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Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study

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Abstract

Background: There are sparse real-world data on severe asthma exacerbations (SAE) in children. This multinational cohort study assessed the incidence of and risk factors for SAE and the incidence of asthma-related rehospitalization in children with asthma.

Methods: Asthma patients 5-17 years old with ≥ 1 year of follow-up were identified in six European electronic databases from the Netherlands, Italy, the UK, Denmark and Spain in 2008-2013. Asthma was defined as ≥ 1 asthma-specific disease code within 3 months of prescriptions/dispensing of asthma medication. Severe asthma was defined as high-dosed inhaled corticosteroids plus a second controller. SAE was

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defined by systemic corticosteroids, emergency department visit and/or hospitalization all for reason of asthma. Risk factors for SAE were estimated by Poisson regression analyses.

Results: The cohort consisted of 212 060 paediatric asthma patients contributing to 678 625 patient-years (PY). SAE rates ranged between 17 and 198/1000 PY and were higher in severe asthma and highest in severe asthma patients with a history of exacerbations. Prior SAE (incidence rate ratio 3-45) and younger age increased the SAE risk in all countries, whereas obesity, atopy and GERD were a risk factor in some but not all countries. Rehospitalization rates were up to 79% within 1 year.

Conclusions: In a real-world setting, SAE rates were highest in children with severe asthma with a history of exacerbations. Many severe asthma patients were rehospitalized within 1 year. Asthma management focusing on prevention of SAE is important to reduce the burden of asthma.

KEYWORDS

asthma: epidemiology, asthma: risk factors, epidemiology: prevalence

1 | INTRODUCTION

Asthma is an important public health problem and is responsible for a high number of missed school and work days; moreover, it can be associated with significant limitations on physical, social and professional/student aspects of life when it is not controlled.^{1,2} Asthma exacerbations represent a decline in lung function with worsening of respiratory symptoms such as shortness of breath, cough and/or chest tightness.² According to a joint statement of the European Respiratory Society and the American Thoracic Society, a severe asthma exacerbation (SAE) is defined as the use of systemic corticosteroids, emergency department (ED) visit or hospitalization all for reason of asthma.³

There are scarce international data on the incidence of SAE in asthma children in the general population. The Asthma Insights and Reality in Europe (AIRE) study was conducted in 1999, in which asthma patients from 7 different European countries were questioned during a telephone interview. It showed differences in SAE rates between countries, as 7%-40% of children with asthma reported an ED visit for asthma and 3%-12% were hospitalized in the previous year.⁴ As this study used interview data, it was susceptible to recall bias. Randomized controlled trials can also provide data on the incidence of severe asthma exacerbations, but these numbers tend to be much lower than in real life due to strict inclusion and exclusion criteria and short follow-up.⁵ Risk factors for SAEs have been studied primarily in adults, and thus, data in children are scarce.

Currently, we still lack reliable instruments or biomarkers to predict SAE in children. Several studies found that the best predictor of future SAE was a history of a previous SAE.^{6,7} This implies that the risk of rehospitalization is probably high.

In this study, we aimed to estimate real-world incidence rates of and risk factors for SAEs, as well as to study the rate and cumulative incidence of asthma rehospitalization in children with asthma and

Key Message

There are few studies on the real-life incidence of severe asthma exacerbations in children and the few available strongly vary in study design. In this large international retrospective cohort study we investigated the incidence of and risk factors for severe asthma exacerbations in 6 European databases using one single protocol and harmonized methods for data extraction and data analysis. We observed exacerbation rates ranging between 17 and 198/1000 person-years in the different databases with high rehospitalization rates. This underscores the importance of enhanced patient care in children with asthma to achieve the ultimate goal of preventing asthma exacerbations.

severe asthma, using one protocol and harmonized methods with regard to data extraction and data analysis, across multiple data sources from five different European countries.

2 | METHODS

A retrospective cohort study was conducted using data from six European electronic healthcare databases, namely the Integrated Primary Care Information Project (IPCI) from the Netherlands, the Health Search Database (HSD) and Pedianet from Italy, Clinical Practice Research Datalink (CPRD) from the UK, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and the Aarhus University Prescription

Database (Aarhus) from Denmark. Detailed descriptions of these databases have been published before and are available in the Appendix S1.8-13 All databases comprise detailed information on drug prescriptions or dispensing, outpatient diagnoses and hospitalizations, comorbidity and measurement data (eg laboratory results, spirometry, BMI). While in most databases children of all ages are captured, in Italy for children 0-6 years old all primary care is provided by paediatricians, and parents can choose between a paediatrician and a GP for children 6-16 years of age. Therefore, Pédianet (primary care paediatrician data) tends to contain younger children, while HSD (GP data) tends to capture older children.

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) database.¹⁴ In all 5 countries, the study protocol was approved by their local institutional review board.

2.1 | Cohort definition

A cohort of patients with asthma was determined in each database within the study period (1 January 2008-31 December 2013). To enter the cohort, patients needed to be 5-17 years old, with a minimum of 1-year database history and diagnosed with asthma. Asthma was defined as physician-diagnosed asthma based on the presence of at least one asthma-specific disease code (see Appendix S1) in combination with prescriptions/dispensing of asthma medications within 3 months of the asthma disease code. Asthma medications 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 receptor antagonist, short-acting muscarinic antagonist (SAMA), fixed combination of SABA + SAMA, xanthines, systemic corticosteroids for the treatment of asthma, and anti-IgE treatment. Information on drug use was retrieved by an ATC-specific search from the drug prescription and/or drug dispensing records. Based on the first date of an asthma disease code, patients were categorized into prevalent or incident asthma.

Within the cohort of patients with asthma, a subcohort of patients with severe asthma was nested. According to international guidelines, severe asthma was defined as asthma requiring treatment with high-dose ICS (as defined in the Global Initiative of Asthma (GINA); see Appendix S1) plus a second controller and/or systemic corticosteroids for at least 120 consecutive days.^{2,15} To account for immortal time bias, the start date of severe asthma was day 120 of high-dose ICS use.

2.2 | Follow-up

Follow-up started at the latest date of the following: the start of the study period, diagnosis of (severe) asthma, age of 5 years or after reaching 365 days of database history. Follow-up ended when

leaving the database, reaching the age of 18, death or end of the study period, whichever came first.

2.3 | Outcomes

An SAE was defined as any of the following: use of systemic corticosteroids, ED visit or hospitalization, all for worsening of asthma.³ The indication of corticosteroid use was retrieved from the prescription/dispensing file or through an automated search on asthma (exacerbation) disease codes in a 7-day window around the prescription date. Continuous use of systemic corticosteroids, defined as consecutive use of at least 30 days, was not considered as an SAE. If the time between exacerbations, of whatever type, was <7 days, it was considered to be one single exacerbation.

Rehospitalization was defined as an asthma-related hospitalization following a previous asthma-related hospitalization. Hospitalizations were based on primary discharge diagnosis codes in SIDIAP, Aarhus and CPRD and were based on manual validation of discharge letters in the other databases.

2.4 | Covariates

We investigated the prevalence of the following comorbidities at the start of follow-up and at each exacerbation, using the complete medical history: atopy (allergic rhinitis and/or atopic eczema/dermatitis), chronic rhinosinusitis, nasal polyposis, gastro-oesophageal reflux disease (GERD), obesity and diabetes mellitus. In addition, we investigated whether or not patients had a history of exacerbations. History of exacerbations was defined as ≥ 2 SAEs in the 1 year prior to entering the (severe) asthma cohort. If patients had <12 months prior to asthma diagnosis or the start of severe asthma, 1 exacerbation or more in the 6 months prior fulfilled the criterion. We also investigated age and gender as covariates.

2.5 | Analysis

The exacerbation rates were calculated by dividing the number of exacerbations by the respective number of person-years of follow-up and additionally stratified by gender and age in years.

Asthma rehospitalization rates in predefined follow-up time windows (30, 180 and 365 days following a previous hospitalization) were calculated. If a patient had more than one exacerbation during that time window, each exacerbation contributed to the numerator. Furthermore, from these rates cumulative incidences were calculated.

Heterogeneity was quantified by the I^2 statistics to assess if it was appropriate to perform a meta-analysis on the overall SAE rates estimated in the databases.

Risk factors for exacerbations were assessed by Poisson regression analyses, adjusting for age, gender and their interaction.

A multivariate model was fitted using the following covariates: age, gender, comorbidity (atopy, obesity, GERD), history of exacerbations and the interaction between age and gender and between age and history of exacerbations. These analyses were repeated after stratification for age: for children 5-11 years old and for children 12-17 years old. Analyses were conducted using SAS® version 9.4.

3 | RESULTS

The cohort comprised 212 060 children with asthma contributing 678 625 patient-years (PY). In total, 14 283 children (6.7%, ranging from 1.6% to 18.3% across databases) with severe asthma were identified.

The mean age at the start of follow-up was 10.4 years (ranging between 7.2 and 14.8 years across databases), and a male preponderance was observed. The prevalence of atopy was 9.6% in Aarhus and ranged between 24.1% and 43.6% in the other databases. In all databases, the prevalence of atopy, GERD and obesity was higher in patients with severe asthma. (Tables 1 and 2).

Of all asthma patients, depending on the database, 2.8%-29.3% had at least one exacerbation during the follow-up. In HSD, SIDIAP and PEDIANET, SAE mostly comprised use of systemic corticosteroids (89%-100%), while in IPCI, Aarhus and CPRD, this proportion

was 57%, 25% and 77%, respectively. Large differences between databases in incidence rates (IR) of SAE were observed especially for the younger age. The overall SAE rates ranged between 17 and 198/1000 PY and were higher in severe asthma patients (range 46-375/1000 PY). SAE rates decreased with age, from age 5 onwards, and this was significant for all databases. (Figure 1 and Table 3) From adolescence on, higher IRs of SAE were observed for women compared to men in CPRD, SIDIAP, IPCI and Aarhus. (Figure 1) The IR ranged between 11 and 131/1000 PY in patients without a history of exacerbations and was higher in children with severe asthma especially with a history of exacerbations (283-1000/1000 PY). (Figure 2 and Table S1) As the heterogeneity of exacerbation rates was substantial ($I^2 > 99\%$), it was not appropriate to pool the data.

3.1 | Risk factors for severe asthma exacerbations

After adjustment for age, gender and their interaction, having atopy, GERD and obesity increased the risk of SAE in some databases. (Table S2) In the multivariate model, the same risk factors remained, but risk estimates were lower. (Table 3) Additionally, the interaction between age and a history of exacerbations showed that in some databases, the risk associated with a history of exacerbations increased

TABLE 1 Baseline characteristics of total asthma cohorts

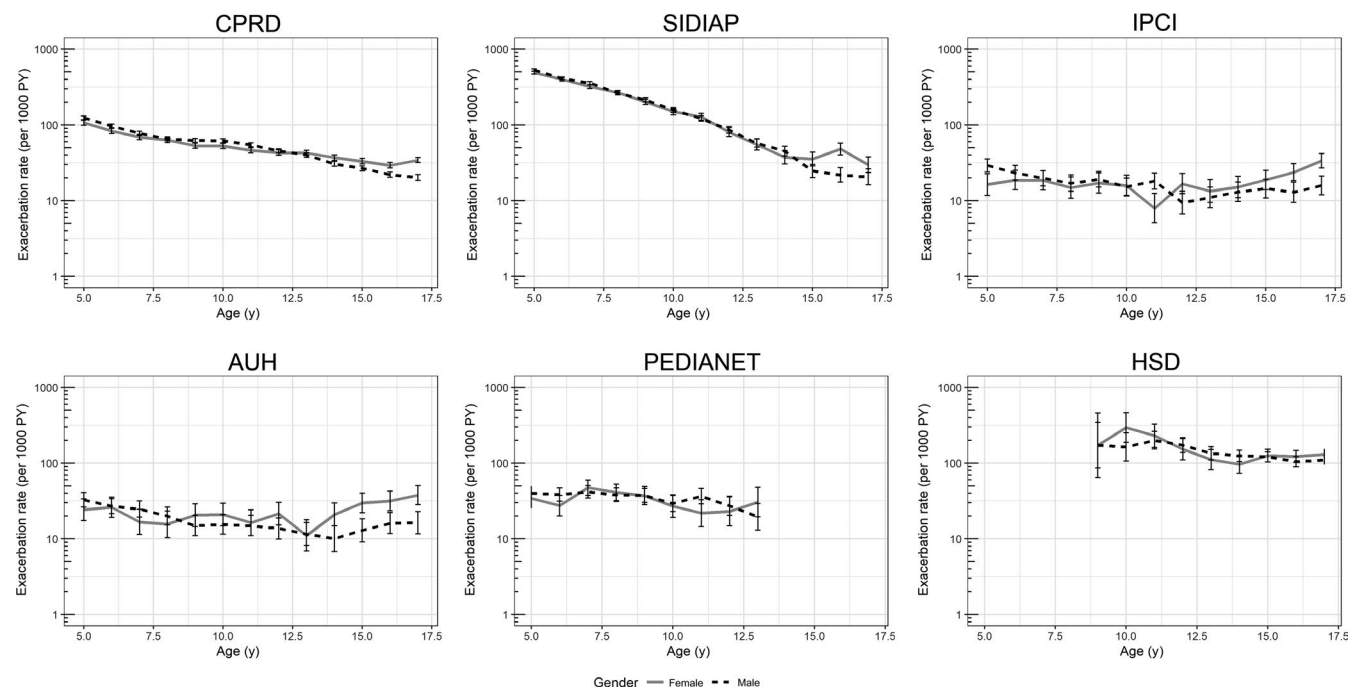
	CPRD (n, %)	SIDIAP (n, %)	IPCI (n, %)	AARHUS (n, %)	PEDIANET (n, %)	HSD (n, %)
Total	124 554	30 749	31 705	12 521	8264	4267
Female	51 667 (41.5)	12 357 (40.2)	13 262 (41.8)	4681 (37.4)	2980 (36.1)	1665 (39.0)
Male	72 887 (58.5)	18 392 (59.8)	18 443 (58.2)	7840 (62.6)	5284 (63.9)	2602 (61.0)
Age (mean, min-max)	10.9 (5.0-17.9)	8.9 (5.0-17.9)	10.2 (5.0-17.9)	9.3 (5.0-17.9)	7.2 (5.0-14.0)	14.8 (6.6-17.9)
Severe asthma	9162 (7.4)	1139 (3.7)	1858 (5.9)	1207 (9.6)	137 (1.7)	780 (18.3)
Incident asthma	23 743 (19.1)	13 062 (42.5)	4604 (14.5)	1392 (11.1)	1892 (22.9)	1302 (30.5)
Prevalent asthma	100 811 (80.9)	17 687 (57.5)	27 101 (85.5)	11 129 (88.9)	6372 (77.1)	2965 (69.5)
History of exacerbations						
Yes	5276 (4.2)	2625 (8.5)	241 (0.8)	408 (3.3)	196 (2.4)	321 (7.5)
No	119 278 (95.7)	28 124 (91.5)	31 464 (99.2)	12 113 (96.7)	8068 (97.6)	3946 (92.5)
Atopy	54 356 (43.6)	9767 (31.8)	11 602 (36.6)	1200 (9.6)	1990 (24.1)	961 (22.5)
GERD	3247 (2.6)	248 (0.8)	510 (1.6)	103 (0.8)	146 (1.8)	55 (1.3)
Diabetes mellitus	294 (0.2)	42 (0.1)	81 (0.3)	43 (0.3)	0	7 (0.2)
Obesity	24 742 (19.9)	12 828 (41.7)	1518 (5.0)	205 (1.6)	3977 (48.1)	265 (6.2)
Chronic rhinosinusitis	4917 (3.9)	33 (0.1)	112 (0.4)	0	0	38 (0.9)
Nasal polyposis	228 (0.2)	0	13 (0.0)	8 (0.1)	0	0
Patients with ≥ 1 exacerbation	12 638 (10.2)	8968 (29.3)	871 (2.8)	756 (6.0)	724 (8.8)	855 (20.0)
Asthma exacerbations (n)	19 530	18 808	1290	1020	1031	1461
Systemic corticosteroids (n, %)	15 049 (77.0)	17 323 (92.1)	739 (57.3)	252 (24.7)	918 (89.0)	1460 (99.9)
ED/ hospitalization (n, %)	4481 (23.0)	1485 (7.9)	551 (42.7)	768 (75.3)	113 (11.0)	1 (0.1)

Abbreviations: ED, emergency department; GERD, gastro-oesophageal reflux disease.

TABLE 2 Baseline characteristics of severe asthma cohorts

	CPRD (n, %)	SIDIAP (n, %)	IPCI (n, %)	AARHUS (n, %)	PEDIANET (n, %)	HSD (n, %)
Total	9162	1139	1858	1207	137	780
Female	3705 (40.4)	481 (42.2)	806 (43.4)	406 (33.6)	34 (24.8)	292 (37.4)
Male	5457 (59.6)	658 (57.8)	1052 (56.6)	801 (66.4)	103 (75.2)	488 (62.6)
Age (mean, min-max)	11.0 (5.0-17.9)	8.60 (5.0-17.9)	13.1 (5.0-17.9)	10.4 (5.0-17.9)	9.3 (5.0-12.9)	14.5 (2.4)
Incident asthma	436 (4.8)	164 (14.4)	122 (6.6)	102 (8.5)	6 (4.4)	79 (10.1)
Prevalent asthma	8726 (95.2)	975 (85.6)	1736 (93.4)	1105 (91.5)	131 (95.6)	701 (89.9)
History of exacerbations						
Yes	562 (6.1)	215 (18.9)	49 (2.6)	40 (1.7)	1 (0.8)	55 (7.1)
No	8600 (93.9)	924 (81.1)	1809 (97.4)	1167 (98.3)	136 (99.3)	725 (92.9)
Atopy	4724 (51.6)	407 (35.7)	789 (42.5)	194 (16.1)	54 (39.4)	190 (24.4)
GERD	375 (4.1)	23 (2.0)	34 (1.8)	14 (1.2)	3 (2.2)	16 (2.1)
Diabetes mellitus	25 (0.3)	2 (0.2)	4 (0.2)	6 (0.5)	0	2 (0.3)
Obesity	2541 (27.7)	522 (45.8)	174 (9.4)	45 (3.7)	60 (43.8)	57 (7.3)
Chronic rhinosinusitis	475 (5.2%)	3 (0.3%)	12 (0.6%)	0	0	7 (0.9%)
Nasal polyposis	31 (0.3%)	0	3 (0.2%)	1 (0.1%)	0	0

Abbreviation: GERD, gastro-oesophageal reflux disease

**FIGURE 1** SAE rate (per 1000 PY) with 95% CI by age and gender in the total asthma cohort per database

with increasing age, and in others, this risk decreased. After stratification for age category, for female gender in 5- to 11-year-olds a decreased risk was found, while in 12- to 17-year-olds there was an increased risk. These findings were less prominent in Pedianet and HSD, possibly due to the limited age range in these databases. No other distinct differences between the age categories were observed (see Appendix S1).

3.2 | Rehospitalization following previous hospitalization for asthma exacerbation

Rehospitalization rates decreased with time following index hospitalization. The asthma rehospitalization rate was highest in SIDIAP (within 1 month: 13.7/10 PY in children with asthma and 88.3/10 PY in children with severe asthma), whereas in the other databases the

TABLE 3 Relative rates for SAE in the total asthma cohort (multivariate analysis)

Characteristic	CPRD		SIDIAP		IPCI		AARHUS		PEDIANET		HSD	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Age	0.89	(0.88, 0.89)	0.78	(0.78, 0.79)	0.94	(0.92, 0.96)	0.95	(0.92, 0.97)	0.94	(0.91, 0.97)	0.95	(0.91, 0.99)
Female	0.68	(0.62, 0.74)	0.83	(0.76, 0.91)	0.43	(0.30, 0.61)	0.39	(0.26, 0.57)	0.88	(0.55, 1.41)	0.46	(0.21, 1.02)
Age*Sex	1.04	(1.03, 1.05)	1.02	(1.01, 1.03)	1.09	(1.06, 1.12)	1.11	(1.07, 1.15)	1.01	(0.95, 1.06)	1.06	(1.00, 1.11)
Atopy	1.37	(1.34, 1.41)	1.09	(1.06, 1.12)	1.51	(1.36, 1.69)	2.07	(1.75, 2.44)	1.17	(1.01, 1.34)	0.92	(0.81, 1.05)
GERD	1.18	(1.09, 1.28)	1.48	(1.30, 1.67)	1.53	(1.08, 2.17)	1.15	(0.57, 2.31)	1	(0.62, 1.61)	1.1	(0.67, 1.80)
Obesity	1.25	(1.21, 1.29)	0.9	(0.88, 0.93)	1.19	(0.94, 1.51)	2.14	(1.55, 2.96)	1.02	(0.90, 1.15)	0.92	(0.73, 1.16)
History of exacerbations	5.76	(5.25, 6.33)	2.53	(2.27, 2.81)	20.04	(12.91, 31.10)	45.71	(31.2, 66.92)	29.36	(16.25, 53.05)	10.07	(4.56, 22.20)
Age*History of exacerbations	1.06	(1.05, 1.07)	1.01	(1.00, 1.03)	1.04	(1.00, 1.08)	0.94	(0.91, 0.97)	0.91	(0.85, 0.98)	0.97	(0.92, 1.02)

Abbreviation: GERD, gastro-oesophageal reflux disease

rehospitalization rate within the first month ranged between 5.4 and 7.7/10 PY in children with asthma and between 14.3 and 15.8/10 PY in children with severe asthma.

The cumulative incidence of rehospitalization within 1 year was 17%-29% in children with asthma, whereas this was much higher, namely 33%-79%, in patients with severe asthma. (Table 4) No data are presented for HSD and PEDIANET as the number of children being hospitalized for asthma exacerbation was too low.

4 | DISCUSSION

In this study, the overall exacerbation rate in children with asthma ranged between 17 and 198/1000 PY across databases, increased in children with severe asthma (range 46-375/1000 PY) and was the highest in those with severe asthma with a history of exacerbations (283-1000/1000 PY). Rehospitalization following a previous hospitalization was high, both in the overall asthma cohort, namely 17%-29% being rehospitalized in a year, and especially in children with severe asthma, as up to 79% were rehospitalized within a year.

We observed large differences in incidence rate of SAE, especially for the youngest age categories, and also large differences in the type of SAE. Large differences in exacerbation rates between European countries have previously been observed in other studies that used questionnaires or interviews to collect data instead of healthcare databases. In line with our results, these studies showed higher severe exacerbation rates in Italy and Spain than in the UK, and higher rates of emergency care in Spain than in the UK. In the Asthma Insights and Reality in Europe (AIR) survey, hospitalization rates in children were higher in Spain and Italy than in The Netherlands and the UK. 16-18 In these studies, many reasons for these differences were suggested: differences in disease management such as asthma prevention plans, lung function measurement, and difference in drug prescriptions, compliance with therapy, environmental differences and cultural differences such as perception of disease burden and healthcare-seeking behaviour.

Our exacerbation rates are in line with a recent study by Suruki et al investigating SAE in adolescent and adult asthma patients.¹⁹ They reported a mean exacerbation rate in asthma patients 12-17 years old of 156/1000 PY based on US claims data and of 77/1000 PY using CPRD data. Comparison with other studies is difficult, as most of these only investigated hospitalizations for asthma, included systemic corticosteroids irrespective of the indication of use or investigated a selective population.^{17,19-24}

Our observation on frequent rehospitalization is in line with data from two cohort studies on hospitalizations for children with asthma in the United States which observed that 17% and 22% of hospitalized children were readmitted within 365 days.^{25,26} The risk factors for SAE were a previous SAE, male gender, youngest age and atopy. In agreement with published literature, in our study a previous exacerbation was the best predictor of a subsequent asthma exacerbation.²⁷⁻²⁹ Other published risk factors for asthma exacerbations

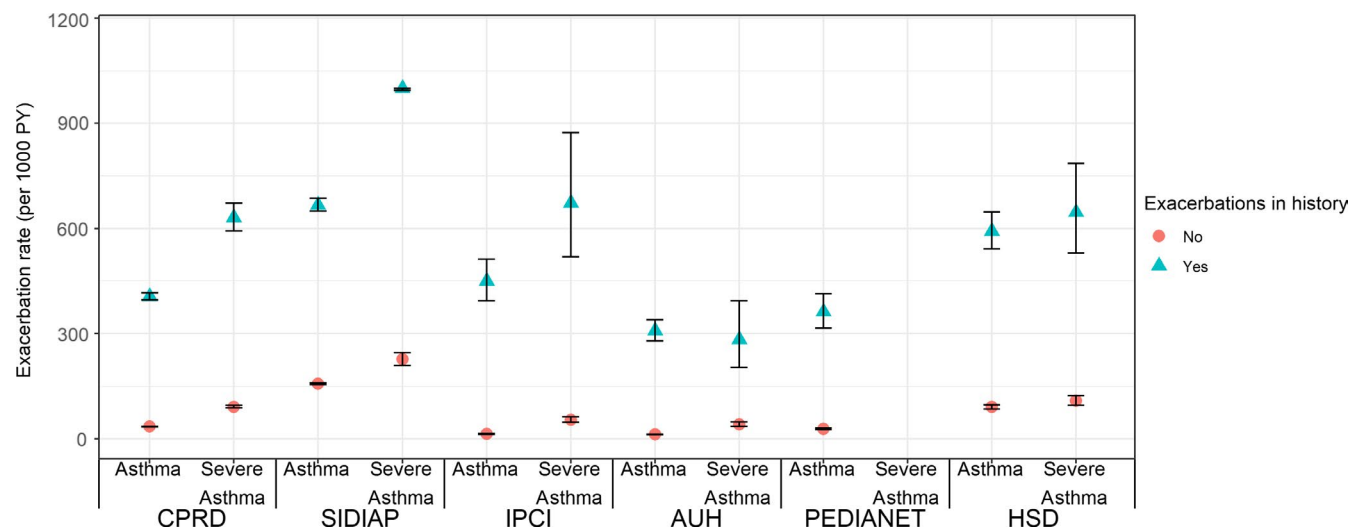


FIGURE 2 SAE rate (per 1000 PY) with 95% CI by history of exacerbations and severity (severe asthma in Pedianet not presented as low numbers)

such as obesity and GERD could not be confirmed as risk factor in all participating databases.^{30,31}

As for all observational studies, our study has strengths and limitations. Major strengths include the large number of children with asthma included in our cohort, from 6 different European databases in 5 countries, using a single protocol and harmonized methods for data extraction and data analysis. Detailed information on important covariates such as drug exposure and underlying comorbidity and on lifestyle factors was collected. The use of real-life data in a heterogeneous asthmatic population increases the external validity of our findings as our data are highly representative of actual practice conditions and likely to minimize Hawthorne and similar effects.³²

However, as this is an observational study, using data from electronic healthcare databases, there is always the potential of bias and/or confounding.

First, we did report large differences in the incidence rates of SAE between countries.

For those databases where automatic linkage with hospital data was available (CPRD, SIDIAP and Aarhus), misclassification of ED visits/hospitalization is unlikely. For the other databases, hospitalization or ED visit was retrieved either via disease-specific codes in combination with codes for hospitalization (HSD and Pedianet) or via review of the discharge letters (IPCI). For prescriptions of systemic steroids, only those with an indication for asthma registered in the database were included. If practices did not report the indication of use or did not report disease codes around the prescription date, we might have underreported the incidence rate. Similar underreporting might have occurred if patients used previously collected systemic corticosteroids.

Also, the large differences in SAE rates might be due to international differences in the use of systemic steroids. For example, in Spain (SIDIAP), a large incidence of SAE based on use of systemic steroids was observed in young children. Despite the fact that these

differences between the databases complicate comparison between countries, we believe that it is better to study six different databases in one identical way than having six different single database studies using different methods because that would make comparison even more difficult.

For Aarhus and SIDIAP, dispensing data instead of prescription data were used, reducing misclassification of exposure. Unfortunately, dosing information is missing in Aarhus and SIDIAP and dosing was derived from the strength per device and the time window between prescriptions. Of course, this method is prone to misclassification, which might explain the relative low proportion of severe asthma patients in SIDIAP.

Because of large numbers, manual validation of asthma was not feasible and asthma was defined based on the presence of disease codes, and thus, potential misclassification of asthma cannot be excluded. However, to ensure good quality of health care, GPs are trained and requested to enter disease codes fitting the actual patient's diagnosis.

Furthermore, for each of the comorbidities of interest, diseases were mapped through the Unified Medical Language System (UMLS) generating a list of disease codes (see Appendix S1) which were verified by the databases prior to extraction.³³ Still we cannot exclude potential misclassification in case certain disease codes were omitted or in case of country-specific differences in disease coding. Despite these potential limitations, we were able to give a good reflection of exacerbations in the general population and found similar trends of risk factors across the databases.

5 | CONCLUSION

In this study, the incidence rates of severe asthma exacerbation in children ranged between 17 and 198/1000 PY and increased in children with severe asthma. In keeping with previous studies,

TABLE 4 Asthma rehospitalization per 10 person-years following discharge from previous asthma hospitalization in different time periods per database (HSD and PEDIANET not presented as low numbers)

		<30 d after hospitalization			<180 d after hospitalization			<365 d after hospitalization		
		Rehospitalizations (n)	Rate/10 PY (95% CI)	Cumulative incidence (%)	Rehospitalizations (n)	Rate/10 PY (95% CI)	Cumulative incidence (%)	Rehospitalizations (n)	Rate/10 PY (95% CI)	Cumulative incidence (%)
CPRD	Asthma	121	5.4 (4.5,6.5)	4.3	257	2.1 (1.9,2.4)	9.8	421	1.9 (1.7,2.1)	17.3
	Severe asthma	58	15.7 (12.2, 20.4)	12.1	100	5.3 (4.4,6.4)	23.0	137	4.0 (3.4,4.8)	33.0
SIDJAP	Asthma	87	13.7 (11.1, 16.9)	10.6	164	5.1 (4.3,5.9)	22.2	205	3.4 (3.0,3.9)	28.8
	Severe asthma	58	88.3 (68.3, 114.2)	51.6	62	25.1 (19.5, 32.2)	71.0	67	15.8 (12.4, 20.0)	79.4
IPCI	Asthma	12	6.4 (3.6, 11.2)	5.1	37	3.9 (2.9,5.4)	17.5	48	3.0 (2.2,3.9)	25.9
	Severe asthma	6	14.3 (6.4, 31.8)	11.1	20	10.8 (7.0, 16.8)	41.3	22	7.3 (4.8, 11.1)	51.8
AARHUS	Asthma	44	7.7 (5.7, 10.3)	6.1	98	3.1 (2.6,3.8)	14.2	133	2.3 (1.9,2.7)	20.0
	Severe asthma	16	15.8 (9.7, 25.7)	12.2	32	6.3 (4.4,8.9)	26.7	46	5.1 (3.8,6.8)	40.0

Abbreviations: 95% CI, 95% confidence interval; PY, person-years.

the most important risk factor for hospitalization was a previous exacerbation.

Rehospitalization for asthma following a previous hospitalization was high, especially in children with severe asthma as up to 50% were rehospitalized within 1 month and up to 79% within 1 year following discharge. This underscores the importance of enhanced patient care in children with asthma to achieve the ultimate goal of preventing asthma exacerbations.

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CONFLICT OF INTEREST

FA, SC, EB, LAE and MKVD are employees of GSK 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. EJB, GP, CG and 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. ME has received grants from GSK and ZonMw. The institutions of MDR, PR, MS and KV have received unconditional research grants from Boehringer-Ingelheim, Novartis, Pfizer, Yamanouchi, Servier and Johnson & Johnson, unrelated to the current manuscript; MDR, MS and KV have received an unconditional grant from GSK to conduct research on the incidence of and risk factors for asthma exacerbations as part of the GSK/EU-ADR Alliance project. HMJ has received grants from NIH and NCFS, participates in studies funded by an unconditional research grant from Vectura, and received travel expenses from Vertex, all unrelated to the current manuscript. ES's institution (Aarhus University) has received a grant from the GSK/EU-ADR Alliance, related to this study.

AUTHOR CONTRIBUTIONS

ME, EJB, MDR, ES, DPA, FL, GP, RS, PR, MS, NB and KV contributed to the study concept and design and acquisition of data and were involved in data analysis and interpretation. FA, EB, LAE, CG, SC, MKVD and EJB contributed to the study concept and design and were involved in data analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the submitted version.

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REFERENCES

1. Blakey JD, Wardlaw AJ. What is severe asthma? *Clin Exp Allergy*. 2012;42(5):617-624.
2. GINA. Pocket guide for asthma management and prevention. 2019.
3. Reddel HK, Taylor DR, Bateman ED, 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*. 2009;180(1):59-99.
4. Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. *Respir Med*. 2002;96(3):142-149.
5. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol*. 2011;128(6):1165-1174.
6. Haselkorn T, Fish JE, Zeiger RS, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the expert panel report 3 guidelines, increases risk for future severe asthma exacerbations in the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *J Allergy Clin Immunol*. 2009;124(5):895-902.e4.
7. Miller MK, Lee JH, Miller DP, Wenzel SE, Group TS. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med*. 2007;101(3):481-489.
8. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med*. 1999;38(4-5):339-344.
9. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus university prescription database. *Clin Epidemiol*. 2010;2:273-279.
10. Cazzola M, Puxeddu E, Bettoncelli G, et al. The prevalence of asthma and COPD in Italy: a practice-based study. *Respir Med*. 2011;105(3):386-391.
11. Cricelli C, Mazzaglia G, Samani F, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med*. 2003;25(3):254-257.
12. Gulliford MC, van Staa T, Dregan A, et al. Electronic health records for intervention research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT study). *Ann Fam Med*. 2014;12(4):344-351.
13. Sorensen HT, Larsen BO. A population-based Danish data resource with possible high validity in pharmacoepidemiological research. *J Med Syst*. 1994;18(1):33-38.
14. Blake KV, Devries CS, Arlett P, Kurz X, Fitt H. 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*. 2012;21(7):690-696.
15. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373.
16. Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. *Respir Med*. 2002;96(3):142-149.
17. Henneberger PK, Mirabelli MC, Kogevinas M, et al. The occupational contribution to severe exacerbation of asthma. *Eur Respir J*. 2010;36(4):743-750.
18. Hyland ME, Sthl E. Asthma treatment needs: a comparison of patients' and health care professionals' perceptions. *Clin Ther*. 2004;26(12):2141-2152.
19. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med*. 2017;17(1):74.

20. Suruki RY, Boudiaf N, Ortega HG. Retrospective cohort analysis of healthcare claims in the United States characterising asthma exacerbations in paediatric patients. *World Allergy Organ J*. 2016;9:18.
21. Bisgaard H, Moller H. Changes in risk of hospital readmission among asthmatic children in Denmark, 1978–93. *BMJ*. 1999;319(7204):229–230.
22. Morrison DS, McLoone P. Changing patterns of hospital admission for asthma, 1981–97. *Thorax*. 2001;56(9):687–690.
23. Kemp T, Pearce N. The decline in asthma hospitalisations in persons aged 0–34 years in New Zealand. *Aust NZ J Med*. 1997;27(5):578–581.
24. Mitchell EA, Cutler DR. Paediatric admissions to Auckland hospital for asthma from 1970–1980. *N Z Med J*. 1984;97(749):67–70.
25. Kenyon CC, Melvin PR, Chiang VW, Elliott MN, Schuster MA, Berry JG. Rehospitalization for childhood asthma: timing, variation, and opportunities for intervention. *J Pediatr*. 2014;164(2):300–305.
26. Auger KA, Kahn RS, Davis MM, Simmons JM. Pediatric asthma readmission: asthma knowledge is not enough? *J Pediatr*. 2015;166(1):101–108.
27. Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy*. 2016;9:1–12.
28. Salamzadeh J, Wong IC, Hosker HS, Chrystyn H. A Cox regression analysis of covariates for asthma hospital readmissions. *J Asthma*. 2003;40(6):645–652.
29. Arabkhazaeli A, Vijverberg SJH, van Erp FC, Raaijmakers JAM, van der Ent CK, Maitland van der Zee AH. Characteristics and severity of asthma in children with and without atopic conditions: a cross-sectional study. *BMC Pediatr*. 2015;15:172.
30. Longo C, Bartlett G, Schuster T, Ducharme FM, MacGibbon B, Barnett TA. The obese-asthma phenotype in children: an exacerbating situation? *J Allergy Clin Immunol*. 2018;141(4):1239–1249.e4.
31. Quinto KB, Zuraw BL, Poon KY, Chen W, Schatz M, Christiansen SC. The association of obesity and asthma severity and control in children. *J Allergy Clin Immunol*. 2011;128(5):964–969.
32. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *BMJ*. 2015;351:h4672.
33. Gu H, Chen Y, He Z, Halper M, Chen L. Quality assurance of UMLS semantic type assignments using SNOMED CT hierarchies. *Methods Inf Med*. 2016;55(2):158–165.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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1

2 **Online Table 1. SAE rate (per 1000 PY) in the total asthma cohort and severe asthma cohort**

	Asthma				Severe asthma			
database	PY	Events	Exacerbation rate/ 1000 PY	95% CI	PY	Events	Exacerbation rate/ 1000 PY	95% CI
CPRD	405,911	19,530	48.1	(47.4, 48.8)	29,515	3,538	119.9	(116.0,123.9)
Female	165,274	7,839	47.4	(46.4, 48.5)	11,701	1,519	129.8	(123.4,136.5)
Male	240,637	11,691	48.6	(47.7, 49.5)	17,814	2,019	113.3	(108.5,118.4)
SIDIAP	94,979	18,808	198.0	(195.2,200.9)	3,178	1,191	374.7	(354.0,396.6)
Female	37,165	7,272	195.7	(191.2,200.2)	1,316	545	414.0	(380.7,450.3)
Male	57,813	11,536	199.5	(195.9,203.2)	1,862	646	346.9	(321.2,374.7)
IPCI	75,127	1,290	17.2	(16.3, 18.1)	3,928	264	67.2	(59.6, 75.8)
Female	30,855	547	17.7	(16.3, 19.3)	1,647	125	75.9	(63.7, 90.5)
Male	44,272	743	16.8	(15.6, 18.0)	2,281	139	60.9	(51.6, 72.0)
AARHUS	52,742	1,020	19.3	(18.2, 20.6)	4,186	201	48.0	(41.8, 55.1)
Female	19,388	430	22.2	(20.2, 24.4)	1,395	89	63.8	(51.8, 78.6)
Male	33,355	590	17.7	(16.3, 19.2)	2,792	112	40.1	(33.3, 48.3)
PEDIANET	29,737	1,031	34.7	(32.6, 36.9)	368	17	46.2	(28.7, 74.4)
Female	10,850	361	33.3	(30.0, 36.9)	94	3	31.9	(10.3, 99.0)
Male	18,887	670	35.5	(32.9, 38.3)	274	14	51.1	(30.3, 86.3)
HSD	11,649	1,461	125.4	(119.1,132.0)	2,329	335	143.8	(129.2,160.1)
Female	4,336	557	128.5	(118.2,139.6)	831	124	149.2	(125.1,177.9)
Male	7,313	904	123.6	(115.8,131.9)	1,498	211	140.8	(123.1,161.2)

3

4 **Online Table 2. Relative rates (IRR) for SAE, age and gender adjusted**

	CPRD			SIDIAP			IPCI			AARHUS			PEDIANET			HSD		
Characteristic	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P
Female Gender	0.98	(0.95,1.00)	0.0999	0.98	(0.95,1.01)	0.1908	1.06	(0.95,1.18)	0.3305	1.25	(1.11,1.42)	0.0004	0.94	(0.83,1.07)	0.3261	1.04	(0.94,1.16)	0.4744
Atopy	1.45	(1.41,1.49)	<.0001	1.11	(1.08,1.14)	<.0001	1.6	(1.43,1.78)	<.0001	2.32	(1.97,2.73)	<.0001	1.11	(0.97,1.28)	0.1312	0.93	(0.82,1.06)	0.2814
Nasal polyposis	0.97	(0.65,1.45)	0.8845	2.18	(1.24,3.84)	0.0069	1.38	(0.19,9.80)	0.7479	1.98	(0.28,14.10)	0.4939	.		.	0	(0.00, .)	0.9987
GERD	1.09	(1.01,1.18)	0.0335	1.52	(1.34,1.72)	<.0001	1.68	(1.18,2.38)	0.0039	0.96	(0.48,1.92)	0.9006	0.99	(0.61,1.60)	0.9712	0.98	(0.60,1.60)	0.9327
Diabetes Mellitus	1.26	(0.93,1.71)	0.1417	0.63	(0.34,1.16)	0.1382	0.31	(0.04,2.23)	0.2465	1.44	(0.60,3.47)	0.4167	0	(0.00, .)	0.9987	0	(0.00, .)	0.9987
Obesity	1.21	(1.17,1.25)	<.0001	0.9	(0.87,0.93)	<.0001	1.31	(1.03,1.66)	0.028	3.94	(2.86,5.43)	<.0001	1.02	(0.90,1.16)	0.7232	0.94	(0.75,1.18)	0.5969
Chronic rhinosinusitis	1.16	(1.08,1.25)	0.0001	0.83	(0.45,1.54)	0.5518	0.5	(0.13,2.02)	0.3329	.		.	.		.	0.77	(0.45,1.33)	0.3538
Smoking-current*	1.25	(1.12,1.40)	0.0001	1.73	(1.49,2.01)	<.0001	2.49	(1.44,4.29)	0.001	6.12	(1.02,36.72)	0.0476	.		.	1.83	(0.98,3.40)	0.0573
Smoking-past*	1.59	(1.45,1.75)	<.0001	0.84	(0.53,1.34)	0.4583	0.45	(0.06,3.26)	0.431	4.19	(0.70,25.18)	0.1171	.		.	0	(0.00, .)	0.9986
Smoking-unknown*	0.75	(0.73,0.78)	<.0001	0.97	(0.91,1.03)	0.2805	0.87	(0.66,1.15)	0.3235	0.07	(0.02,0.20)	<.0001	.		.	1.14	(0.94,1.40)	0.1875
Smoking-overall	.		<.0001	.		<.0001	.		0.0022	.		<.0001	.		.	.		0.1488
History of exacerbations	9.88	(9.58,10.20)	<.0001	2.77	(2.68,2.86)	<.0001	30.54	(26.43,35.29)	<.0001	25.2	(22.23,28.57)	<.0001	13.52	(11.61,15.74)	<.0001	6.47	(5.80,7.22)	<.0001

5 Analyses adjusted for age and gender except for gender .*current smoking as reference category

6 GERD= gastro esophageal reflux; CI= confidence interval

7 Online Table 3. Relative rates (IRR) for SAE, multivariate model after stratification for age
8

Age category		CPRD			SIDIAP			IPCI			AUH			PEDIANET			HSD		
		IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P	IRR	95% CI	P
5-11	Age	0.9	(0.89, 0.91)	<.0001	0.81	(0.81, 0.82)	<.0001	0.91	(0.88, 0.95)	<.0001	0.87	(0.84, 0.91)	<.0001	0.94	(0.91, 0.97)	0.0003	1.1	(0.87, 1.38)	0.4298
	Female gender	0.92	(0.88, 0.95)	<.0001	0.95	(0.92, 0.98)	0.0023	0.83	(0.71, 0.97)	0.016	0.9	(0.76, 1.06)	0.2101	0.9	(0.78, 1.03)	0.1121	1.03	(0.73, 1.47)	0.8617
	Atopy	1.34	(1.29, 1.39)	<.0001	1.11	(1.08, 1.15)	<.0001	1.59	(1.37, 1.83)	<.0001	2.19	(1.74, 2.75)	<.0001	1.25	(1.08, 1.45)	0.0028	0.73	(0.44, 1.21)	0.2226
	GERD	1.16	(1.05, 1.27)	0.0031	1.47	(1.29, 1.66)	<.0001	2	(1.36, 2.94)	0.0004	1.75	(0.87, 3.52)	0.1185	0.79	(0.46, 1.36)	0.3941	7.46	(1.81, 30.70)	0.0054
	Obesity	1.18	(1.13, 1.24)	<.0001	0.92	(0.89, 0.95)	<.0001	1.31	(0.86, 1.99)	0.2031	1.89	(1.23, 2.88)	0.0033	1.01	(0.89, 1.15)	0.8659	0.77	(0.24, 2.50)	0.6663
	History of exacerbations	8.32	(8.01, 8.65)	<.0001	2.71	(2.62, 2.80)	<.0001	26.7	(22.17, 32.15)	<.0001	27.55	(23.42, 32.40)	<.0001	13.89	(11.82, 16.32)	<.0001	10.73	(7.64, 15.08)	<.0001
12-17	Age	0.92	(0.91, 0.93)	<.0001	0.79	(0.77, 0.81)	<.0001	1.13	(1.08, 1.19)	<.0001	1.09	(1.03, 1.16)	0.0029	0.89	(0.60, 1.31)	0.5416	0.98	(0.95, 1.02)	0.3689
	Female gender	1.21	(1.16, 1.27)	<.0001	1.09	(0.99, 1.20)	0.0666	1.46	(1.23, 1.73)	<.0001	1.62	(1.33, 1.97)	<.0001	1.05	(0.71, 1.56)	0.8162	1.02	(0.92, 1.14)	0.6877
	Atopy	1.43	(1.37, 1.50)	<.0001	0.9	(0.80, 1.00)	0.0518	1.44	(1.22, 1.71)	<.0001	1.89	(1.49, 2.39)	<.0001	0.66	(0.39, 1.10)	0.1081	0.94	(0.83, 1.08)	0.3998
	GERD	1.21	(1.04, 1.41)	0.0115	2.39	(1.36, 4.23)	0.0026	0.69	(0.28, 1.65)	0.4008	0	(0.00, .)	0.999	3.81	(1.37, 10.63)	0.0106	0.97	(0.57, 1.64)	0.9036
	Obesity	1.33	(1.26, 1.40)	<.0001	0.79	(0.72, 0.87)	<.0001	1.15	(0.86, 1.55)	0.3452	2.42	(1.47, 3.99)	0.0006	1.07	(0.73, 1.58)	0.7144	0.93	(0.74, 1.18)	0.5525
	History of exacerbations	13.99	(13.27, 14.74)	<.0001	4.23	(3.67, 4.87)	<.0001	34.08	(27.04, 42.94)	<.0001	19.95	(16.21, 24.55)	<.0001	10.28	(6.42, 16.48)	<.0001	6.09	(5.42, 6.85)	<.0001

9 Online supplement: Description of databases

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

20 The Health Search CSD Longitudinal Patient Database (HSD), is a longitudinal
21 observational database that is representative of the Italian general population. HSD
22 contains data from computer-based patient records from a selected group of GPs
23 (covering a total of 1.5 million patients) located throughout Italy. The database includes
24 information on age, gender, patient and GP identification, which is linked to prescription
25 information, clinical events and diagnoses and date of death. All diagnoses are coded
26 according to the International Classification of Diseases, 9th Revision. Drug names are
27 coded according to the ATC classification. ^(1, 2)

28 In 1998 Pedianet has been established in Italy to collect epidemiological information for
29 clinical research from family paediatricians. Pedianet is a paediatric general practice
30 research database that contains the clinical, demographic, prescription and outcome
31 data of the children routinely seen by about 130 PCPs equally distributed throughout
32 Italy (all Italian children aged less than six years are registered with a PCP as part of the
33 country's national health service), and which has been used for various epidemiological
34 and pharmacovigilance studies. The data are generated during routine patient care
35 using common software, and are anonymously sent monthly to a centralised database
36 for validation. The reasons for the contacts and diagnoses (free text or coded using the
37 ICD-9 system) are recorded in the medical file, and the database also contains
38 information about specialist referrals, procedures, hospitalizations, medical
39 examinations, health status (according to the Guidelines of Health Supervision of the
40 American Academy of Paediatrics), and centile diagrams.

41 Clinical Practice Research Datalink (CPRD) is a large validated computerized database
42 of anonymized longitudinal medical records for primary care. Data comprise
43 approximately 12 million patients with around 5.4 million of these being currently alive
44 and registered from 680 primary care practices spread throughout the UK. The
45 database contains the entire anonymized electronic medical record of each patient,
46 including medical codes associated with consultations and referrals; details of all
47 medications prescribed; life style factors and laboratory tests. ⁽³⁾ Information on
48 hospitalization is collected through linkage HES and information on mortality is retrieved
49 through linkage with the Office of National Statistics (ONS) Mortality data.

50 The Aarhus University Prescription Database comprises clinical and prescription data
51 from the Central Denmark Region and the North Denmark Region. This population

covers a total of 1.2 million inhabitants and is representative of the population of Denmark ⁽⁴⁾. Data are available on demographics, life style 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 of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures.

The SIDIAP 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 factors, laboratory test results, and hospital admissions and their major outcomes.⁽⁵⁾

68 **Online supplement:**

69 **Asthma**

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

72

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			663N.00 663N000 663N100 663N200	
Asthma disturbs sleep frequently			663O.00	
Asthma not disturbing sleep			663O000	
Asthma never disturbs sleep			66YP.00	
Asthma night-time symptoms			66Yq.00	
Asthma causes night time symptoms			66Yr.00	
Asthma causes symptoms most nights			66Ys.00	
Asthma never causes night symptoms				
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 hospitalization for reasons of asthma exacerbation. To identify patients with a severe asthma exacerbation defined as ED visit or hospitalization 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 hospitalization. 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	493.01	H33z000
	J45.22	493.11	
	J45.32	493.21	
	J45.42	493.91	
	J45.52		
	J45.902		
Severe asthma attack			H33z011
Asthma accident and emergency attendance since last visit			663m.00
Emergency asthma admission since last appointment			663d.00

87

88 Atopy

89 Atopy is defined as any of the following: atopic dermatitis/eczema or allergic rhinitis.

90 The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for
91 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	

92 *means all codes falling under this category

93 Chronic rhinosinusitis

94 The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for
95 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

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

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*

108 *means all codes falling under this category

109 In addition, BMI was retrieved from the measurement table in all databases.

110 Cut-off values for obesity or overweight were as following:

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

111

112

113 **Online supplement:**

114 **Cut off values for high ICS dose**

Drug	Daily dose (mcg)
Adolescents (≥12 years)	
Beclometasone dipropionate (HFA)	>400
Budesonide (DPI)	>800
Ciclesonide (HFA)	>320
Fluticasone furoate (DPI)	≥200
Fluticasone propionate (DPI)	>500
Fluticasone propionate (HFA)	>500
Mometasone furoate	>440
Triamcinolone acetonide	>2000
Children <12 years	
Beclometasone dipropionate (HFA)	>200
Budesonide (DPI)	>400
Budesonide (nebules)	>1000
Ciclesonide	>160
Fluticasone propionate (DPI)	>400
Fluticasone propionate (HFA)	>500
Mometasone furoate	≥440
Triamcinolone acetonide	>1200

115 DPI: dry powder inhaler, HFA: hydrofluoroalkane propellant

116 Global Initiative for Asthma (GINA) 2018, box 3-6