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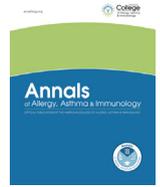
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Asthma exacerbation trajectories and their predictors in children with incident asthma

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ABSTRACT

Background: Asthma exacerbation trajectories in children after incident asthma diagnosis are understudied.
Objective: To identify trajectories of asthma exacerbation and predictors of these trajectories in children with incident asthma.
Methods: Children from the National Longitudinal Survey of Children and Youth, Canada, with incident asthma were followed-up for up to 12 years during childhood. Latent class growth modeling was used to identify distinct asthma exacerbation trajectory groups. Multinomial logistic regression was performed to identify predictors of trajectory group membership.
Results: The mean age at asthma diagnosis among 403 children was 5.9 years. Three distinct trajectories were identified: low increasing (21.3% of children), medium decreasing (45.8% of children), and high decreasing (32.8% of children). Asthma attack probability increased gradually after diagnosis in low increasing group, decreased from moderate level after diagnosis to almost zero probability at the end of follow-up in the medium decreasing group, and decreased after diagnosis but remained higher in the high decreasing group than the other 2 groups at 12 years after diagnosis. Children having more siblings at home were more likely to belong to the medium decreasing and high decreasing trajectory groups, whereas children older at asthma diagnosis were less likely to belong to the medium decreasing and high decreasing trajectory groups than the low increasing trajectory group.
Conclusion: Our results suggest that children with incident asthma follow 3 distinct trajectories of asthma exacerbations after asthma diagnosis. The trajectory group with initial moderate exacerbation probability has better long-term prognosis.

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Introduction

Asthma, a chronic disease characterized by periodic exacerbations and remissions, accounts for substantial medical and economic burden in children. Asthma exacerbations cause considerable suffering in children and can result in unscheduled emergency department visits, outpatient visits, hospitalizations, and even death.[1] Furthermore, asthma exacerbations can have extra-medical consequences such as school absenteeism and loss of parental or caregiver's productivity.[2,3] Much of the clinical-epidemiological literature on asthma has focused on the trajectories of wheezing to identify wheeze phenotypes and their subsequent association with asthma development in children,[4–6] and a few studies followed-up children since birth and attempted to identify trajectories of asthma prevalence according to age.[7–9] However, none have examined the trajectories of asthma course in children using time since asthma diagnosis as the time scale to inform the course after diagnosis.

The trajectories of asthma course in terms of exacerbations in children remain understudied. Qualitatively distinct groups of asthma exacerbation trajectories are possible among children with incident asthma. Identifying the trajectory groups and their predictors could enhance physicians' ability to better prognosticate the

course of asthma. The objectives of this study were to identify trajectories of exacerbation in children with incident asthma and to identify the predictors of these trajectories at the time of asthma diagnosis.

Methods

Data Source

Ethical approval was not needed, because the study relied on anonymous and "secondary" data from Statistics Canada. The data source for this study was the National Longitudinal Survey of Children and Youth (NLSCY), Canada. Details of the NLSCY are available elsewhere.[10] Briefly, the NLSCY used a multi-stage cluster sampling to select households in 10 Canadian provinces in 1994 to 1995 (cycle 1) with children aged 0 to 11 years. Of the 22,831 children surveyed in cycle 1, 15,405 children were followed-up for 14 years and surveyed every 2 years through the final survey (cycle 8) in 2008 to 2009, when they were 14 to 25 years old. A maximum of 2 children (siblings) were selected from each household. One person most knowledgeable about a child (aged 0-15 years) and older children (>15 years) responded to survey questionnaires administered to collect sociodemographic and lifestyle, environment, and health-related data.

Study Sample

An affirmative response to the question "Has this child ever had asthma that was diagnosed by a health professional?" asked to the person most knowledgeable for children aged 0 to 15 years in survey cycles indicated the presence of asthma. An affirmative response to the question "Have you ever had asthma that was diagnosed by a health professional?" asked to children aged older than 15 years in survey cycles 4 to 5 indicated the presence of asthma. The first-time report of asthma during survey cycles 2 through 8 indicated incident asthma diagnosed at some point during the 2 years before the survey. Children meeting the following criteria were included in our study: having a biological parent as the person most knowledgeable (parent hereafter), no asthma at survey cycle 1, and reported asthma diagnosed by a health professional during follow-up. Children with the following conditions were excluded from the study: not having a parent as the person most knowledgeable (parent hereafter) (n = 958); asthma at survey cycle 1 (n = 1530), missing asthma information at survey cycle 1 (n = 178); no health professional—diagnosed asthma during the follow-up (n = 10,617); information on asthma at less than 4 survey cycles (to be able to assess cubic pattern of the trajectories)[11] (n = 1538); and inconsistent response ("no" after "yes") on "ever diagnosed with asthma" question between surveys (n = 161). Another 20 children were excluded because of missing asthma information between surveys with a "no" and a "yes" response on asthma, which precluded identification of time of incident asthma; older child from households with 2 children to allow longer follow-up of the younger child, and children whose reported sex changed between surveys before asthma diagnosis. A total of 403 children diagnosed with incident asthma were retained for the analysis to identify trajectories during childhood. Follow-up of a child for our study started at asthma diagnosis and lasted for 6 to 12 years (up to 17 years of age), depending on the age at survey cycle 1 and the age at asthma diagnosis.

Description of Variables

"Asthma attack" was considered as the measure of asthma exacerbation. An affirmative response to the question "Has he/she had an attack of asthma in the last 12 months?" asked to parents of 0- to 15-year-old children with asthma at each survey cycle, or

"Have you had an attack of asthma in the last 12 months?" asked to 16- to 17-year-old children with asthma in survey cycles 4 or 5 was considered as having an asthma attack. The following baseline variables measured at or before incident asthma diagnosis were considered as potential predictors for trajectory group membership based on review of literature on prognostic factors in asthma[12–17] and available information in the NLSCY: sex of the child, child having health professional—diagnosed allergy as a proxy for allergen sensitization or atopy of the child, at least 1 biological parent with a history of health professional—diagnosed asthma or allergy, smoking habit of parent or spouse as a proxy for exposure to environmental tobacco smoke at home, number of siblings at home, and age at asthma diagnosis. Except age at asthma diagnosis, predictor information from the survey cycle before asthma diagnosis was used, considering a 12-month recall period for asthma attack and because predictors should be established at the time of asthma diagnosis (ie, at the beginning of period of trajectory).[18] Available information from a prior survey cycle was used to replace missing predictor data, assuming the condition remained the same at the survey cycle before asthma diagnosis. Age at asthma diagnosis and number of siblings were treated as continuous variables, and the other predictors were represented by binary variables.

Statistical Analysis

At first, a hierarchical logistic regression model was used to assess the overall pattern of asthma attack after diagnosis.[19,20] Latent class growth modeling, a semi-parametric approach, was then used to identify distinct groups of children with similar patterns of asthma exacerbations over time.[18,21] Latent class growth modeling attempts to identify trajectory groups in the population even if these trajectory groups are latent ("not identifiable ex ante on the basis of measured characteristics")[18] and thus unobservable. We first attempted to identify the number of latent trajectory groups by testing models with up to 5 latent trajectory groups. Each model included the linear, quadratic, and cubic polynomial terms for time since asthma diagnosis, to allow for the possibility of an S-shaped pattern of the relation between the logit of the probability of asthma attack and time since asthma diagnosis. Among these, the model having the lowest Bayesian Information Criterion was selected (eTable 1).[18,22] Examination of the results of statistical-significance testing of the 3 polynomial terms for time since asthma diagnosis revealed that the quadratic and cubic terms were not statistically significant. Thus, these terms were dropped from the model,[11,18] so the final model only included a linear term, suggesting a straight-line (rather than parabolic or S-shaped) pattern of the relation between the logit of the probability of asthma attack and time since asthma diagnosis. We used time since asthma diagnosis as the time axis in both hierarchical modeling and group-based trajectory modeling. Details of these analytic methods are provided in eMethods. Finally, multinomial logistic regression modeling was performed to identify the predictors of trajectory group membership. Data on parental history of asthma or allergies and exposure to environmental tobacco smoking at home were missing in 7% and 1% of children, respectively. We first performed a complete-case analysis, restricted to children having information on all predictors. We also performed sensitivity analysis after conducting 10 imputations for the missing risk factor values employing multivariate imputation using chained equations.[23]

We conducted a secondary analysis to identify asthma exacerbation trajectories restricted to children with asthma diagnosed after 6 years of age, because some preschool children with diagnosed asthma may outgrow their asthma after 6 years of age.[24,25] To identify predictors of trajectory group membership, we fitted logistic regression models. We performed a complete-case and

sensitivity analyses, which involved conducting 15 imputations for missing risk factors using multivariate imputation using chained equations.

Hierarchical logistic regression modeling was performed using SAS's PROC GLIMMIX procedure with Laplace estimation to obtain maximum likelihood estimation of the parameters (SAS Institute, Inc., Cary, NC).[26] Latent class growth modeling was performed using the PROC TRAJ procedure and multinomial logistic regression in SAS.[27] Sensitivity analysis was performed using Stata software (StataCorp LP, College Station TX). All statistical-significance tests were carried out at the alpha level of 0.05 (2-sided).

Results

We report findings on the trajectories and predictors following the recommended guidelines for reporting on latent trajectory studies, including studies using latent class growth modeling.[28]

Characteristics of Children at Asthma Diagnosis

Among 403 children retained in the analysis, the mean age at asthma diagnosis was 5.9 years; most children (61%) were male, and one fifth (20%) of the children had allergies at or before asthma diagnosis (Table 1). The mean duration of follow-up was 8 years; 170 (42%) children contributed data for 6 years, 104 (26%) children contributed data for 8 years, 79 (20%) children contributed data for 10 years, and the remaining 50 (12%) children contributed data for 12 years of follow-up. Of the 403 children, 177 (44%) were aged older than 6 years at asthma diagnosis. Among these 177 children, 136 (77%) contributed data for 6 years, and 41 (23%) contributed data for 8 years of follow-up.

Average Asthma Trajectory from Hierarchical Modeling

Table 2 presents the parameter estimates from the hierarchical logistic regression model. The fixed-effects parameter estimate for the intercept was 0.68, implying that the estimated probability of asthma attack was 0.66 at asthma diagnosis. The fixed-effects parameter estimate for time since asthma diagnosis was −0.358, implying that the odds of having had asthma attack decreased by 30% with each year increase in time since asthma diagnosis. The random-effects parameter estimates for between-child variance in both the intercept and "growth" rate of asthma attack over time since asthma diagnosis were statistically significant (Table 2, random effects) suggesting that asthma attack probability at diagnosis and asthma attack probabilities across time since asthma diagnosis vary across children. The overall trajectory of asthma attack plotted from the fitted model suggested that the probability of asthma attack decreased with time after asthma diagnosis, from 0.63 at asthma diagnosis to 0.11 at 12 years after diagnosis (Fig 1).

Table 1
Characteristics of Children at Asthma Diagnosis, National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995—2008/2009

Characteristics	Frequency (%) (n = 403)
Sex, male	246 (61)
Child has allergy	82 (20)
Parent has asthma or allergy	114 (34)
Exposure to environmental tobacco smoke at home	192 (48)
Number of siblings at home, mean (SD)	1.02 (0.83)
Age of child at asthma diagnosis in years, mean (SD)	5.90 (2.55)

SD, standard deviation.

Table 2
Parameter Estimates from the Hierarchical Logistic Regression Model, National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995—2008/2009

Parameter	Estimate (SE)	P
Fixed effects		
Intercept	0.68 (0.14)	<.0001
Time[a]	−0.36 (0.03)	<.0001
Random effects		
Between-child variance in intercepts	2.91 (0.49)	<.0001
Between-child variance in "growth" rate of asthma attack over time[a]	0.04 (0.02)	.003
Fit statistics		
BIC	2291.93	
−2 Log likelihood	2267.94	

SE, standard error; BIC, Bayesian information criterion.
[a]Time since asthma diagnosis.

Trajectory Groups of Asthma Attack from Latent Class Growth Modeling

Asthma attack over time was best fitted by a 3-group model. Figure 2A presents the trajectories of each of the 3 groups, and eTable 2 presents the estimates of the trajectory parameters and model adequacy information. The first trajectory group (*low increasing*) comprised 21.3% of children who had an initial low level of asthma attack probability that gradually increased after diagnosis and remained higher than the asthma attack probability for the second trajectory group from approximately 7 years after asthma diagnosis (Fig 2A). The second trajectory group (*medium decreasing*) comprised 45.8% of children having a moderate level of initial asthma attack probability with initial steep decrease followed by gradual decrease with almost zero asthma attack probability at the end of the 12-year follow-up. The third trajectory group (*high decreasing*) comprised 32.8% of children having very high initial asthma attack probability that decreased gradually and had a higher level of asthma attack probability than *low increasing* and *medium decreasing* trajectory groups at 12 years after asthma diagnosis. The predicted and observed trajectories for the 3 trajectory groups suggested good fit (Fig 2B). Among 104 children in the *low increasing* trajectory group, the mean age of asthma diagnosis was 6.5 (standard deviation [SD], 2.4) years, and 57 (54.8%) children had asthma diagnosed after 6 years of age; among 168 children in the *medium decreasing* trajectory group, the mean age at asthma diagnosis was 5.9 (SD 2.4) years, and 99 (58.9%) children had asthma diagnosed before 6 years of age; and among 131 children in the *high decreasing* trajectory group, the mean age at
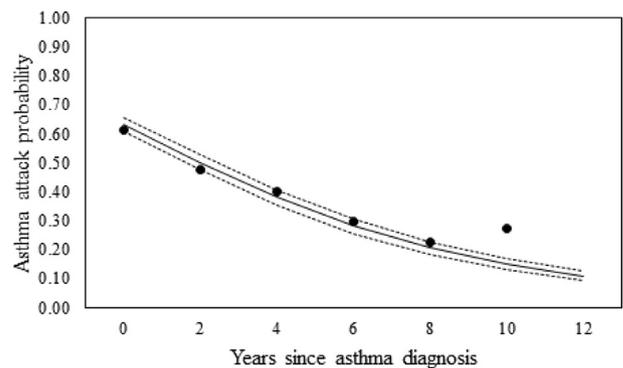
Figure 1. Overall trajectory of estimated probability of asthma attack, hierarchical logistic regression model, National Longitudinal Survey of Children and Youth, Canada, 1994/1995—2008/2009. Solid line represents the point estimate of the probability, and dashed lines represent the 95% confidence interval estimates. Black circles represent observed proportion of asthma attack. Proportion at 12 years since asthma diagnosis is not reportable because of a small sample size (n < 15) in this subpopulation.

A Asthma attack probability
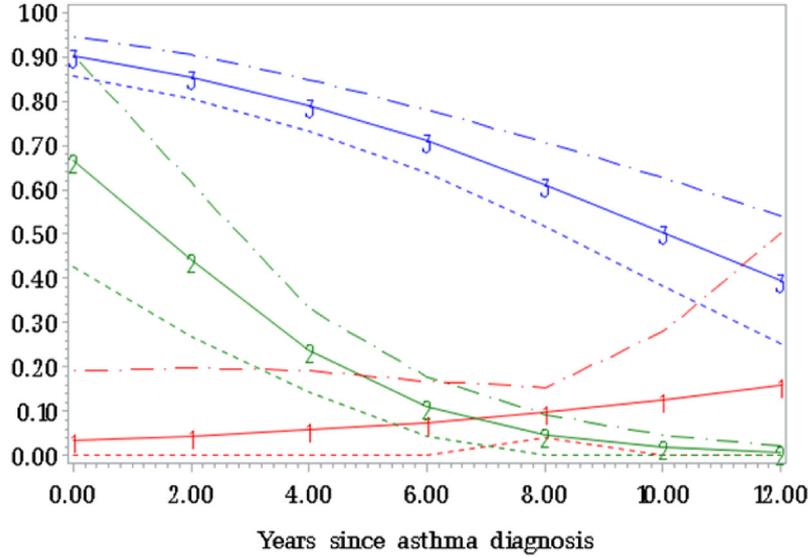
Number at each time point

Low increasing	104	99	101	100	60	27	*
Medium decreasing	167	164	159	165	107	55	28
High decreasing	131	122	131	129	78	57	27

*Frequency not reportable because of small sample size (n<15)

Low increasing (21.3%)   Medium decreasing (45.8%)   High decreasing (32.8%)

B Asthma attack probability

Number at each time point

Low increasing	104	99	101	100	60	27	*
Medium decreasing	167	164	159	165	107	55	28
High decreasing	131	122	131	129	78	57	27

*Frequency not reportable because of small sample size (n<15)

Low increasing (21.3%)   Medium decreasing (45.8%)   High decreasing (32.8%)

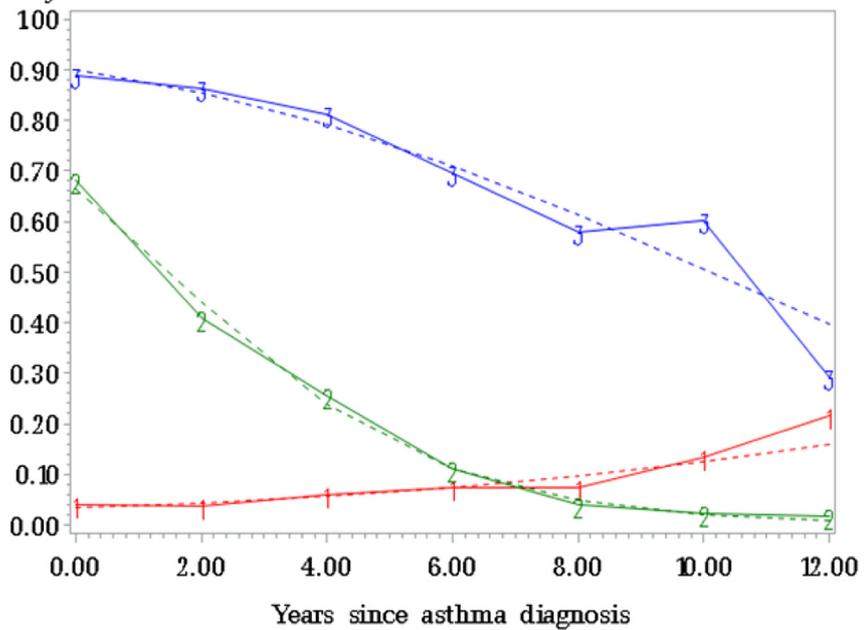**Figure 2.** Trajectories of asthma attack, latent class growth modeling, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009. **A,** Solid line depicts predicted trajectory and dashed line 95% confidence interval. **B,** Solid line depicts observed trajectory and dashed line the predicted trajectory.

asthma diagnosis was 5.4 (SD 2.8) years, and 80 (61.1%) children had asthma diagnosed before 6 years of age.

Predictors of Trajectory Groups

A total of 371 children had information on all potential predictors. According to the multivariable model, children having more siblings at home were more likely to belong to the *medium decreasing* and *high decreasing* trajectory groups, and children older at asthma diagnosis were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups than *low increasing* trajectory group (Table 3). The magnitude of the estimated association was largest for having more siblings. Male children were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups compared with the *low increasing* group, but the 95% confidence intervals were wide to allow meaningful interpretation. Similarly, imprecise results were obtained for children having allergy and exposure to environmental tobacco smoke at home, although there were positive associations with the probability of belonging to the *medium decreasing* and *high decreasing* trajectory groups. The association between having parents with asthma or allergy and trajectory group membership was ambiguous: children having parents with asthma or allergy were less likely to belong to the *medium decreasing* trajectory group but more likely to belong to the *high decreasing* trajectory group. Sensitivity analysis with imputed data for missing predictors yielded similar results (Table 3).

Asthma Attack Trajectory Groups and Predictors in Children with Asthma Diagnosed after Six Years of Age

Among 177 children with asthma diagnosed after 6 years of age, the pattern of asthma attack over time was best represented by a 2-group model. Figure 3A depicts the trajectories of these two groups, and eTable 2 depicts the estimates of the trajectory

parameters and model adequacy statistics. The first trajectory group (*low decreasing*) comprised 59.7% of children having a low level of asthma attack probability that gradually decreased during the follow-up (Fig 3A). The second trajectory group (*high decreasing*) comprised 40.3% of children having very high initial asthma attack probability that decreased gradually over the 8 years of follow-up and had a higher level of asthma attack probability than the *low decreasing* trajectory group throughout the follow-up. The predicted and observed trajectories for the 2 trajectory groups suggested good fit (Fig 3B).

In the complete-case analysis (N = 160), male children were less likely to belong to the *high decreasing* trajectory group, whereas children having allergy, having parents with asthma or allergy, with exposure to tobacco smoke at home, having more siblings at home, and being older at asthma diagnosis were more likely to belong to the *high decreasing* trajectory group compared with the *low stable* trajectory group (Table 3). Similar results were obtained with imputed data.

Discussion

Using data from a population-based longitudinal survey, we identified 3 distinct trajectories of asthma attack in children for a period of up to 12 years after incident asthma diagnosis: *low increasing, medium decreasing,* and *high decreasing*. We also identified 2 predictors of the trajectory group membership: number of siblings at home and age at asthma diagnosis. Knowledge on the trajectories could help physicians foresee disease course at the time of asthma diagnosis.

Although one fifth of the children belonged to the *low increasing* trajectory group, most of the children belonged to the *medium decreasing* and *high decreasing* trajectory groups, with substantially high probabilities of asthma attack during the initial phase of follow-up immediately after asthma diagnosis. The mean age of

Table 3

Predictors of Trajectory Groups of Asthma Attack in Children with Asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Group	Predictor	Odds ratio (95% confidence interval)			
		Complete case analysis (N = 371)		Sensitivity analysis (N = 403)	
		Bivariate	Multivariable	Bivariate	Multivariable
All children[a]					
Medium decreasing	Sex of the child, male	0.76 (0.45-1.33)	0.74 (0.42-1.29)	0.94 (0.57-1.56)	0.91 (0.54-1.53)
	Child has allergy	1.07 (0.57-2.02)	1.19 (0.62-2.30)	1.26 (0.68-2.34)	1.38 (0.73-2.60)
	Parent has asthma/allergy	0.69 (0.39-1.23)	0.67 (0.37-1.24)	0.69 (0.39-1.21)	0.64 (0.36-1.16)
	Exposure to environmental tobacco smoke at home	1.33 (0.79-2.24)	1.28 (0.75-2.18)	1.21 (0.74-1.99)	1.15 (0.69-1.91)
	Siblings at home	1.37 (0.99-1.90)	1.60 (1.11-2.30)	1.36 (0.99-1.86)	1.53 (1.08-2.16)
	Age at asthma diagnosis (years)	0.92 (0.83-1.02)	0.87 (0.78-0.98)	0.44 (0.84-1.02)	0.88 (0.79-0.98)
High decreasing	Sex of the child, male	0.83 (0.47-1.46)	0.70 (0.39-1.26)	1.01 (0.60-1.72)	0.87 (0.50-1.50)
	Child has allergy	1.02 (0.53-1.99)	1.11 (0.55-2.22)	1.11 (0.57-2.14)	1.14 (0.58-2.26)
	Parent has asthma/allergy	1.45 (0.82-2.56)	1.36 (0.75-2.49)	1.47 (0.83-2.58)	1.36 (0.76-2.44)
	Exposure to environmental tobacco smoke at home	1.41 (0.82-2.42)	1.21 (0.69-2.13)	1.27 (0.75-2.15)	1.11 (0.64-1.92)
	Siblings at home	1.26 (0.90-1.78)	1.59 (1.09-2.33)	1.34 (0.96-1.86)	1.62 (1.13-2.32)
	Age at asthma diagnosis (years)	0.83 (0.74-0.93)	0.80 (0.71-0.90)	0.85 (0.77-0.94)	0.82 (0.74-0.92)
		Complete case analysis (N = 160)		Sensitivity analysis (N = 177)	
		Bivariate	Multivariable	Bivariate	Multivariable
Children with asthma diagnosed after 6 years of age[b]					
High decreasing	Sex of the child, male	0.83 (0.44-1.56)	0.69 (0.35-1.38)	0.89 (0.49-1.61)	0.75 (0.40-1.43)
	Child has allergy	1.72 (0.85-3.50)	1.71 (0.81-3.61)	1.55 (0.78-3.08)	1.53 (0.75-3.15)
	Parent has asthma/allergy	1.28 (0.65-2.54)	1.31 (0.62-2.79)	1.26 (0.64-2.48)	1.27 (0.60-269)
	Exposure to environmental tobacco smoke at home	1.57 (0.83-2.98)	1.79 (0.92-3.51)	1.52 (0.83-2.79)	1.70 (0.91-3.20)
	Siblings at home	1.57 (1.03-2.41)	1.54 (0.99-2.39)	1.45 (0.97-2.17)	1.44 (0.95-2.18)
	Age at asthma diagnosis (years)	1.22 (0.94-1.59)	1.23 (0.93-1.62)	1.18 (0.93-1.49)	1.20 (0.93-1.53)

[a]Multinomial logistic regression, low increasing trajectory is the comparison group.
[b]Logistic regression, low decreasing trajectory is the comparison group.

asthma diagnosis in children was 5.9 years. Virus-induced wheezing is prevalent in the preschool years, and symptoms may abate soon afterward.[24,29,30] We would expect *low increasing* trajectory group with low exacerbation rate to have predominance of children with asthma diagnosed at a younger age. However, the mean age at asthma diagnosis was higher in children in the *low increasing* trajectory group compared with the mean age at asthma diagnosis in children in the *medium decreasing* and *high decreasing* trajectory groups, contrary to our expectation. Our finding of children with asthma diagnosed before 6 years of age belonging to the *medium decreasing* and *high decreasing* trajectory groups are comparable to the findings from previous studies that an earlier age at asthma onset may lead to persistent asthma in childhood.[29,31] The reason for the low level of exacerbation probability in children in the *low increasing* trajectory group warrants exploration in future studies. Children belonging to the *low increasing* group may require attention several years after asthma diagnosis to decrease the increasing probabilities of asthma attacks, and children belonging to the *medium decreasing* and *high decreasing* trajectory groups could particularly benefit from reduction in exacerbation frequency during the initial period after diagnosis. Overall, children belonging to the *medium decreasing* trajectory group have better long-term prognosis than children belonging to the other 2 trajectory groups. Lack of similar studies on individuals with diagnosed asthma and with follow-up beginning right after asthma diagnosis in children or adults precluded us comparing exacerbation trajectories identified in our study.

Having more siblings at home was positively associated with membership in the *medium decreasing* and *high decreasing* trajectory groups compared with the *low increasing* trajectory group. Having more siblings at home may have increased exposure to

respiratory infections via contact with the siblings resulting in more asthma exacerbation immediately after asthma diagnosis. Our finding is similar to the finding that larger sibship was associated with severe asthma symptoms in children aged 6 to 7 years and 13 to 14 years in a worldwide study.[32] Nevertheless, our finding seems contrary to the finding from a study reporting that exposure to older siblings was associated with an increased rate of asthma remission in childhood.[33] Assessing a factor for asthma remission measured at a particular age or time does not provide information on the role of the factor over the course of asthma. In our study, children older at asthma diagnosis experienced milder asthma course, because they were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups that had higher probabilities of asthma attack. In other studies, younger age was found to be a risk factor for asthma attack[34] and a predictor of severe asthma exacerbation in children.[35] These findings are consistent with the results from our study. However, age at asthma diagnosis was only weakly associated with frequent episodic asthma in children in another study.[36]

Exposure to environmental tobacco smoke is known to be positively associated with asthma severity and hospitalization with asthma exacerbation[37,38] and negatively associated with asthma remission.[14] In our study, the estimated association between exposure to environmental tobacco smoke at home and trajectory group membership in our study was imprecise. Nevertheless, a study reported that exposure to second-hand smoke was "not associated" with frequent episodic asthma compared with infrequent asthma in children.[36] Although exposure to environmental tobacco smoke is time-varying and can change during the course of asthma, we considered exposure to environmental tobacco smoke before asthma diagnosis as a predictor to be able to predict trajectory group membership at the time of asthma diagnosis. An imprecise association was also found between allergy in child and trajectory group membership. Parent-reported allergy in a child may have led to inaccurate documentation of child's allergy status, potentially resulting in an underestimation of the association. The point estimates suggested that allergy in a child was a weak predictor, but the upper limits of the 95% confidence interval indicated that our data are compatible with relatively strong associations too. In addition, strong predictors of asthma course may not necessarily be strong predictors of our outcome, "trajectory group." Among children with asthma diagnosed after 6 years of age, nearly three-fifths of the children belonged to the *low decreasing* trajectory group with better prognosis compared with the two-fifths of the children belonging to the *high decreasing* trajectory group. Our results weakly support the association between exposure to environmental tobacco smoke at home, siblings at home, and age at asthma diagnosis, with high decreasing trajectory group membership.

This study has several strengths. To our knowledge, this is the first study to identify trajectories of exacerbation in children after incident asthma diagnosis using a group-based trajectory method that takes into account the dynamic nature of asthma course. Use of population-based data enabled us to follow-up with children up to 12 years after asthma diagnosis. We were able to capture less severe asthma attacks that may not have necessitated urgent medical care and would have been excluded if administrative data were used. Asthma attacks managed at home, not seeking medical care, or medical care received from non–fee-for-service physicians who do not remit service information are not captured in administrative data.[39] Information on the predictors of the trajectory groups identified in this study would be readily available to the physicians even at a primary care setting.

The findings of this study need to be interpreted in light of some limitations. Our sample size was relatively small, which led to considerable uncertainty in estimated trajectory patterns, as
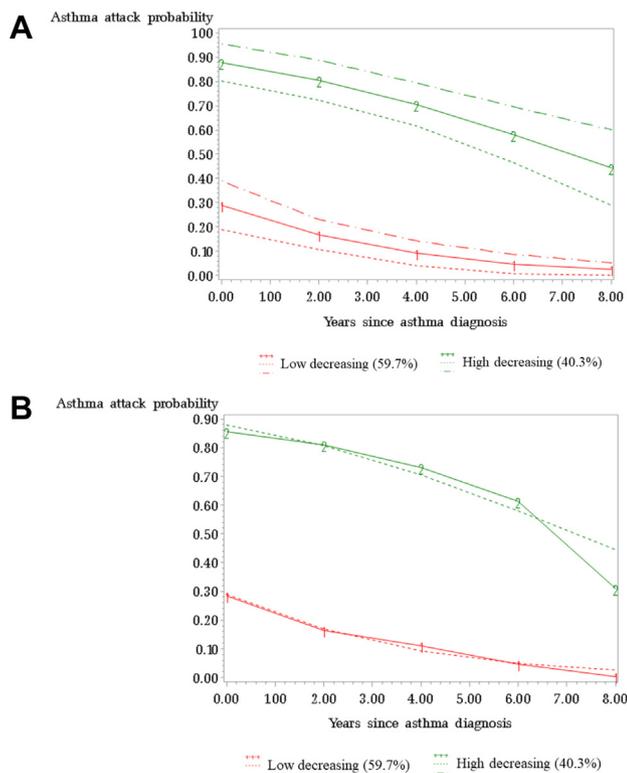

Figure 3. Trajectories of asthma attack in children with asthma diagnosed after 6 years of age, latent class growth modeling, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009. **A,** Solid line depicts predicted trajectory and dashed line 95% confidence interval. **B,** Solid line depicts observed trajectory and dashed line the predicted trajectory.

reflected by the wide confidence intervals of the trajectory curves. The small sample size also may have precluded us from identifying predictors that distinguished between *high decreasing* and *medium decreasing* trajectory groups. Thus, replication of our results in future studies is warranted. Asthma diagnosis was based on parental and child report and subject to recall bias. The prevalence of parent-reported physician-diagnosed asthma has been found to be lower than the prevalence based on health administrative data (16% vs 21%) in urban Canadian school children in cross-sectional setting.[40] However, validity of parent report of diagnosed asthma in longitudinal setting remains undetermined. Some discrepancies in response regarding the child ever having asthma over the course of the NLSCY cycles was seen, suggesting that the questions asked may not have been perceived by the respondents in the way they were intended. We excluded children with discrepant responses to obtain conservative estimates. We could not ascertain the exact age at asthma diagnosis because the question on ever having asthma was asked every 2 years, and information on exact age or date of asthma diagnosis was not available. Possibly children may have been younger than the age we considered to have asthma diagnosis. The recall period for asthma attack was 12 months before the interview, which has the potential for recall bias. Because asthma attacks affect day-to-day lives of children and caregivers with or without necessitating medical care, parents likely reliably recalled any asthma attack event. Nevertheless, we were unable to quantify asthma attack and ascertain severity because of a lack of this information. Children younger at NLSCY cycle 1 or asthma diagnosed at a younger age contributed more to the follow-up than children older at cycle 1 or asthma diagnosed at an older age. Different contribution to the follow-up by the children may have resulted in misclassification of trajectory group membership. We employed the traditional 3-step method for identifying latent trajectories and their predictors, which does not take into account the uncertainty (classification error) in group allocation.[28] However, the odds of classification error for the trajectory groups in our final models exceeded the threshold and suggest fewer classification errors. We were unable to consider some potential baseline predictors of the trajectory groups, such as respiratory tract infection, objective markers of atopy and bronchial hyper-responsiveness, severity of asthma, and asthma medication because of lack of information in the dataset.[12] Future studies should assess all potential predictors for trajectory group membership. Missing predictor values could bias the association between predictors and trajectory group membership.[41] We performed sensitivity analysis after imputing missing predictor values, and the results were similar.

In conclusion, our study suggests that children with asthma follow 3 distinct trajectories of asthma exacerbation. Membership in 2 of these trajectories was associated with 2 predictors at asthma diagnosis (number of siblings at home and age at asthma diagnosis), although the predictors were not able to distinguish between these 2 trajectories. Knowledge on the trajectories at the time of asthma diagnosis could help prognosticate the course and supplement the current paradigm of asthma management based on symptom control. Further studies on children with asthma in other settings, following children from birth through their entire childhood and using accurate measures of asthma and asthma attack, would provide further evidence on distinctive asthma exacerbation trajectories in children and enable comparison. Future studies are warranted to identify distinct predictors of the trajectory groups to predict an individual child's exacerbation trajectory pattern. A comprehensive risk assessment model should be developed in the future, incorporating predictors from this study and future studies to aid prediction of distinct asthma exacerbation trajectory groups.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.anai.2019.05.013.

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eMethods

A 2-level hierarchical logistic regression model[19,20] with repeated observations as level 1 units nested within individuals as level 2 units was performed to assess the overall pattern of asthma attack over time after asthma diagnosis and examine between-subject variability in trajectories. The combined level 1 and level 2 model included fixed effects for intercept and time since asthma diagnosis, and random effects for intercept and time since asthma diagnosis. The intercept in a logistic regression model is the log odds of the dependent variable when all of the independent variables are set to zero. Because we have 1 independent variable, "time since asthma diagnosis," in our hierarchical model, the intercept can be interpreted as the log odds of having an asthma attack around the time of asthma diagnosis. The fitted model was used to estimate time-specific probabilities of having an asthma attack, which were then plotted to depict the average trajectory of asthma attack after asthma diagnosis.

We used a logistic model for binary logit distribution in latent class growth modeling[18]: $\alpha_{it}^{j} = \frac{e^{\beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3}}{1 + e^{\beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3}}$ where α_{it}^{j} is the probability of the observed binary outcome $y_{it} = 1$ given membership in group j, $p^j(y_{it} = 1)$ with the assumption that the observed binary outcome $y_{it} = 1$ (individual i had asthma in time t) if the latent variable $y_{it}^{*} > 0$ and $y_{it} = 0$ (individual i did not have asthma in time t) if $y_{it}^{*} \leq 0$. Trajectory parameters were estimated using maximum likelihood with default start values. Identification of the trajectory groups involved a 2-stage process.[18] In the first stage, the number of latent trajectory groups to include in the model was chosen. We tested 5 candidate models with cubic polynomial function in each model: the first model with 1 latent trajectory group, the second model with 2 latent trajectory groups, the third model with 3 latent trajectory groups, the fourth model with 4 latent trajectory groups, and the fifth model with 5 latent trajectory groups (eTable 1). Among the 5 models tested, we chose the model with the lowest Bayesian Information Criterion (BIC). The BIC is a commonly used criterion for model selection, and it is calculated as $\log(L) - 0.5k \log(N)$, where L is the value of the model's maximized likelihood, N is the sample size, and k is the number of parameters estimated by the model; the model with the lowest BIC is preferred.[18,22] In the second stage, we chose the order of the polynomial defining the shape of each trajectory group in the model selected in the first stage. Including cubic polynomial function in the models in the first stage allowed for the possibility of an S-shaped pattern of relationship between the logit of the probability of asthma attack and time since asthma diagnosis. Nonsignificant quadratic and cubic terms were removed but linear terms were retained in the model regardless of significance.[11] Thus, the final model included a linear term, depicting a straight-line trajectory pattern for each trajectory group. Adequacy of the final model was assessed by 3 diagnostics: average posterior probability of each group exceeded 0.70, odds of correct classification exceeded 5, and the model estimated probability of group membership differed by less than 50% from the proportion assigned to a group based on largest posterior probability.

eTable 1
Models Tested in Latent Class Growth Modeling

No. of trajectory groups	BIC[a]	Sample size per group based on most likely group membership
All children (N = 403)		
1	−1294.47	403
2	−1163.76	251/152
3	−1160.35	232/108/63
4	−1170.10	—[b]
5	−1182.41	—[b]
Children with asthma diagnosed after 6 years of age (N = 177)		
1	−486.79	177
2	−438.52	99/78
3	−450.37	64/45/68
4	−461.57	—[b]
5	−475.74	—[b]

BIC, Bayesian information criterion.
[a]Lowest BIC is preferable.
[b]Indicates values not reportable because of small sample size (n < 15) in 1 or more groups.

eTable 2
Latent Trajectory Groups of Asthma Attack in Children with Asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Groups	Model estimated group membership, %	Assigned group membership using maximum probability rule, n(%)	Average posterior probability (AvePP)	Odds of correct classification	Parameter	Estimate (SE)	t statistic	BIC
All children (N = 403)								
Low increasing	21.3	104 (25.8)	0.72	9.48	Intercept	−3.36 (2.48)	−1.36	−1154.05
					Time to asthma diagnosis	0.14 (0.31)	0.46	
Medium decreasing	45.8	168 (41.7)	0.84	6.20	Intercept	0.69 (0.55)	1.26	
					Time to asthma diagnosis	−0.46 (0.12)	−3.95	
High decreasing	32.8	131 (32.5)	0.88	15.01	Intercept	2.21 (0.26)	8.59	
					Time to asthma diagnosis	−0.22 (0.04)	−5.89	
Children with asthma diagnosed after 6 years of age (n = 177)								
Low decreasing	59.7	99 (55.9)	0.96	16.20	Intercept	−0.90 (0.25)	−3.60	−430.29
					Time to asthma diagnosis	−0.35 (0.08)	−4.21	
High decreasing	40.3	78 (44.1)	0.87	9.92	Intercept	1.97 (0.36)	5.47	
					Time to asthma diagnosis	−0.27 (0.07)	−4.16	

BIC, Bayesian information criterion; SE, standard error.

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