Respiratory Medicine 165 (2020) 105919

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

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

Marjolein Engelkes [a], Maria AJ de Ridder [a], Elisabeth Svensson [b], Klara Berencsi [b], Daniel Prieto-Alhambra [c,d], Francesco Lapi [e], Carlo Giaquinto [f], Gino Picelli [f], Nada Boudiaf [g], Frank C Albers [h], Sarah M Cockle [i], Eric S Bradford [j], Robert Y Suruki [k], Guy GO Brusselle [l,m], Peter R. Rijnbeek [a], Miriam CJM Sturkenboom [n], Katia MC Verhamme [a,**]

[a] Medical Informatics, ErasmusMC, Rotterdam, the Netherlands
[b] Clinical Epidemiology, Aarhus, Denmark
[c] GREMPAL Research Group, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Spain
[d] Musculoskeletal Pharmaco and Device Epidemiology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, UK
[e] SIMG, Florence, Italy
[f] Pedianet, Padova, Italy
[g] Research and Development, GlaxoSmithKline, Middlesex, UK
[h] Global Respiratory Franchise, GlaxoSmithKline, Research Triangle Park, NC, United States
[i] Research and Development, GlaxoSmithKline, Brentford, UK
[j] Research and Development, GlaxoSmithKline, Research Triangle Park, NC, United States
[k] UCB Biosciences, Raleigh, NC, USA
[l] Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
[m] Departments of Epidemiology and Respiratory Medicine, ErasmusMC, Rotterdam, the Netherlands
[n] Department of Epidemiology, Julius Center, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Asthma epidemiology
Severe asthma
Mortality
Cohort studies

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 January 1, 2008–December 31, 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 9.5/1000 person-years (PY) in asthma, and between 11.3 and 14.8/1000 PY in severe asthma. The all-cause mortality rate in the first week following a severe asthma exacerbation ranged between 14.1 and 59.9/1000 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.

1. Introduction

Asthma is a highly prevalent and chronic respiratory condition

* Corresponding author. Department of Medical Informatics, Na2603, ErasmusMC, Dr Molewaterplein 50, 3000, CA Rotterdam, the Netherlands.
E-mail address: k.verhamme@erasmusmc.nl (K.M. Verhamme).

https://doi.org/10.1016/j.rmed.2020.105919
Received 16 June 2019; Received in revised form 24 February 2020; Accepted 26 February 2020
Available online 2 March 2020

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].

List of abbreviations

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

The Global Initiative for 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.

2. Methods

2.1. 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].

2.2. 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 December 31, 2013.

2.3. 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.

2.4. 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.

2.5. 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.

2.6. 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].

2.7. 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 $\geq$ 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, 31–90 days, 91–365 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.

3. Results

3.1. 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 (Fig. 1).

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 and 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

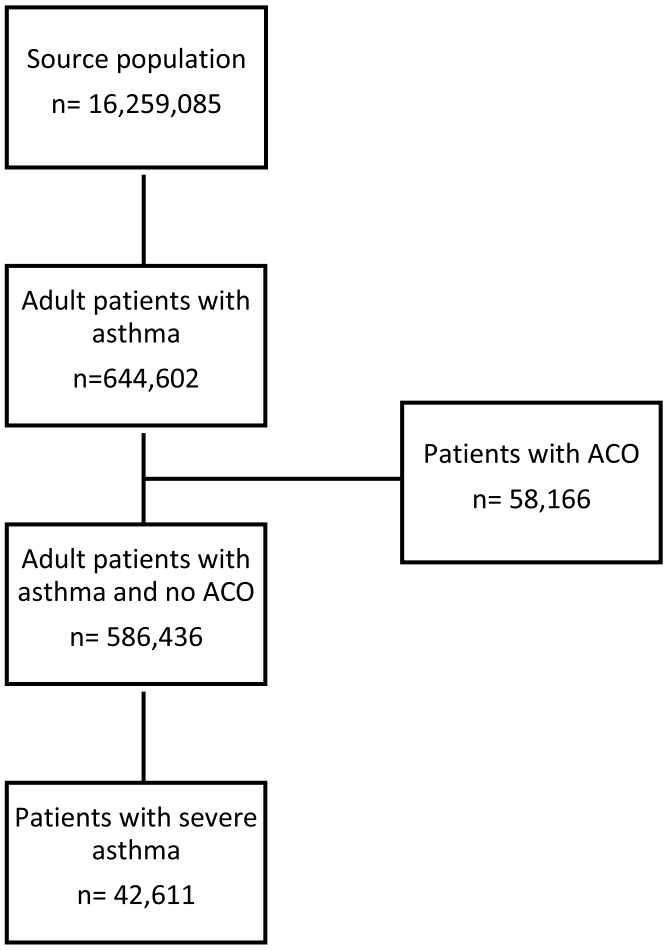

Fig. 1. Patient flowchart
ACO = Asthma COPD overlap.

Table 1
Baseline characteristics of total asthma cohorts.

	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)	4083 (29.1)	15,842 (42.8)	77,884 (19.8)	42,086 (61.7)
Prevalent asthma	57,241 (77.9)	9958 (70.9)	21,161 (57.2)	315,776 (80.2)	26,140 (38.3)
Female	44,394 (60.4)	8172 (58.2)	21,959 (59.3)	226,026 (57.4)	43,857 (64.3)
Male	29,112 (39.6)	5869 (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[a]	10,899 (26.3)	112 (23.5)	5227 (26.2)	84,449 (21.9)	12,992 (25.0)
Current[a]	20,878 (50.4)	227 (47.6)	11,416 (57.2)	177,469 (45.9)	31,768 (61.1)
Never[a]	9616 (23.2)	138 (28.9)	3328 (16.7)	124,512 (32.2)	7236 (13.9)
Past Smoking status unknown	32,113 (43.7)	13,564 (96.6)	17,032 (46.0)	7230 (1.8)	16,230 (23.8)
Atopy	22,679 (30.9)	2119 (15.1)	6175 (16.7)	140,710 (35.7)	11,731 (17.2)
Chronic rhinosinusitis	2235 (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	4756 (6.5)	498 (3.5)	4162 (11.3)	34,576 (8.8)	1362 (2.0)
Diabetes mellitus	5001 (6.8)	548 (3.9)	2244 (6.1)	20,317 (5.2)	4901 (7.2)
Obesity	19,358 (26.3)	1281 (9.1)	7436 (20.1)	231,604 (58.8)	34,265 (50.2)
Anxiety/ Depression	9440 (12.8)	336 (2.4)	7144 (19.3)	108,229 (27.5)	15,910 (23.3)
Cardiovascular disease	3265 (4.4)	839 (6.0)	577 (1.6)	17,844 (4.5)	1095 (1.6)
Cerebrovascular disease	1666 (2.3)	421 (3.0)	828 (2.2)	7555 (1.9)	1121 (1.6)
Cancer	3870 (5.3)	590 (4.2)	731 (2.0)	13,418 (3.4)	2467 (3.6)

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

Table 2
Baseline characteristics of severe asthma cohorts.

	IPCI (NL) (n, %)	AARHUS (DK) (n,%)	HSD (IT) (n, %)	CPRD (UK) (n, %)	SIDIAP (SP) (n, %)
Total	6446 (100.0)	1633 (100.0)	1895 (100.0)	31,214 (100.0)	1423 (100.0)
Incident asthma	443 (6.9)	205 (12.6)	91 (4.8)	1705 (5.5)	362 (25.4)
Prevalent asthma	6003 (93.1)	1428 (87.5)	1804 (95.2)	29,509 (94.5)	1061 (74.6)
Female	4030 (62.5)	997 (61.1)	1123 (59.3)	19,474 (62.4)	994 (69.9)
Male	2416 (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	1029 (23.3)	5 (13.9)	203 (19.8)	6136 (19.7)	123 (10.1)
Current[a]	2197 (49.7)	7 (19.4)	588 (57.3)	12,156 (39.0)	913 (74.8)
Never[a]	1193 (27.0)	24 (66.7)	235 (22.9)	12,871 (41.3)	184 (15.1)
Past[a]	2027 (31.5)	1597 (97.8)	869 (45.9)	51 (0.2)	203 (14.3)
Smoking status unknown	2084 (32.3)	223 (13.7)	282 (14.9)	11,808 (37.8)	163 (11.5)
Atopy	260 (4.0)	14 (0.9)	44 (2.3)	4396 (14.1)	14 (1.0)
Chronic rhinosinusitis	62 (1.0)	50 (3.1)	77 (4.1)	1924 (6.2)	43 (3.0)
Nasal polyposis	564 (8.8)	66 (4)	279 (14.7)	4712 (15.1)	58 (4.1)
GERD	669 (10.4)	75 (4.6)	161 (8.5)	3082 (9.9)	229 (16.1)
Diabetes mellitus	2424 (37.6)	147 (9.0)	417 (22.0)	22,952 (73.5)	1016 (71.4)
Obesity	957 (14.9)	32 (2.0)	421 (22.2)	11,319 (36.3)	337 (23.7)
Anxiety/ Depression	407 (6.3)	126 (7.7)	39 (2.1)	2938 (9.4)	60 (4.2)
Cardiovascular disease	175 (2.7)	74 (4.5)	52 (2.7)	1242 (4.0)	50 (3.5)
Cerebrovascular disease	406 (6.3)	97 (5.9)	70 (3.7)	1826 (5.9)	113 (7.9)
Cancer					

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

eczema and/or allergic rhinitis) ranged between 15.1 and 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).

3.2. 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 5.2/1000 PY (95% CI 4.9–5.5) in HSD, 5.5/1000 PY (95% CI 5.1–5.8) in IPCI, 6.4/1000 PY (95% CI 6.1–6.7) in SIDIAP, 6.5/1000 PY (95% CI 6.4–6.6) in CPRD and 9.5/1000 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 and 14.8/1000 PY across databases (Table 3).

All-cause mortality rates increased with age both for the total asthma cohort and the severe asthma cohort (Online Table 2). 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 0.3/1000 PY (95% CI 0.2–0.5) and highest in Aarhus (DK) namely 1.0/1000 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 and 59.9/1000 PY across databases. All-cause mortality rates remained high in the first month following a severe asthma exacerbation and decreased thereafter (Table 4).

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.

3.3. 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

Table 3
Crude and age & sex standardized mortality rate (distribution of CPRD as reference population) (Mortality Rates (MR) = number of deaths/per 1000 PY).

	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

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

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).

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).

The 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 (Fig. 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 (Fig. 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).

4. 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 and 9.5/1000 PY over databases and doubled in patients with severe asthma (range 11.3–14.8/1000 PY). The all-cause mortality rate in the first 7 days following a severe asthma exacerbation ranged between 14.1 and 59.9/1000 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 and 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 0.3–1.0/1000 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 9.9/1000 PY in 1999 to 8.5/1000 PY in 2009 which is comparable to the age and sex standardized mortality rate as reported for Aarhus (9.5/1000 PY) but higher than the mortality rate as reported for the other databases (5.2–6.5/1000 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 1000 person years. This is slightly higher than the standardized mortality rate that we reported namely 6.5 per 1000 PY but Gayle et al. studied mortality using CPRD data between 2005 and 2015 whereas our study period was from 2008 to 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 and 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 and 2.5) mortality in all databases except Aarhus, stressing the relevance of smoking cessation in patients with asthma. A 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 1000 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, hospitalisation 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

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

	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%

MR = mortality rate per 1,000 PY. CumInc = cumulative incidence. 95% CI = 95% confidence interval, NL= Netherlands, DK = Denmark, IT= Italy, UK= United Kingdom, SP= Spain.

Table 5
Patient characteristics and mortality (multivariate analysis).

	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			8965			2097			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	

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

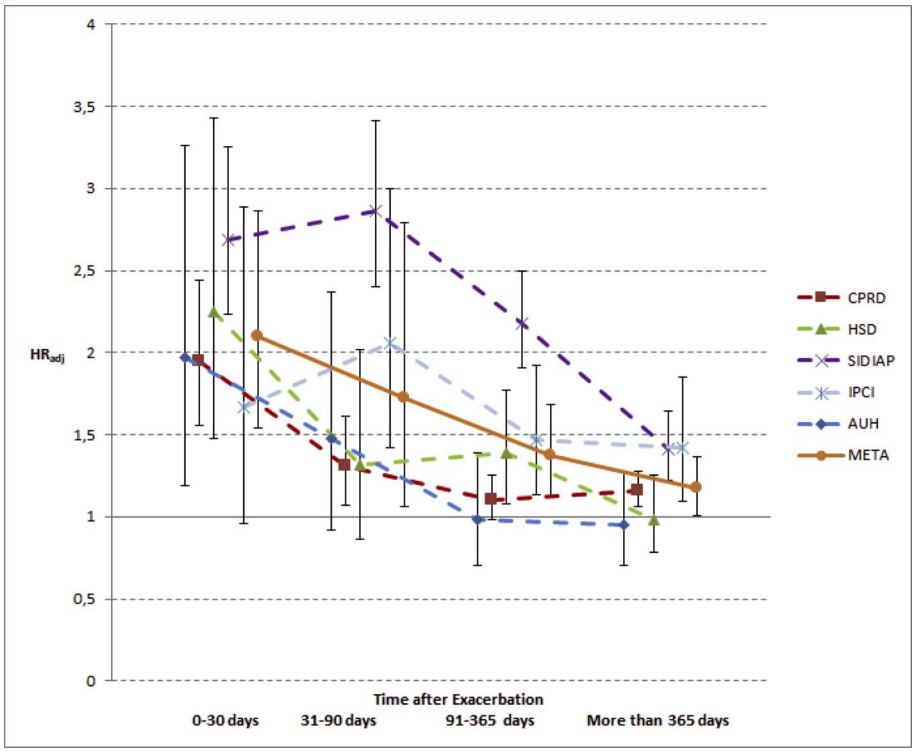

Fig. 2. Hazard ratios of mortality in adult asthmatic patients for time periods after severe asthma exacerbation (0–30, 31–90, 91–365, >365 days after severe asthma exacerbation) compared to time before any exacerbation.
* adjusted for sex, age at start follow-up, asthma severity, history of cancer, history of cardiovascular disease, history of cerebrovascular disease, history of diabetes mellitus, history of obesity, incident or prevalent and smoking. ⊤ ⊥ represent 95% CI.

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 hospitalisation 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.

Funding

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.

Declaration of competing 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.

CRediT authorship contribution statement

Marjolein Engelkes: Methodology, Validation, Data curation, Writing - review & editing, Visualization, Conceptualization. **Maria AJ de Ridder:** Methodology, Software, Formal analysis, Writing - review & editing, Visualization, Conceptualization. **Elisabeth Svensson:** Methodology, Validation, Data curation, Writing - review & editing. **Klara Berencsi:** Methodology, Validation, Data curation, Writing - review & editing. **Daniel Prieto-Alhambra:** Methodology, Validation, Data curation, Writing - review & editing. **Francesco Lapi:** Methodology, Validation, Data curation, Writing - review & editing. **Carlo Giaquinto:** Methodology, Validation, Data curation, Writing - review & editing. **Gino Picelli:** Methodology, Validation, Data curation, Writing - review & editing. **Nada Boudiaf:** Methodology, Validation, Data curation, Writing - review & editing. **Frank C Albers:** Methodology, Writing - review & editing, Conceptualization. **Sarah M Cockle:** Methodology, Writing - review & editing, Conceptualization. **Eric S Bradford:** Methodology, Writing - review & editing, Conceptualization. **Robert Y Suruki:** Methodology, Writing - review & editing, Supervision, Conceptualization. **Guy GO Brusselle:** Methodology, Writing - review & editing. **Peter R. Rijnbeek:** Methodology, Software, Validation, Data curation, Writing - review & editing, Visualization. **Miriam CJM Sturkenboom:** Methodology, Writing - review & editing, Supervision, Conceptualization. **Katia MC Verhamme:** Methodology, Software, Validation, Data curation, Writing - review & editing, Visualization, Supervision, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.105919.

References

[1] WHO, Chronic Respiratory Diseases.
[2] Global Asthma Report, Global Asthma Network, 2018.
[3] T. To, et al., Global asthma prevalence in adults: findings from the cross-sectional world health survey, BMC Publ. Health 12 (2012) 204.
[4] GINA, Global Strategy for Asthma Management and Prevention, 2019.
[5] D.J. Jackson, et al., Asthma exacerbations: origin, effect, and prevention, J. Allergy Clin. Immunol. 128 (6) (2011) 1165–1174.
[6] J.I. Ivanova, et al., Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma, J. Allergy Clin. Immunol. 129 (5) (2012) 1229–1235.
[7] S.P. Peters, et al., Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment, Respir. Med. 100 (7) (2006) 1139–1151.
[8] A.S. Rebuck, The global decline in asthma death rates: can we relax now? Asia Pac. Allergy 3 (3) (2013) 200–203.
[9] M. Masoli, et al., The global burden of asthma: executive summary of the GINA Dissemination Committee report, Allergy 59 (5) (2004) 469–478.
[10] S. Ebmeier, et al., Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012), Lancet 390 (10098) (2017) 935–945.
[11] T.A. Omachi, et al., Risk factors for death in adults with severe asthma, Ann. Allergy Asthma Immunol. 101 (2) (2008) 130–136.
[12] P.M. Sturdy, et al., Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study, Thorax 57 (12) (2002) 1034–1039.
[13] R.E. Lemmetyinen, et al., Higher mortality of adults with asthma: a 15-year follow-up of a population-based cohort, Allergy 73 (7) (2018) 1479–1488.
[14] S. Huang, et al., Asthma, airflow limitation and mortality risk in the general population, Eur. Respir. J. 45 (2) (2015) 338–346.
[15] A.E. Vlug, et al., Postmarketing surveillance based on electronic patient records: the IPCI project, Methods Inf. Med. 38 (4–5) (1999) 339–344.
[16] V. Ehrenstein, S. Antonsen, L. Pedersen, Existing data sources for clinical epidemiology: Aarhus university prescription database, Clin. Epidemiol. 2 (2010) 273–279.
[17] M. Cazzola, et al., The prevalence of asthma and COPD in Italy: a practice-based study, Respir. Med. 105 (3) (2011) 386–391.
[18] C. Cricelli, et al., Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases, J. Publ. Health Med. 25 (3) (2003) 254–257.
[19] M.C. Gulliford, et al., Electronic health records for intervention research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT study), Ann. Fam. Med. 12 (4) (2014) 344–351.
[20] H.T. Sorensen, B.O. Larsen, A population-based Danish data resource with possible high validity in pharmacoepidemiological research, J. Med. Syst. 18 (1) (1994) 33–38.
[21] K.V. Blake, et al., Increasing scientific standards, independence and transparency in post-authorisation studies: the role of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, Pharmacoepidemiol. Drug Saf. 21 (7) (2012) 690–696.
[22] K.F. Chung, et al., International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma, Eur. Respir. J. 43 (2) (2014) 343–373.
[23] GINA, Pocket Guide for Asthma Management and Prevention, 2014.
[24] S. Suissa, Immortal time bias in pharmaco-epidemiology, Am. J. Epidemiol. 167 (4) (2008) 492–499.
[25] H.K. Reddel, et al., An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice, Am. J. Respir. Crit. Care Med. 180 (1) (2009) 59–99.
[26] H. Gu, et al., Quality assurance of UMLS semantic type Assignments using SNOMED CT hierarchies, Methods Inf. Med. 55 (2) (2016) 158–165.
[27] L.R. Curtin, R.J. Klein, Direct standardization (age-adjusted death rates), Health People 1995 (6) (2000) 1–10. Stat Notes.
[28] A. Gasparrini, B. Armstrong, M.G. Kenward, Multivariate meta-analysis for non-linear and other multi-parameter associations, Stat. Med. 31 (29) (2012) 3821–3839.
[29] E. Pennington, et al., Trends in asthma mortality in the United States: 1999 to 2015, Am. J. Respir. Crit. Care Med. 199 (12) (2019) 1575–1577, https://doi.org/10.1164/rccm.201810-1844LE.
[30] T. To, et al., Asthma deaths in a large provincial health system. A 10-year population-based study, Ann. Am. Thorac. Soc. 11 (8) (2014) 1210–1217.
[31] A.V. Gayle, et al., Changing causes of death for patients with chronic respiratory disease in England, Thorax 74 (5) (2019) 483–491, 2005-2015.
[32] V. Krishnan, et al., Mortality in patients hospitalized for asthma exacerbations in the United States, Am. J. Respir. Crit. Care Med. 174 (6) (2006) 633–638.
[33] B.P. Kaur, et al., Asthma: hospitalization trends and predictors of in-hospital mortality and hospitalization costs in the USA (2001-2010), Int. Arch. Allergy Immunol. 168 (2) (2015) 71–78.
[34] J.M. Strid, et al., Hospitalization rate and 30-day mortality among patients with status asthmaticus in Denmark: a 16-year nationwide population-based cohort study, Clin. Epidemiol. 5 (2013) 345–355.
[35] Z. Ali, C.G. Dirks, C.S. Ulrik, Long-term mortality among adults with asthma: a 25-year follow-up of 1,075 outpatients with asthma, Chest 143 (6) (2013) 1649–1655.
[36] G. D'Amato, et al., Asthma-related deaths, Multidiscip. Respir. Med. 11 (2016) 37.
[37] H. Backman, et al., A population-based cohort of adults with asthma: mortality and participation in a long-term follow-up, Euro. Clin. Respir. J. 4 (2017).