00	

*means all codes falling under this category

Arterial Hypertension

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for arterial hypertension.

Terms	**ICD10**	**ICD9CM**	**Read Codes**	**ICPC**
Hypertensive diseases	I10-I15.9	401-405.99	Gyu2. G2...*	
high blood pressure	I10			
Uncomplicated hypertension				K86
Hypertension with involvement target organs				K87
Renovascular hypertension	I15.0			
Secondary hypertension	I15	405	G24..	
Secondary hypertension, unspecified	I15.9		G24z.	
Malignant essential hypertension		401.0	G200.	
Essential (primary) hypertension	I10	401		
Hypertension NOS		401.9		
Benign hypertension		401.1	G201.	
Other secondary hypertension	I15.8	405.99	Gyu20	
Malignant secondary hypertension		405.0	G240.	
		405.09	G240z	
Benign secondary hypertension		405.1	G241	
		405.19	G241z	
Malignant hypertension			Xa3fQ G200.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertension monitoring			662..*	

*means all codes falling under this category

Heart Failure

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for heart failure.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart failure	I50	428.*	G58..	K77
Heart failure, unspecified	I50.9	428.9		
Congestive heart failure	I50.0	428.0	G580.00	
Congestive heart disease	I50.9			
Left ventricular failure	I50.1	428.1	G581.00	
Acute heart failure			G582.	
			G5800	
Admit heart failure emergency			8H2S.00	
Chronic congestive heart failure[#]			G5801	
H/O: heart failure[#]			14A6.00	
			14AM.00	
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01	G21z011	
		402.91		
Hypertensive heart and renal disease with (congestive) heart failure	I13.0	402.11	G232.00	
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2	404.01		
		404.91		
Heart failure confirmed			1O1..00	
Heart failure resolved[#]			2126400	
Heart failure management			661M500	
			661N500	
New York Heart Association classification - class II			662g.00	
New York Heart Association classification - class III			662h.00	
New York Heart Association classification - class IV			662i.00	
New York Heart Assoc classification heart failure symptoms			ZRad.00	
Heart failure monitoring			662p.00	
			662T.00	
			662W.00	
			679W100	
			679X.00	
			67D4.00	
			8CL3.00	
			8CMK.00	
Heart failure follow-up			8HBE.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			8Hg8.00	
			8HgD.00	
			8HHb.00	
			8HHz.00	
			8Hk0.00	
			8HTL.00	
			8IB8.00	
			8IE0.00	
			8IE1.00	
			9N0k.00	
			9N2p.00	
Heart failure quality indicators			9hH..00	
			9hH0.00	
			9hH1.00	
Cardiomegaly			G5y3.00	
Post cardiac operation heart failure NOS			G5y4z00	
Heart failure confirmed via echography			G5yy900	
			G5yyA00	
			G5yyC00	

*means all codes falling under this category

Myocardial infarction

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for myocardial infarction.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cardiac infarction	I22*			
Cardiac infarction	I21*			
Acute myocardial infarction	I21*	410*	G30*	K75
Old myocardial infarction	I25.2	412*	G32*	K76.02
			14A3.00	
			14A4.00	
			14AH.00	
			14AT.00	
Healed myocardial infarction			G32..11	
Subsequent/recurrent myocardial infarction			G35*	
Subsequent myocardial infarction of unspecified site			Gyu3600	
Subsequent myocardial infarction of other sites			Gyu3500.	
Acute transmural myocardial infarction of unspecified site			Gyu34	
			G30X.00	
ECG: old myocardial infarction			3232.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Acute widespread myocardial infarction			X200S	
ECG: myocardial infarction			323*	
Postoperative myocardial infarction			G38*	
Postmyocardial infarction syndrome			G310.00	
Complications following myocardial infarction			G36*	

*means all codes falling under this category

Stroke

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for stroke.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64*			
Stroke NOS	I63.9			K90
Intracerebral hemorrhage		431*	G61..	
Cerebrovascular accident (CVA)			G66..13	
Stroke and cerebrovascular accident unspecified			G66..00	
Stroke NOS			G66..12	
Sequelae of stroke, not specified as hemorrhage or infarction	I69	342	Gyu6C	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Other and unspecified intracranial hemorrhage	I62*	432*	G62..00 G62z.00	
Cerebral infarction	I63*		G64..	
Personal history of stroke			ZV125	
Sequelae of stroke NOS	I69.3			
H/O: Stroke			14A7.00 14A7.11	
Cerebral infarct due to thrombosis of precerebral arteries		433*	G63y000 G63y000	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits	Z86.73	V12.54		
Sequelae of cerebral infarction			G683.00	
Sequelae of stroke, not specified as hemorrhage or infarction		438.*	G68X.00/Gyu6C00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300 G6X..00/Gyu6G00	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		434.*		
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	
Hemiplegia and hemiparesis		342.*		
Acute, but ill-defined, cerebrovascular disease		436.*		

*means all codes falling under this category

TIA

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for TIA.

Terms	ICD10	ICD9CM	Read Codes	ICPC
TIA - Transient ischemic attack	G45*	435.*	G65..12	K89
Transient cerebral ischemia			G65**00	
Drop attack			G65*.11	
H/O: TIA			14AB.00 ZV12D00	
Amaurosis fugax			F423600	
Retinal transient arterial occlusion NOS			F423700	
Other transient cerebral ischemic attacks and related syndromes			Fyu55	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits	Z86.73	V12.54	ZV12D00	

*means all codes falling under this category

Definition of cancer

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for cancer.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignancy	C*		B*	
Malignant neoplasm without specification of site	C80*	199*	ByuC8 XE20H B59..	A79
Cancer			X78ef	
Malignant neoplasm				
Malignant neoplasm of bladder	C67*	188*	B49..	U76

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of breast	C50*-C50.9		Byu6.	X76
Breast cancer			X78WM	
Malignant tumor of breast			XE1zL	
Malignant neoplasm of colon	C18*	153*	B13..	D75
Malignant tumour of colon			XE1xd	
			XE1vV	
Malignant neoplasm of larynx	C32*	161*	B21..	
			XE1yD	
Carcinoma of the rectum	C20*	154*	XE1vW	
			X78OK	
Malignant neoplasm of skin	C44*		Byu43	S77
			X78gs	
			B33z.	
Malignant neoplasm of thyroid gland	C73*	193*	B53..	T71
Malignant neoplasm of cervix uteri	C53*	180*	XE1vi	X75
			B41z.	
Malignant neoplasm of stomach	C16*	151*	X78gA	D74
Gastric cancer			XE1vR	
			XE1xJ	
			B11z.	
Malignant neoplasm of vagina	C52*	184.0	B450.	
Malignant neoplasm of oropharynx	C10*	146*	B06..	
Malignant neoplasm of nasopharynx	C11*	147*	B07..	
Malignant neoplasm of pharynx	C14*	149.0	X78fO	
Malignant neoplasm of duodenum	C17*	152.0	/B120.	
Malignant neoplasm of caecum	C18.0	153.4	XE1vU	
Malignant neoplasm of peritoneum	C48.2	158.9	Byu57	
			X78Pq	
Malignant neoplasm of trachea	C33*	162.0	B220.	
Malignant neoplasm of pleura	C38.4	163*	B23..	
Bone cancer	C40*	170*	XE1vd	
	C41*			
Malignant neoplasm of liver	C22*	155*	Xa97q	
			B152.	
Malignant neoplasm of intestinal tract, part unspecified	C26.0	159.0	Byu12	
			X78gK	
			B1z0.	
Malignant neoplasm of pancreas	C25*	157*	B17..	D76
			XE1y5	
Malignant neoplasm of vertebral column	C41.2		B302.	
Malignant neoplasm of prostate	C61*	185*	B46..	Y77
Malignant neoplasm of oesophagus	C15*	150.9	B10..	
			X78g3	
			XE1vQ	
Malignant neoplasm of ovary	C56*	183.0	B440.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of uterus	C55*	179*	B43..	
Malignant melanoma of skin (not basal cell carcinoma nor epidermoid epithelioma)	C43*	172*	Byu41 B32..	
Malignant neoplasm of brain	C71*	191*	B51z. XE2vS	N74
Malignant tumor of kidney	C64*	189.0	X78iu	U75
Hodgkin's disease	C81*	201*	B61.. XaC2n BBjA.	B72
Leukemia	C95*	208*	BBr00 X78e2	B73
Lung cancer	C34.9	162*	Xa0KG	R84
Malignant neoplasm of bronchus and lung		162.9	B22.. Byu20 XE1vc	
Oat cell carcinoma of			X78QO	
Small cell carcinoma of lung			X78QN	
Secondary malignant neoplasm of lung	C78.0	197.0	B570	
Non-small cell lung cancer			X78QS	
Malignant neoplasm of hilus of lung			B2211	
Malignant neoplasm of upper lobe of lung			B2221	
Malignant neoplasm of middle lobe of lung			B2231	
Malignant neoplasm of lower lobe of lung			B2241	
Malignant neoplasm of upper lobe, bronchus or lung	C34.1	162.3	B222z XE1vb	
Malignant neoplasm of middle lobe, bronchus or lung	C34.2	162.4	B223. B223z	
Malignant neoplasm of lower lobe, bronchus or lung	C34.3	162.5	B224. B224z	
Malignant neoplasm of other parts of bronchus or lung		162.8	B22y.	
Malignant neoplasm overlapping bronchus and lung sites	C34.8		B225.	
Personal history of malignant neoplasm of lung			ZV101	

*means all codes falling under this category

Diabetes mellitus

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus type 1.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus type 1	E10	250.*1	C108***	T90.01
		250.*3	C10E***	
Diabetes mellitus, juvenile type			C10*000	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Brittle Diabetes			66AJ100	

*means all codes falling under this category

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus type 2.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus type 2	E11	250.*0	C10*.100	T90.02
		250.*2	C10F***	
			C109***	

*means all codes falling under this category

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus type 1 and/or 2 or other specified diabetes.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus	E08- E13	250.**	C10../Cyu.00	T90
Unstable diabetes			66AJ.11	
Diabetic neuropathy	E**.42	357.2/250.6		N94.02
Secondary diabetes mellitus		249		
Nephrotic syndrome in diabetes mellitus		581.81	K01x1	
Diabetic cataract		366.41		
History of diabetes			1434.00	
Foot abnormality dm related			2G51000 2G5C.00	
Diabetes with neurological manifestations			X00Ag	

*means all codes falling under this category

Multinational cohort study of mortality in patients with asthma and severe asthma

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Keywords: asthma epidemiology, severe asthma, mortality, cohort studies

Word count:

List of abbreviations

Term	Abbreviation
Asthma-COPD overlap	ACO
DK	Denmark
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance	ENCePP
Emergency department	ED
Gastro-oesophageal reflux disease	GERD
Global Initiative of asthma	GINA
Inhaled corticosteroids	ICS
IT	Italy
leukotriene modifier	LTRA
Long-acting β_2 agonists	LABA
NL	The Netherlands
Person-years	PY
Short-acting β_2 agonists	SABA
Short-acting muscarinic antagonist	SAMA
SP	Spain
UK	United Kingdom
World Health organisation	WHO

Declarations:

Acknowledgement: This work was carried out through the EU-ADR Alliance. The authors wish to acknowledge Eva Molero and Natasha Yefimenko (Synapse Research Management Partners) for their contributions to managing the study protocol during the development of this manuscript.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Interest

Funding for this study was provided by GSK (PRJ2284) and ZonMw (ME and KV) (113201006).

Author's contribution

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. This work was carried out through the EU-ADR Alliance.

Conflicts of interest

FA, SC, and EB are GSK employees and own stocks/shares in GSK.

NB and RS were employees of GSK at the time this research was conducted and own stocks/shares in GSK.

GP, CG, KB have no conflicts to declare.

FL has received grants from Chiesi, GSK and Novartis.

DPA has received research grants from Amgen, Bioiberica and GSK and speaker/advisory fees from Amgen and Bioiberica, paid to his department.

KV has received grants from GSK and ZonMw.

MR, PR, MS and KV's institution has received unconditional research grants from Boehringer-Ingelheim, Novartis, Pfizer, Yamanouchi, Servier, and Johnson & Johnson, unrelated to the current manuscript; MR, PR, MS and KV's received an unconditional grant from GSK to conduct research on incidence and risk factors of asthma exacerbations as part of the GSK/EU-ADR alliance.

ES's institution (Aarhus University) has received a grant from the GSK/EU-ADR alliance related to this study.

GB has received fees for lectures and/or advisory boards of AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Sanofi and Teva.

ABSTRACT

Background: Data on the risk of death following an asthma exacerbation are scarce. With this multinational cohort study, we assessed all-cause mortality rates, mortality rates following an exacerbation, and patient characteristics associated with all-cause mortality in asthma.

Methods: Asthma patients aged ≥18 years and with ≥1 year of follow-up were identified in 5 European electronic databases from the Netherlands, Italy, UK, Denmark and Spain during the study period 1st January 2008 – 31st December 2013. Patients with asthma-COPD overlap were excluded. Severe asthma was defined as use of high dose ICS + use of a second controller. Severe asthma exacerbations were defined as emergency department visits, hospitalizations or systemic corticosteroid use, all for reason of asthma.

Results: The cohort consisted of 586,436 asthma patients of which 42,611 patients (7.3%) had severe asthma. The age and sex standardized all-cause mortality rates ranged between databases from 5.2 to 9.5/1,000 person-years (PY) in asthma, and between 11.3-14.8/1,000 PY in severe asthma. The all-cause mortality rate in the first week following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY. Mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. Higher age, male gender, comorbidity, smoking, and previous severe asthma exacerbations were associated with mortality.

Conclusion: All-cause mortality following a severe exacerbation is high, especially in the first month following the event. Smoking cessation, comorbidity-management and

asthma-treatment focusing on the prevention of exacerbations might reduce associated mortality.

Abstract word count: 243

INTRODUCTION

Asthma is a highly prevalent and chronic respiratory condition affecting 300-400 million people worldwide.[1, 2] Asthma is a major cause of disability, health resource utilization, and significantly reduces the patient's quality of life.[3] There is no cure for asthma, but it can generally be controlled through treatment as described by existing asthma management guidelines.[4] Real world surveys among asthmatic patients indicate that the incidence of exacerbations is much higher than observed in clinical trials.[5] Asthma exacerbations are associated with increased healthcare costs, reductions in health related quality of life, and increased mortality.[6] Although asthma-related mortality has decreased over the last decades, still on a global scale it is estimated that asthma accounts for about 250,000 deaths per year.[7, 8]

The Global Initiative of Asthma (GINA) published in 2004 mortality estimates of 5.2 per 100,000 asthma patients aged 5-34 years in the United States, with wide variations across Europe (e.g. 1.6 per 100,000 in Finland and 9.3 per 100,000 in Denmark).[9]

A more recent report based on data from the WHO mortality database using mortality data from 46 countries in the entire population of 5-34 years old (thus not necessarily diagnosed with asthma), report a reduction in asthma mortality rates from 0.44 deaths per 100,000 in 1993 to 0.19 deaths per 100,000 in 2006 with a stagnation in asthma mortality rates from 2006 on.[10]

Increasing age, lower socio-economic status, smoking status, low FEV_1 and poor asthma control have been associated with increased mortality.[11-14] Although there is a considerable amount of data on mortality rates in patients with asthma, data on all-cause mortality rates and mortality rates following asthma exacerbations is scarce.

In this study we aimed to estimate all-cause and asthma-related mortality, mortality rates following severe asthma exacerbations and patient characteristics associated with mortality in adult patients with asthma and severe asthma, using one protocol and harmonized methods with regard to data extraction and data analysis, across five different European countries.

METHODS

Design and setting

A retrospective cohort study was conducted using data from five European electronic health care databases: i) the Integrated Primary Care Information Project (IPCI) from the Netherlands, ii) the Health Search Database (HSD) from Italy, iii) Clinical Practice Research Datalink (CPRD) from the UK, iv) the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and v) the Aarhus University Prescription Database (Aarhus) from Denmark. Detailed descriptions of these databases have been published before [15-20] and are available in the online supplement. All databases comprise detailed information on drug prescriptions or dispensing, outpatient diagnoses and hospitalizations, comorbidity and measurement data (e.g. lab results, spirometry, BMI). Weaknesses and major differences of the registers are further commented on in the discussion section.

These databases contain information on mortality either through linkage with hospital data and death registries (Aarhus, SIDIAP and CPRD), via information from discharge letters (HSD and IPCI) or via information from death records as registered by the GP (CPRD, IPCI and SIDIAP). All participating databases comply with EU guidelines on the use of medical data for research and are registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database.[21]

Cohort definition

A cohort of patients with asthma was defined in each database. To enter the cohort, patients needed to be at least 18 years old, with a minimum of 1-year database history. Asthma was defined as physician diagnosed asthma based on the presence of at least

one asthma specific disease code (see online supplement) in combination with prescriptions/dispensing of asthma drugs within 3 months before or after an asthma disease code. Asthma drugs consisted of the following: inhaled corticosteroids (ICS), short-acting β_2 agonists (SABA), long-acting β_2 agonists (LABA), fixed combination of ICS+LABA, leukotriene modifier (LTRA), short-acting muscarinic antagonist (SAMA), fixed combination of SABA+SAMA, xanthines, and anti-IgE treatment. Information on drug use was retrieved by an ATC specific search from either the drug prescription or drug dispensing records. Based on the asthma index date (first date of an asthma disease code), patients were categorized into prevalent or incident asthma. Patients having both disease codes for asthma and disease codes for COPD, considered as patients with asthma-COPD overlap (ACO), were excluded from the analysis.

Within the cohort of patients with asthma, a sub-cohort of patients with severe asthma was identified. According to GINA guidelines, severe asthma was defined as asthma requiring treatment with high dose ICS plus a second controller (and/or systemic corticosteroids).[4, 22, 23] For each prescription of an ICS we were able to label this prescription as “use of high dose ICS” based on the dosing information and the strength and according to GINA guidelines [4]. Next, for each prescription of both ICS and controller therapy, the legend duration was derived from the information on strength, dosing and volume. Only those patients who fulfilled the criteria of high dose ICS plus a second controller therapy for a consecutive period of at least 120 days were included in the severe asthma cohort. The study period started on the first of January 2008 and ended on 31st December 2013.

Follow-up

For each patient, cohort follow-up started from the latest date of the following; start of study period, diagnosis of (severe) asthma, age of 18 years or after reaching a minimum of 365 days of database history. To account for immortal time bias, follow-up in the severe asthma cohort started on day 120 of consecutive use of high dose ICS with additional controller therapy.[24] Follow-up ended when leaving the database, death or end of the study period whichever came first.

For the analysis of mortality following severe asthma exacerbations, follow-up ran from the date of a severe asthma exacerbation until the end of the predefined time windows following the severe asthma exacerbation (7, 30, 90, 180 or 365 days), a next severe asthma exacerbation, end of study period, or death, whichever came first.

Severe asthma exacerbations

Severe asthma exacerbation was defined as any of the following: acute use of systemic corticosteroids, ED visit or hospitalisation for an asthma exacerbation.[25]

The indication of corticosteroid use was retrieved from the prescription/dispensing file or through an automated search on asthma or asthma exacerbation disease codes in a 7-day window before or after the prescription date. Continuous use of systemic corticosteroids, defined as consecutive use of 30 days or more, was not considered as a severe asthma exacerbation. If the time between 2 prescriptions of systemic corticosteroids was less than 2 weeks, this was considered as one single severe asthma exacerbation.

All cause and asthma-related mortality

In all databases, death and date of death are well documented but information on cause of death was only systematically available for IPCI and Aarhus (up to 2011). In SIDIAP,

cause of death (i.e. asthma-related deaths) was only identifiable through hospital admissions data linkage, and therefore they only represent “in-hospital deaths". Where available, cause of death was classified into “asthma-related” or “non-asthma-related death”. Asthma-related death was defined as death with as main cause asthma and/or asthma exacerbation.

Covariates

We investigated the prevalence of the following comorbidities: atopy (allergic rhinitis, atopic eczema/dermatitis), chronic rhinosinusitis, nasal polyposis, gastro-oesophageal reflux disease (GERD), depression and anxiety, overweight and obesity, diabetes mellitus, cardio- and cerebrovascular diseases and cancer. Smoking status was classified as “current smoker”, “past smoker”, “non-smoker” or “smoking status unknown”. Comorbidities and smoking status were assessed at the start of follow up (using information in the entire period prior, even before start of study period). For each of the comorbidities of interest, diseases were mapped through the Unified Medical Language System (UMLS) generating a list of disease codes (see online supplement) which were verified by the databases prior to extraction.[26]

Analysis

Categorical data were presented in counts and proportions. For continuous data, the number of observations (n), mean, and standard deviation were presented.

The overall mortality rate was calculated by dividing the number of deaths by the respective number of person-years of follow-up. Mortality rates were calculated by age category (18-<35 years and subsequent 10-year age categories).

To account for differences in age and sex distribution between databases, direct standardization was applied using the largest population (CPRD) as reference population.[27]

Mortality rates were also calculated in predefined windows (7, 14, 30, 90, and 365 days) following the severe asthma exacerbation.

Patient characteristics associated with mortality were assessed by means of univariate and multivariate Cox regression analysis, including the following covariates: age at start of follow-up, sex, smoking status, comorbidity (cancer, cardiovascular and cerebrovascular disease, obesity (defined as a BMI of >=30) and diabetes mellitus), whether the patient had incident or prevalent asthma at start of follow-up and two time-dependent covariates; time since previous severe asthma exacerbation (classified in up to 30 days, 31 to 90 days, 91 to 365 days and more than 365 days) and asthma severity. At T=0 (start of follow-up), severity was either “yes” or “no”. From the time patients with non-severe asthma became severe, their severity was coded as “yes”.

Maximum follow-up in this analysis was restricted to 5 years. Pooled results for all hazard ratios were obtained using multivariate meta-analysis.[28]

As the duration of asthma disease might be an important risk factor of all-cause mortality, the analysis was repeated in patients with incident asthma only, i.e. without asthma diagnosis prior to study entry as the correct date of asthma onset was not always well documented in prevalent cases.

All analyses were done using the software package SAS version 9.2, SAS Institute Inc., Cary, NC.

RESULTS

Study population and baseline characteristics

The source population comprised 16,259,085 individuals with active follow-up during the study period of which 644,602 adult patients were diagnosed with asthma. As patients with ACO (n=58,166) were excluded, 586,436 patients remained of which 42,611 patients (7.3%) with severe asthma were identified. (Figure 1)

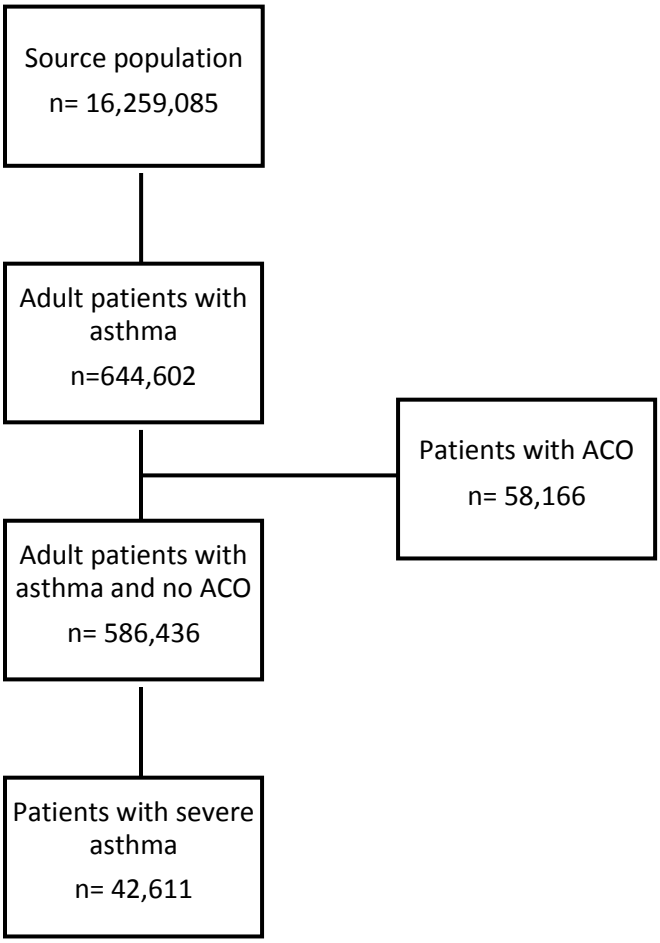

Figure 1: Patient flowchart
ACO= Asthma COPD overlap

The percentage of severe asthma was the highest in Aarhus (11.6%) and the lowest in SIDIAP (2.1%). Baseline characteristics of the asthma cohorts are further described in Table 1 and Table 2. Briefly, the mean age at start of follow up ranged between 45.2 -

48.3 years. In all databases, there was a preponderance of females (57.4-64.3% females) which remained when studying patients with severe asthma (59.3-69.9% females). The prevalence of atopy (consisting of atopic eczema and/or allergic rhinitis) ranged between 15.1-35.7% and did not increase in patients with severe asthma (11.5-37.8%). The prevalence of chronic rhinosinusitis and nasal polyposis ranged between 0.3%-9.9% and 0.5-2.8% respectively and increased in patients with severe asthma (0.9-14.1% and 1.0-6.8% respectively).

	IPCI (NL) (n,%)	AARHUS (DK) (n,%)	HSD (IT) (n,%)	CPRD (UK) (n,%)	SIDIAP (SP) (n,%)
Total	73,506 (100.0)	14,041 (100.0)	37,003 (100.0)	393,660 (100.0)	68,226 (100.0)
Incident asthma	16,265 (22.1)	4,083 (29.1)	15,842 (42.8)	77,884 (19.8)	42,086 (61.7)
Prevalent asthma	57,241 (77.9)	9,958 (70.9)	21,161 (57.2)	315,776 (80.2)	26,140 (38.3)
Female	44,394 (60.4)	8,172 (58.2)	21,959 (59.3)	226,026 (57.4)	43,857 (64.3)
Male	29,112 (39.6)	5,869 (41.8)	15,044 (40.7)	167,634 (42.6)	24,369 (35.7)
Age (mean,sd)	45.5 (16.9)	46.4 (17.6)	47.9 (18.0)	45.2 (18.4)	48.3 (18.9)
Smoking status*					
Current	10,899 (26.3)	112 (23.5)	5,227 (26.2)	84,449 (21.9)	12,992 (25.0)
Never	20,878 (50.4)	227 (47.6)	11,416 (57.2)	177,469 (45.9)	31,768 (61.1)
Past	9,616 (23.2)	138 (28.9)	3,328 (16.7)	124,512 (32.2)	7,236 (13.9)
Smoking status unknown	32,113 (43.7)	13564 (96.6)	17,032 (46.0)	7,230 (1.8)	16,230 (23.8)
Atopy	22,679 (30.9)	2,119 (15.1)	6,175 (16.7)	140,710 (35.7)	11,731 (17.2)
Chronic rhinosinusitis	2,235 (3.0)	42 (0.3)	628 (1.7)	38,980 (9.9)	398 (0.6)
Nasal polyposis	338 (0.5)	208 (1.5)	383 (1.0)	11,133 (2.8)	940 (1.4)
GERD	4,756 (6.5)	498 (3.5)	4,162 (11.3)	34,576 (8.8)	1,362 (2.0)
Diabetes mellitus	5,001 (6.8)	548 (3.9)	2,244 (6.1)	20,317 (5.2)	4,901 (7.2)
Obesity	19,358 (26.3)	1,281 (9.1)	7,436 (20.1)	231,604 (58.8)	34,265 (50.2)
Anxiety/Depression	9,440 (12.8)	336 (2.4)	7,144 (19.3)	108,229 (27.5)	15,910 (23.3)
Cardiovascular disease	3,265 (4.4)	839 (6.0)	577 (1.6)	17,844 (4.5)	1,095 (1.6)
Cerebrovascular disease	1,666 (2.3)	421 (3.0)	828 (2.2)	7,555 (1.9)	1,121 (1.6)
Cancer	3,870 (5.3)	590 (4.2)	731 (2.0)	13,418 (3.4)	2,467 (3.6)

Table 1: Baseline characteristics of total asthma cohorts

* Percentage of patients for whom smoking is available.

	IPCI (NL) (n,%)	AARHUS (DK) (n,%)	HSD (IT) (n,%)	CPRD (UK) (n,%)	SIDIAP (SP) (n,%)
Total	6,446 (100.0)	1,633 (100.0)	1,895 (100.0)	31,214 (100.0)	1,423 (100.0)
Incident asthma	443 (6.9)	205 (12.6)	91 (4.8)	1705 (5.5)	362 (25.4)
Prevalent asthma	6,003 (93.1)	1,428 (87.5)	1,804 (95.2)	29,509 (94.5)	1,061 (74.6)
Female	4,030 (62.5)	997 (61.1)	1,123 (59.3)	19,474 (62.4)	994 (69.9)
Male	2,416 (37.5)	636 (39.0)	772 (40.7)	11,740 (37.6)	429 (30.2)
Age (mean,sd)	50.8 (16.0)	53.2 (16.5)	55.0 (17.5)	55.8 (17.3)	66.3 (14.9)
Smoking status					
Current*	1,029 (23.3)	5 (13.9)	203 (19.8)	6,136 (19.7)	123 (10.1)
Never*	2,197 (49.7)	7 (19.4)	588 (57.3)	12,156 (39.0)	913 (74.8)
Past*	1193 (27.0)	24 (66.7)	235 (22.9)	12,871 (41.3)	184 (15.1)
Smoking status unknown	2,027 (31.5)	1,597 (97.8)	869 (45.9)	51 (0.2)	203 (14.3)
Atopy	2,084 (32.3)	223 (13.7)	282 (14.9)	11,808 (37.8)	163 (11.5)
Chronic rhinosinusitis	260 (4.0)	14 (0.9)	44 (2.3)	4,396 (14.1)	14 (1.0)
Nasal polyposis	62 (1.0)	50 (3.1)	77 (4.1)	1,924 (6.2)	43 (3.0)
GERD	564 (8.8)	66 (4)	279 (14.7)	4,712 (15.1)	58 (4.1)
Diabetes mellitus	669 (10.4)	75 (4.6)	161 (8.5)	3,082 (9.9)	229 (16.1)
Obesity	2,424 (37.6)	147 (9.0)	417 (22.0)	22,952 (73.5)	1,016 (71.4)
Anxiety/Depression	957 (14.9)	32 (2.0)	421 (22.2)	11,319 (36.3)	337 (23.7)
Cardiovascular disease	407 (6.3)	126 (7.7)	39 (2.1)	2,938 (9.4)	60 (4.2)
Cerebrovascular disease	175 (2.7)	74 (4.5)	52 (2.7)	1,242 (4.0)	50 (3.5)
Cancer	406 (6.3)	97 (5.9)	70 (3.7)	1,826 (5.9)	113 (7.9)

Table 2: Baseline characteristics of severe asthma cohorts

* Percentage of patients for whom smoking is available. NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Death and mortality rates

In total, 15,349 deaths were observed during follow-up. Characteristics of patients who died are further described in Online table 1. Asthma-related death was reported in 4.1% of deaths with known cause in Aarhus, 0.2% in IPCI, 4.1% in SIDIAP (hospital deaths only), and 2.0% in CPRD. However, it should be noted that cause of death was not reported in a substantial proportion of deaths in SIDIAP (58.6%) and CPRD (80.0%).

The overall age and sex standardized all-cause mortality rates were 5.2/1,000 PY (95% CI 4.9-5.5) in HSD, 5.5/1,000 PY (95% CI 5.1-5.8) in IPCI, 6.4/1,000 PY (95% CI 6.1-6.7) in SIDIAP, 6.5/1,000 PY (95% CI 6.4-6.6) in CPRD and 9.5/1,000 PY (95% CI 8.8-10.2) in Aarhus. These standardized all-cause mortality rates were higher in patients with severe asthma, ranging between 11.3-14.8/1,000 PY across databases. (Table 3)

	Asthma			Severe asthma		
	Overall MR	**Overall MR - Standardized**	**95% CI**	**Overall MR**	**Overall MR - Standardized**	**95% CI**
IPCI (NL)	4.9	5.5	5.1-5.8	7.3	11.3	9.2-13.7
AARHUS (DK)	9.2	9.5	8.8-10.2	12.2	14.6	11.8-17.9
HSD (IT)	6.0	5.2	4.9-5.5	11.9	11.6	9.2-13.9
CPRD (UK)	6.5	6.5	6.4-6.6	14.8	14.8	14.1-15.5
SIDIAP (SP)	8.8	6.4	6.1-6.7	25.3	13.0	10.5-20.6

Table 3: Crude and age & sex standardized mortality rate (distribution of CPRD as reference population) (Mortality Rates (MR) = number of deaths/per 1,000 PY)

NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

All-cause mortality rates increased with age both for the total asthma cohort and the severe asthma cohort (Online table 2). In order to compare our data to the WHO data on patients up to the age of 35, we defined an age category of patients 18-<35 years of age.[9] The all-cause mortality rate in asthma patients of this age group was the lowest in HSD (IT) namely 0.3/1,000 PY (95% CI 0.2-0.5) and highest in Aarhus (DK) namely 1.0/1,000 PY (95% CI 0.7-1.5).

The all-cause mortality rate in the first 7 days following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY across databases. All-cause mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. (Table 4)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI
ALL ASTHMA mortality following severe asthma exacerbation															
< 7 days	25.3	0.0%	0.0-0.1%	59.9	0.1%	0.1-0.2%	14.1	0.0%	0-0.1%	15.4	0.0%	0.0-0.0%	56.9	0.1%	0.1-0.1%
< 15 days	30.6	0.1%	0.1-0.2%	28.1	0.1%	0.1-0.2%	22.8	0.1%	0.1-0.1%	13.3	0.1%	0.0-0.1%	47.6	0.2%	0.2-0.2%
< 30 days	23.5	0.2%	0.1-0.3%	28.5	0.2%	0.1-0.4%	17.4	0.1%	0.1-0.2%	11.8	0.1%	0.1-0.1%	41.2	0.3%	0.3-0.4%
< 90 days	14.9	0.4%	0.3-0.5%	21.0	0.5%	0.4-0.7%	12.7	0.3%	0.2-0.4%	9.7	0.2%	0.2-0.3%	41.1	1.0%	0.9-1.1%
< 365 days	11.5	1.1%	1.0-1.4%	15.5	1.5%	1.2-1.9%	10.2	1.0%	0.9-1.2%	7.9	0.8%	0.7-0.9%	32.8	3.2%	3.0-3.5%
SEVERE ASTHMA mortality following severe asthma exacerbation															
< 7 days	61.4	0.1%	0.0-0.3%	80.6	0.2%	0.0-0.6%	0	0.0%	0.0-0.0%	18.0	0.0%	0.0-0.1%	28.4	0.1%	0.0-0.4%
< 15 days	57.8	0.2%	0.1-0.5%	37.8	0.2%	0.0-0.6%	26.5	0.1%	0.0-0.4%	14.1	0.1%	0.0-0.1%	26.7	0.1%	0.0-0.4%
< 30 days	33.4	0.3%	0.1-0.5%	28.8	0.2%	0.1-0.7%	26.9	0.2%	0.1-0.6%	19.5	0.2%	0.1-0.2%	27.1	0.2%	0.1-0.6%
< 90 days	15.3	0.4%	0.2-0.7%	24.4	0.6%	0.3-1.3%	17.8	0.4%	0.2-0.9%	16.7	0.4%	0.3-0.5%	53.8	1.3%	0.8-2.1%
< 365 days	11.1	1.1%	0.7-1.7%	17.8	1.8%	1.1-2.9%	15.1	1.5%	0.9-2.4%	13.1	1.3%	1.1-1.5%	56.8	5.5%	4.1-7.4%

Table 4: Mortality rate and cumulative incidence of mortality following severe asthma exacerbation

MR=mortality rate. CumInc=cumulative incidence. 95% CI= 95% confidence interval, NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

This was also observed in patients with severe asthma, except for SIDIAP, probably because of low numbers.

From the all-cause mortality rates, the cumulative incidences of death were calculated (Table 4). Within seven days following a severe asthma exacerbation 0.0-0.1% of asthma patients died. Within one year following severe asthma exacerbation, 0.8-3.2% of asthma patients and 1.1-5.5% of severe asthma patients died.

Patient characteristics associated with mortality

In total 13,449 patients with asthma died during the first 5 years of follow up and the results of the univariate analysis of patient characteristics and mortality, adjusted for age at start follow-up, are documented in the Online table 3. In the multivariate analysis, age at start follow-up, male gender, previous severe exacerbations, smoking status, underlying comorbidity (history of cancer, cerebrovascular disease and history of diabetes) were associated with increased all-cause mortality in most databases. (Table 5)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)			Meta-analysis		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226			586,436		
Deaths in 5 years (n)	923			571			893			8,965			2,097			13,449		
Parameter	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age	1.10	1.09-1.11	<.0001	1.10	1.09-1.11	<.0001	1.11	1.11-1.12	<.0001	1.10	1.10-1.10	<.0001	1.12	1.11-1.12	<.0001	1.11	1.10-1.11	<.0001
Female gender	0.73	0.64-0.84	<.0001	0.93	0.78-1.10	0.3872	0.74	0.64-0.86	<.0001	0.81	0.78-0.85	<.0001	0.70	0.63-0.78	<.0001	0.78	0.70-0.86	<.0001
Previous severe asthma exacerbation																		
No previous exacerbations	1.00		<.0001	1.00		0.0465	1.00		0.0002	1.00		<.0001	1.00		<.0001			<.0001
30 days after exacerbation	1.67	0.96-2.89	.	1.97	1.19-3.26	.	2.25	1.48-3.43	.	1.95	1.56-2.44	.	2.69	2.23-3.25	.	2.10	1.72-2.55	
31-90 days after exacerbation	2.06	1.42-3.00	.	1.48	0.92-2.37	.	1.32	0.86-2.02	.	1.31	1.07-1.61	.	2.86	2.40-3.41	.	1.72	1.25-2.37	
91-365 days after exacerbation	1.47	1.13-1.92	.	0.98	0.70-1.39	.	1.39	1.08-1.77	.	1.10	0.98-1.25	.	2.18	1.91-2.50	.	1.37	1.04-1.81	
>365 days after exacerbation	1.42	1.09-1.85	0.0092	0.95	0.70-1.27	0.7114	0.98	0.78-1.25	0.8960	1.16	1.06-1.28	0.0021	1.41	1.22-1.64	<.0001	1.17	0.97-1.40	
Comorbidity																		
History of cancer	2.08	1.78-2.42	<.0001	1.81	1.46-2.25	<.0001	2.18	1.75-2.71	<.0001	2.06	1.95-2.18	<.0001	1.66	1.47-1.88	<.0001	1.95	1.75-2.16	<.0001
History of cardiovascular disease	1.03	0.87-1.22	0.7070	1.13	0.91-1.40	0.2818	1.13	0.85-1.49	0.4055	1.41	1.34-1.49	<.0001	1.62	1.39-1.89	<.0001	1.26	1.06-1.49	0.0097
History of cerebrovascular disease	1.38	1.13-1.68	0.0015	1.74	1.37-2.20	<.0001	1.44	1.17-1.78	0.0007	1.48	1.39-1.58	<.0001	1.64	1.42-1.90	<.0001	1.53	1.39-1.68	<.0001
History of diabetes mellitus	2.14	1.82-2.52	<.0001	1.57	1.21-2.05	0.0008	1.18	0.99-1.41	0.0693	1.70	1.61-1.80	<.0001	1.66	1.50-1.84	<.0001	1.61	1.33-1.95	<.0001
Obesity	0.70	0.59-0.82	<.0001	1.25	0.90-1.73	0.1857	1.52	1.31-1.78	<.0001	0.78	0.74-0.82	<.0001	0.69	0.63-0.76	<.0001	0.93	0.67-1.29	0.67
Prevalent asthma	1.11	0.93-1.31	0.2588	0.72	0.60-0.87	0.0008	0.98	0.85-1.13	0.7393	1.19	1.11-1.27	<.0001	0.96	0.88-1.05	0.3449	0.98	0.83-1.16	0.83
Severe asthma	1.05	0.86-1.28	0.6394	0.92	0.73-1.16	0.4800	1.21	0.96-1.52	0.1026	1.33	1.26-1.41	<.0001	0.98	0.81-1.20	0.8785	1.09	0.95-1.26	0.22
Smoking status																		
Smoking never	1.00		<.0001	1.00		0.5796	1.00		0.0198	1.00		<.0001	1.00		<.0001			<.0001
Smoking current	2.45	1.96-3.05	.	0.91	0.11-7.55	.	1.49	1.15-1.92	.	2.40	2.25-2.57	.	2.23	1.86-2.67	.	1.96	1.56-2.48	

Smoking past	1.45	1.17-1.79	.	0.36	0.07-1.80	.	1.16	0.94-1.43	.	1.10	1.05-1.16	.	1.13	0.95-1.34	.	1.13	0.97-1.32	
Smoking status unknown	1.54	1.30-1.83	.	0.99	0.43-2.25	.	1.15	0.98-1.35	.	1.21	0.87-1.69	.	1.14	1.02-1.28	.	1.25	1.10-1.42	

Table 5: Patient characteristics and mortality (multivariate analysis)

NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Current smoking increased the risk of all-cause mortality with 50-150% in IPCI, HSD, CPRD and SIDIAP. This association was not observed for Aarhus (HR_{adj} 0.91, 95% CI 0.11-7.55) but it should be noted that the smoking status of patients in Aarhus was often unknown. (96.6% - table 1)

Hazard ratios for all-cause mortality in adults with asthma for the different periods after severe asthma exacerbation are shown both per database as well as the result of the meta-analysis of these results. (Figure 2) Compared to follow-up with no previous severe asthma exacerbation the pooled meta-analysis HR_{adj} of dying decreased from 2.10 (95% CI 1.72-2.55) in the first 30 days following a severe asthma exacerbation to 1.17 (95% CI 0.97-1.40) after one year. (Figure 2)

When the analysis was repeated in patients with incident asthma only (n=156,160, 2843 patients died) similar results with regard to risk estimates, but with wider 95% CI were obtained (online table 4).

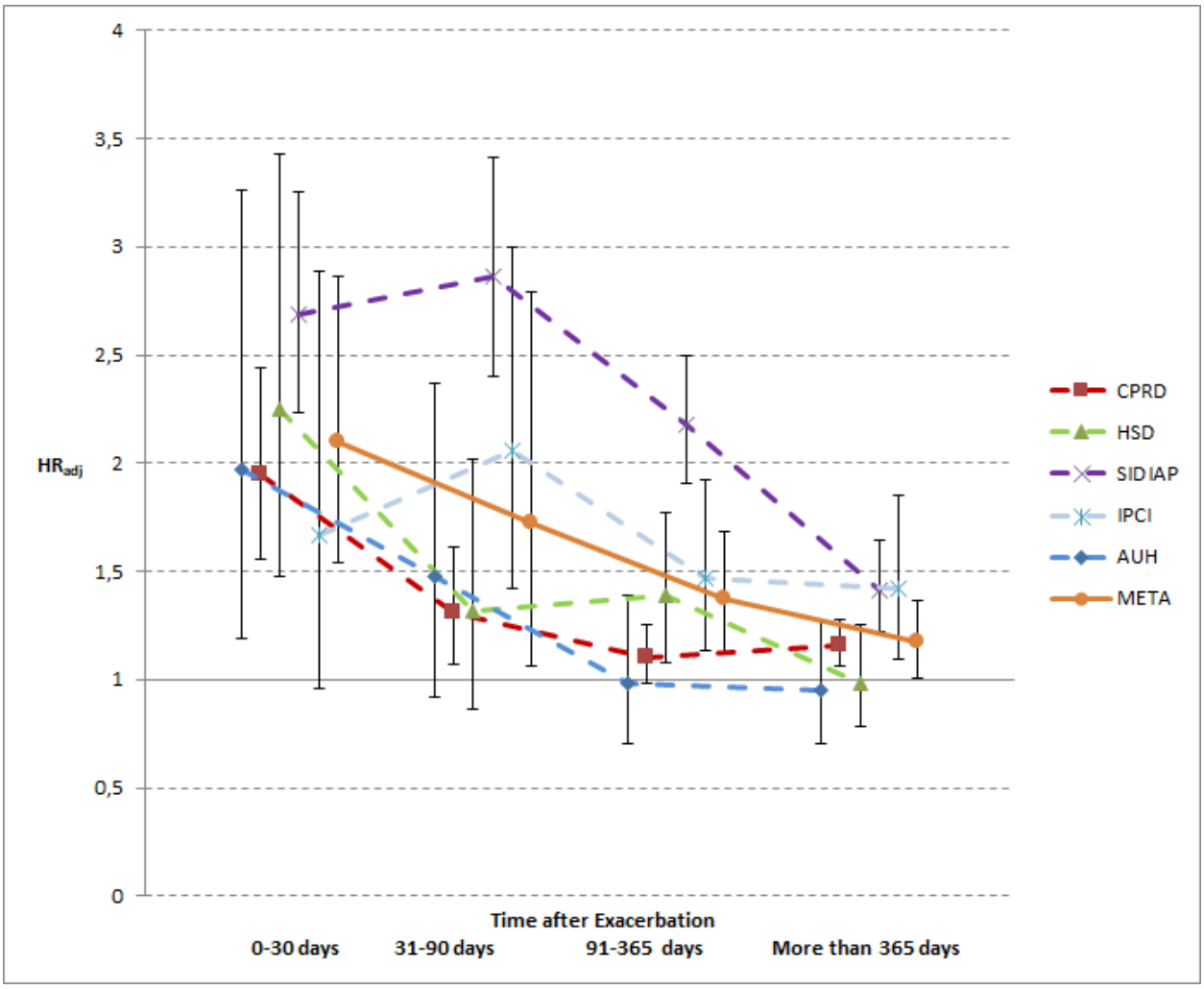

Figure 2: Hazard ratios of mortality in adult asthmatic patients for time periods after severe asthma exacerbation (0-30, 31-90, 91-365, >365 days after severe asthma exacerbation) compared to time before any exacerbation.

* adjusted for sex, age at start follow-up, asthma severity, history of cancer, history of cardiovascular disease, history of cerebrovascular disease, history of diabetes mellitus, history of obesity, incident or prevalent and smoking. ⊤⊥ represent 95% CI

DISCUSSION

In this study, we investigated all-cause mortality rates and all-cause mortality rates following a severe asthma exacerbation in five asthma cohorts from five European countries, using one protocol and harmonized methods for data extraction and data analysis.

The overall age and gender standardized all-cause mortality rate in patients with asthma ranged between 5.2-9.5/1,000 PY over databases and doubled in patients with severe asthma (range 11.3 to 14.8/1,000 PY). The all-cause mortality rate in the first 7 days following a severe asthma exacerbation ranged between 14.1-56.9/1,000 PY across databases. All-cause mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter. This was also observed in the meta-analysis on patient characteristics and mortality where the association with mortality was 2-fold higher in the month following a severe asthma exacerbation using patients without a previous severe asthma exacerbation as a reference.

In a publication on WHO data considering all individuals and not only patients with asthma, the age standardised asthma-related mortality in people aged 5-34 years in the period 2008-2012, ranged between 0-0.17/100,000 people when considering Italy, the UK, Spain, the Netherlands and Denmark only.[10] As could be expected, these mortality rates are much lower than the overall mortality rates that we report for these respective countries and for comparable age categories (18-<35 years) (database range 0.3-1.0/1,000 PY) not only because the WHO data considered all individuals in the denominator and not only individuals with asthma but more importantly because the WHO report only investigated asthma-related mortality.

Asthma-related-mortality is higher in the US based on findings from a recent publication exploring data from the Center for Disease Control and Prevention and reporting an overall asthma related mortality rate of 1.5/100,000 people during the study period 1999-2015.[29] In 2014, To et al. reported the results of a ten-year population study on asthma-related mortality and all-cause mortality using data from the health administrative database from Ontario, Canada. The age and sex standardized, all-cause mortality in individuals with asthma declined from 9.9/1,000 PY in 1999 to 8.5/1,000 PY in 2009 which is comparable to the age and sex standardized mortality rate as reported for Aarhus (9.5/1,000 PY) but higher than the mortality rate as reported for the other databases (5.2-6.5/1,000 PY) .[30] A recent study on mortality rates in patients with chronic respiratory diseases in the UK, using CPRD data reported an age-standardized all-cause mortality rate of 8.6 per 1,000 person years. This is slightly higher than the standardized mortality rate that we reported namely 6.5 per 1,000 PY but Gayle et al. studied mortality using CPRD data between 2005-2015 whereas our study period was from 2008-2013.[31]

In 2006, Krishnan et al. published US data on mortality following hospital admission for asthma and reported an in-house mortality of 0.5%.[32] Similar results were recently described by Kaur et al. who reported that in the US, 1% of patients die in hospital following admission for severe asthma exacerbation.[33] In 2013, age-standardized mortality rates within 30 days following an admission for status asthmaticus in Denmark were published.[34] Between 2008-2011, the 30-day mortality rate was 1.5 % which is higher than the 0.2% (95% CI 0.1-0.4%) that we reported for Denmark but in our

definition of severe asthma exacerbation we did not limit to ED admission and/or hospitalisation only.

We studied patient characteristics in association with mortality in patients with asthma and in particular investigated the effect of lifestyle factors (smoking), asthma severity, previous severe asthma exacerbations and underlying comorbidity. Underlying comorbidity, higher age, male gender and a previous severe asthma exacerbation were associated with mortality in most databases. In addition, current smoking was associated with (HR_{adj} between 1.5-2.5) mortality in all databases except Aarhus, stressing the relevance of smoking cessation in patients with asthma. Previous severe asthma exacerbation was also associated with mortality in all databases. This is in line with the study by Ali et al. who followed more than 1,000 Danish asthma patients over 25 years and reported a relative risk of dying of 2.9 in patients who had a history of acute hospital contacts for reason of asthma.[35] In a recent review article, hospitalization or emergency care visit for asthma in the past year was considered an important risk factor of asthma-related mortality.[36] The OLIN (Obstructive Lung Disease in Northern Sweden) study followed a cohort of asthma patients in Sweden up to 28 years and reported a cumulative mortality of 22.7%. Similar to our study, independent risk factors of mortality were age, male gender, current smoking, and underlying comorbidity.[37]

Our observational study has strengths and limitations. Major strengths are the fact that we included a large number of patients from different European databases that collect detailed information on drug exposure. However, our study has also several weaknesses. Firstly, an important weakness is the fact that there are major differences

between databases with respect to accurate information on important covariates such as lifestyle factors (e.g. smoking) obesity (BMI) and underlying comorbidity. Indeed, country-specific differences in the prevalence of comorbidities are more likely due to consequences of weaknesses in the registers (e.g. incomplete information) than due to real differences between countries. In several databases, the prevalence of comorbidities such as atopy, anxiety, depression, chronic rhinosinusitis and nasal polyposis are underestimates of the true prevalence of these comorbidities in patients with (severe) asthma due to incomplete data.

Secondly, as this is an observational study, using data from electronic health care databases, there is a potential risk of bias and/or confounding. As for all electronic health care databases, it should be noted that the primary aim of data collection is patient management and not research. This implies that only events that are deemed to be relevant to the patient's care are collected, and thus accurate information on concomitant diseases could be lacking. For those databases without linkage with hospital databases (HSD and IPCI), severe asthma exacerbations were retrieved either via disease specific codes in combination with codes for hospitalization or via review of the discharge letters. Underestimation of severe asthma exacerbations is likely for HSD where incidence rates of severe asthma exacerbations were indeed low.

A third weakness is the fact that the risk analyses between patient characteristics and mortality are based on incomplete information for instance with regard to smoking status and comorbidity, implicating that the results of the risk analyses must be taken with caution. Lastly, we have used the GINA definition of severe asthma, i.e. use of high

dose ICS plus a second controller (most frequently a LABA). In contrast, the ERS/ATS definition of severe asthma is more stringent, since it requires that the diagnosis of asthma has been confirmed, comorbidities have been addressed and it distinguishes well-controlled from uncontrolled severe asthma [22] As a consequence, our estimate of the prevalence of severe asthma in primary care (7.3%) most probably overestimates the true prevalence of severe asthma.

The main outcome in this study was mortality, assessed either through direct linkage with death registries (CPRD, and Aarhus) or administrative data (SIDIAP), or via information as collected by the GP. Unfortunately, the cause of death was frequently missing in particular in HSD (100%), CPRD (80%) and SIDIAP (60%) and the number of patients with known asthma-related death was low hampering the analysis of asthma-related mortality rates.

In conclusion, our data demonstrate that 1) mortality in patients with asthma, and especially severe asthma, is substantial and 2) is highest in the first month following a severe asthma exacerbation. Moreover, 3) patient characteristics such as a history of severe asthma exacerbation, increasing age, smoking and underlying comorbidity were associated with mortality but replication is needed as information on comorbidity and lifestyle factors is not completely captured within the databases. In addition to smoking cessation and management of comorbidities, asthma treatment focusing on the prevention of severe asthma exacerbations might reduce mortality.

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Online supplement

Online Table 1. Characteristics of asthma patients who died

	IPCI (NL) (n,%)		AARHUS (DK) (n,%)		HSD (IT) (n,%)		CPRD (UK) (n,%)		SIDIAP (SP) (n,%)	
	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma
	n=971	n=118	n=652	n=101	n=1,001	n=99	n=10,278	n=1,760	n=2,331	n=126
Cause of Death										
-Asthma-related*	2 (0.2)	2 (1.9)	17 (4.1)	2 (2.9)			42 (2.0)	21 (6.3)	40 (4.1)	2 (3.8)
- Other*	879 (99.8)	102 (98.1)	401 (95.9)	67 (97.1)			2,013 (98.0)	311 (93.7)	925 (95.9)	50 (96.2)
- Unknown	90 (9.3)	14 (11.9)	234 (35.9)	32 (31.7)	1,001 (100.0)	99 (100.0)	8,223 (80.0)	1,428 (81.1)	1,366 (58.6)	74 (58.7)
Gender										
- Female	595 (61.3)	68 (57.6)	403 (61.8)	58 (57.4)	592 (59.1)	53 (53.5)	6,172 (60.1)	1,122 (63.8)	1,721 (73.8)	83 (65.9)
- Male	376 (38.7)	50 (42.4)	249 (38.2)	43 (42.6)	409 (40.9)	46 (46.5)	4,106 (40.0)	638 (36.3)	610 (26.2)	43 (34.1)
Smoking status										
- Current*	157 (24.4)	22 (26.5)	38 (29.2)	5 (29.4)	91 (13.2)	10 (17.2)	1,434 (14.0)	194 (11.0)	163 (7.8)	3 (2.6)
- Never*	269 (41.8)	31 (37.4)	31 (23.9)	3 (17.7)	408 (59.1)	29 (50.0)	3,570 (34.8)	628 (35.7)	1,682 (80.6)	99 (85.3)
- Past*	218 (33.9)	30 (36.1)	61 (46.9)	9 (52.9)	191 (27.7)	19 (32.8)	5,263 (51.3)	937 (53.3)	241 (11.6)	14 (12.1)
- Smoking status unknown	327 (33.7)	35 (29.7)	522 (80.1)	84 (83.2)	311 (31.1)	41 (41.4)	11 (0.1)	1 (0.1)	245 (10.5)	10 (7.9)
Atopy	175 (18.0)	28 (23.7)	34 (5.2)	7 (6.9)	66 (6.6)	8 (8.1)	2,771 (27.0)	534 (30.3)	142 (6.1)	7 (5.6)
Chronic rhinosinusitis	21 (2.2)	3 (2.5)	2 (0.3)	1 (1.0)	15 (1.5)	1 (1.0)	1,328 (12.9)	270 (15.3)	8 (0.3)	1 (0.8)
Nasal polyposis	3 (0.3)	2 (1.7)	8 (1.2)	3 (3.0)	11 (1.1)	3 (3.0)	478 (4.7)	116 (6.6)	17 (0.7)	1 (0.8)
GERD	110 (11.3)	24 (20.3)	43 (6.6)	4 (4.0)	185 (18.5)	19 (19.2)	1,931 (18.8)	357 (20.3)	66 (2.8)	2 (1.6)
Diabetes mellitus	274 (28.2)	45 (38.1)	92 (14.1)	12 (11.9)	228 (22.8)	26 (26.3)	2,229 (21.7)	385 (21.9)	667 (28.6)	45 (35.7)
Obesity	355 (36.6)	51 (43.2)	112 (17.2)	15 (14.9)	472 (47.2)	44 (44.4)	7,326 (71.3)	1,291 (73.4)	1,628 (69.8)	95 (75.4)
Anxiety/Depression	160 (16.5)	23 (19.5)	90 (13.8)	13 (12.9)	338 (33.8)	31 (31.3)	3,590 (34.9)	648 (36.8)	706 (30.3)	31 (24.6)

	IPCI (NL) (n,%)		AARHUS (DK) (n,%)		HSD (IT) (n,%)		CPRD (UK) (n,%)		SIDIAP (SP) (n,%)	
	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma	asthma	severe asthma
	n=971	n=118	n=652	n=101	n=1,001	n=99	n=10,278	n=1,760	n=2,331	n=126
Cardiovascular disease	223 (23.0)	28 (23.7)	155 (23.8)	20 (19.8)	79 (7.9)	9 (9.1)	2,867 (27.9)	524 (29.8)	247 (10.6)	17 (13.5)
Cerebrovascular disease	191 (19.7)	20 (17.0)	133 (20.4)	21 (20.8)	168 (16.8)	14 (14.1)	1,698 (16.5)	284 (16.1)	306 (13.1)	15 (11.9)
Cancer	383 (39.4)	44 (37.3)	244 (37.4)	45 (44.6)	257 (25.7)	27 (27.3)	3,618 (35.2)	552 (31.4)	630 (27.0)	30 (23.8)

All characteristics measured at moment of death. * Percentage of patients for whom cause of death/smoking is available, NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Online Table 2. Number of persons, deaths and mortality rates (number of patients who died/1000 PY) by age category

	Asthma				Severe asthma			
	Number of persons (%)	**Number of deaths (%)**	**MR**	**95 %CI**	**Number of persons (%)**	**Number of deaths (%)**	**MR**	**95 %CI**
IPCI (NL)								
Overall	73,506	973	4.9	4.6-5.2	6,446	118	7.3	6.1-8.8
18-<35 yrs.	22,039 (30.0)	20 (2.0)	0.4	0.2-0.6	1,088 (16.9)	1 (0.8)	0.4	0.1-3.0
35-<45 yrs.	15,415 (21.0)	27 (2.8)	0.7	0.5-1.0	1,251 (19.4)	3 (2.5)	1.1	0.3-3.3
45-<55 yrs.	15,105 (20.5)	73 (7.5)	1.7	1.3-2.1	1,618 (25.1)	10 (8.5)	2.4	1.3-4.4
55-<65 yrs.	10,621 (14.4)	134 (13.8)	4.3	3.7-5.1	1,230 (19.1)	19 (16.1)	5.9	3.8-9.3
65-<75 yrs.	6,335 (8.6)	189 (19.4)	10.2	8.9-11.8	773 (12.0)	23 (19.5)	10.8	7.2-16.3
>=75 yrs.	3,991 (5.4)	530 (54.5)	44.9	41.2-48.9	486 (7.5)	62 (52.5)	48.3	37.7-62.0
AARHUS (DK)								
Overall	14,041	657	9.2	8.6-10.0	1,633	101	12.2	10.0-14.8
18-<35 yrs.	4,164 (29.7)	21 (3.2)	1	0.7-1.5	234 (14.3)	1(1.0)	0.8	0.1-5.9
35-<45 yrs.	2,704 (19.3)	19 (2.9)	1.5	0.9-2.3	254 (15.6)	1 (1.0)	1.0	0.1-7.0
45-<55 yrs.	2,586 (18.4)	60 (9.1)	4.6	3.5-5.9	344 (21.1)	10 (9.9)	6.0	3.2-11.1
55-<65 yrs.	2,271 (16.2)	78 (11.9)	7.0	5.6-8.7	402 (24.6)	13 (12.9)	6.3	3.7-10.9
65-<75 yrs.	1,421 (10.1)	120 (18.3)	14.9	12.4-17.8	242 (14.8)	17 (16.8)	11.7	7.3-18.8
>=75 yrs.	895 (6.4)	359 (54.6)	77.1	69.5-85.5	157 (9.6)	59 (58.4)	65.9	51.1-85.1
HSD (IT)								
Overall	37,003	1002	6.0	5.7-6.4	1,895	99	12.0	9.8-14.6
18-<35 yrs.	10,081 (27.2)	13 (1.3)	0.3	0.2-0.5	292 (15.4)	0 (0.0)	Nap	Nap
35-<45 yrs.	7,798 (21.1)	22 (2.2)	0.7	0.4-1.0	286 (15.1)	0 (0.0)	Nap	Nap
45-<55 yrs.	6,523 (17.6)	50 (5.0)	1.6	1.2-2.1	359 (18.9)	2 (2.0)	1.2	0.3-4.9
55-<65 yrs.	5,185 (14.0)	83 (8.3)	3.5	2.8-4.4	354 (18.7)	14 (14.1)	8.9	5.3-15.0
65-<75 yrs.	4,113 (11.1)	149 (14.9)	8.0	6.8-9.4	324 (17.1)	19 (19.2)	13.2	8.4-20.7
>=75 yrs.	3,303 (8.9)	685 (68.4)	45.6	42.3-49.1	280 (14.8)	64 (64.6)	46.5	36.4-59.4

	Asthma				Severe asthma			
	Number of persons (%)	**Number of deaths (%)**	**MR**	**95 %CI**	**Number of persons (%)**	**Number of deaths (%)**	**MR**	**95 %CI**
CPRD (UK)								
Overall	393,660	10,346	6.5	6.4-6.6	31,214	1.770	14.8	14.1-15.5
18-<35 yrs.	138,693 (35.2)	218 (2.1)	0.4	0.4-0.5	4,284 (13.7)	15 (0.8)	1.2	0.7-1.9
35-<45 yrs.	73,462 (18.7)	306 (3.0)	1.2	1.0-1.3	4,767 (15.3)	28 (1.6)	1.8	1.3-2.6
45-<55 yrs.	64,517 (16.4)	595 (5.8)	2.1	1.9-2.3	5,898 (18.9)	90 (5.1)	4.0	3.3-4.9
55-<65 yrs.	51,960 (13.2)	1,044 (10.1)	4.6	4.3-4.9	6,206 (19.9)	163 (9.2)	6.7	5.7-7.8
65-<75 yrs.	35,196 (8.9)	1,877 (18.1)	10.5	10.1-11.0	5,285 (16.9)	344 (19.4)	14.6	13.1-16.2
>=75 yrs.	29,832 (7.6)	6,306 (61.0)	43.7	42.7-44.8	4,774 (15.3)	1,130 (63.8)	54.6	51.5-57.8
SIDIAP (SP)								
Overall	68,226	2.347	8.8	8.4-9.2	1,423	126	25.3	21.3-30.2
18-<35 yrs.	20,811 (30.5)	33 (1.4)	0.4	0.3-0.6	48 (3.4)	0 (0.0)	Nap	Nap
35-<45 yrs.	13,506 (19.8)	53 (2.3)	1.0	0.7-1.3	109 (7.7)	0 (0.0)	Nap	Nap
45-<55 yrs.	9,519 (14.0)	84 (3.6)	2.1	1.7-2.6	158 (11.1)	2 (1.6)	3.9	1.0-15.7
55-<65 yrs.	8,747 (12.8)	123 (5.3)	3.7	3.1-4.4	277 (19.5)	3 (2.4)	3.3	1.1-10.1
65-<75 yrs.	7,914 (11.6)	297 (12.7)	9.5	8.5-10.6	372 (26.1)	18 (14.3)	14.4	9.1-22.9
>=75 yrs.	7,729 (11.3)	1,744 (74.7)	54.5	52.0-57.1	459 (32.3)	103 (81.7)	56.2	46.3-68.1

Yrs= Years, NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Online Table 3. Patient characteristics and mortality (univariate analysis)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226		
Deaths in 5 years (n)	923			571			893			8,965			2,097		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age															
18-<25	1	Ref	<.0001	1	Ref	<.0001	1	Ref	<.0001	1	Ref	<.0001	1	Ref	<.0001
25-<35	1.19	0.50-2.82		2.09	0.74-5.93		2.07	0.56-7.63		1.87	1.42-2.44		1.26	0.61-2.61	
35-<45	2.25	1.08-4.69		3.32	1.27-8.69		3.92	1.17-13.11		3.51	2.75-4.46		2.41	1.22-4.77	
45-<55	5.74	2.88-11.42		7.24	2.89-18.18		11.27	3.52-36.10		7.24	5.75-9.10		5.64	2.92-10.89	
55-<65	14.59	7.44-28.59		12.65	5.12-31.28		22.95	7.25-72.62		15.49	12.39-19.36		10.41	5.48-19.79	
65-<75	33.18	16.99-64.77		29.48	12.02-72.32		63.79	20.37-199.7		36.49	29.27-45.49		31.04	16.56-58.20	
>=75	135.3	69.92-261.7		160.4	66.29-388.30		287.8	92.52-895.10		140.0	112.7-173.9		152.2	81.70-283.4	
Female gender	0.69	0.61-0.79	<.0001	0.93	0.78-1.10	0.4129	0.65	0.56-0.74	<.0001	0.76	0.73-0.79	<.0001	0.64	0.58-0.71	<.0001
Exacerbation history															
No previous exacerbations	1	Ref	<.0001	1	Ref	0.0286	1	Ref	0.0002	1	Ref	<.0001	1	Ref	<.0001
30 days after exacerbation	1.74	1.00-3.01		2.07	1.25-3.41		2.25	1.48-3.42		1.97	1.58-2.46		2.70	2.24-3.26	
31-90 days after exacerbation	2.14	1.48-3.11		1.53	0.95-2.46		1.32	0.86-2.01		1.29	1.05-1.59		2.79	2.34-3.33	
91-365 days after exacerbation	1.49	1.15-1.94		1.02	0.73-1.43		1.39	1.09-1.78		1.08	0.96-1.22		2.13	1.86-2.44	

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226		
Deaths in 5 years (n)	923			571			893			8,965			2,097		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
>365 days after exacerbation	1.45	1.12-1.88		1.02	0.76-1.37		0.98	0.77-1.24		1.14	1.04-1.25		1.39	1.20-1.61	
Comorbidity															
History of cancer	2.12	1.82-2.47	<.0001	1.80	1.45-2.23	<.0001	2.56	2.07-3.17	<.0001	2.07	1.96-2.18	<.0001	1.75	1.55-1.98	<.0001
History of cardiovascular disease	1.21	1.02-1.43	0.0260	1.26	1.01-1.56	0.0376	1.28	0.97-1.69	0.0807	1.56	1.49-1.64	<.0001	1.76	1.51-2.05	<.0001
History of cerebrovascular disease	1.48	1.21-1.80	0.0001	1.85	1.46-2.33	<.0001	1.46	1.19-1.80	0.0004	1.65	1.54-1.76	<.0001	1.73	1.50-2.01	<.0001
History of diabetes mellitus	1.69	1.46-1.97	<.0001	1.74	1.34-2.25	<.0001	1.22	1.02-1.45	0.0274	1.75	1.66-1.84	<.0001	1.57	1.42-1.73	<.0001
Obesity	0.82	0.72-0.95	0.0059	1.43	1.05-1.96	0.0243	1.50	1.30-1.73	<.0001	0.86	0.83-0.90	<.0001	0.72	0.66-0.79	<.0001
Prevalent asthma	1.03	0.87-1.22	0.7324	0.72	0.60-0.86	0.0003	0.93	0.81-1.06	0.2813	1.18	1.10-1.26	<.0001	0.92	0.85-1.01	0.0767
Severe asthma	1.12	0.92-1.36	0.2714	0.91	0.73-1.14	0.4257	1.27	1.01-1.58	0.0376	1.38	1.31-1.46	<.0001	1.05	0.86-1.27	0.6406
Smoking status															
Smoking never	Ref		<.0001	Ref		0.7725	Ref		<.0001	Ref		<.0001	Ref		<.0001
Smoking current	2.55	2.05-3.16		1.00	0.12-8.33		1.55	1.20-1.99		2.54	2.38-2.71		2.58	2.16-3.08	
Smoking past	1.54	1.25-1.90		0.47	0.09-2.31		1.46	1.20-1.77		1.20	1.15-1.26		1.39	1.18-1.62	

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)		
Asthma patients (n)	73,506			14,041			37,003			393,660			68,226		
Deaths in 5 years (n)	923			571			893			8,965			2,097		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Smoking status unknown	1.56	1.33-1.84		0.72	0.32-1.63		1.04	0.89-1.21		1.36	0.97-1.89		1.25	1.12-1.39	

Adjusted for age at start of follow-up (except for univariate analysis of age categories), NL= Netherlands, DK= Denmark, IT= Italy, UK= United Kingdom, SP= Spain

Online Table 4. Patient characteristics and mortality - incident asthma patients only (Multivariate analysis)

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)			Meta-analysis		
Incident asthma patients (n)	16,265			4,083			15,842			77,884			42,086					
Deaths in 5 years (n)	165			176			375			1,047			1,080					
Parameter	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age at asthma diagnosis	1.12	1.10-1.13	<.0001	1.11	1.09-1.12	<.0001	1.11	1.10-1.13	<.0001	1.10	1.09-1.10	<.0001	1.12	1.11-1.12	<.0001	1.11	1.10-1.12	<.0001
Female gender	0.68	0.49-0.95	0.0224	0.82	0.60-1.12	0.2173	0.70	0.56-0.88	0.0020	0.91	0.80-1.03	0.1371	0.71	0.61-0.82	<.0001	0.76	0.66-0.87	<.0001
Previous severe asthma exacerbation																		
No previous exacerbations	1.00		0.0380	1.00		0.7366	1.00		0.1709	1.00		0.0005	1.00		<.0001			0.0001
30 days after exacerbation	1.89	0.57-6.21	.	1.51	0.68-3.36	.	1.42	0.69-2.92	.	1.78	1.01-3.14	.	2.56	1.95-3.37	.	1.82	1.34-2.46	
31-90 days after exacerbation	2.52	1.21-5.22	.	0.67	0.24-1.84	.	1.33	0.74-2.36	.	1.20	0.74-1.97	.	2.81	2.20-3.59	.	1.61	1.05-2.47	
91-365 days after exacerbation	1.50	0.89-2.52	.	1.10	0.66-1.83	.	1.45	1.04-2.03	.	1.39	1.09-1.77	.	1.91	1.58-2.32	.	1.48	1.22-1.79	
>365 days after exacerbation	1.48	0.91-2.42	0.1150	0.90	0.53-1.52	0.6918	1.10	0.80-1.50	0.5567	1.37	1.13-1.66	0.0015	1.49	1.21-1.82	0.0001	1.28	1.08-1.51	
Comorbidity																		
History of cancer	1.64	1.13-2.37	0.0085	1.48	0.97-2.25	0.0667	2.09	1.50-2.93	<.0001	2.04	1.74-2.40	<.0001	1.58	1.34-1.87	<.0001	1.79	1.54-2.08	<.0001
History of cardiovascular disease	0.89	0.60-1.32	0.5771	1.17	0.81-1.69	0.4074	1.40	0.96-2.03	0.0788	1.49	1.28-1.73	<.0001	1.51	1.21-1.87	0.0002	1.28	1.05-1.57	0.0161
History of cerebrovascular disease	0.84	0.49-1.43	0.5102	1.38	0.89-2.13	0.1531	1.47	1.09-1.98	0.0106	1.71	1.42-2.06	<.0001	1.82	1.50-2.20	<.0001	1.44	1.13-1.83	0.003
History of diabetes mellitus	1.75	1.18-2.60	0.0055	1.69	1.08-2.63	0.0209	1.27	0.98-1.65	0.0695	1.79	1.53-2.09	<.0001	1.62	1.41-1.86	<.0001	1.60	1.37-1.86	<.0001
Obesity	0.81	0.55-1.18	0.2664	1.00	0.59-1.69	0.9936	1.82	1.45-2.29	<.0001	0.75	0.65-0.85	<.0001	0.66	0.58-0.76	<.0001	0.95	0.65-1.38	0.782
Severe asthma	0.56	0.27-1.14	0.1102	0.77	0.43-1.39	0.3839	1.02	0.56-1.86	0.9577	1.26	1.02-1.55	0.0285	0.98	0.72-1.33	0.8952	0.91	0.67-1.22	0.5162
Smoking status																		
Smoking never	1.00		0.0627	1.00		0.5618	1.00		0.0259	1.00		<.0001	1.00		<.0001			<.0001
Smoking current	2.02	1.19-3.43	.	0.98	0.12-8.23	.	1.58	1.09-2.28	.	2.62	2.18-3.14	.	2.30	1.81-2.91	.	2.07	1.66-2.59	

	IPCI (NL)			AARHUS (DK)			HSD (IT)			CPRD (UK)			SIDIAP (SP)			Meta-analysis		
Incident asthma patients (n)	16,265			4,083			15,842			77,884			42,086					
Deaths in 5 years (n)	165			176			375			1,047			1,080					
Parameter	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Smoking past	1.11	0.70-1.77	.	0.39	0.08-1.96	.	0.93	0.66-1.30	.	1.04	0.90-1.19	.	1.11	0.89-1.39	.	1.02	0.90-1.16	
Smoking status unknown	1.32	0.89-1.98	.	1.09	0.47-2.54	.	1.26	0.98-1.63	.	1.51	0.48-4.73	.	1.14	0.97-1.36	.	1.30	1.12-1.50	

NL= Netherlands, DK= Denmark, IT=Italy, UK= United Kingdom, SP= Spain

Online supplement: Description of databases

The **Integrated Primary Care Information** (IPCI) database is a Dutch database containing the complete medical record of more than 1.5 million patients provided by more than 450 GPs geographically spread over the Netherlands. [15] In the Netherlands, all citizens are registered with a GP practice which acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care. The International Classification of Primary Care (ICPC) is the coding system but diagnoses and complaints can also be entered as free text. Prescription data contain information on product name, quantity prescribed, dosage regimens, strength, indication and ATC codes.

The **Health Search Database** (HSD). is a longitudinal observational database that is representative of the Italian general population. HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.5 million patients) located throughout Italy. The database includes information on age, gender, patient and GP identification, which is linked to prescription information, clinical events and diagnoses and date of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision. Drug names are coded according to the ATC classification. [17, 18]

Clinical Practice Research Datalink (CPRD) is a large validated computerized database of anonymized longitudinal medical records for primary care. Data comprise approximately 12 million patients with around 5.4 million of these being currently alive and registered from 680 primary care practices spread throughout the UK. The database contains the entire anonymized electronic medical record of each patient, including medical codes associated with consultations and referrals, details of all drugs prescribed, lifestyle factors and laboratory tests. [19]. Information on hospitalization is collected through linkage HES and information on mortality is retrieved through linkage with the Office of National Statistics (ONS) Mortality data.

The **Aarhus University Prescription Database** comprises clinical and prescription data from the Central Denmark Region and the North Denmark Region. It covers a total of 1.2 million inhabitants and is representative of the population of Denmark [16]. Data are available on demographics, lifestyle factors, dispensing data, hospitalizations and procedures. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data are linked to the national registry [38] of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures to the Central Registration system [39] that records information on mortality and to the Danish Registry of Cause of death. [20]

The **SIDIAP** (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria) **Database** comprises the electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices. The SIDIAP data comprises the clinical and referral events (coded by ICD-10), demography information, prescription and dispensing, specialist referrals, lifestyle factors, laboratory test results, and hospital admissions and their major outcomes. [40]

Online supplement: Disease codes

Asthma

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for asthma

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493*	H33*..	R96
Asthma confirmed			1O2..00	
Extrinsic asthma with asthma attack			663d.00 663m.00	
Asthma severity			663V*	
Number of asthma exacerbations in past year			663y.00	
Emergency admission. asthma			8H2P.00	
Status asthmaticus	J46			
Induced asthma			173A.00	
Asthma trigger			173c.00 173d.00 178*.00	
Asthma accident and emergency attendance since last visit			663m.00	
Emergency asthma admission since last appointment			663d.00	
Asthma and exercise			663e.00 663e000 663e100 663f.00 663w.00 663x.00	
Asthma currently dormant			663h.00	
Asthma currently active			663j.00	
Asthma treatment compliance satisfactory			663n.00	
Asthma treatment compliance unsatisfactory			663p.00	
Asthma disturbing sleep Asthma causing night waking Asthma disturbs sleep weekly Asthma disturbs sleep frequently Asthma not disturbing sleep Asthma never disturbs sleep Asthma night-time symptoms Asthma causes night time symptoms Asthma causes symptoms most nights Asthma never causes night symptoms			663N.00 663N000 663N100 663N200 663O.00 663O000 66YP.00 66Yq.00 66Yr.00 66Ys.00	
Asthma limits activities			663P*	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma daytime symptoms			663q.00	
Asthma not limiting activities			663Q.00	
Asthma causes night symptoms 1 to 2 times per month			663r.00	
Asthma never causes daytime symptoms			663s.00	
Asthma causes daytime symptoms 1 to 2 times per month			663t.00	
Asthma causes daytime symptoms 1 to 2 times per week			663u.00	
Asthma causes daytime symptoms			663v.00	
Asthma prophylactic medication used			663W.00	
Asthma medication review			8B3j.00	
Absent from work or school due to asthma			66YC.00	
Number days absent from school due to asthma in past 6 months			66Yu.00	
Health education - asthma			679J.*	
Asthma control			8793.00 8794.00 8795.00 8796.00 8797.00 8798.00	
Asthma quality indicators			9hA*.00	

*means all codes falling under this category

Asthma exacerbation

Definition of severe asthma exacerbation

Asthma exacerbation was defined as the use of acute systemic corticosteroids, ED visit, or hospitalisation for reasons of asthma exacerbation. To identify patients with a severe asthma exacerbation defined as ED visit or hospitalisation for reasons of asthma, an automated search was done on codes specific for severe asthma exacerbation. In addition, the medical file was searched for asthma specific disease codes (thus not only asthma exacerbation codes) in combination with codes for hospitalisation. Hospitalization was retrieved either via linkage with hospital admission/discharge database (Aarhus. CPRD (➔ HES)).combination of disease codes with information from hospital referral (HSD. SIDIAP and IPCI) and discharge letters (SIDIAP and IPCI) or combination of disease codes with source codes (hospital discharge letters) (CPRD ➔ for those patients where we did not have HES).

The following disease codes also did fit the criteria of asthma exacerbation:

Terms	ICD10	ICD9CM	Read Codes	ICPC
Emergency admission. asthma			8H2P.00	

Status asthmaticus	J46 J45.22 J45.32 J45.42 J45.52 J45.902	493.01 493.11 493.21 493.91	H33z000
Severe asthma attack			H33z011
Asthma accident and emergency attendance since last visit			663m.00
Emergency asthma admission since last appointment			663d.00

Atopy

Atopy is defined as any of the following: atopic dermatitis/eczema or allergic rhinitis.
The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for atopy.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atopy				
Atopic dermatitis/eczema	L20*	691*	M111.00 M112.00 M113.00 M114.00 M11z.00	S87
Allergic rhinitis	J30* (excluding J30.0)	477*	H17* H120.11	R97
Asthma with allergic rhinitis (nasal congestion)	J45.909			
Other allergic rhinitis			Hyu2100 Hyu2000	
Allergic eczema			M114.00	

*means all codes falling under this category

Chronic rhinosinusitis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for chronic rhinosinusitis.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic rhinitis			H120*	
Chronic allergic sinusitis			H 13..11	R75.02
Allergic sinusitis			H17..00	
Other chronic sinusitis			Hyu2200	
Chronic sinusitis, unspecified	J32.9	473.9		
Chronic sinusitis			H13*	

Allergic rhinosinusitis			H17..12	

*means all codes falling under this category

COPD

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for COPD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease	J44			R95
Chronic airway obstruction		496.*		
Obstructive chronic bronchitis		491.2*	H312z00	
Chronic obstructive lung disease			H3...00	
Chronic obstructive airways disease			H3...11	
			H3z..00	
Other specified chronic obstructive pulmonary disease	J44.8		Hyu31	
			H3z..11	
Chronic obstruct pulmonary dis with acute lower respiratory infection			H3y0.00	
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1		H3y1.00	
Mild chronic obstructive pulmonary disease			H36..00	
Moderate chronic obstructive pulmonary disease			H37..00	
Severe chronic obstructive pulmonary disease			H38..00	
Very severe chronic obstructive pulmonary disease			H39..00	
End stage chronic obstructive airways disease			H3A..00	
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0		H3y0.00	
COPD exacerbation			66Yd.00	
			66Ye.00	
			66Yf.00	
			8H2R.00	
			H3y1.00	
			H312200	
Multiple COPD emergency hospitalisations			66Yi.00	

*means all codes falling under this category

Gastroesophageal reflux disease

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for GERD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Gastroesophageal reflux disease	K21*	530.81		
Reflux esophagitis			J101100	
Acid reflux			J101111	
Gastroesophageal reflux with esophagitis	K21.0	530.81	J101112	
Gastroesophageal reflux without esophagitis	K21.9	530.81	J101112	

Esophageal reflux with esophagitis		530.11	J101113	D84.03
Esophageal reflux without (mention) of esophagitis			J10y400	D84.02
Esophageal reflux	K21.9		J10y411	
Gastroesophageal reflux	K21.9		J10y412	
Acid reflux	K21.9	530.81	J10y413	
Peptic esophagitis			J101114	
Regurgitant oesophagitis			J101115	
Gastric reflux			1957.00	

*means all codes falling under this category

Nasal Polyposis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for nasal polyps.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Nasal Polyps	J33*	471*	H11*	R99.02
Nasal polyp present			2D33.00	
Nasal polypectomy			7406000	
			7402900	
			7402911	
			7406700	
			7416F00	

*means all codes falling under this category

Depression and anxiety

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for depression.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Depression			E2B*.00	P76
			E112*	
Major depressive disorder, recurrent	F33*	296.3*	E113*	
Major depressive disorder, single	F32*	296.2*	E112*	
Depressive episode			Eu32*	
Recurrent episode of depressive reaction			Eu33*	
			Eu3y111	
Depressive disorder, nos		311*	Eu34112	
Chronic depressive personality disorder		301.12	E2112000	
Post schizophrenic depression			Eu20400	
History of depression			1465.00	
History of manic depressive disorder			146D.00	
Other and unspecified manic depressive disorder			E11y.00 E11y.000 E11y.200	
Psychotic reactive depression			E130.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Agitated depression			E135.00	
Mild anxiety depression			Eu41211	

*means all codes falling under this category --- Post-natal depression not included

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for anxiety.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Phobic anxiety disorders	F40*	300*	E202.12	P74
Other anxiety disorders	F41*			
Anxiety states			E200*	
Organic anxiety disorder			Eu05400	
Phobic anxiety disorders			Eu40*	
Other anxiety disorders			Eu41*	

*means all codes falling under this category

Overweight and obesity

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for obesity.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Overweight and Obesity bmi>30	E66*	278.0*	C38*	T83
Adipositas				T82
Body mass index (BMI > 40.0-44.9)	Z68.4*	278.01	22K7.00	
Body mass index (BMI 45.0-49.9)	Z68.42			
Body mass index (BMI >30)		V85.3*	22K5.00	
Body mass index (85th<95th percentile)	Z68.53	V85.53		
Body mass index (=>95th percentile)	Z68.54	V85.54		
Other obesity			Cyu7*	

*means all codes falling under this category

In addition, BMI was retrieved from the measurement table in all databases.
Cut-off values for obesity or overweight were as following:

	Adults (>19)
Obese	BMI>=30
Overweight	BMI between 25 and 29.9

Angina pectoris

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for angina pectoris.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina pectoris	I20*	413*	G33*	K74

Other acute and subacture ischaemic heart disease	I24*		G31***00	
Atherosclerotic heart disease of native coronary artery with angina pectoris	I25.11 I25.7*			
Ischemic heart disease		411*	G3...00 G3...13	
Dressler's syndrome			G310.11 G31y.00 G34..00 G3y..00 G3z..00 G340*	
Other forms of angina pectoris			Gyu3000	
Other forms of ischemic heart disease			Gyu3.00	
Intermediate coronary syndrome				K76.01
H/O angina pectoris			14A5. 14AJ.00	

*means all codes falling under this category

Arterial Hypertension

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for arterial hypertension.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive diseases	I10-I15.9	401-405.99	Gyu2. G2...*	
high blood pressure	I10			
Uncomplicated hypertension				K86
Hypertension with involvement target organs				K87
Renovascular hypertension	I15.0			
Secondary hypertension	I15	405	G24..	
Secondary hypertension, unspecified	I15.9		G24z.	
Malignant essential hypertension		401.0	G200.	
Essential (primary) hypertension	I10	401		
Hypertension NOS		401.9		
Benign hypertension		401.1	G201.	
Other secondary hypertension	I15.8	405.99	Gyu20	
Malignant secondary hypertension		405.0	G240.	
		405.09	G240z	
Benign secondary hypertension		405.1	G241	
		405.19	G241z	
Malignant hypertension			Xa3fQ G200.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertension monitoring			662..*	

*means all codes falling under this category

Heart Failure

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for heart failure.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart failure	I50	428.*	G58..	K77
Heart failure, unspecified	I50.9	428.9		
Congestive heart failure	I50.0	428.0	G580.00	
Congestive heart disease	I50.9			
Left ventricular failure	I50.1	428.1	G581.00	
Acute heart failure			G582.	
			G5800	
Admit heart failure emergency			8H2S.00	
Chronic congestive heart failure[#]			G5801	
H/O: heart failure[#]			14A6.00	
			14AM.00	
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01	G21z011	
		402.91		
Hypertensive heart and renal disease with (congestive) heart failure	I13.0	402.11	G232.00	
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2	404.01		
		404.91		
Heart failure confirmed			1O1..00	
Heart failure resolved[#]			2126400	
Heart failure management			661M500	
			661N500	
New York Heart Association classification - class II			662g.00	
New York Heart Association classification - class III			662h.00	
New York Heart Association classification - class IV			662i.00	
New York Heart Assoc classification heart failure symptoms			ZRad.00	
Heart failure monitoring			662p.00	
			662T.00	
			662W.00	
			679W100	
			679X.00	
			67D4.00	
			8CL3.00	
			8CMK.00	
Heart failure follow-up			8HBE.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			8Hg8.00	
			8HgD.00	
			8HHb.00	
			8HHz.00	
			8Hk0.00	
			8HTL.00	
			8IB8.00	
			8IE0.00	
			8IE1.00	
			9N0k.00	
			9N2p.00	
Heart failure quality indicators			9hH..00	
			9hH0.00	
			9hH1.00	
Cardiomegaly			G5y3.00	
Post cardiac operation heart failure NOS			G5y4z00	
Heart failure confirmed via echography			G5yy900	
			G5yyA00	
			G5yyC00	

*means all codes falling under this category

Myocardial infarction

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for myocardial infarction.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cardiac infarction	I22*			
Cardiac infarction	I21*			
Acute myocardial infarction	I21*	410*	G30*	K75
Old myocardial infarction	I25.2	412*	G32*	K76.02
			14A3.00	
			14A4.00	
			14AH.00	
			14AT.00	
Healed myocardial infarction			G32..11	
Subsequent/recurrent myocardial infarction			G35*	
Subsequent myocardial infarction of unspecified site			Gyu3600	
Subsequent myocardial infarction of other sites			Gyu3500.	
Acute transmural myocardial infarction of unspecified site			Gyu34	
			G30X.00	
ECG: old myocardial infarction			3232.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Acute widespread myocardial infarction			X200S	
ECG: myocardial infarction			323*	
Postoperative myocardial infarction			G38*	
Postmyocardial infarction syndrome			G310.00	
Complications following myocardial infarction			G36*	

*means all codes falling under this category

Stroke

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for stroke.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64*			
Stroke NOS	I63.9			K90
Intracerebral hemorrhage		431*	G61..	
Cerebrovascular accident (CVA)			G66..13	
Stroke and cerebrovascular accident unspecified			G66..00	
Stroke NOS			G66..12	
Sequelae of stroke, not specified as hemorrhage or infarction	I69	342	Gyu6C	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Other and unspecified intracranial hemorrhage	I62*	432*	G62..00 G62z.00	
Cerebral infarction	I63*		G64..	
Personal history of stroke			ZV125	
Sequelae of stroke NOS	I69.3			
H/O: Stroke			14A7.00 14A7.11	
Cerebral infarct due to thrombosis of precerebral arteries		433*	G63y000 G63y000	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits	Z86.73	V12.54		
Sequelae of cerebral infarction			G683.00	
Sequelae of stroke, not specified as hemorrhage or infarction		438.*	G68X.00/Gyu6C00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300 G6X..00/Gyu6G00	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		434.*		
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	
Hemiplegia and hemiparesis		342.*		
Acute, but ill-defined, cerebrovascular disease		436.*		

*means all codes falling under this category

TIA

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for TIA.

Terms	ICD10	ICD9CM	Read Codes	ICPC
TIA - Transient ischemic attack	G45*	435.*	G65..12	K89
Transient cerebral ischemia			G65**00	
Drop attack			G65*.11	
H/O: TIA			14AB.00 ZV12D00	
Amaurosis fugax			F423600	
Retinal transient arterial occlusion NOS			F423700	
Other transient cerebral ischemic attacks and related syndromes			Fyu55	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits	Z86.73	V12.54	ZV12D00	

*means all codes falling under this category

Definition of cancer

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for cancer.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignancy	C*		B*	
Malignant neoplasm without specification of site	C80*	199*	ByuC8 XE20H B59..	A79
Cancer			X78ef	
Malignant neoplasm				
Malignant neoplasm of bladder	C67*	188*	B49..	U76

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of breast	C50*-C50.9		Byu6.	X76
Breast cancer			X78WM	
Malignant tumor of breast			XE1zL	
Malignant neoplasm of colon	C18*	153*	B13..	D75
Malignant tumour of colon			XE1xd	
			XE1vV	
Malignant neoplasm of larynx	C32*	161*	B21..	
			XE1yD	
Carcinoma of the rectum	C20*	154*	XE1vW	
			X78OK	
Malignant neoplasm of skin	C44*		Byu43	S77
			X78gs	
			B33z.	
Malignant neoplasm of thyroid gland	C73*	193*	B53..	T71
Malignant neoplasm of cervix uteri	C53*	180*	XE1vi	X75
			B41z.	
Malignant neoplasm of stomach	C16*	151*	X78gA	D74
Gastric cancer			XE1vR	
			XE1xJ	
			B11z.	
Malignant neoplasm of vagina	C52*	184.0	B450.	
Malignant neoplasm of oropharynx	C10*	146*	B06..	
Malignant neoplasm of nasopharynx	C11*	147*	B07..	
Malignant neoplasm of pharynx	C14*	149.0	X78fO	
Malignant neoplasm of duodenum	C17*	152.0	/B120.	
Malignant neoplasm of caecum	C18.0	153.4	XE1vU	
Malignant neoplasm of peritoneum	C48.2	158.9	Byu57	
			X78Pq	
Malignant neoplasm of trachea	C33*	162.0	B220.	
Malignant neoplasm of pleura	C38.4	163*	B23..	
Bone cancer	C40*	170*	XE1vd	
	C41*			
Malignant neoplasm of liver	C22*	155*	Xa97q	
			B152.	
Malignant neoplasm of intestinal tract, part unspecified	C26.0	159.0	Byu12	
			X78gK	
			B1z0.	
Malignant neoplasm of pancreas	C25*	157*	B17..	D76
			XE1y5	
Malignant neoplasm of vertebral column	C41.2		B302.	
Malignant neoplasm of prostate	C61*	185*	B46..	Y77
Malignant neoplasm of oesophagus	C15*	150.9	B10..	
			X78g3	
			XE1vQ	
Malignant neoplasm of ovary	C56*	183.0	B440.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of uterus	C55*	179*	B43..	
Malignant melanoma of skin (not basal cell carcinoma nor epidermoid epithelioma)	C43*	172*	Byu41 B32..	
Malignant neoplasm of brain	C71*	191*	B51z. XE2vS	N74
Malignant tumor of kidney	C64*	189.0	X78iu	U75
Hodgkin's disease	C81*	201*	B61.. XaC2n BBjA.	B72
Leukemia	C95*	208*	BBr00 X78e2	B73
Lung cancer	C34.9	162*	Xa0KG	R84
Malignant neoplasm of bronchus and lung		162.9	B22.. Byu20 XE1vc	
Oat cell carcinoma of			X78QO	
Small cell carcinoma of lung			X78QN	
Secondary malignant neoplasm of lung	C78.0	197.0	B570	
Non-small cell lung cancer			X78QS	
Malignant neoplasm of hilus of lung			B2211	
Malignant neoplasm of upper lobe of lung			B2221	
Malignant neoplasm of middle lobe of lung			B2231	
Malignant neoplasm of lower lobe of lung			B2241	
Malignant neoplasm of upper lobe, bronchus or lung	C34.1	162.3	B222z XE1vb	
Malignant neoplasm of middle lobe, bronchus or lung	C34.2	162.4	B223. B223z	
Malignant neoplasm of lower lobe, bronchus or lung	C34.3	162.5	B224. B224z	
Malignant neoplasm of other parts of bronchus or lung		162.8	B22y.	
Malignant neoplasm overlapping bronchus and lung sites	C34.8		B225.	
Personal history of malignant neoplasm of lung			ZV101	

*means all codes falling under this category

Diabetes mellitus

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus type 1.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus type 1	E10	250.*1 250.*3	C108*** C10E***	T90.01
Diabetes mellitus, juvenile type			C10*000	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Brittle Diabetes			66AJ100	

*means all codes falling under this category

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus type 2.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus type 2	E11	250.*0	C10*.100	T90.02
		250.*2	C10F***	
			C109***	

*means all codes falling under this category

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus type 1 and/or 2 or other specified diabetes.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus	E08- E13	250.**	C10../Cyu.00	T90
Unstable diabetes			66AJ.11	
Diabetic neuropathy	E**.42	357.2/250.6		N94.02
Secondary diabetes mellitus		249		
Nephrotic syndrome in diabetes mellitus		581.81	K01x1	
Diabetic cataract		366.41		
History of diabetes			1434.00	
Foot abnormality dm related			2G51000	
			2G5C.00	
Diabetes with neurological manifestations			X00Ag	

*means all codes falling under this category

Dear Prof Lundbäck,

First of all, we want to thank the editor to provide us the chance to resubmit a revised version of the manuscript.

Please find below our answers to the comments/questions raised which we addressed point by point. Corrections have been added to the manuscript and changes have been marked via the “track changes” feature in word.

We do hope that we have successfully answered to all the questions and we do hope that you will consider publishing this manuscript in Respiratory Medicine.

0th February 2020 - Manuscript Number: YRMED-D-19-00518R1
Manuscript Title: Multinational cohort study of mortality and related risk factors in patients with asthma and severe asthma Respiratory Medicine

Dear Dr. Verhamme,

I have now again evaluated your paper. I am sorry for keeping you waiting, but I have been overloaded.
The problem with your paper (the revised version) is the second half of the Discussion section and partly the title. Otherwise only a few small minor changes are required before I can make a final decision about publication.

Major comment:

The validity, or lack of validity, regarding the information included in the registers has to some extend been discussed by the authors, but the severe lack of important information that not at all were included in the registers has not been discussed in an appropriate way. Instead the authors state that for health care data basis:
"…it should be noted that the primary aim of data collection is patient management and not research. This implies that only events that are deemed to be relevant to the patient's care are collected. However this also means that collected data are highly representative of actual practice conditions…" (!). So, one database has almost no information about smoking habits and two of the five data bases have such information from about half of the included subjects. Information about comorbidity is obviously poor in several databases. Some examples: in three of the five data bases only about 15% of the asthmatics had atopy (mean age at inclusion 40-50 years) which contrasts to results from all populations studied giving results on that issue, and very low proportions of even severe asthmatics had rhinosinusitis and nasal polyposis.
The authors further discuss "country-specific differences in prevalence of comorbidities" as they are real differences between countries instead of consequences of weaknesses in registers. Much attention is paid to the small Danish data base regarding anxiety and depression and some other aspects. The UK register of obesity coding is highlighted (about 60% are obese) without any hint if those in the register really are representative for the UK asthmatics.

So, the text of the Discussion from the last para on page 27 to the end of the Discussion is nothing but a long talkative defense not appropriately discussing real weaknesses. As the risk analysis are based on severely incomplete information, the authors must clearly state that the results particularly regarding the results of the risk analyses must be taken with caution.

So:

1/ Please re-write the second part of the discussion section. You can make it shorter but you must discuss weaknesses more appropriately.

Answer to the reviewer – We have rewritten the second part of the discussion session and discussed the weaknesses/limitations more clearly. Changes in the discussion has been highlighted as requested.

2/ As the results of the risk analysis are hazardous, please omit "and related risk factor" form the title of the paper, so the title will read:

"Multinational cohort study of mortality in patients with asthma and severe asthma".
This will not at all exclude you from giving results from the risk analysis. You can still include the results and tables on risks as you have done in case you discus the uncertainty much more appropriately.

Answer to the reviewer – Risk factors have been removed from the title of the paper. In the manuscript we now address this as an analysis on the association between patient characteristics and mortality and we have removed the term "risk factors" from the paper. Also within the discussion, we addressed the uncertainty around this association as information on smoking and comorbidity was not systematically collected.

3/ Please, mention in one or two sentences in the Methods section that weaknesses and major differences of the registers will be further discussed in the Discussion section.

Answer to the reviewer – In the method section on the covariates, we now refer to the discussion session where weaknesses and major differences of the registers are discussed

4/ Be more careful in the conclusions both in abstract and in the end of the discussion section.

Answer to the reviewer – We have reworded the conclusion in the abstract and the end of the discussion as following:

"Conclusion abstract: All-cause mortality following a severe exacerbation is high, especially in the first month following the event. Smoking cessation, comorbidity-management and asthma-treatment focusing on the prevention of exacerbations might reduce associated mortality."

"In conclusion, our data demonstrate that 1) mortality in patients with asthma, and especially severe asthma, is substantial and 2) is highest in the first month following a severe asthma exacerbation. Moreover, 3) patient characteristics such as a history of severe asthma exacerbation, increasing age, smoking and underlying comorbidity were associated with mortality but replication is needed as information on comorbidity and lifestyle factors is not completely captured within the databases. In addition to smoking cessation and management of comorbidities, asthma treatment focusing on the prevention of severe asthma exacerbations might reduce mortality."

Minor comments:

5/ The definition of severe asthma is based on the GINA definition, which results in a greater proportion of severe asthmatics than for instance when using the ERS/ATS definition. All pharma companies, in this case GSK, keep to the GINA probably as it results in more severe asthmatics. Please comment in the text why the GINA definition was selected, and why only 120 consecutive days of "high" dose treatment (together with concomitant controller) was required for being included among those classified as having severe asthma.

Answer to the reviewer – The choice of applying the GINA definition and the potential consequence on the proportion of patients with severe asthma has been addressed as limitation in the discussion and now reads as following:

"Lastly, we have used the GINA definition of severe asthma, i.e. use of high dose ICS plus a second controller (most frequently a LABA). In contrast, the ERS/ATS definition of severe asthma is more stringent, since it requires that the diagnosis of asthma has been confirmed, comorbidities have been addressed and it distinguishes well-controlled from uncontrolled severe asthma [22] As a consequence, our estimate of the prevalence of severe asthma in primary care (7.3%) most probably overestimates the true prevalence of severe asthma."

With regard to the choice of 120 consecutive days of high dose treatment + controller therapy, as treatment step-up is often initiated for a trial period of at least 12 weeks, it was decided to request consecutive treatment of high dose ICS + second controller for at least 120 days.

6/ In opposite to one of the previous reviewers, I strongly argue against the use of that precise estimate of 235 million asthmatics in society worldwide, and also use of other very precise estimates. Further, the numbers given are probably underestimates. The Global Asthma Report from 2018 says the number to be 339 million. You could refer to that and say that 300-400 million have asthma (first line of Introduction). I´ll e-mail the report to you.

Answer to the reviewer – The number of patients with asthma has been corrected in the introduction and reference to the Global Asthma Report 2018 has been added

Multinational cohort study of mortality in patients with asthma and severe asthma – Highlights

- All-cause mortality, especially in patients with severe asthma is substantial.
- All-cause mortality following a severe asthma exacerbation is high, especially in the first month following the event
- Higher age, male gender, comorbidity, smoking, and previous severe asthma exacerbations were associated with mortality.

Van: Brusselle Guy <Guy.Brusselle@uzgent.be>
Verzonden: Saturday, 22 February 2020 11:47
Aan: Laura Gardner; guy.brusselle@ugent.be
CC: K.M.C. Verhamme; Melissa Van Dyke; Shbana Ahmad; z.FW Respiratory
Onderwerp: Re: EU-ADR mortality ms: agreement to be included as an author - response requested

Dear Laura,

I agree to be included as an author.

Kind regards,

Guy Brusselle

Van: Laura Gardner <laura.gardner@fishawack.com>
Verzonden: vrijdag 21 februari 2020 18:43:10
Aan: guy.brusselle@ugent.be
CC: K.M.C. Verhamme; Melissa Van Dyke; Shbana Ahmad; z.FW Respiratory
Onderwerp: EU-ADR mortality ms: agreement to be included as an author - response requested

Dear Professor Brusselle,

Owing to your contribution to the revision of the manuscript entitled 'Multinational cohort study of
mortality in patients with asthma and severe asthma' we believe you qualify for authorship and propose
including you as an author on this publication. Please could you confirm you agree to be included as an
author by replying to this email?

If you have any queries please do not hesitate to get in touch.

Best wishes,
Laura

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Multinational cohort study of mortality in patients with asthma and severe asthma - Credit Author Statement

Author's contribution

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. This work was carried out through the EU-ADR Alliance.

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