

The course of asthma activity: A population study

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Background: Unlike most chronic diseases, which tend to progress over time, asthma is known to persist, possibly resolve, and/or present with any combination of remissions and relapses. As a result, its course has been difficult to characterize and its prognosis difficult to predict.

Objective: To quantify the proportion of individuals with asthma who have active disease and, of those, the proportion who experience significant gaps in their asthma activity; and to determine factors associated with asthma activity.

Methods: Universal population health administrative databases were used to identify all individuals with asthma living in Ontario, Canada, in 1993 and follow them for 15 years. Active asthma was indicated by 1 or more physician claims for asthma.

Results: Of 613,394 individuals with asthma in 1993, 504,851 (82.3%) had active disease in subsequent years. Of those who had complete follow-up, 74.6% experienced a gap of 2 or more years in their asthma activity. Previous asthma claims, older and younger age, and a codiagnosis of chronic obstructive pulmonary disease correlated with greater asthma activity.

Conclusion: Over 15 years, most individuals with asthma in Ontario, Canada, had active disease that was interspersed by periods of inactivity when they did not require medical attention and were likely in remission. These analyses offer insight into the natural course of asthma activity that may help improve the ability to predict an individual's course of disease. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Asthma, health services use, remission, natural history

Abbreviations used

COPD: Chronic obstructive pulmonary disease

SES: Socioeconomic status

Asthma is a chronic respiratory disease with significant morbidity that affects more than 10% of the North American population.^{1,2} Unlike most chronic diseases, which tend to affect older adults and get progressively worse over time, asthma may onset at any age (most commonly in children) and is known to clinically persist, possibly resolve, and/or present any combination of remissions and relapses over time. Thus, the course of asthma activity has been difficult to characterize and, as a result, its prognosis difficult to predict. Little is known about the course of asthma activity and inactivity and its correlated factors. Such information would help affected patients and health care providers anticipate the course of asthma and be proactive in its management.

Previous longitudinal, population-based studies that have attempted to characterize the course of asthma activity have shown that asthma activity persists for decades but is commonly interspersed with periods of remission.³⁻⁹ These studies, however, have been limited by being able to assess asthma activity only at preselected points of time (with little detail on activity in between)^{3,4} and/or following only small, select populations.^{6,7,9} Most also had relatively short follow-up times.⁸ A longitudinal cohort study that could follow a large asthma population and capture information about individual day-to-day disease activity over a lifetime would be ideal to confirm these early findings and learn more about the natural history of asthma activity; however, the resources needed to conduct such a study would be prohibitive. Health administrative data that capture health information on an entire population can provide an alternate and more practical way of capturing daily information about clinically relevant asthma activity over many years that is highly generalizable, albeit not as detailed. This is particularly true for a health care system with universal, single-payer health care insurance where cost is not a barrier to seeking medical attention and all encounters are captured. Therefore, we used health administrative data to conduct a longitudinal retrospective cohort study to characterize asthma activity in individuals living in the province of Ontario, Canada (population approximately 12 million at the time of the study), over 15 years. Specifically, we were interested in the proportion of individuals who had active asthma, as indicated by their asthma-related health services use, the proportion of those with active asthma who experienced significant gaps in their asthma activity, and patient characteristics associated with asthma activity.

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METHODS

Study design and setting

A longitudinal, retrospective cohort study was conducted in Ontario, a province of Canada with a multicultural population of approximately 12 million people in 2010.

Data sources

Residents of Ontario have universal public health insurance under the Ontario Health Insurance Plan, the single payer for all medically necessary services across the full spectrum of residents, providers, and hospitals. Service details are captured in a few health administrative databases that can be linked on an individual level to provide a complete health services profile for each resident. The Registered Persons Database contains basic demographic information and date of death. The Canadian Institute of Health Information Discharge Abstract database contains information on all discharges from acute care hospitals. The Ontario Health Insurance Plan Physician Claims database contains information about all services provided by fee-for-service physicians and "shadow-billings" for physicians paid under alternate payment plans. Data are collated by fiscal year (April 1 to March 31 of the following year). Of note, prescription medication claim records are available only for residents on welfare or who are age 65 years and older, and were therefore not used in this study.

Subjects

The Ontario Asthma Surveillance Information System database is a validated registry of all Ontario residents diagnosed with asthma generated by using the health administrative databases described above.^{10,11} Individuals with asthma were identified by using a previously validated asthma case-definition (described in detail elsewhere), which yielded 89% sensitivity and 72% specificity in children (age 0-17 years) and 84% sensitivity and 76% specificity in adults (age 18 years or older) when compared with clinical evaluation by a physician.¹²⁻¹⁴ Only those individuals who were identified as having asthma in fiscal year 1993 (April 1, 1993, to March 31, 1994—the earliest year that individuals with asthma could be identified) were followed from April 1, 1994 (the index date), until they left the province, died, or March 31, 2009, at which point they were censored. Thus, the cohort consisted of subjects of all ages having asthma of various duration, severity, and control.

Outcomes

The primary outcome was active asthma as indicated by 1 or more physician claims for asthma (*International Classification of Diseases, 9th Revision*, diagnostic code 493 or *International Statistical Classification of Diseases, 10th Revision*, diagnostic codes J45 or J46). Such asthma claims were presumed to be the result of active or treated asthma of sufficient severity to seek medical attention and occurred when a physician took care of a patient in any location including a doctor's office, during an emergency department visit, or during a hospitalization. Nonasthma claims were not considered. The secondary outcome was a clinically significant gap in asthma activity, which was defined as a duration of 2 years or more between asthma health-care claims. A duration of 2 years was chosen because physicians are unlikely to renew asthma medications for patients they had not seen for more than 2 years because of it being both poor clinical care and medicolegally indefensible. Two years has also been used by previous studies to define asthma remission.^{3,9} Persistent asthma was asthma where a 2-year gap between asthma claims never occurred.

Covariables

Individuals were characterized in terms of several sociodemographic factors, obtained in the index year from the health administrative data. Socioeconomic status (SES) was based on the average household income of patients' neighborhood derived from the Canadian census and categorized into quintiles, with quintile 1 representing the lowest and quintile 5 the highest.¹⁵

Individuals' primary address was defined as rural or urban according to Statistics Canada's definition of rural.¹⁶ A codiagnosis of allergy was determined if an individual had 1 or more outpatient claims for allergy (*International Classification of Diseases, 9th Revision*, codes 477, 691-693). Finally, a codiagnosis of chronic obstructive pulmonary disease (COPD) was determined if a subject met a previously validated case-definition of COPD at any time during the study period.¹⁷

Analyses

Population characteristics according to asthma activity in the follow-up period were described by using frequencies and proportions and differences tested by using chi-square tests of association. The cumulative proportion of individuals with active asthma over time was determined. Gaps between asthma claims, which by definition could occur only in individuals with active asthma, were calculated. Since most clinical interest lies in how long (as opposed to how short) gaps in asthma activity are, for individuals with multiple gaps, only the longest gaps were reported overall and by patient characteristics. Since patients who died or left the province could contribute only shorter gaps in asthma activity, to avoid bias in reporting, only gaps in individuals with complete follow-up were described.

The adjusted hazards of repeated asthma health care claims across individual characteristics were determined by using multivariable, recurrent-event survival analysis, controlling for sociodemographic and clinical characteristics. All statistical tests were 2-sided, with statistical significance defined as a *P* value of less than .05 and performed by using SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

Sensitivity analysis

To address the concern that using a single asthma-related claim may overestimate clinically relevant asthma activity, the primary analysis was repeated twice, with active asthma defined as having 2 and then 3 physician visits for asthma. The date of the later claim was used to denote the time of asthma activity. To account for the fact that it would be impossible for an individual without a first claim to have a second, or an individual without a second claim a third, a second analysis examined the cumulative proportion of individuals who had first and second claims and went on to have, respectively, second and third claims.

Ethics statement

Research ethics approval was obtained from the institutional review boards at The Hospital for Sick Children and Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

RESULTS

Subjects

There were 613,934 individuals identified as having asthma in Ontario as of April 1, 1994, of whom 114,572 (19%) died or left the province during the 15-year follow-up period at which time they were censored (Fig 1). Most were female and lived in an urban center. Approximately one fifth were age 5 years or younger, 24% were age between 6 and 17 years, and only 11% were age 65 years and older (Table I). Compared with those with complete follow-up, those who died or left the province were older, of lower SES, more likely to have COPD, and less likely to be atopic (data not shown).

Active asthma

During the study period, 504,851 (82.3%) individuals had active asthma (at least 1 physician claim for asthma; Fig 1), accruing a total of 5,121,597 asthma-related claims (3% hospital

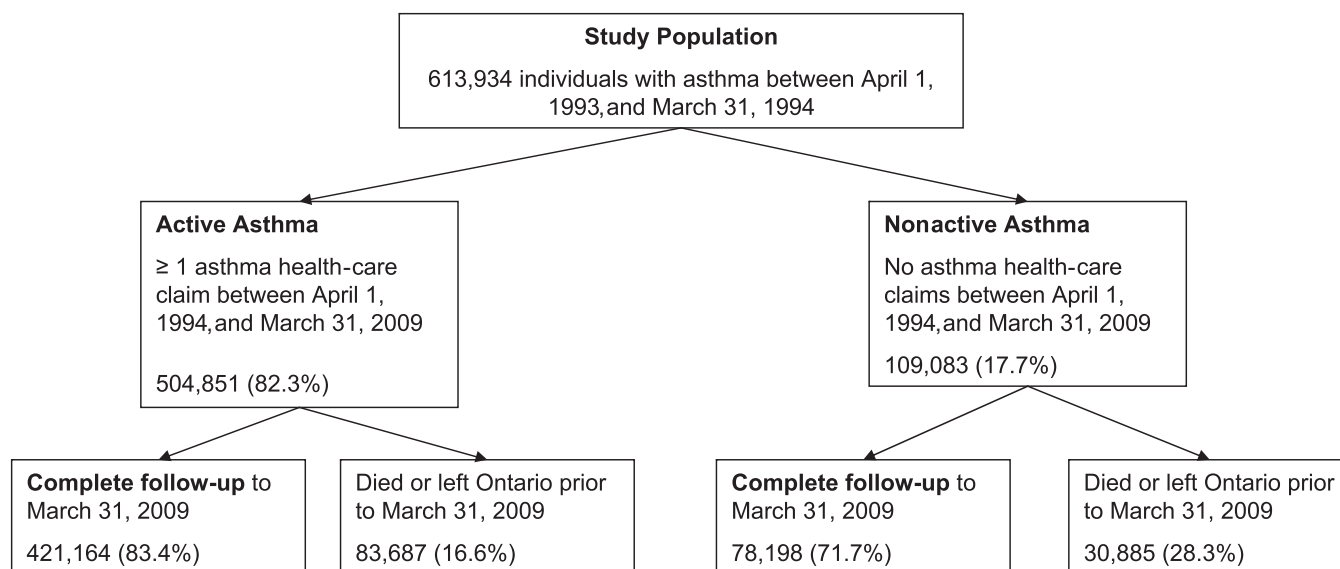


FIG 1. Flow diagram of study population.

discharges, 97% ambulatory claims). The individual median total number of asthma-related health care claims was 4 (interquartile range, 1-11). Over the study period, higher claim rates were seen in the first years of follow-up across all age groups, ranging from 870 per 1000 population among 6- to 17-year-olds to 1579 per 1000 among those aged 65 years and older (Fig 2). By the 15th year of follow-up, claim rates leveled off, ranging from 195 per 1000 among those aged 0 to 5 years at study inception to 572 per 1000 among those aged 18 to 64 at study inception. The median time from the index date to first claim was 0.71 years, and 64% of individuals had at least 1 claim within the first 2 years of follow-up (Fig 3). Compared with those with inactive asthma, those with active asthma were more likely to be female, live in an urban location, and have COPD (Table I).

Gaps in asthma activity

Among the 421,164 people with active asthma with complete follow-up (Fig 1), 314,167 (74.6%) had a gap of 2 years or more between asthma claims and the remainder had persistent asthma. Overall, 25.4% had persistent asthma, 44% a longest gap between 2 and 4 years, 25.1% a longest gap between 5 and 9 years, and 5.9% a longest gap between 10 and 15 years. The median duration of longest gaps was 3.6 years (interquartile range, 1.9-5.7 years). Females were more likely than males to have longer gaps, as were middle-aged adults and those without COPD (see Table II). Very similar distributions of longest gaps were seen for urban/rural residence. Although differences across SES and allergy groups were statistically significant, they were small (see Table II).

Characteristics associated with asthma activity

Controlling for all other variables, individuals with more prior physician claims for asthma were much more likely to have active asthma and as the frequency of physician claims increased, so did the likelihood of future asthma claims (see Table III). Adults 65

years and older and children younger than 5 years were also significantly more likely to have greater asthma activity (hazard ratio 1.36, 95% confidence interval 1.33-1.40; and hazard ratio 1.30, 95% confidence interval 1.28-1.31, respectively, when compared with those aged 6-17 years). Rates of asthma claims were also higher among patients with COPD (hazard ratio 1.47, 95% confidence interval 1.44-1.49). Lower SES and allergy had modest associations with asthma activity (see Table III).

Sensitivity analysis

When 2 and 3 asthma claims were used as indicators of asthma activity, 397,151 (76%) and 334,572 (67%) individuals, respectively, were found to have active asthma over the 15 years. The median time from the index date to the second claim was 2.3 years and to the third claim was 4.5 years (Fig 3). Approximately 87% of the population who had a first asthma health services claim had a second, and 88% of individuals who had a second asthma claim had a third (Fig 4).

DISCUSSION

We followed all individuals with asthma living in Ontario, Canada, in 1993 for 15 years to document their asthma activity—as indicated by their asthma health services use—and found that the majority had active disease that was interrupted by gaps of inactivity, often lasting years, when they were likely in remission. We also found that a history of previous claims for asthma and a codiagnosis of COPD were associated with greater asthma activity. Since there have been no major advances in altering the natural history of asthma over the last several years, these results are likely generalizable to individuals with asthma in years after 1993 as well.¹⁸ They offer insight into the natural history of asthma activity and potentially asthma remission and can be used to predict the course of asthma activity and be proactive in its management.

TABLE I. Characteristics of asthma population according to asthma activity

Characteristic	All individuals with asthma in 1993			P value
	Overall	Active asthma*	Nonactive asthma	
Overall, n (%)	613,934 (100.0)	504,851 (82.3)	109,083 (17.3)	
Female (%)	52.9	53.6	49.8	<.001
Age in 1993 (y) (%)				
5 or younger	19.1	18.6	21.3	<.001
6-17	23.9	23.7	25.1	
18-64	46.0	47.1	40.4	
65 or more	11.0	10.6	13.2	
Rural (vs urban) (%)	12.9	12.7	14.3	<.001
Socioeconomic status (%)				
Quintile 1 (lowest)	21.7	21.7	21.4	.003
Quintile 2	20.3	20.4	20.1	
Quintile 3	20.1	20.1	20.2	
Quintile 4	19.3	19.2	19.4	
Quintile 5 (highest)	18.6	18.5	18.9	
Allergy (%)	30.1	30.0	30.2	.172
COPD (%)	27.0	28.7	18.5	<.001

*Active asthma was defined as having at least 1 physician claim for asthma.

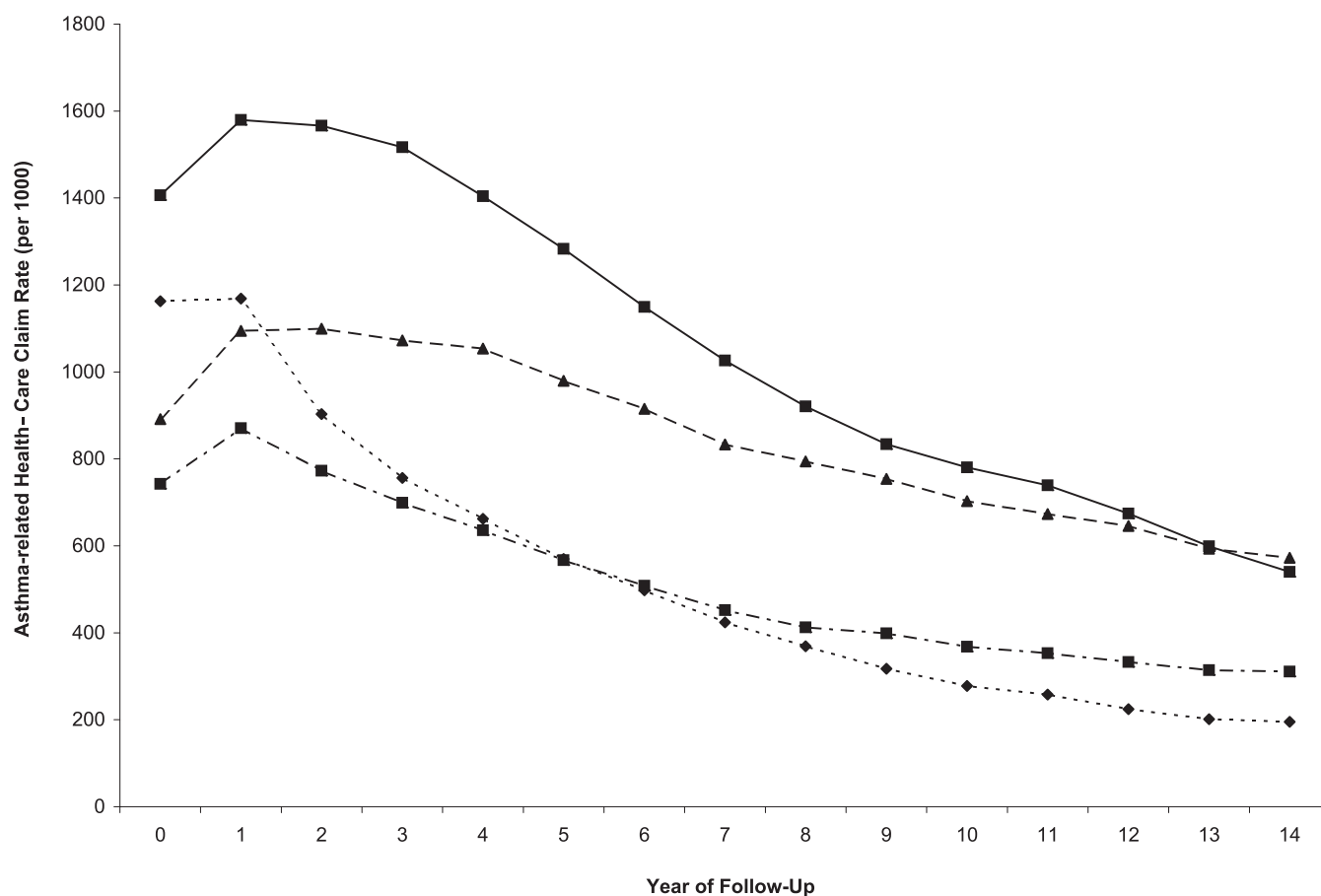


FIG 2. Annual asthma-related health care claim rate over 15 years of follow-up stratified by age at April 1, 1994. *Dotted line* indicates 0- to 5-year-old patients, *dash-dotted line* indicates 6- to 17-year old patients, *dashed line* indicates 18- to 64-year-old patients, and *solid line* indicates patients aged 65 years and older.

The high proportion of individuals with active asthma in our study is in accordance with previous work, suggesting that people diagnosed with asthma will continue to have it for life. De Marco et al⁹ followed 856 young adults with asthma for an average of 9

years and found that 88% continued to have persistent or intermittent asthma. Likewise, Horak et al⁶ found that of 168 children diagnosed with asthma between age 7 and 10 years, 79% continued to have asthma at age 42 years. Stern et al⁷ conducted a birth

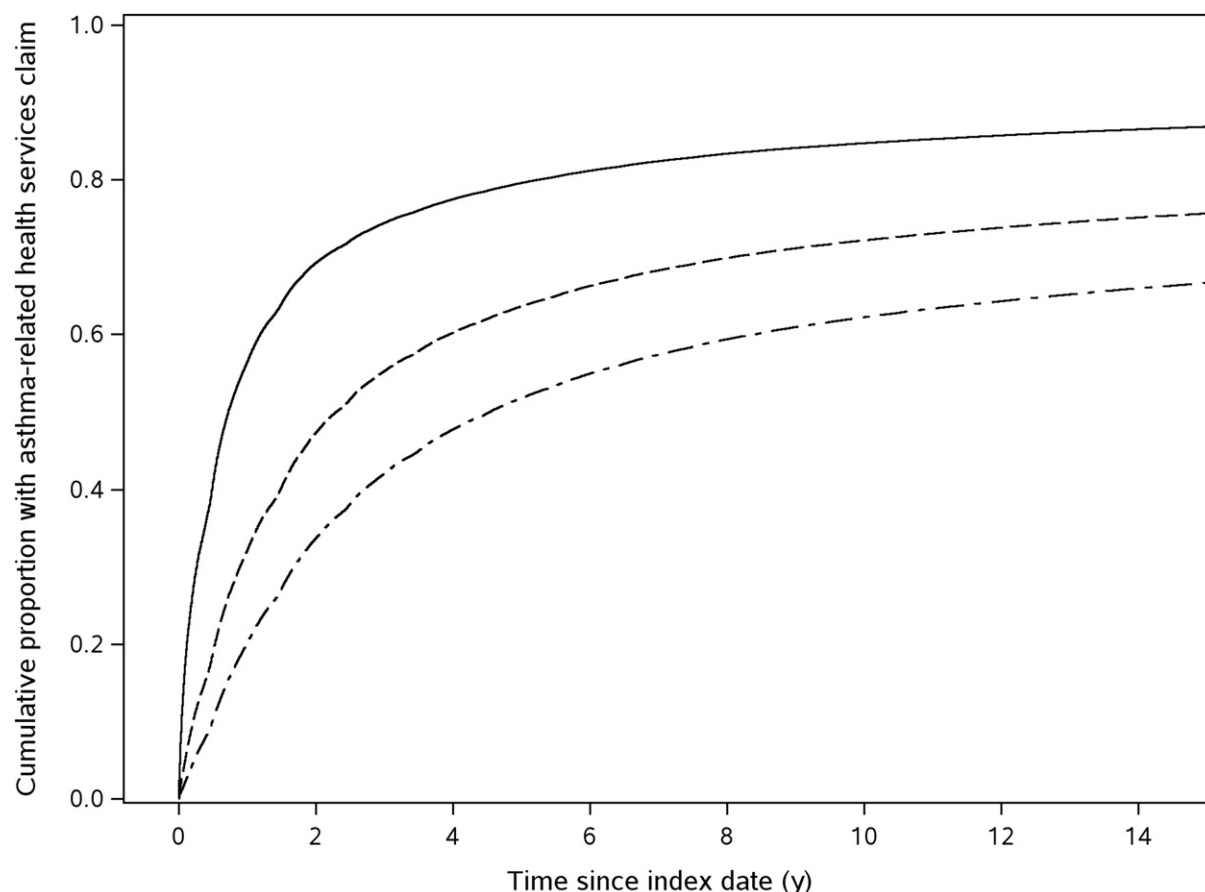


FIG 3. Cumulative proportion of individuals who experienced a first, second, and third asthma health services claim. *Solid line* indicates first asthma health services claim following index date, *dashed line* indicates second claim, and *long and short dashed line* indicates third asthma health services claim.

cohort study and found that more than 70% of 181 people with asthma at 22 years had wheezing in early life. Using a methodology similar to that used for the current study, our research group followed 34,126 children born in 1994 and found that more than 50% of those diagnosed with asthma by age 6 years had an asthma health care claim within 1 year.⁸ Supporting the “asthma-for-life” hypothesis, studies have also demonstrated that inflammatory changes found in the lungs of individuals with asthma continue to persist even when their asthma appears to be in clinical remission or have resolved.^{19,20} Our study expands on these previous findings by demonstrating that over the course of 15 years a high proportion of individuals in a large complete, provincial asthma population had active asthma.

Most individuals in our asthma population had active asthma over the study duration; however, there was a minority (17.7%) who did not. This could have been for 3 possible reasons: because they were in prolonged remission, because their asthma had resolved, or because they had mistakenly been included in our asthma cohort when they did not, in fact, have asthma. We plan to determine whether the first 2 possibilities are true by continuing to follow those individuals to see whether they have future asthma claims. We believe, however, the last possibility as the most plausible as the health administrative database case definition we used has been shown to be associated with a limited amount of misclassification.^{13,14} If those who did not have active

asthma were removed because they were misclassified, it would make the proportion with active asthma even higher than previously noted.

Our study also found that about three quarters of those with active asthma and complete follow-up experienced a gap of 2 years or more between physician visits. This suggests that the rate of remission in our asthma population was higher than other rates of remission quoted in the literature. Previous studies have found rates ranging from 15% to 50%.^{3,21-23} The difference could be because other studies measured the rate of remission at 1 or, in some cases, 2 points in time while our study measured the proportion of individuals who had gaps in their asthma activity at any time over 15 years. It could also be because other studies measured clinical remission, while our study lacked such detail.

The strength of our study was its ability to examine clinically significant asthma activity of an entire population through its longitudinal use of health services. Thus, it used data that were highly generalizable, not subject to individual recollection (ie, self-report), and had inherent significance because it represented real-life physician visits. Such data, and our study, also have important limitations that merit emphasis. To begin, our measure of asthma activity relied on the presumption that individuals use health services for asthma when (and only when) they have active disease or are on treatment, which may not always be the case.

TABLE II. Percentage of individuals with longest gaps in asthma activity of various durations, overall and by gender, age group, urban/rural residence, socioeconomic status, and codiagnosis of allergy and COPD*

Characteristic	Durations of longest gap between physician claims for asthma				P value
	Less than 2 y	2-4 y	5-9 y	10-15 y	
n	106,997	185,186	105,731	23,250	
Overall	25.4	44.0	25.1	5.5	–
Sex					
Female	23.3	44.3	26.4	5.9	<.001
Male	27.8	43.6	23.6	5.1	
Age group (y)					
5 or younger	30.4	41.2	23.3	5.1	<.001
6-17	27.5	42.3	24.7	5.5	
18-64	22.1	45.9	26.3	5.8	
65 or more	26.3	46.5	22.9	4.4	
Residence					
Rural	25.3	44.1	25.2	5.5	.839
Urban	25.4	44.0	25.1	5.5	
Socioeconomic status					
Quintile 1 (lowest)	26.2	43.9	24.5	5.4	<.001
Quintile 2	25.6	43.9	25.0	5.5	
Quintile 3	25.3	43.9	25.2	5.6	
Quintile 4	25.2	44.2	25.1	5.6	
Quintile 5 (highest)	24.7	44.0	25.9	5.5	
Allergy					
Yes	26.0	43.2	25.2	5.6	<.001
No	25.1	44.4	25.1	5.5	
COPD					
Yes	24.5	47.7	23.4	4.5	<.001
No	25.7	42.9	25.6	5.8	

*Analysis limited to individuals with complete 15-y follow-up.

People may choose not to use health services when their disease is active and, alternatively, they may choose to use health services for preventive care when their disease is inactive. The former would make it appear that gaps in care or remissions are more common than they actually are, and the latter would make it appear that asthma is more active than it actually is. Nonetheless, given that there is very little preventive care offered for asthma in remission and that our study took place in Ontario, Canada, where health care coverage is universal and barriers to its use relatively low, we believe that there would be relatively few exceptions to our presumption. Unfortunately, prescription medication claim records were available only for subjects on welfare or who were aged 65 years or older, and so these could not be used to confirm asthma activity for the whole population. In addition, privacy legislation governing access to our data strictly forbids identifying or directly contacting patients, and so we were unable to verify that gaps in care were due to remission rather than just lack of physician visits.

A second limitation was that active asthma was defined as having 1 or more physician claims—a definition that might not accurately indicate clinically relevant asthma activity over 15 years. To address this, we broadened our definition of active asthma to include 2 and then 3 claims and still found that a majority of individuals had active disease (Fig 3). Furthermore, we found that the large majority of individuals who had a first or second claim went on to have, respectively, a second and third

TABLE III. Association between patient characteristics and asthma activity

Characteristic	Recurrent event hazard ratio* (95% CI)	P value
Age (y)		
5 or younger	1.20 (1.18-1.22)	<.001
6-17	1.00	Ref
18-64	1.05 (1.04-1.07)	<.001
65 or more	1.35 (1.31-1.39)	<.001
Female	1.20 (1.18-1.22)	<.001
Rural (vs urban) residence	0.99 (0.97-1.01)	.233
Socioeconomic status		
Quintile 1 (lowest)	1.04 (1.02-1.07)	<.001
Quintile 2	1.04 (1.02-1.07)	<.001
Quintile 3	1.04 (1.01-1.06)	<.001
Quintile 4	1.01 (0.99-1.04)	.093
Quintile 5 (highest)	1.00	Ref
Allergy	1.07 (1.06-1.09)	<.001
COPD	1.49 (1.47-1.52)	<.001
Previous physician claim for asthma		
1	1.00	Ref
2	3.09 (3.05-3.13)	<.001
3	3.12 (3.08-3.16)	<.001
4-6	3.26 (3.22-3.30)	<.001
7 or more	4.40 (4.34-4.46)	<.001

CI, Confidence interval.

*Hazard of having an asthma-related health-services claim.

within a short period of time (Fig 4). This along with the increasing slope of our accumulative incident curves suggests that if we had more years of follow-up data, more individuals would have gone on to have subsequent asthma claims. Finally, although we did not specifically focus on repeated asthma claims in our descriptive analysis, our finding that most individuals had active asthma over the 15 years is corroborated by the fact that very few had gaps lasting more than 10 years between asthma claims.

A third limitation was that, as mentioned above, our case definition based on health administrative data was subject to potential misclassification when compared with clinical evaluation by a physician. This misclassification was possibly compounded by the fact that physicians do not always accurately diagnose asthma. Since asthma has been shown to be both overdiagnosed and underdiagnosed by physicians, it is not clear how such possible misdiagnosis influenced our results.²⁴⁻²⁶

A fourth limitation is that physicians in Ontario are able to submit only one diagnostic code per health services claim. Therefore, patients presenting with asthma and a coexisting medical problem (such as an upper respiratory tract infection or pneumonia) may have had their visit coded as the other diagnosis. This situation, however, would have biased our study toward finding a smaller proportion of individuals with active asthma and suggests that the already quite high level of asthma activity we observed was an underestimate.

In summary, over 15 years, we found that most individuals with asthma in Ontario, Canada, had active disease that was interrupted by gaps of inactivity, often lasting years, when they were likely in remission. These findings offer some insight into the course of asthma activity and support the hypothesis that once a person has asthma, he or she will continue to have it for life. Further study is needed to confirm these results by using detailed clinical data so that asthma patients, and their health care workers,

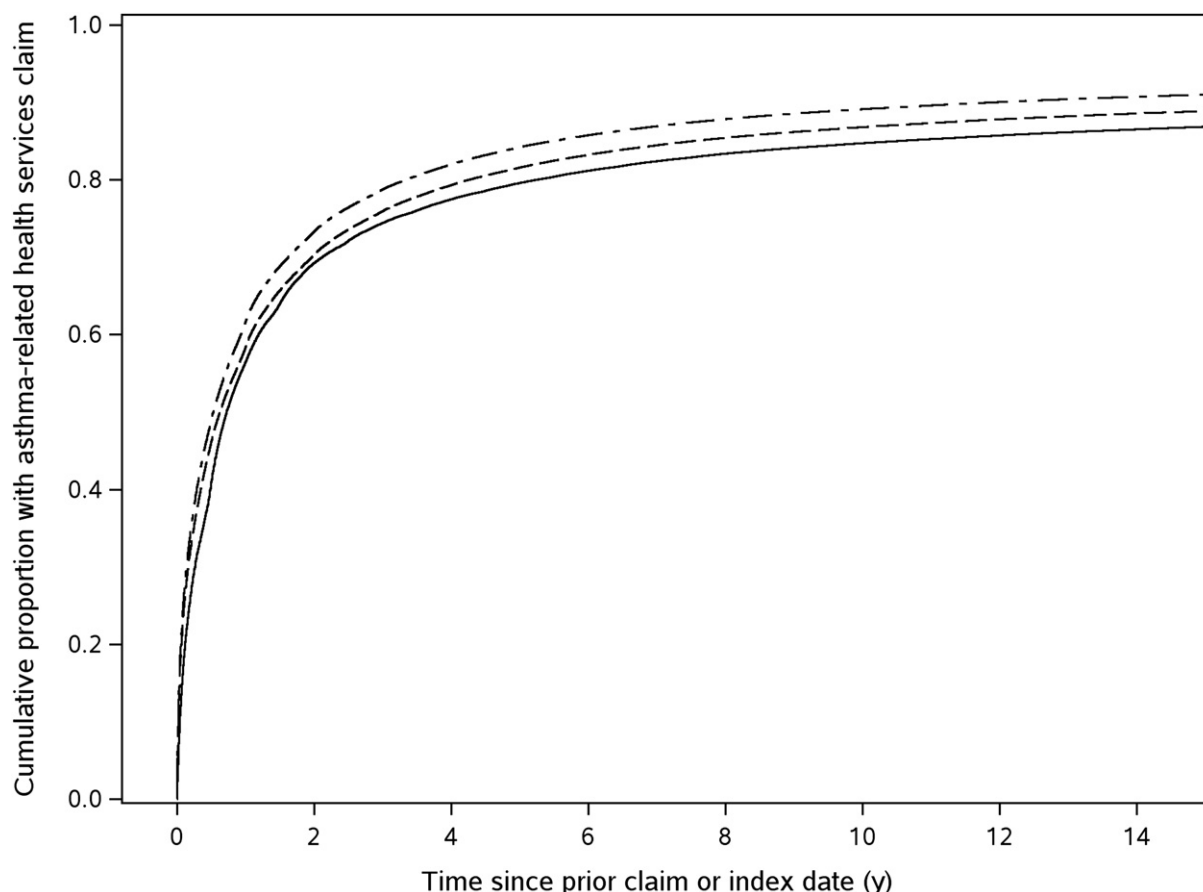


FIG 4. Cumulative proportion of individuals experiencing a first, second, and third asthma health services claims from the index date or prior claim. *Solid line* indicates first asthma health services claim following index date, *dashed line* indicates second subsequent asthma health services claim (among those experiencing a first claim), and *long and short dashed line* indicates third asthma health services claim (among those experiencing a second claim).

can accurately prognosticate and be proactive in the management of their asthma.

Clinical implications: Over a 15-year period, most patients with asthma may expect to have active disease that is interspersed by periods of time lasting years when they do not require medical attention and are likely in remission.

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