



Real life data on incidence and risk factors of severe asthma exacerbations in children in primary care



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ABSTRACT

Real-life data on the incidence rates (IR) and risk factors of severe asthma exacerbations in children are sparse. We aimed to assess IR and risk factors of severe asthma exacerbations in children in real life.

We conducted a population-based cohort study using a Dutch GP database containing complete medical records of >1 million patients. All records of children with physician-diagnosed asthma aged 5–18 years between 2000 and 2012 were examined for exacerbations, defined as either hospitalization, emergency department visit or need of systemic steroids for asthma. IR was expressed as number of exacerbations per person year (PY).

We identified 14,303 asthmatic children with 35,118 PY of follow-up and 732 exacerbations. The overall IR was 2.1/100PY (95% CI 1.9–2.2), 4.1/100PY (3.8–4.4) for children on asthma treatment. Re-exacerbation occurred in 2% (1.3–4.3) of patients within 1 month, in 25% (20.6–28.8) within 1 year. Predictors for (frequent) exacerbations were age, medication use and prior exacerbations (all $p < 0.001$).

The overall IR of severe asthma exacerbations was 4/100PY in children on asthma treatment, highest in spring and fall. 25% of the patients with an exacerbation will experience a next exacerbation within 1 year. More severe asthma is a predictor of subsequent and future exacerbations.

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1. Introduction

Asthma continues to be a public health concern due to its high prevalence in industrialized countries [1,2]. Poor asthma control resulting from inadequate treatment or non-response to available treatments was associated with adverse long-term outcomes [3]. Asthma can usually be well controlled by treatment as described in asthma management guidelines [4]. A severe asthma exacerbation is defined as a hospitalization or emergency department (ED) visit because of worsening asthma, or need of systemic corticosteroids because of asthma [5]. Reported frequencies of severe asthma exacerbations in the literature vary by the definition of an exacerbation, patient population, the severity of asthma, degree of asthma control, and the data source and incidence rates (IR) are sparse [6]. Most data on IR of severe asthma exacerbation derive from adults in clinical trials. These showed IRs ranging between 0.24 and 0.92/PY

[7–11] and in cross-sectional data, IRs that ranged between 0.23 and 0.41/PY [12,13]. As far as we know, only 4 studies investigated the rate of exacerbation in children, showing IR ranging from 0.04 to 0.64/PY. This broad range can be explained by differences in patient selection, sample size or study duration [7,14,15]. Asthma related hospitalization rates in asthmatic children ranged from 4 to 15% per year, depending on factors like age, sex, and asthma severity [12,16]. The CAMP study observed an exacerbation-requiring-hospitalization-rate of 2.5/100 PY in children from 5 to 12 years of age with mild-to-moderate asthma [17]. Surveys in real-life indicated that the true incidence of severe asthma exacerbations may be higher than in clinical trials [6]. Insight in the real life incidence of severe asthma exacerbations and characteristics of children with frequent exacerbations is important to optimize management in those who are prone to exacerbations. Hence, the purpose of the present study was to evaluate the incidence of severe asthma exacerbations and to identify characteristics of children with severe asthma exacerbations over a 12 year period in a large cohort of children with physician-diagnosed asthma.

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2. Methods

We conducted a retrospective population-based cohort study within the Integrated Primary Care Information (IPCI) database, a longitudinal observational dynamic database containing the complete electronic medical records of more than 450 general practitioners (GPs) throughout the Netherlands, the study population and the GPs participating in the study are representative for the Dutch population. In the Dutch health care system, people are registered with a single GP who has a crucial role as a gatekeeper for and receiver of information from secondary care [18]. Details of the database have been published elsewhere [19,20]. Briefly, the database contains the complete electronic medical records of approximately 1,500,000 patients, containing anonymous longitudinal data on demographics, symptoms and diagnosis in coded and free text, referrals, laboratory findings, discharge letters, and drug prescriptions. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiological studies [20]. The scientific and ethical advisory board of the IPCI database approved the present study. (no 07/55 2011).

2.1. Asthma cohort

The dynamic source population ($n = 176,516$) comprised all children aged 5–18 years with a database history of at least 12 months. The study period was from the 1st of January 2000 until the 1st of January 2012.

Within this population a cohort of children with asthma was identified. Asthma cases were retrieved by an automated search on both International Classification of Primary Care asthma codes [21] (ICPC code, R96) and free text that was relevant to asthma. Asthma was defined as “definite” if diagnosed by a pediatrician. “Probable asthma” was defined as asthma diagnosed by the GP with at least 2 additional records/prescriptions of asthma medications in the 1 year following the initial diagnosis of asthma. A patient was labeled to have “possible asthma” in case of only 1 asthma record or inconsistency between records. Children were classified as not having asthma if the identified symptoms were not related to asthma or if the symptoms could be ascribed to other respiratory conditions (e.g. pneumonia, cystic fibrosis). If at any time during the follow-up asthma was diagnosed, the child was considered asthmatic from date of first diagnosis until the end of follow-up.

As this automated search resulted in a high number of potential asthma cases ($n = 63,618$), we used machine learning to facilitate the validation, as described in detail elsewhere [22]. Follow-up started on the latest of the following dates: start of study period, date on which the required 1 year of follow-up was obtained, the 5th birthday, or date of asthma diagnosis (for prevalent asthma cases, who had diagnosis before start of study period asthma diagnosis was not used as criterion) All patients were followed from study entry until the earliest of the following dates: end of the study period, transferring out of GP practice or age 18 years.

2.2. Severe asthma exacerbations

Severe asthma exacerbations were defined as any of the following; hospitalization, emergency department (ED) visit, or prescription of systemic corticosteroids for at least 3 days, all because of asthma. In case there were less than 7 days between two exacerbations, these were considered as one single exacerbation.

All potential exacerbations were identified in the electronic medical records and validated by a medical doctor (ME). To identify patients with ED visit or hospitalization for reasons of asthma, the medical file was searched for asthma-specific disease codes in

combination with information on hospitalization, hospital referral and discharge letters. Use of systemic corticosteroids was retrieved from prescriptions via an automated search on the corresponding ATC codes. The indication of use was searched for in a window of 7 days before and 7 days after the prescription date.

2.3. Covariates

Covariates included age at study start, gender, age at time of exacerbation, eczema (ICPC code S87), allergic rhinitis (ICPC code R97), conjunctivitis (ICPC code F71), number of respiratory infections, number of prescriptions for any asthma medication, number of prescriptions for inhaled corticosteroids (ICS), eosinophil count (<150 cells/uL, $150–300$ cells/uL, ≥ 300 cells/uL and eosinophil count unknown) number of specialist visits for asthma and number of prior severe asthma exacerbations. Comorbidity was assessed by searching for the respective ICPC disease codes in the patient's file. Baseline covariates were retrieved in the 365 days prior to cohort entry.

2.4. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD). We used t -test, χ^2 test or Mann-Whitney test to compare baseline characteristics of children with and without exacerbations.

Three different regression techniques were used: (1) Poisson regression for count outcomes (=count of exacerbation), (2) Logistic regression for the binomial outcome (comparison of episodes with <2 exacerbations to episodes with ≥ 2 exacerbations) and (3) Cox regression for time to first exacerbation. The techniques are discussed in more detail below.

2.5. Rates of exacerbations

For each child the person time (in years, PY) of follow-up was stratified by calendar year, calendar month, gender and age (on January 1st of each year). Because of the dynamic nature of the population we used PY rather than persons. The incidence rate (IR) of exacerbations was calculated by dividing the number of exacerbations by the person time.

To assess seasonal effects monthly IRs were compared. Then to further assess interaction of seasonal rates with age, we compared monthly IRs in primary school (<13 years) and high school children (≥ 13 years of age) using Poisson regression.

IR for re-exacerbation was assessed in the following time-windows: 0–30, 0–90, 0–180 and 0–365 days after exacerbation, and in subsequent 90 day time-windows: 0–90, 90–180, 180–270 and 270–365 days. Cumulative incidences for re-exacerbation were calculated by multiplying the IR with the time duration.

2.6. Risk factors for exacerbations

Risk factors for exacerbations were estimated using Poisson regression. For the analysis of the total cohort, follow-up of each child was divided in episodes by year of age, the first episode started at the date of asthma diagnosis, or study entry whichever came last. For analysis of episodes after a previous exacerbation, follow up started was at the first exacerbation or at study entry (for prevalent cases), whichever was last. Subsequent episodes started at each birthday. Covariates were retrieved during the 365 days prior to the start of each episode and could change over time for the different episodes. The analysis incorporated the potential effect of age, gender and interaction between age and gender. Age was introduced as a quadratic term as the relation between age and

exacerbation IR was a parabolic function (online Fig. 1). First univariate analyses were performed, adjusted for age. Second, a multiple regression was conducted with all covariates with a p-value <0.10 in the first analysis. Poisson regression analyses were repeated in the subgroup of patients with 1 or more exacerbations before or during follow-up.

Logistic regression was used to evaluate possible predictors of frequent exacerbations by comparing episodes with ≥ 2 versus <2 exacerbations per episode. A sensitivity analysis was done using ≥ 3 versus <3 exacerbations per episode. First univariate analyses were performed, adjusted for age. Second, a multiple regression was conducted with all covariates with a p-value <0.10 in the first analysis.

Finally, a Cox regression was performed to determine risk factors for first exacerbation. For this analysis, only time to first severe asthma exacerbation during follow-up was considered. First univariate analyses were performed, adjusted for age and gender. Second, a multiple regression was conducted with all covariates with a p-value <0.10 in the first analysis.

A p-value of <0.05 was considered statistically significant. Analyses were conducted with SPSS 20.0 for Windows (SPSS Inc Chicago).

3. Results

The source population comprised 176,516 children aged 5–18 years. After validation the asthma cohort consisted of 14,303 asthmatic children with 35,118 PY of follow-up (median 2.33 PY), resulting in a prevalence of 6.7%.

Baseline characteristics of the asthma cohort and cases with exacerbation (n = 481) are described in Table 1. Cases had a total of 733 exacerbations during follow-up, the median number of exacerbations per patient was 1 (range 1–18). Detailed numbers of

exacerbations and follow-up time of the cases are shown in online Table 1.

The overall incidence rate of exacerbations was 2.1 per 100 PY (95%CI 1.9–2.2) and increased to 4.1 when restricted to children who did not only had a diagnosis of asthma but had also medications (Fig. 1). In both groups the rate was highest in the youngest and oldest children. ($p < 0.001$ for quadratic term with age). The IR did not change over different years in the study period ($p = 0.19$) (Fig. 2). Significant seasonal effects ($p = 0.005$ for calendar month) were observed with peaks in March–April and September–November, with highest rates (IR = 2.8/100 PY) in November and lowest (IR = 1.6/100 PY) in June. (Fig. 3). The seasonal effect was not significantly different between pre-school or high-school aged children. (data not shown).

3.1. Re-exacerbation

The incidence rate of re-exacerbation was constant over time. The cumulative incidence shows that within one year of a severe asthma exacerbation, 25% (95%CI 20.55–28.82) of the patients will have a new exacerbation (Online Table 2).

3.2. Risk factors

Risk factors for severe asthma exacerbations estimated by Poisson regression analyses are shown in Table 2. Each Poisson model included age and age². As both gender and the interaction term between age and gender were not significant, we did not include these. Covariates that remained independent risk factors of exacerbations after adjustment for age in the univariate models were number of visits to the specialist, number of prescriptions of any asthma medication and specifically of ICS, and number of exacerbations in the previous year. No significant associations were

Table 1
Baseline characteristics of the total asthma cohort and of the subgroups without and with exacerbation during follow-up.

Baseline characteristics (N,%) unless stated otherwise	Total asthma cohort	≥ 1 exacerbation during FU	No exacerbation during FU	p-value ^b
Patients (N)	14,303	481	13,822	
Gender (female)	5,903 (41.3)	196 (40.7)	5,707 (41.3)	ns
Age at cohort entry (years) (mean, sd)	10.5 (4.1)	10.1 (3.8)	10.5 (4.1)	0.016
Follow-up (years) (mean, sd)	2.46 (1.56)	1.17 (1.25)	2.44 (1.55)	<0.001
<i>Prior to cohort entry:</i>				
Conjunctivitis	821 (5.7)	26 (5.4)	795 (5.8)	ns
Eczema	3,852 (26.9)	159 (33.1)	3,693 (26.7)	0.002
Allergic rhinitis	2,541 (17.8)	77 (16.0)	2,464 (17.8)	ns
Exacerbations ever	1,868 (13.1)	481 (100.0)	1,387 (10.0)	<0.001
<i>In 12 months prior to cohort entry:</i>				
Exacerbations	415 (2.9)	129 (26.8)	286 (2.1)	<0.001
Pediatrician visits for asthma (yes/no)	995 (7.0)	103 (21.4)	892 (6.5)	<0.001
Prescription for asthma medication ^a	9,275 (64.8)	410 (85.2)	8,865 (64.8)	<0.001
Children on ICS	5,547 (38.8)	262 (54.5)	5,285 (38.2)	<0.001
Children on LABA	292 (2.0)	27 (5.6)	265 (1.9)	<0.001
- LABA + ICS	211 (1.5)	24 (5.0)	187 (1.4)	
- LABA only	81 (0.6)	3 (0.6)	78 (0.6)	
Children on LTRA	357 (2.5)	40 (8.3)	317 (2.3)	<0.001
Children on FDC-LABA/ICS	1,481 (10.4)	81 (16.8)	1,400 (10.1)	<0.001
Children on SABA	7,027 (49.1)	345 (71.7)	6,682 (48.3)	<0.001
Blood eosinophilia				0.026
- unknown	13,434 (94)	450 (94)	12,983 (94)	
- <150 cells/uL	197 (1)	2 (0.4)	195 (1.4)	
- 150 to <300 cells/uL	244 (2)	6 (1.2)	238 (1.7)	
- ≥ 300 cells/uL	429 (3)	23 (4.8)	406 (2.9)	

N = number, FU = follow up, % = percentage, sd = standard deviation, ns = not significant.

ICS = inhaled corticosteroids, LABA = long acting β_2 agonists, LTRA = leukotriene receptor antagonist, FDC-LABA/ICS = fixed dose combination SABA = short acting beta agonists.

^a asthma medication consisting of prescriptions for ICS, LABA, LTRA, fixed combination LABA/ICS, SABA, cromoglycate, LAMA, SAMA and SAMA combination – The 4 last categories are not presented separately as numbers were low.

^b P-value based on the χ^2 or t-test comparing characteristics of the patients with no exacerbation during follow-up with patients with ≥ 1 exacerbation during follow-up.

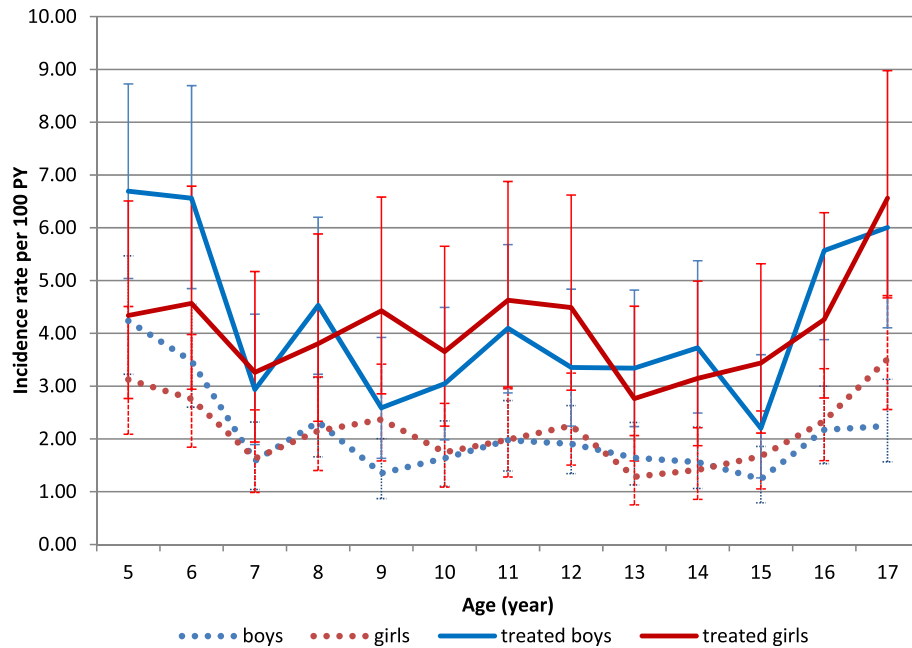


Fig. 1. Incidence rate with 95% CI for exacerbation by age and gender, all children and children on asthma treatment (≥ 1 prescription for asthma medication during follow-up).

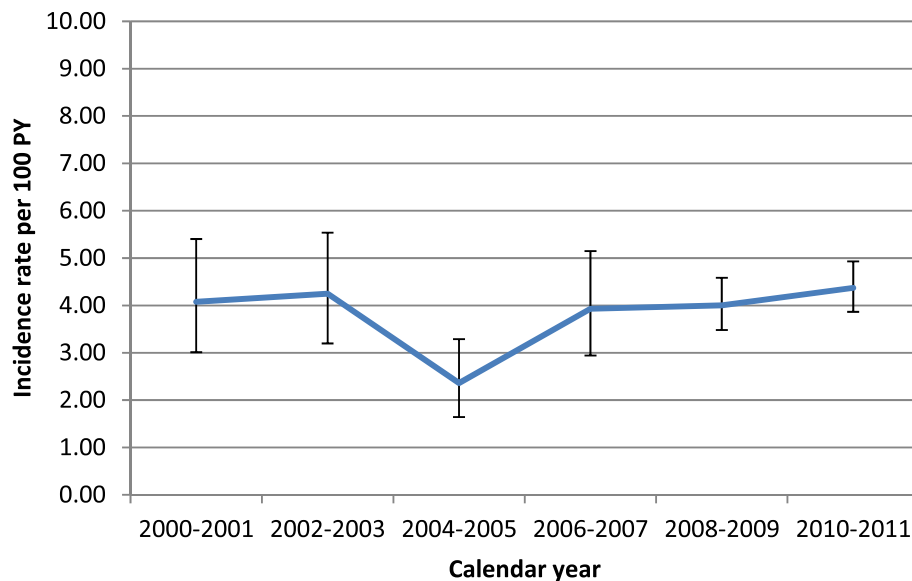


Fig. 2. Severe asthma exacerbation incidence rates with 95% CI for treated cohort by calendar year.

observed with gender, blood eosinophilia, eczema, allergic rhinitis, conjunctivitis, or respiratory infections. In the multivariate model, exacerbations in the previous year and use of any asthma medication remained significant. When repeating the Poisson regression analyses in only patients with exacerbations, the same risk factors as in the total cohort were found (Table 2).

Factors that were associated with frequent exacerbation episodes estimated by univariate logistic regression, were specialist visits, prescriptions of any asthma medication, prescriptions of ICS and exacerbations during the previous year (Table 3). In the multivariate model, use of any asthma medication and exacerbation during the previous year remained significant.

Eczema, respiratory infections, eczema, high blood eosinophilia (≥ 300 cells/ul), specialist visits for asthma, exacerbations, and ICS

prescriptions were significant predictors adjusted for gender and age and their interaction, when studying predictors of first exacerbation during follow-up using Cox-regression, both in the univariate analysis as well as in the multivariate analysis (Table 4).

4. Discussion

This longitudinal population-based study covering 12 calendar years showed patterns, rates and risk factors of asthma exacerbations and demonstrated rates vary by season but are similar over the 12 calendar years, the most important risk factor/predictor of exacerbation is having a prior exacerbation. Patients with an exacerbation have 25% chance to have a subsequent exacerbation within a year.

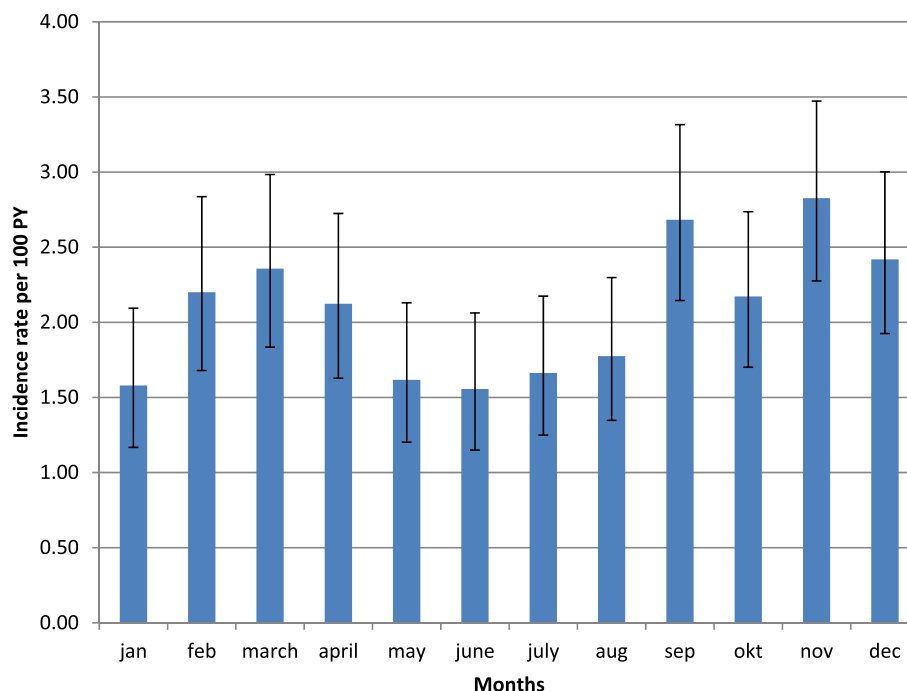


Fig. 3. Severe asthma exacerbation incidence rates with 95% CI by calendar month for the total asthma cohort.

Table 2

Risk factors for severe asthma exacerbation for all episodes of the total asthma cohort and for episodes of children with ≥ 1 severe asthma exacerbation.

	Total asthma cohort				Children with ≥ 1 exacerbation ever			
Patients (N)	14,303				1868			
Episodes (N)	46,423				5940			
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Basic model:								
Age	0.67	0.48–0.92	0.68	0.50–0.92	0.72	0.54–0.96	0.75	0.57–1.00
Age ²	1.02	1.00–1.03	1.02	1.00–1.03	1.02	1.00–1.03	1.01	1.00–1.03
	Model 1		Model 2		Model 1		Model 2	
Gender	1.02	0.69–1.50	Na		0.86	0.59–1.26	Na	
Conjunctivitis	1.36	0.70–2.65	Na		1.15	0.62–2.14	Na	
Eczema	0.76	0.42–1.36	Na		0.68	0.39–1.18	Na	
Allergic rhinitis	0.75	0.47–1.21	Na		0.75	0.47–1.18	Na	
Respiratory infections	1.04	0.97–1.12	Na		1.03	0.97–1.10	Na	
Blood eosinophilia								
- unknown	0.68	0.14–3.29	Na		0.95	0.17–5.34	Na	
- <150 cells/uL	Ref	Ref	Na		Ref	Ref	Na	
- 150 to <300 cells/uL	1.06	0.18–6.12	Na		2.74	0.34–22.15	Na	
- ≥ 300 cells/uL	1.91	0.33–10.92	Na		3.04	0.48–19.41	Na	
Specialist visits for asthma	1.66	1.33–2.07	0.91	0.64–1.29	1.25	1.16–1.34	1.01	0.87–1.18
Prior exacerbations	1.99	1.40–2.83	2.17	1.30–3.60	1.60	1.37–1.88	1.52	1.19–1.94
ICS prescriptions*	1.25	1.18–1.33	1.01	0.89–1.15	1.16	1.09–1.22	0.98	0.88–1.09
Any asthma treatment	1.16	1.12–1.19	1.14	1.06–1.22	1.10	1.07–1.13	1.10	1.05–1.16

N = number, RR = relative rate, 95%CI = 95% confidence interval Na = not applicable. Estimates in bold are statistically significant. Model 1 = adjusted for age and age², model 2 = adjusted for age, age², specialist visits, prior exacerbations, ICS prescriptions and any asthma treatment. *p < 0.05.

Our asthma exacerbation incidence rates are consistent with the rates observed in the CAMP study [17] and study of Blais et al. [7] Zeiger et al. studied a cohort of children with persistent asthma and reported a threefold higher rate than we observed [15], this may be explained by their inclusion of only patients with severe asthma. The annual IR of exacerbation remained stable over time, which is in line with recent findings in a cohort of asthmatic adults, where the number of exacerbations per subject per year did not change between 2007 and 2011 [23]. An earlier study showed a decrease in hospital admissions over time, however this study used data from 1990 to 2001 [24]. Our study confirms seasonal

variability within a year with exacerbation peaks in spring and autumn. Exposure to grass pollen and other aeroallergens (e.g. elm, alder and willow pollen in March) may account for the observed peaks. In September the increase was more obvious among children of kindergarten- and school age although the interaction with age was not significant. In other studies this September peak was related to the start of the school year [6].

In the present study, the most important risk factors for severe asthma exacerbation and frequent exacerbations were prior exacerbation, which is in agreement with prior studies [9,23,25] Other risk factors of severe asthma exacerbation were the number of ICS

Table 3

Risk factors for frequent exacerbation episodes compared to non frequent exacerbation episodes.

Episodes (N)	<2 versus ≥2 exacerbations				<3 versus ≥3 exacerbations			
	5,801 versus 139				5,873 versus 67			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Basic model:								
Age	0.77	0.55–1.06	0.81	0.57–1.15	1.02	0.63–1.65	1.13	0.68–1.89
Age ²	1.01	1.00–1.03	1.01	1.00–1.03	1.00	0.98–1.02	1.00	0.97–1.02
Adjusted	Model 1		Model 2		Model 1		Model 2	
Gender	1.06	0.70–1.61	Na		1.07	0.58–1.96	Na	
Eczema	0.65	0.30–1.39	Na		0.90	0.37–2.16	Na	
Allergic rhinitis	0.70	0.34–1.44	Na		0.82	0.30–2.23	Na	
Respiratory infections	0.99	0.89–1.10	Na		1.05	0.93–1.20	Na	
Blood eosinophilia								
- unknown	1.56	0.20–12.30	Na		0.63	0.11–3.78	Na	
- <150 cells/uL	Ref	Ref	Na		Ref	Ref	Na	
- 150 to <300 cells/uL	3.71	0.39–35.28	Na		0.70	0.04–10.92	Na	
- ≥300 cells/uL	4.34	0.54–34.60	Na		2.10	0.30–14.85	Na	
Specialist visits								
because of asthma	1.31	1.15–1.50	1.00	0.80–1.25	1.47	1.28–1.69	1.11	0.88–1.41
Exacerbations	2.11	1.66–2.68	1.93	1.42–2.63	2.43	1.84–3.23	1.99	1.35–2.94
ICS prescriptions	1.15	1.08–1.24	0.92	0.79–1.07	1.21	1.12–1.31	1.02	0.86–1.22
Any asthma treatment	1.11	1.08–1.15	1.14	1.06–1.22	1.12	1.08–1.17	1.09	1.01–1.19

N = number, OR = odds ratio, 95%CI = 95% confidence interval, Na = not applicable as not significant in model 1.

Estimates in bold are statistically significant. Model 1 = adjusted for age and age² model 2 = adjusted for age, age², specialist visits, prior exacerbations, ICS prescriptions and any asthma treatment.**Table 4**

Risk factors for time until an exacerbation (Cox-regression).

	HR	95% CI	HR	95% CI
Gender	0.57	0.33–0.96	0.79	0.47–1.35
Age	0.97	0.94–1.00	1.02	0.98–1.05
Age * gender	1.06	1.01–1.11	1.03	0.98–1.08
Variables retrieved prior to baseline				
	Model 1		Model 2	
Conjunctivitis	0.94	0.63–1.39	Na	
Eczema	1.28	1.06–1.55	1.26	1.04–1.52
Allergic rhinitis	0.92	0.72–1.18	Na	
Respiratory infections within 1year prior to baseline	1.13	1.05–1.21	1.09	1.02–1.17
Specialist visits because of asthma within 1year prior to baseline	2.53	2.24–2.85	1.19	1.02–1.40
Exacerbations within 1year prior to baseline	4.04	3.68–4.43	3.73	3.24–4.31
ICS prescriptions within 1year prior to baseline	1.18	1.14–1.23	1.17	1.12–1.22
Blood eosinophilia				
- unknown	2.93	0.73–11.76	2.89	0.72–11.62
- <150 cells/uL	Ref	Ref	Ref	Ref
- 150 to <300 ce	2.37	0.48–11.76	1.94	0.39–9.64
- ≥300 cells/uL	5.26	1.24–22.34	4.66	1.10–19.80

HR = hazard ratio, 95%CI = 95% confidence interval, Na = not applicable as not significant in model 1.

Variables in bold are statistically significant.

Model 1 = adjusted for age, gender and age*gender. Model 2 = adjusted for age, gender, age*gender, eczema, respiratory infections, specialist visits, prior exacerbations, and ICS prescriptions.

prescriptions and the number of specialist visits, factors which we consider as proxy for asthma control. There is evidence that other comorbidities e.g. environmental factors such as smoking, and disease symptoms are associated with a risk of severe asthma exacerbations, however these were not available in our database. Also, in contrast to other publications, we did not observe an association between allergic rhinitis and risk of severe asthma exacerbations [26,27]. However the association between allergic rhinitis and asthma exacerbation is probably influenced by treatment and especially control of allergic rhinitis which was difficult to assess in our database. As is reflected in the fact that the incidence of allergic rhinitis in this pediatric asthma cohort was much lower compared to adult cohorts in which this association was observed.

In line with other publications, we observed that high eosinophil counts is a risk factor of severe asthma exacerbation [27].

However, in our dataset, the number of asthma children for which eosinophil counts were available was low (6%) explaining why the association between high eosinophil levels and outcomes such as repeated exacerbations is not always statistically significant.

The main strength of the present study is the size of the cohort with more than 14,000 children with asthma and the validation of the asthma diagnosis and asthma exacerbations which limits the risk of false positives. Incidence and prevalence rates of asthma are in agreement with international data. Selection bias was unlikely as almost all inhabitants of the Netherlands are registered with one GP and data are collected as part of routine patient care, irrespective of any research question. Still, as this is an observational study using data from electronic healthcare data, the risk of bias and/or confounding is substantial. As the IPCI database has no linkage with hospital admission- and discharge data, hospitalization and ED visits for asthma were retrieved either via disease-

specific codes in combination with codes for hospitalization or via review of the discharge letters. Within the prescription file, information on the indication of prescribing of systemic corticosteroids was not always complete. If missing, we searched for asthma disease codes in a window of 7 days before or after the prescription date. Treatment information may be misclassified as the database captures prescribing data not dispensing data, patients can refill the drugs but may not actually take the drugs, and specialist initiated prescriptions may be missed if this is not captured in the records. Both issues might underestimate the number of exacerbations, however this was probably minimal as in the Netherlands, the GP plays a central and coordinating role in patient's care. This implies that if a patient wants to see a specialist, a referral is needed from the GP. The GP is thus informed about all specialist visits and prescriptions as initiated by the specialist will often be continued by the GP [28]. Another reason why our number of exacerbations was considerably low, is the fact that we used a lifetime definition of asthma, instead of an episodic definition. In our data set it was not possible to identify whether a patient had asthma in remission as the ICPC codes do not have a code for resolved asthma in contrast to e.g. the READ codes in the UK. This might lead to an overestimation of the prevalence of 'active' asthma and consequently an underestimation of the rate of exacerbations patients with asthma. The overestimation of "active asthma" also explains why the incidence rate of asthma exacerbations was higher in patients on asthma medications which is not only a proxy of more severe asthma but also a proxy of "active asthma".

What is the clinical relevance of our findings? This study showed that 4 out of 100 children on asthma treatment will have a severe asthma exacerbation when followed over 1 year. Furthermore, 25% of all children with an asthma exacerbation will have a next exacerbation within 1 year. In this study the IR of exacerbation was stable over time, which suggest that treatment should not be stepped down up to one year after exacerbation, especially in frequent exacerbaters, however this might be confounded by recent guidelines that asthma medications should be increased directly after exacerbation and stepped down 6 months thereafter. The most important risk factors for exacerbations were prior exacerbations, which emphasizes the importance of close monitoring of children after a severe asthma exacerbation.

Authors' contributions

All authors contributed extensively to the work presented in this paper. ME, HJ, KV and MR analysed data and wrote the manuscript, KV, MS and JC designed the study and supervised the project.

Conflict of interest statements

ME has nothing to disclose, JJ had nothing to disclose. HJ received grants outside the submitted work from Philips, Chiesi, Novartis, and Gilead. MR received grants outside the submitted work from Novartis and GSK. MS received grants outside the submitted work from Novartis, Boehringer, Pfizer, and GSK. KV had received grants outside the submitted work from Novartis Pfizer, Yanouchi, and GSK.

Role of funding source

Zonmw (funder) did not have a role in this research.

Ethics committee approval

The scientific and ethical advisory board of the IPCI database

approved the present study. (no 07/55 2011).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.08.016>.

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Online Table 1. Number of exacerbations, follow up time, cases and incidence rate per gender, per total asthma cohort and per patients with asthma treatment.

agecategory	gender	All patients			Patients with treatment		
		exacerbations (n)	Follow up time (days)	Incidence rate all	exacerbations (n)	Follow up time (days)	Incidence rate treated
5	1	55	474358	4.23	51	278318	6.69
5	2	26	303910	3.12	21	176770	4.34
6	1	49	514926	3.48	45	250565	6.56
6	2	26	344359	2.76	22	175976	4.57
7	1	24	552919	1.59	22	273825	2.93
7	2	17	380984	1.63	16	179198	3.26
8	1	37	582058	2.32	36	290184	4.53
8	2	23	390387	2.15	18	172814	3.80
9	1	22	595705	1.35	20	282048	2.59
9	2	26	400987	2.37	22	181475	4.43
10	1	27	603820	1.63	23	275847	3.05
10	2	19	397315	1.75	18	179945	3.65
11	1	34	628654	1.98	33	294192	4.10
11	2	22	404889	1.98	22	173729	4.63
12	1	34	651655	1.91	26	283131	3.35
12	2	26	421936	2.25	23	187145	4.49
13	1	30	667628	1.64	26	284234	3.34
13	2	15	426870	1.28	14	185000	2.76
14	1	28	655235	1.56	26	254869	3.73
14	2	17	439407	1.41	16	185714	3.15
15	1	21	619243	1.24	14	232191	2.20
15	2	20	437183	1.67	18	191178	3.44
16	1	34	571721	2.17	32	209881	5.57
16	2	28	437317	2.34	23	197101	4.26
17	1	32	520578	2.25	29	176360	6.01
17	2	41	426438	3.51	36	200443	6.56

OnlineTable 2. Number of re-exacerbations, IR of asthma re-exacerbation (per PY) and cumulative incidence in percentage (%).

Time Window after exacerbation	Number of re- exacerbations	IR / PY	95% CI	Cumulative incidence (%)	95% CI
<30 days	12	0.31	0.16-0.54	2.5	1.31-4.34
<90 days	28	0.26	0.17-0.37	6.1	4.11-8.72
<180 days	53	0.26	0.20-0.34	12.1	9.39-15.44
<270 days	78	0.28	0.22-0.35	18.6	15.02-22.81
<365 days	99	0.28	0.23-0.34	24.7	20.55-28.82

IR= incidence rate, PY= person years, 95%CI= 95% confidence interval

Online figure 1: Association between age and incidence rate of exacerbations.

