

Long-Term Trajectories of Mild Asthma in Adulthood and Risk Factors of Progression



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What is already known about this topic? Long-term prognosis of mild asthma, especially if developed in younger age, is generally benign.

What does this article add to our knowledge? One-tenth of patients with mild asthma will transition to more severe disease over 10 years, with older age at onset and inappropriate use of rescue medications being associated with higher likelihood of such a transition.

How does this study impact current management guidelines? Patients with mild asthma can generally be reassured of good long-term prognosis. There is a pressing need for clinicians to consider regular use of low-dose inhaled corticosteroids in patients with mild asthma who require frequent rescuer therapy.

BACKGROUND: Most patients with asthma have mild disease. However, the clinical course of mild asthma and risk factors for progression are not well studied.

OBJECTIVE: To examine the long-term trajectories of mild asthma and the effects of early-stage risk factors on the subsequent disease course.

METHODS: From the administrative health data of British Columbia, Canada, we identified patients aged 14 to 45 years with newly diagnosed mild asthma between January 1997 and December 2012. For each follow-up year, we categorized a patient's asthma severity into mild/dormant, moderate, or severe on the basis of the intensity of asthma medications and occurrence of exacerbations. Ordinal logistic regression was used to estimate the probability of severity or all-cause death in the next year as a function of a patient's severity history in the past 3 years and selected baseline risk factors.

RESULTS: The study included 70,829 patients with incident mild asthma (62% women; mean age, 31 years). Over 10 years, 8% of these patients transitioned to moderate or severe asthma. Inappropriate use of rescue medications and older age were the most influential determinants for progression from mild asthma (odds ratios, 1.79; 95% CI, 1.68-1.90; $P < .001$; 1.24 per 10-year increase in age; 95% CI, 1.22-1.27; $P < .001$), whereas the presence of allergic rhinitis had no significant effects (odds ratio, 0.95; 95% CI, 0.91-1.00; $P = .063$). **CONCLUSIONS:** Mild asthma remains largely stable over time. However, potentially modifiable factors such as inappropriate use of rescue medications are associated with a worsened prognosis. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2024-32)

Key words: Mild asthma; Prognosis; Natural history; Disease progression; Risk factors; Rescue medication; Controller medication

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Conflicts of interest: J. M. FitzGerald is a member of the Global Initiative for Asthma Executive and Science committees; has served on advisory boards for Novartis, Pfizer, AstraZeneca, Boehringer Ingelheim, and Merck; has been a member of speakers' bureaus for AstraZeneca, Boehringer Ingelheim, Novartis, and Merck; and has received research funding paid directly to the University of British Columbia from AstraZeneca, Glaxo-SmithKline, Boehringer Ingelheim, Merck,

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Abbreviations used

BC- British Columbia
CCI- Charlson comorbidity index
ICS- inhaled corticosteroid
LABA- long-acting beta-agonist
OR- odds ratio
SABA- short-acting beta-agonist
SES- socioeconomic status

INTRODUCTION

As one of the most prevalent chronic diseases worldwide,¹ asthma imposes substantial economic and humanistic burden.²⁻⁴

Asthma severity refers to the intrinsic variability of the intensity of disease (symptoms, exacerbation frequency) among individuals, or within an individual over time. Mild asthma is the most common form of asthma, representing 50% to 75% of all patients with asthma.⁵ According to the Global Initiative for Asthma classification,⁶ mild asthma can be intermittent or persistent and is characterized by the presence of symptoms for at least 1 year without the regular use of bronchodilators and not associated with airflow limitation. Patients with mild asthma may occasionally use acute rescue treatment (ie, short-acting beta-agonists [SABAs]), and/or receive continuous low-dose inhaled corticosteroid (ICS) therapy (≤ 500 $\mu\text{g}/\text{d}$ beclomethasone or equivalent⁷), but they rarely experience exacerbations (≤ 1 per year).⁵ The occurrence of exacerbations that lead to hospitalization or use of oral corticosteroids precludes the classification of asthma as mild.⁵

The long-term trajectory of asthma according to its degree of severity is not well understood. Current evidence regarding asthma progression is predominantly focused on longitudinal changes in lung function parameters and on phenotypic changes from childhood to adulthood.^{5,8-11} The severity of asthma in adulthood is considered a relatively stable phenomenon over time.¹²⁻¹⁴ However, we and others have previously shown that there is a large “regression to the mean” phenomenon in severe asthma as many patients with newly diagnosed severe asthma tend to experience milder asthma over long-term.¹⁵ To what extent mild asthma remains stable over time and what risk factors affect such stability are not well studied. Using administrative health data from a large province of Canada, we aimed to examine the long-term trajectory of mild asthma in adults older than 16 years and to identify demographic, clinical, and treatment-related factors during the earlier stages of disease that are associated with asthma progression, that is, the worsening of disease severity.

METHODS

Data sources

This study is based on the provincial health administrative databases of British Columbia (BC, Canada, 4.6 million residents as of 2016¹⁶) for the period between January 1, 1997, and December 31, 2012. Because BC has a publicly funded health care system, data for all legal residents are collected within these databases. We therefore retrieved the linked, individual-level data of all BC residents from databases that contain information including registration status and demographic characteristics, vital statistics, hospitalizations, outpatient physician services, and prescription medication dispensations¹⁷⁻²¹ (see Data Source, available in this article's Online Repository at www.jaci-inpractice.org). Previous analyses have showed a very low prevalence of missing data, underreporting, and misclassification in these

databases.^{22,23} All inferences, opinions, and conclusions drawn in this study are those of the authors and do not reflect the opinions or policies of the data steward(s). Ethical approval was obtained from the University of British Columbia Human Ethics Board (H15-00062).

Study sample

This was a prospective cohort study of patients aged between 14 and 45 years who developed incident (ie, a new occurrence of) mild asthma. We first used a validated case definition to identify patients with asthma in general. This algorithm is based on the presence of 1 or more asthma-related hospitalizations (with the most responsible diagnosis being due to asthma), or 2 or more asthma-related outpatient visits (on different dates, with asthma as the primary diagnosis), or 3 or more asthma-specific filled prescriptions, during any rolling 12-month period.²⁴ Asthma diagnosis was based on the *International Classification of Diseases* codes (*International Classification of Diseases, Ninth Revision* code 493.x; *International Classification of Diseases, Tenth Revision* codes J45.x and J46.x). Asthma-specific medications were extracted on the basis of a prespecified list (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

For each patient in the cohort, we defined the cohort entry date as the day of the patient's first asthma-related resource use. From this date forward, we calculated asthma severity according to health care resource use records for every 12-month period on the basis of a validated algorithm (see next section, *asthma severity classification*).²⁵ We then selected patients who had new-onset mild asthma, with *new onset* defined as having their first 12-month period after entry date being classified as mild asthma, and with at least 3 years of full registration in the province before the entry date. The unit of observation was the adjacent 12-month periods since entry date. We followed patients until death, the last date of registration with the health care services program, or the end of available data (December 31, 2012), whichever came first. We removed any period in which the patient was not fully registered unless they died during that period.

Asthma severity classification

From the entry date onward, we classified each 12-month period into 3 asthma severity states (mild/dormant, moderate, or severe) on the basis of intensity of asthma-related health care resource utilization. The severity algorithm, developed by Firoozi et al,²⁵ was designed on the basis of Canadian administrative health data and was validated against the Canadian Asthma Consensus Guidelines.²⁶ Such resource-based severity classification has been used in previous asthma prognosis studies.^{15,27} Medication intensity was calculated as the averaged, dispensed doses per patient-year, which was a surrogate for actual use.²⁵ In each patient-year, mild asthma was defined on the basis of filled prescriptions of ICS corresponding to a mean daily dose of up to 500 $\mu\text{g}/\text{d}$ beclomethasone equivalent,⁷ or below 250 $\mu\text{g}/\text{d}$ if receiving additional controller medications, while SABA was used for no more than 3 doses/wk and there was no moderate-to-severe exacerbation. One dose of SABA was equivalent to 2 inhalations of salbutamol from a metered dose inhaler (100 $\mu\text{g}/\text{inhalation}$). A moderate-to-severe exacerbation was defined as an acute episode of progressive worsening of asthma symptoms that required hospitalization, emergency room visit, or use of an oral corticosteroid. The definition of mild asthma also includes dormant asthma, which, for each 12-month period, was defined as not requiring any asthma medication and not having experienced an exacerbation during the period. Severe asthma was defined by the use of high doses of an ICS (≥ 1000 $\mu\text{g}/\text{d}$), or the presence of difficult-to-control asthma (ie, ≥ 10 doses/wk of a SABA

TABLE I. Characteristics of the study sample in the index year

Characteristic	Patients with mild asthma (N = 70,829)
Age (y), mean $\pm$ SD	30.5 $\pm$ 9.7
Sex, n (%)	
Female	43,891 (62)
Male	26,938 (38)
Socioeconomic status, n (%)	
Low	29,993 (42)
Middle	14,430 (20)
High	26,406 (37)
Comorbidity, n (%)	
None (CCI score = 0)	62,342 (88)
Mild (CCI score = 1)	7,266 (10)
Moderate (CCI score = 2)	873 (1)
High (CCI score $\geq$ 3)	348 (0.5)
Allergic rhinitis, n (%)	9,398 (13)
Inappropriate SABA use,* n (%)	
No	42,186 (59)
Yes	8,399 (12)
No ICS or SABA use	20,244 (29)
ICS vs ICS + LABA use, n (%)	
ICS	24,522 (35)
ICS + LABA	8,253 (12)
Both	906 (1)
No ICS use	37,148 (52)
ICS-adjusted daily dose,† mean $\pm$ SD	82.9 $\pm$ 115.4
No. of other controllers/wk,‡ mean $\pm$ SD	0.0 $\pm$ 0.0
No. of SABA doses/wk,§ mean $\pm$ SD	2.3 $\pm$ 2.4
Moderate-to-severe exacerbations, mean $\pm$ SD	0.1 $\pm$ 0.3
No. of nonasthma hospitalizations, mean $\pm$ SD	1.2 $\pm$ 4.6
No. of nonasthma physician visits, mean $\pm$ SD	12.8 $\pm$ 13.9
No. of nonasthma medications, mean $\pm$ SD	71.3 $\pm$ 256.4

*Defined as high dose of SABA and low dose of ICS: using 2 or more puffs of SABA per week in the absence of ICS use or 9 or more canisters of SABA and less than 100 μ g of ICS daily doses.

†Daily dose of ICS in beclomethasone-chlorofluorocarbon equivalent.

‡Number of dispensed other controllers per week, including LABA, theophylline, or leukotriene receptor antagonists.

§Average number of SABA doses per week; 1 dose of SABA was equivalent to 2 inhalations of salbutamol from a metered dose inhaler (100 μ g/inhalation).

||Events of asthma-related emergency department visits or hospital admission, or filled prescriptions of oral corticosteroids.

while still experiencing at least 1 moderate-to-severe exacerbation during the 12-month period). Moderate asthma was defined as not meeting the criteria for either mild or severe asthma, such as the use of moderate doses of ICS ($\geq$ 250 μ g/d) and SABA ($\leq$ 10 doses/wk), or low-to-moderate doses of ICS ($\leq$ 1000 μ g/d) with the presence of uncontrolled asthma (ie, either $\geq$ 10 doses/wk of a SABA or $\geq$ 1 moderate-to-severe exacerbation, but not both). In addition, each period in which a death (of any cause) occurred was labeled as death, irrespective of asthma severity before death.

Assessment of prognostic risk factors

We evaluated a candidate set of exposure variables that was hypothesized to affect the long-term trajectory of asthma and specifically, the transitioning from mild to more severe asthma. We evaluated 2 variables representative of drug therapy. The first factor was the excessive use of rescue medications relative to the controller therapy.

Following a previously published and highly cited definition in claims data analysis,^{28,29} we defined such pattern as the “inappropriate prescription of rescue medication,” which was indicated by 2 or more puffs of SABA per week in the absence of ICS use in the first year of asthma diagnosis (index year), or 9 or more canisters of SABA with under 100 μ g of ICS daily. Such definition of inappropriate SABA use has been used by multiple studies to characterize the prevalence, predictors, and outcomes of imbalanced use of controller and rescue medications.^{28,30-32} The second drug-related variable was the utilization of ICS versus ICS/long-acting beta-agonist (LABA) combination therapy in the index year. Further variables included sociodemographic factors (age, sex, socioeconomic status [SES]), all of which were measured in the index year. On the basis of neighborhood (postal-code based) income quintiles, SES was categorized into 3 levels: low (lowest 2 quintiles), middle (the third quintile), and high (the highest 2 quintiles). This variable has been shown to correlate well with individual- and household-level SES and has been previously used to investigate SES-related disparities in asthma outcomes.^{33,34} In addition, we measured comorbidity in the 12 months preceding mild asthma diagnosis. We first calculated the Charlson comorbidity index (CCI, excluding asthma from the score)³⁵ and categorized it into 4 levels using commonly used cutoff points³⁶: none (CCI score = 0), low (score = 1), moderate (score = 2), and high (score $\geq$ 3). We also evaluated the presence of allergic rhinitis (on the basis of a validated case definition using *International Classification of Diseases, Ninth Revision* code 477.x; *International Classification of Diseases, Tenth Revision* code J30.x and prescription dispensation of antihistamine and/or nasal corticosteroids³⁷) because of its previously reported association with adult-onset asthma and its potential prognostic value for long-term natural history of asthma.³⁸

Statistical analysis

The main analysis followed a previously established approach for projecting long-term trajectory of asthma and associating early-stage factors to each long-term projection.¹⁵ Briefly, a Markov model with time cycles of 1 year was used to model a sequence of dynamic transitions between severity states (0 = mild/dormant, 1 = moderate, 2 = severe, 3 = dead [the only absorbing state]) over time, with patients all starting with mild asthma. Dead was an absorbing state but otherwise patients could transition into any severity state from any other severity state.

To populate the Markov model, first an ordinal logistic model was created to model the severity/dead state in any given period. The severity state in the next period (year) was treated as the (ordinal) dependent variable, whereas severity histories in the current period and the past 2 periods, calendar year, baseline age, sex, CCI category, rhinitis, SES, inappropriate SABA use, and ICS versus ICS/LABA treatment were included as the independent variables. The choice of using 3-year history was because it satisfied the Markovian property; that is, the probability of transitioning to a future disease state depended only on disease states in the past 3 periods.³⁹ This was not the case for models that included only the current period or the current and previous periods' history.

Generalized estimating equations were used to account for correlation between clustered observations (multiple periods for each patient).⁴⁰ Regression results were presented in terms of the odds ratios (ORs) affecting the transitioning from a milder to a more severe state. For each independent variable, the effect on future severity was estimated as the ORs of transitioning to moderate/severe asthma or dead state versus to mild asthma; to severe/dead state versus to mild/moderate asthma; and to dead state versus to mild/

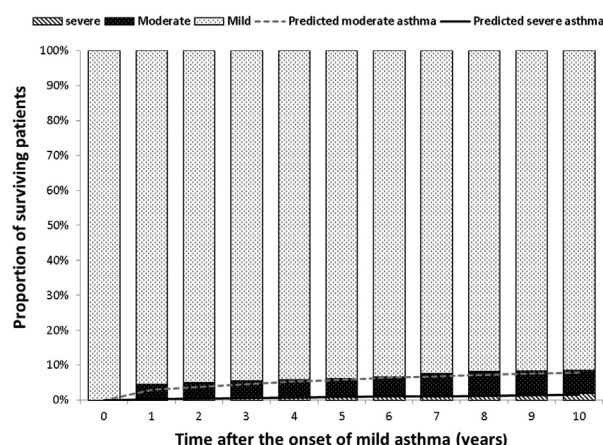


FIGURE 1. Proportions of surviving patients with incident asthma at different severity states over time. The dead state was not shown in the graph because of its very small contribution (only 0.1% had died over 10 years).

moderate/severe asthma. We evaluated the proportional odds assumptions; that is, ORs should be constant across all 3 possible transitions, for all independent variables. For variables that did not meet the proportional odds assumption, we allowed their effects to vary across different transitions.

Because this regression model satisfied the Markovian assumption, it could be used to model complete natural history of individuals over time on the basis of their baseline characteristics history of asthma in the first 3 years. The transition probabilities across severity states governing such a Markov process were derived from the predicted probabilities for each patient from the above-mentioned ordinal regression. Severity trajectory was plotted as the probability of being in each of the 4 severity/dead states at a given 12-month follow-up period over the next 10 years. Model fit was assessed by comparing the observed versus predicted trajectories of severity of the entire sample.

We quantified the effects of baseline risk factors (variables) on the severity trajectories by comparing the accumulated follow-up years staying in a given severity state between different levels of baseline risk factors. To make such projections for a given risk factor profile, we updated the risk factor variable of all individuals in the sample to the given profile (eg, all individuals being inappropriate SABA users) and calculated the corresponding transition probabilities from the ordinal regression, repeating the analysis with the alternative value of the risk factor (eg, no patient being inappropriate SABA user). All statistical analyses were performed under SAS (Version 9.3, SAS Institute Inc, Cary, NC).

RESULTS

Among 361,501 individuals who satisfied the case definition of asthma, there were 70,829 incident cases of mild asthma (for a flowchart of cohort selection, see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org). These patients contributed 380,161 patient-years, with an average follow-up of 5.4 years. Baseline mean age was 30.5 ± 9.7 years and 62% were women. Most patients (88%) had a CCI score of 0 at baseline, and 0.5% had a CCI score above 3; 13% had allergic rhinitis. Approximately 42% were living in low SES neighborhoods (the first 2 quintiles).

Inappropriate use of rescue medication was present in 12% of patients, and 52% of patients did not use any ICS treatment in the index year; 35% used ICS monotherapy, 12% used an ICS and a LABA in combination, and 1% used both types ([Table I](#)).

The observed and regression-fitted trajectories of the cohort are shown in [Figure 1](#). The observed and predicted trajectories aligned well, indicating satisfactory model fit.

Among patients with incident mild asthma, most (91.6%) remained in the mild state over the next 10 years, whereas 8.4% transitioned to a more severe state (6.7% to moderate state, 1.7% to a severe state by year 10). The proportion of patients transitioning to moderate and severe asthma, respectively, slowly increased over time. Meanwhile, fewer than 0.2% patients died during follow-up ($n = 99$).

[Table II](#) presents the ORs of transitioning from milder to severe or dead states in the next 12-month period on the basis of baseline risk factors. Inappropriate use of rescue medications (OR, 1.79; 95% CI, 1.68-1.90), comorbidity ([compared with CCI score = 0], OR ranges for CCI score ≥ 1 -3: 1.07 [95% CI, 1.02-1.13] to 1.25 [95% CI, 1.01-1.54]), and the age at diagnosis (OR, 1.24 per 10-year increase in age; 95% CI, 1.22-1.27) were associated with the greatest likelihood of worsened asthma. Notably, ICS/LABA combination therapy was associated with a reduced risk of progression compared with ICS monotherapy (OR, 0.92; 95% CI, 0.87-0.97). Being male and having low SES were associated with a worse prognosis but the effect sizes were small, while the presence of allergic rhinitis was not associated with progression to more severe asthma (OR, 0.95; 95% CI, 0.91-1.00; $P = .063$).

[Figures 2 to 5](#) plot the 10-year trajectories of mild asthma according to inappropriate use of rescue medications, age, comorbidity, and monotherapy versus combination therapy with ICS (and LABA). For other variables, their impact on long-term trajectory was negligible. Over 10 years, for every 1000 patients who developed mild asthma, inappropriate SABA use would lead to 38 (4%) extra patients transitioning to more severe states as compared with appropriate users. The corresponding figures were 38 (4%) for 40-year-olds relative to 20-year-olds, 15 (2%) for having comorbidity (CCI score ≥ 1) relative to no comorbidity, and 8 (1%) for ICS monotherapy relative to ICS/LABA combination therapy in the baseline year.

DISCUSSION

Among a population-based cohort of mild asthma, we found that most patients (92%) with incident mild asthma remained in the mild state over the next 10 years. Inappropriate use of rescue medications, older age, and comorbidity were independently associated with an increased risk of disease progression over time. Male sex and low SES were also associated with such transition but their effects were clinically trivial. However, patients initially treated with ICS/LABA combination therapy had a slightly better prognosis than those who received ICS monotherapy, while the presence of allergic rhinitis did not alter the long-term trajectories of mild asthma. Several factors that were shown here to be associated with long-term trajectory of mild asthma are potentially modifiable, signaling an opportunity for preventing adverse asthma outcomes through risk factor management and treatment.

Several early life-to-adulthood studies have reported a benign course for mild asthma.^{12,41} These findings are supported by our

TABLE II. Effects of selected baseline risk factors on future severity of asthma

Risk factors in the index year	OR of transitioning to a severity state in any future year					
	Transition to moderate/severe/dead (relative to mild)		Transition to severe/dead (relative to mild/moderate)		Transition to dead (relative to mild/moderate/severe)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 10- y increase)	1.24 (1.22-1.27)	<.0001	1.24 (1.19-1.29)	<.0001	1.98 (1.51-2.60)	<.0001
Sex (male vs female)	1.05 (1.01-1.08)	.006	1.05 (1.01-1.08)	0.006	1.05 (1.01-1.08)	.006
SES						
Low	Reference					
Middle	0.93 (0.89-0.98)	.003	0.90 (0.82-1.00)	.047	1.00 (0.60-1.67)	.99
High	0.95 (0.92-0.99)	.011	0.83 (0.76-0.90)	<.0001	0.80 (0.50-1.27)	.34
Comorbidity						
CCI score = 0	Reference					
CCI score = 1	1.07 (1.02-1.13)	.010	1.06 (0.95-1.19)	.30	1.31 (0.73-2.33)	.36
CCI score = 2	1.11 (0.97-1.27)	.122	1.45 (1.12-1.89)	.005	3.88 (1.55-9.72)	.004
CCI score $\geq$ 3	1.25 (1.01-1.54)	.039	1.25 (1.01-1.54)	.018	11.34 (4.94-26.05)	<.0001
Allergic rhinitis (yes vs no)	0.95 (0.91-1.00)	.063	0.95 (0.91-1.00)	.063	0.95 (0.91-1.00)	.063
Inappropriate SABA use*						
No	Reference					
Yes	1.79 (1.68-1.90)	<.0001	1.29 (1.16-1.44)	<.0001	1.15 (0.61-2.16)	.68
No ICS or SABA use	0.63 (0.59-0.68)	<.0001	1.00 (0.89-1.13)	0.98	1.16 (0.71-1.87)	.55
ICS therapy						
ICS only	Reference					
ICS-LABA	0.92 (0.87-0.97)	.004	0.92 (0.87-0.97)	<.0001	0.92 (0.87-0.97)	<.0001
Both	0.96 (0.84-1.10)	.56	0.96 (0.84-1.10)	.56	0.96 (0.84-1.10)	.56
None	0.73 (0.69-0.78)	<.0001	0.73 (0.69-0.78)	<.0001	0.73 (0.69-0.78)	<.0001

F, Female; ICS-LABA, ICS and LABA combination therapy; M, male.

*Defined as high dose of SABA and low dose of ICS—using 2 or more puffs of SABA per week in the absence of ICS use, or 9 or more canisters of SABA and less than 100 μ g of ICS daily doses.

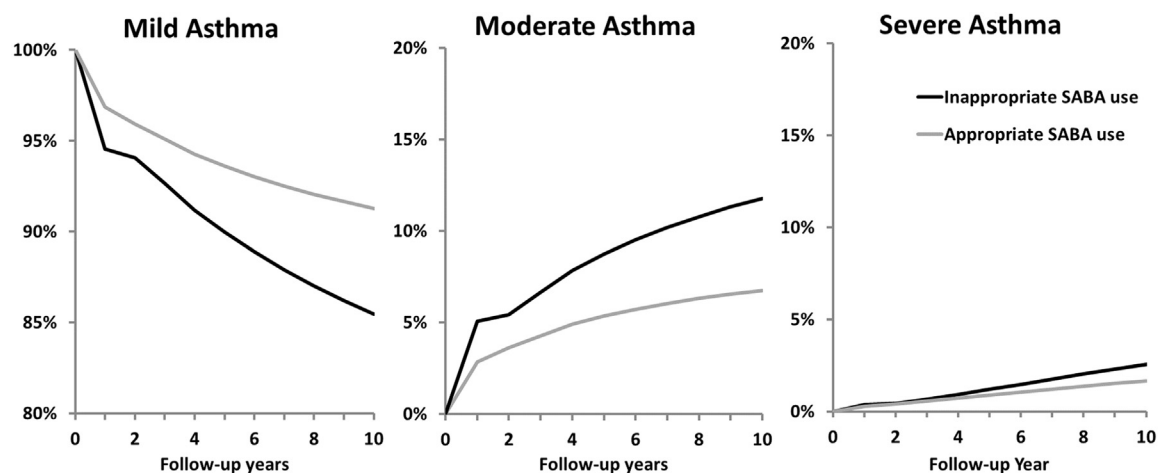


FIGURE 2. The influences of rescue medication use in the index year on the long-term trajectory of patients with incident mild asthma. Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. Probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma.

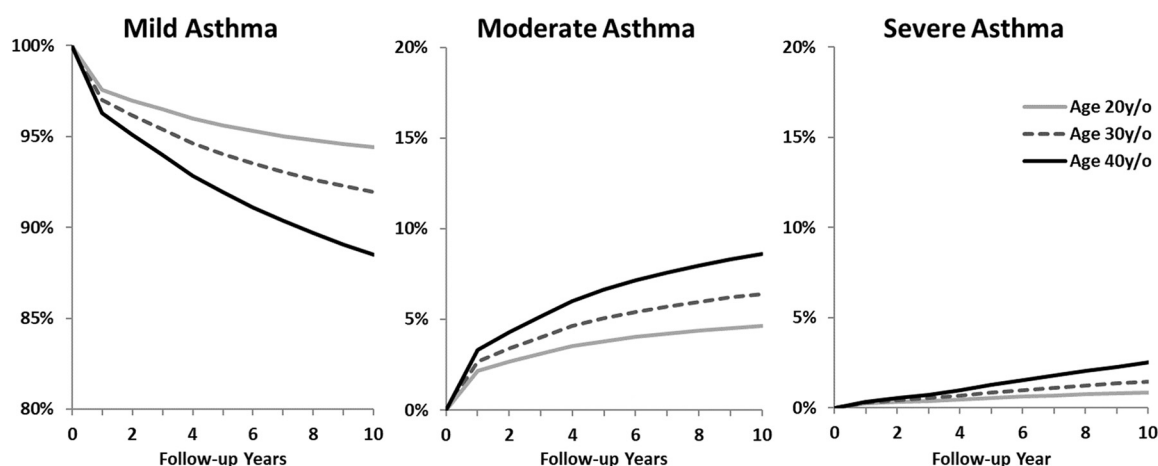


FIGURE 3. The influence of baseline age on long-term trajectory of patients with incident mild asthma. Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. Probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma. y/o, Years of age.

analysis and by an earlier population-based study,⁴² both of which showed that mild asthma is generally stable but can occasionally evolve to severe states. Both studies were based on large, population-based administrative data and defined asthma severity on the basis of intensity of asthma therapy. However, our study had a much longer follow-up period. Moreover, with the use of a flexible, multistate Markov model, for the first time we projected the long-term trajectories of incident mild asthma and quantified the effects of multiple risk factors at early stage on the subsequent disease course, including the effects of sociodemographic characteristics, clinical features, and early treatment. The stability of mild asthma phenotype over time is in contrast with the pattern observed in severe asthma. A previous study using

similar methodology has shown that more than 80% patients with incident severe asthma would transition to milder states over 10 years.¹⁵

Inappropriate use of rescue medications essentially refers to excessive doses of acute-reliever medications (eg, SABAs) and inadequate doses of controller medications.²⁹ Reddel et al⁴³ recently found that patients with early mild symptoms also benefit from daily low-dose ICS use with a reduction in exacerbations.⁴³ Our study supports this recommendation because we found that inappropriate SABA use might lead to transition to worse states over time, although like any other observational study, we could not rule out the possibility of residual confounding by disease severity. Such bias might exist if there was

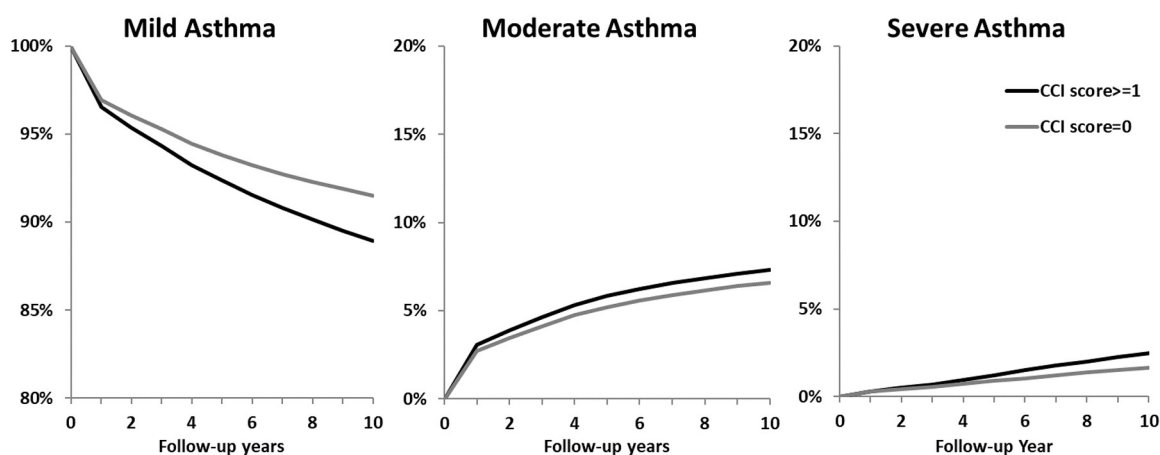


FIGURE 4. The influence of baseline comorbidity status on long-term trajectory of patients with incident mild asthma. Comorbidity was represented by the CCI (excluding asthma) scores: none (CCI score = 0), comorbidity (CCI score ≥ 1). Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. Probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma.

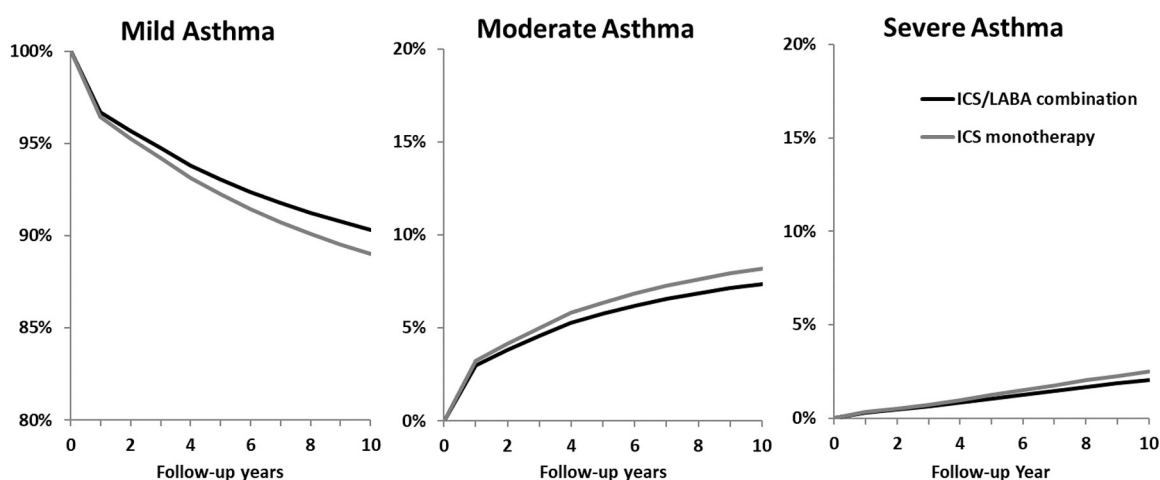


FIGURE 5. The influences of controller medication use in the index year on long-term trajectory of patients with incident mild asthma. Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. The probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma. ICS/LABA, ICS and LABA combination therapy.

heterogeneity in patients who were initially classified as having mild asthma, with inappropriate SABA use indicating more severe disease within the mild category. However, the association between ICS + LABA (vs ICS alone) and better asthma prognosis was reassuring that such residual confounding was minimal. Given the high prevalence of mild asthma and the proportion of patients who filled inappropriate doses of SABA,²⁸ the potential for causal association between inappropriate SABA use in early mild asthma and adverse long-term prognosis can have a large impact and thus should be further studied. We also found that ICS/LABA combination use was associated with a slightly more benign course of mild asthma compared with the use of ICS monotherapy. This finding might be explained by the better

long-term adherence to ICS/LABA use than to monotherapy with ICS,⁴⁴ which merits further investigation. It also has a mechanistic support: ICS/LABA combination is found to improve pulmonary function, reduces symptoms, and decreases the use of SABA as compared with ICS monotherapy.^{45,46}

Current understanding of age being an important modulator of asthma has mainly focused on young patients, demonstrating disease remission during late childhood children⁴⁷ and adolescence.⁴² Our findings confirm such age effect and extend this evidence base from childhood to adulthood. Comorbidity was another factor associated with disease progression,^{48,49} which has previously been shown to also be a risk factor for worse prognosis of severe asthma.¹⁵ However, in our mild asthma sample, only

12% patients had a CCI score above 1; thus the absolute impact of this factor may not be substantial. However, the finding that allergic rhinitis had no significant effect was somewhat surprising considering its important role in adult-onset asthma.³⁸ It is possible that patients who received an asthma diagnosis have their rhinitis more closely monitored and more appropriately treated.

This study has important clinical and policy implications. Because mild asthma represents most patients with asthma,⁵ focusing on modifiable factors that prevent its transition to severe states over time can provide substantial population-level benefits. Particularly, there is a pressing need for clinicians to consider regular use of low-dose ICS in patients with mild asthma, because one-tenth of these patients showed signs of unmet medical need demonstrated as excess reliever use. The benefits of using low-dose combination inhaler therapy for this patient population are also worth considering and is currently being evaluated in a number of studies.⁵⁰ However, although other factors such as age and comorbidity are more difficult to modify, they can be used as covariates in prediction tools for prognosticating the course of mild asthma.

The current findings need to be interpreted within the context of this study's limitations. Intrinsic limitations of the algorithm we used to classify asthma severity have been previously discussed,¹⁵ including that this classification is only an approximate for clinical severity because asthma symptoms and lung function were unavailable in the administrative data. The first consideration was confounding by severity/indication, which is ubiquitous in observational studies. For instance, disease intensity could still vary within mild asthma, and medication usage pattern that was labeled as inappropriate SABA use could indicate more severe disease. However, such confounding might have been largely controlled for, because our analysis already showed that ICS + LABA use was associated with a better prognosis as compared with ICS, whereas confounding by indication should have shown the opposite direction of association (ie, toward ICS + LABA being associated with worse prognosis). Second, we calculated the average dispensed doses of prescription drugs to classify severity,²⁵ which might not reflect the actual pattern of use. For instance, patients could have used SABA only during fall and/or winter episodes. Although the Firoozi et al²⁵ severity classification has been validated against pulmonary function measurements and established clinical severity indices, misclassification could still occur when patients did not strictly follow clinical advice, such as filling more prescriptions than needed (eg, stockpiling medications) and thus being misclassified as more severe. However, the simultaneous use of markers of exacerbations in the severity algorithm²⁵ can prevent misclassifying patients as milder than their true level of severity. Third, the prevalence of allergic rhinitis could be underestimated because administrative data could not capture the use of over-the-counter antihistamines. Finally, several risk factors of interest including obesity⁵¹ and smoking status⁵² were not captured by the administrative data and hence not examined in our analysis.

Notwithstanding these limitations, our findings confirm the generally benign course of mild asthma in adults with incident mild asthma. Importantly, we quantified the effects of risk factors at an early stage on the subsequent development of mild asthma over time. Inappropriate use of rescue medications, older age, comorbidity, and ICS + LABA versus ICS therapy were among

the factors that were shown to affect the long-term course of mild asthma. Because our findings were based on administrative data and population-level analysis, individualized clinical judgment needs to be considered together with current findings in real-world patient care. For better-informed decision making, further studies should focus on different phenotypes of mild asthma and provide a deeper mechanistic investigation of disease progression and in particular document the most effective interventions to modify such as lung function decline and measures of airway inflammations. In addition, parallel validation studies using international data sources in other jurisdictions can further improve the generalizability of current findings.

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ONLINE REPOSITORY

DATA SOURCE

A provincial health insurance program provides universal health care coverage to all legal residents of BC, Canada, one of the largest provinces, representing 13% of the Canadian population (4.6 million residents as of 2016^{E1}). We retrieved data from the BC provincial health administrative databases for the period of January 1997 to December 2012 (16 years). These databases are linked at individual level and provide information on health care encounters of all legal residents of BC. We used registration files (capturing the status of insurance coverage of individuals),^{E2} vital statistics (capturing

births and deaths),^{E3} the hospital discharge database (capturing inpatient encounters),^{E4} Medical Services Plan payment information (capturing outpatient encounters with physicians),^{E5} and PharmaNET (capturing all medication dispensations outside of hospital pharmacies, and regardless of any third-party insurance coverage).^{E6} Previous analyses have shown a very low prevalence of missing data, under-reporting, and misclassification in these databases.^{E7,E8} All inferences, opinions, and conclusions drawn in this study are those of the authors and do not reflect the opinions or policies of the Data Steward(s). Ethical approval was obtained from the University of British Columbia Human Ethics Board (H15-00062).

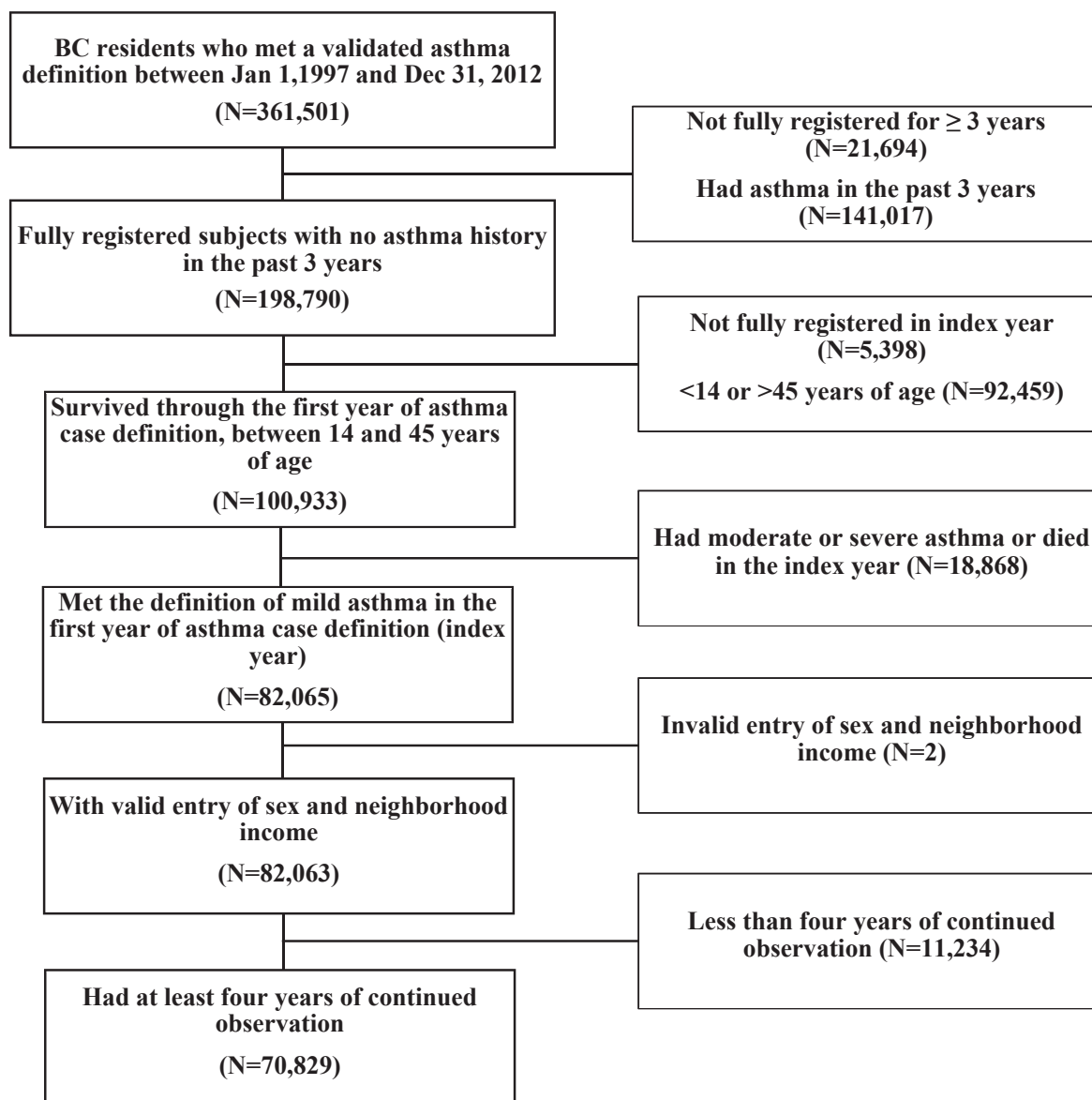


FIGURE E1. A cohort of individuals with newly diagnosed asthma was created from the BC health administrative data in fiscal years 1997 to 2013. *N*, Number of identified subjects.

TABLE E1. List of asthma-related medications used for asthma case definition

Medication category	Medication type	Active ingredient(s)	ATC	DIN	Used in case definition?
ICSs	Controller	Beclomethasone	R03BA01	2242030, 2242029, 374407, 828521, 828548, 872334, 893633, 897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039, 2215047, 2215055, 2216531	Y
		Budesonide	R03BA02	2229099, 1978918, 1978926, 852074, 851752, 851760	Y
		Fluticasone	R03BA05	2237247, 2237246, 2237245, 2237244, 2244293, 2244292, 2244291, 2174731, 2174758, 2174766, 2174774, 2213583, 2213591, 2213605, 2213613	Y
		Ciclesonide	R03BA08	2285614, 2285606, 2303671	Y
SABAs	Reliever	Salbutamol	R03AC02	790419, 812463, 832758, 832766, 851841, 860808, 867179, 897345, 1926934, 1938851, 1938878, 1945203, 1947222, 1986864, 2022125, 2046741, 2048760, 2069571, 2084333, 2148617, 2154412, 2173360, 2208229, 2208237, 2208245, 2212315, 2212323, 2213400, 2213419, 2213427, 2213478, 2213486, 2214997, 2215004, 2215616, 2215624, 2215632, 2216949, 2231430, 2231488, 2231678, 2231783, 2231784, 2232570, 2232987, 2236931, 2236932, 2236933, 2239365, 2239366, 2241497, 2243115, 2243828, 2244914, 2245669, 2259583, 2326450	Y
			R03CC02	620955, 620963, 874086, 894249, 894257, 1932691, 2035421, 2063689, 2091186, 2146843, 2146851, 2164434, 2164442, 2165368, 2165376, 2212390, 2213435, 2213443, 2213451, 2261324	Y
		Terbutaline	R03AC03	786616	Y
		Orciprenaline	R03CB03	249920, 3891, 2236783, 2229862, 2152568, 2192675	Y
LABAs	Controller	Salmeterol	R03AC12	2211742, 2214261, 2231129, 2136139, 2136147	Y
		Formoterol	R03AC13	2230898, 2237224, 2237225	Y
ICS and LABA in combination (ICS + LABA)	Controller	Budesonide, formoterol	R03AK07	2245385, 2245386	Y
		Fluticasone, salmeterol	R03AK06	2240835, 2245126, 2245127, 2240836, 2240837	Y
Leukotriene receptor antagonists	Controller	Montelukast	R03DC03	2247997, 2238217, 2243602, 2238216	Y
Anti-IgE mAb	Controller	Zafirlukast	R03DC01	2236606	Y
		Omalizumab	R03DX05	2260565	Y
Inhaled mast cell stabilizers	Controller	Cromoglicic acid (cromolyn)	R03BC01	2231431, 2231671, 2046113, 534609, 555649, 261238, 638641, 2049082, 2219468	Y
Theophylline	Controller	Choline theophyllinate	R03DA02	346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366, 476390, 476412, 503436, 511692, 536709, 565377, 589942, 589950, 792934	Y
		Theophylline	R03DA04	156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223, 556742, 575151, 599905, 627410, 631698, 631701, 692689, 692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616, 1926640, 1966219, 1966227, 1966235, 1966243, 1966251, 1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087	Y
Inhaled anticholinergics	Reliever	Aminophylline	R03DA05	14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450, 2014270, 2014289	Y
		Ipratropium bromide	R01AX03	2246084, 2246083, 2163705, 2163713, 2240508, 2240072	N

(continued)

TABLE E1. (Continued)

Medication category	Medication type	Active ingredient(s)	ATC	DIN	Used in case definition?
			R03BB01	2126222, 2243827, 2231494, 731439, 576158, 2247686, 824216, 2026759, 1950681, 2239131, 2216221, 2210479, 2231785, 2236934, 2236935, 2237134, 2237135, 2239627, 2231135, 2231136, 2231245, 2231244, 2097141, 2097176, 2097168	N
		Ipratropium bromide, fenoterol	R03AK03	02148633	N
		Tiotropium bromide	R03BB04	02246793	N
Other beta-agonists	Reliever	Epinephrine	R03AA01	2017555, 466417, 525103, 1927582	N
		Ephedrine	R03CA02	2237085, 2229698, 2100231, 2100258, 2243148, 2236722, 2229678, 2219743, 2012111, 2229711, 38121, 2242961, 876534, 893323, 893331, 438847, 2242639, 2126419, 2126400	N
		Isoprenaline	R03AB02	2017652	N
		Orciprenaline	R03AB03	1923870, 1928449, 2017660, 254134, 3859	N
Other corticosteroids	Controller	Cortisone	H02AB10	280437, 16241, 16446, 16438	N
		Triamcinolone	H02AB08	2194090, 15016, 15024, 2194082	N
		Prednisone	H02AB07	610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434, 868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381	N
		Prednisolone	H02AB06	21679, 2230619, 2152541, 2245532	N
		Methylprednisolone	H02AB04	1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406, 2245400, 2245408, 2245407, 2241229, 2231893, 2231894, 2231895, 2232750, 2232748, 2063727, 2063697, 2063719, 2063700, 36137, 2230210, 2230211, 30678, 30651, 30643	N
		Betamethasone	H02AB01	2237835, 36366, 2063190, 176834, 28096, 28185	N
		Hydrocortisone	H02AB09	888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539, 878618, 878626, 30635, 30600, 30619, 30627	N
		Dexamethasone	H02AB02	2261081, 2250055, 213624, 16462, 354309, 716715, 874582, 1977547, 664227, 2204274, 2204266, 295094, 285471, 489158, 2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046, 2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900, 751863, 2311267, 2240687, 2240685, 2240684	N
Other xanthines	Controller	Theophylline, combination	R03DA54	545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718, 640093, 828726, 828742, 307548	N
Other antiallergic agents	Antiallergic	Levocabastine	R01AC02	2020017	N
		Ketotifen	R06AX17	2221330, 2176084, 2230730, 2218305, 2231680, 2231679, 600784, 577308	N

ATC, Anatomical therapeutic chemical; DIN, drug identification number; N, no; Y, yes.

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