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Different seasonal effect on asthma trajectories: a population-based birth cohort study

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Running title: Seasonal effect on asthma trajectories

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To the Editor:

Research has reported heterogeneity in longitudinal wheezing patterns arising in childhood.

Data-driven approaches have also identified 4 wheezing trajectory phenotypes in childhood asthma in 2 longitudinal cohorts when the types of transient early and prolonged early wheezing were

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grouped together.^{1,2} However, a large-scale study following patients from birth to the age of 10

years revealed 3 asthma trajectory phenotypes.³ The number of wheezing or asthma trajectory

subgroups was not consistent within these studies of Western countries, whereas the information is

lacking in Asian people.

Childhood asthma trajectory phenotypes vary in their association with atopic status and vulnerability

to ambient air pollution.¹⁻³ On the other hand, seasonal exacerbation patterns of asthma have been

associated with different seasonal factors.⁴ We aimed to discover trajectories of asthma from birth

to adolescence in an Asian population and to test whether seasonal exacerbation patterns,

urbanization trends and comorbid diseases are different among the identified asthma trajectories.

This study was approved by the Research Ethics Committee at the National Taiwan University

Hospital.

The sampling cohort data set was obtained from the Longitudinal Health Insurance Database of

Taiwanese National Health Insurance (NHI) Research Database. We used the database for

admissions and outpatient visits to establish a cohort retrieving all births from 1998 to 2001, tracked

from birth until the end of 2013.

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Urbanization levels in Taiwan are divided according to a Taiwan National Health Research Institute

publication.⁵ The comorbid diseases of identified asthma trajectories were defined as the proportion

of atopic dermatitis (ICD-9, 691.8; A Code, A429) and allergic rhinitis (ICD-9, 477.9; A Code, A319)

ever diagnosed and numbers of upper or lower respiratory tract infections (ICD-9, 460–466,

480–487; A Code, A310–312, A320–322).

Asthma diagnoses were identified from outpatient visit and hospital discharge records (ICD-9, 493; A

Code, A323). Patients with a minimum of 2 outpatient visits in a rolling 12-month period or a

minimum of 1 hospital admission due to asthma were defined as asthma cases each year during

periods of follow-up. The method used to identify asthma cases was found to be associated with

treated asthma⁶ and similar to that used in a study.³ In our study, diagnoses of asthma (63.5%) or

respiratory tract diseases (32.2%) constituted 95.7% of the primary diagnoses for those with a

primary or secondary asthma diagnosis. Because asthma was often comorbid with respiratory tract

diseases, we used primary and secondary diagnoses to identify asthma cases in accordance with the

literature.⁶

The prevalence of asthma was defined as the percentage of identified current asthma cases in the study population in a rolling 12-month period. Emergency department (ED) visits due to asthma were used to represent asthma exacerbation, identified by asthma cases with a copayment code for emergency care. The monthly exacerbation rate of asthma trajectory was defined as the number of ED visits averaged over the number of patients for each trajectory in the calendar month.

We used group-based trajectory modeling (GBTM) to estimate the distribution of asthma prevalence conditional on age over time. Statistical analyses were performed using Stata 14.1 software and a Stata program for estimating GBTM.⁷ The detailed description of methodology is provided in supporting information.

The onset of asthma exacerbation could be attributed to seasonal factors during the month prior to exacerbation. To reveal the seasonal effect on asthma exacerbation, the weighted monthly rate of ED visits per patient with asthma for different asthma trajectories was calculated using a weighting factor of 2/3 for the monthly rate of ED visits and 1/3 for the rate of the following month.

We used the NHI data of 1 million individuals to obtain a birth cohort of 48,473 patients born between 1998 and 2001. After the exclusion of 1,603 patients who had withdrawn from the insurance during the follow-up period, a total of 46,870 patients were enrolled.

The population prevalence of asthma was 3.8% at the age of 0 years. The prevalence then rose until the age of 6 years, at which point the prevalence (9.4%) decreased until the end of the 16-year follow-up (0.25%). We identified 5 trajectory subgroups (Figure 1, supplementary Table S1): one with no asthma (never or infrequent), representing 81.3% of the cohort; one with early-onset transient asthma (<1 yr; 7.4%); one with early-onset chronic asthma (<1 yr; 2.4%); one with late-onset transient asthma (<3 yr; 6.0%); and one with intermediate-onset chronic asthma (<1 yr; 2.9%). The characteristics of these subgroups are summarized in supplementary Table S2.

Regarding the proportions of asthma, we observed a significant increasing trend from living in a more urbanized area toward a less urbanized area in terms of early-onset transient asthma. By contrast, we observed a significant decreasing trend in terms of the other types of asthma (Table 1).

The main island of Taiwan is bisected by Tropic of Cancer and the climate ranges from tropics to subtropics in the plain. Briefly, two pollen seasons appeared in March and September and the incidence of respiratory infections peaked in January and June. Students returned to schools after winter and summer vacations on January and September, respectively.

Early-onset chronic asthma had the highest monthly exacerbation rate among the 4 asthma trajectories. The exacerbation rates of the 2 transient types were lower than those of the 2 chronic types. Seasonal peaks in early spring, middle summer, and middle and late autumn were significantly higher in chronic asthma than in transient asthma. Seasonal peaks were observed similarly in boys and girls, during ages of 0—5 years and 6—10 years. However, the seasonal peak was not obviously observed during ages of 11—15 years (Figure 2, supplementary Table S3). Thus we reasoned that the confounding effect of ages and sex on seasonal peaks of chronic asthma was small. Early-onset chronic asthma, constituting the smallest proportion of the population (2.4%), contributed to approximately 40% of ED visits associated with asthma for each month (supplementary Table S4).

In an Asian population, we identified 4 asthma trajectory phenotypes from birth to the age of 15 years, confirming findings from the United Kingdom and the Netherlands.^{1,2} These phenotypes are different in frequencies of acute exacerbation and attack seasons. The prevalence of asthma at the age of 15 years is lower than that in the 2015 data of the Centers for Disease Control and Prevention (CDC) from the United States.⁸

Compared with early-onset transient asthma, the distinctness of late-onset transient asthma identified in our study was confirmed by the proportion of comorbid allergic rhinitis and an opposite trend of proportions of asthma related to urbanization levels (Table 1). However, a study in Canada³ did not identify later-onset transient asthma.

The population prevalence of asthma at the age of 0 years (3.8%) observed in our study is comparable to the prevalence revealed by the 2015 CDC data from the United States (4.7% at the age of < 4 years). However, the same CDC data indicated an asthma prevalence of 10.2% in adolescents aged 15 to 19 years in the United States, which is much higher than the prevalence of asthma in Taiwanese adolescents in 2013. In the present study, the average prevalence of asthma at

the age of 12–15 years was 1.8%, which is comparable to a decreasing trend reported by a

Taiwanese study for the periods 1995–1996 and 2001, with the corresponding figures being 5.0%

and 4.0%, respectively.⁹ In addition, the finding is in agreement with the racial differences in asthma

prevalence in the United States.¹⁰

For asthma exacerbation among children, some factors are crucial throughout the year, such as a

pulmonary function test and previous exacerbations, whereas others vary by season, such as allergic

sensitizations.⁴ From the analysis of the different seasonal exacerbation patterns across the asthma

trajectories, seasonal factors appear to contribute differentially to the asthma subgroups.

In conclusion, 5.3% and 13.4% of children would develop chronic asthma and transient asthma,

respectively. Chronic asthma and transient asthma were differentiated by frequencies of acute

exacerbation and attack seasons. The findings could provide potential for personalized prevention.

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Table 1. Distribution of demographic factors and comorbid diseases by asthma trajectory phenotypes (N = 46,870)

	Nonasthmatic (n = 39,043)	Early-onset transient asthma (n = 2,906)	Intermediate-onset chronic asthma (n = 1,202)	Late-onset transient asthma (n = 2,641)	Early-onset chronic asthma (n = 1,078)
Age, mean (SD)	14.1 (1.1)	14.0 (1.1)	14.1 (1.1)	14.0 (1.1)	13.9 (1.1)
Female	19,310 (86.3)	1,131 (5.1)	449 (2.0)	1,115 (5.0)	364 (1.6)
Male	19,733 (80.5)	1,775 (7.2)	753 (3.1)	1,526 (6.2)	714 (2.9)
Geographic region					
North	18,588 (80.4)	1,612 (7.0)	704 (3.0)	1,515 (6.6)	701 (3.0)
Central	7,956 (86.7)	475 (5.2)	172 (1.9)	454 (4.9)	124 (1.4)
South	11,559 (85.8)	770 (5.7)	285 (2.1)	628 (4.7)	232 (1.7)
East	940 (85.8)	49 (4.5)	41 (3.7)	44 (4.0)	21 (1.9)

Urbanization level						
1 (most urbanized)	11,107 (82.8)	757 (5.6)	402 (3.0)	799 (6.0)	348 (2.6)	
2	11,458 (82.3)	893 (6.4)	378 (2.7)	821 (5.9)	376 (2.7)	
3	7,033 (84.4)	522 (6.3)	167 (2.0)	441 (5.3)	171 (2.1)	
4 (least urbanized)	9,342 (84.3)	733 (6.6)	254 (2.3)	577 (5.2)	182 (1.6)	
trend P for	<0.0001	<0.01	<0.0001	<0.01	<0.0001	
urbanization†						
ULRI, mean (SD)‡	161.1 (94.0)	215.9 (106.8)	223.0 (109.4)	222.3 (107.1)	263.9 (127.0)	
Atopic eczema§	9,026 (23.1)	1,027 (35.3)	478 (39.8)	970 (36.7)	545 (50.6)	
Allergic rhinitis¶	25,671 (65.8)	2,651 (91.2)	1,133 (94.3)	2,505 (94.9)	1,055 (97.9)	

Data are shown in n (row %) unless otherwise stated.

Some percentages do not total 100 because of rounding, and the total number of patients in the urbanization levels is not equal to 46870 because of missing data.

†Cochran–Armitage test

‡There was significant difference indicated by Tukey test between members of each pair ($p < 0.001$) except for “IOCA vs. EOTA”, “LOTA vs. EOTA” and “LOTA vs. IOCA”.

§p for trends of >0.005 (Bonferroni correction, for IOCA vs. EOTA, LOTa vs. EOTA, and LOTa vs. IOCA); p for trends of <0.005 (for EOCA vs. EOTA, EOCA vs. IOCA, EOCA vs. LOTa, EOTA vs. nonasthmatic, IOCA vs. nonasthmatic, LOTa vs. nonasthmatic, and EOCA vs. nonasthmatic). Data are shown in n (column %).

¶p for trends of >0.005 (Bonferroni correction, for LOTa vs. IOCA); p for trends of <0.005 (for IOCA vs. EOTA, LOTa vs. EOTA, EOCA vs. EOTA, EOCA vs. IOCA, EOCA vs. LOTa, EOTA vs. nonasthmatic, IOCA vs. nonasthmatic, LOTa vs. nonasthmatic, and EOCA vs. nonasthmatic). Data are shown in n (column %).

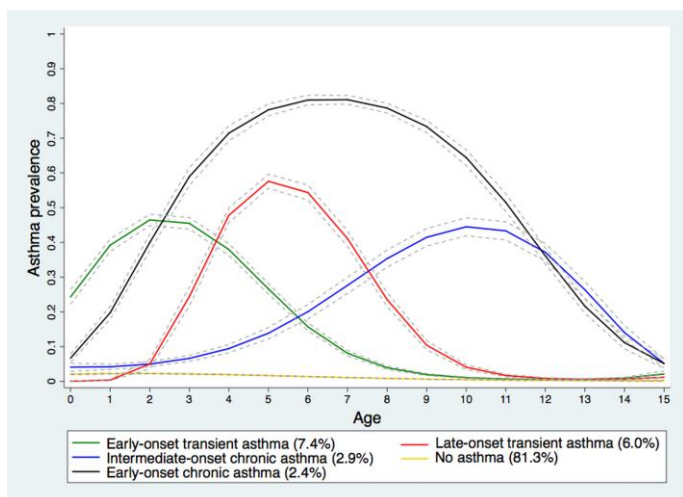
ULRI: numbers of upper or lower respiratory infections per patient throughout the follow-up periods.

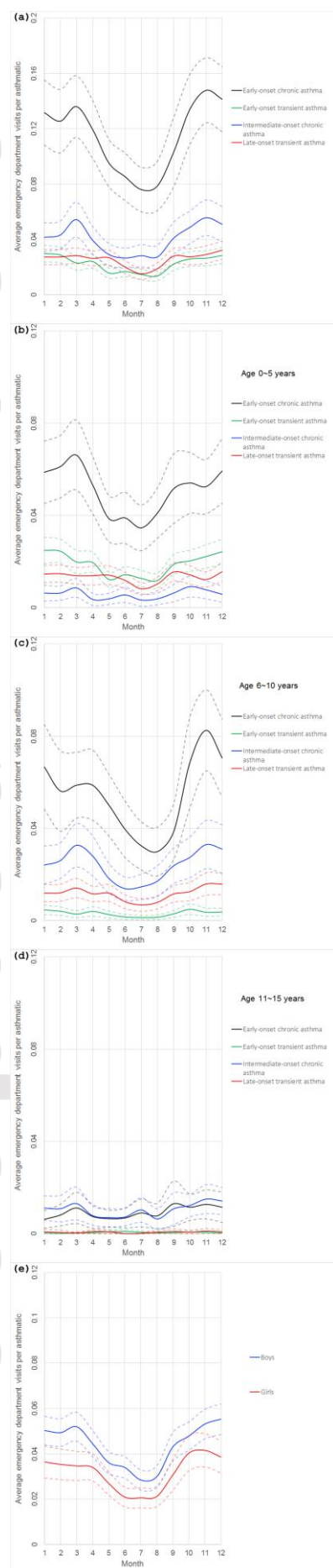
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Figure legends

Figure 1. Trajectories and 95% confidence intervals (dashed lines) for the posterior distributions of asthma prevalence from the age of 0 to 15 years in the study cohort. Asthma prevalence denotes the proportion of patients ever having a minimum of 2 outpatient visits or a minimum of one hospital admission due to asthma in a rolling year.

Figure 2. Number of emergency department visits and 95% confidence intervals (dashed lines) for asthma exacerbations distributed per month per patient with asthma by asthma trajectories (a), by trajectories and ages of 0—5 years (b), by trajectories and ages of 6—10 years (c), by trajectories and ages of 11—15 years (d), and by sex (e).





Supplementary Material

Different seasonal effect on asthma trajectories: a population-based birth cohort study

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Group-based trajectory modeling

We used group-based trajectory modeling (GBTM) to estimate the distribution of asthma prevalence conditional on age over time. Statistical analyses were performed using Stata 14.1 software and a Stata program developed by Jones and Nagin for estimating GBTM.⁷ Heterogeneity in asthma prevalence trajectories within a single population was assumed, and the population distribution of trajectories was modeled from a finite mixture of latent asthma trajectory subgroups. The unique patterns of subgroup asthma prevalence can be described using a polynomial function of age. We used binary logit distribution for the analysis of longitudinal data on a dichotomous outcome variable in terms of whether the patients fulfilled the definition of asthma at each year of age.

For model selection, we first determined the number of trajectory subgroups, followed by estimating the shape of each trajectory subgroup. The model parameters used to determine the shape of the subgroup trajectory were estimated with maximum likelihood.⁷ We started with 3 groups to fit the model repeatedly in a stepwise manner according to the literature.³

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Table S1: Model fit statistics for selection of trajectory.

	Groups [†]	Order [‡]	BIC
Model 1	3	2 2 2	-109774.2
Model 2	3	3 3 3	-109752.6
Model 3	4	2 2 2 2	-108629.4
Model 4	4	3 3 3 3	-108587.2
Model 5	5	2 2 2 2 2	-107683.5
Model 6	5	3 3 3 3 3	-107357.4

[†] Number of trajectories.

[‡] The selection of shape for each trajectory was evaluated with the selection of order (2 for quadratic and 3 for cubic).

Table S2: Posterior probability and 95% confidence intervals for asthma trajectories (EOTA: Early-onset transient asthma; IOCA: Intermediate-onset chronic asthma; LOTA: Late-onset transient asthma; EOCA: Early-onset chronic asthma) †

Age	Nonasthmatic		EOTA		IOCA		LOTA		EOCA	
0	0.02	[0.02~0.02]	0.24	[0.22~0.26]	0.04	[0.03~0.05]	0.00	[0.00~0.00]	0.07	[0.06~0.08]
1	0.02	[0.02~0.02]	0.39	[0.37~0.41]	0.04	[0.03~0.05]	0.00	[0.00~0.01]	0.20	[0.18~0.22]
2	0.02	[0.02~0.02]	0.46	[0.45~0.48]	0.05	[0.04~0.06]	0.05	[0.04~0.06]	0.40	[0.38~0.42]
3	0.02	[0.02~0.02]	0.46	[0.44~0.47]	0.07	[0.06~0.07]	0.24	[0.22~0.27]	0.59	[0.56~0.61]
4	0.02	[0.02~0.02]	0.38	[0.36~0.40]	0.09	[0.08~0.11]	0.48	[0.46~0.50]	0.71	[0.69~0.74]
5	0.02	[0.02~0.02]	0.27	[0.25~0.28]	0.14	[0.12~0.15]	0.58	[0.56~0.60]	0.78	[0.76~0.80]
6	0.01	[0.01~0.01]	0.16	[0.14~0.17]	0.20	[0.18~0.22]	0.54	[0.52~0.57]	0.81	[0.80~0.82]
7	0.01	[0.01~0.01]	0.08	[0.07~0.09]	0.28	[0.25~0.30]	0.41	[0.39~0.43]	0.81	[0.80~0.82]
8	0.01	[0.01~0.01]	0.04	[0.03~0.04]	0.35	[0.33~0.38]	0.24	[0.22~0.26]	0.79	[0.77~0.80]
9	0.01	[0.01~0.01]	0.02	[0.02~0.02]	0.41	[0.39~0.44]	0.10	[0.09~0.12]	0.73	[0.72~0.75]
10	0.00	[0.00~0.00]	0.01	[0.01~0.01]	0.44	[0.42~0.47]	0.04	[0.03~0.05]	0.64	[0.62~0.67]
11	0.00	[0.00~0.00]	0.01	[0.01~0.01]	0.43	[0.41~0.46]	0.02	[0.01~0.02]	0.52	[0.49~0.54]
12	0.00	[0.00~0.00]	0.01	[0.00~0.01]	0.37	[0.35~0.40]	0.01	[0.01~0.01]	0.36	[0.34~0.38]
13	0.00	[0.00~0.00]	0.01	[0.00~0.01]	0.26	[0.24~0.29]	0.01	[0.00~0.01]	0.22	[0.20~0.24]
14	0.00	[0.00~0.00]	0.01	[0.01~0.01]	0.14	[0.12~0.16]	0.01	[0.00~0.01]	0.11	[0.09~0.13]
15	0.00	[0.00~0.00]	0.02	[0.01~0.03]	0.05	[0.04~0.06]	0.01	[0.00~0.02]	0.05	[0.04~0.07]

†The subgroup that had a lifetime posterior probability of asthma less than or equal to 0.02 was classified as no asthma; the asthma subgroups that had a posterior probability greater than 0.04 at the age of 0 years were classified as early-onset asthma; the asthma subgroup that had a posterior probability of 0.04 at the age of 0 years was classified as intermediate-onset asthma; the asthma subgroup in which the posterior probability was 0 at the age of 0 years and subsequently increased to more than 0.02 was classified as late-onset asthma; and the asthma subgroups in which the posterior probability ever declined to 0 after asthma onset were classified as transient asthma, and otherwise, they were classified as chronic asthma. Among these asthma subgroups, 2 transient types of asthma reached remission at the ages of 9 and 11 years, respectively. The posterior probability of early-onset and intermediate-onset chronic asthma declined rapidly after the age of 12 years.

Table S3. Tukey's post hoc tests of difference between group means and 95% confidence intervals of monthly exacerbation rates for asthma trajectories, sex, and ages.

	Jan		Feb		Mar		Apr		May		Jun	
IOCA vs EOTA	0.01	[-0.01~0.03]	0.01	[0.00~0.03]	0.03	[0.01~0.05]	0.02	[0.00~0.03]	0.01	[0.00~0.03]	0.01	[0.00~0.02]
LOTA vs EOTA	0.00	[-0.02~0.01]	0.00	[-0.02~0.01]	0.01	[-0.01~0.02]	0.00	[-0.01~0.02]	0.01	[0.00~0.02]	0.00	[-0.01~0.01]
EOCA vs EOTA	0.10	[0.08~0.12]	0.10	[0.08~0.12]	0.11	[0.09~0.13]	0.10	[0.08~0.11]	0.08	[0.07~0.09]	0.07	[0.05~0.08]
LOTA vs IOCA	-0.01	[-0.03~0.00]	-0.02	[-0.03~0.00]	-0.03	[-0.04~-0.01]	-0.01	[-0.03~0.00]	0.00	[-0.02~0.01]	-0.01	[-0.02~0.01]
EOCA vs IOCA	0.09	[0.07~0.11]	0.08	[0.06~0.10]	0.08	[0.06~0.10]	0.08	[0.06~0.10]	0.07	[0.05~0.08]	0.06	[0.04~0.07]
EOCA vs LOTA	0.10	[0.08~0.12]	0.10	[0.08~0.12]	0.11	[0.09~0.13]	0.09	[0.08~0.11]	0.07	[0.05~0.08]	0.07	[0.05~0.08]
Girl vs Boy	-0.01	[-0.02~0.00]	-0.01	[-0.02~0.00]	-0.02	[-0.03~-0.01]	-0.01	[-0.02~0.00]	-0.01	[-0.02~0.00]	-0.01	[-0.02~-0.01]
6~10 vs 0~5 yr	0.00	[-0.01~0.00]	-0.01	[-0.01~0.00]	0.00	[-0.01~0.00]	0.00	[-0.01~0.00]	0.00	[0.00~0.00]	0.00	[-0.01~0.00]
11-15 vs 0~5 yr	-0.02	[-0.02~-0.02]	-0.02	[-0.02~-0.02]	-0.02	[-0.02~-0.01]	-0.02	[-0.02~-0.01]	-0.01	[-0.02~-0.01]	-0.01	[-0.02~-0.01]
11~15 vs 6~10 yr	-0.02	[-0.02~-0.01]	-0.01	[-0.02~-0.01]	-0.02	[-0.02~-0.01]	-0.02	[-0.02~-0.01]	-0.01	[-0.02~-0.01]	-0.01	[-0.01~-0.01]
	Jul		Aug		Sep		Oct		Nov		Dec	
IOCA vs EOTA	0.01	[0.00~0.03]	0.01	[0.00~0.03]	0.02	[0.00~0.04]	0.02	[0.00~0.04]	0.03	[0.01~0.05]	0.02	[0.00~0.04]
LOTA vs EOTA	0.00	[-0.01~0.01]	0.01	[-0.01~0.02]	0.01	[-0.01~0.02]	0.00	[-0.01~0.02]	0.00	[-0.01~0.02]	0.00	[-0.01~0.02]
EOCA vs EOTA	0.06	[0.05~0.07]	0.07	[0.05~0.08]	0.08	[0.06~0.10]	0.11	[0.09~0.13]	0.12	[0.10~0.14]	0.11	[0.09~0.13]
LOTA vs IOCA	-0.01	[-0.03~0.00]	-0.01	[-0.02~0.01]	-0.01	[-0.03~0.01]	-0.02	[-0.04~0.00]	-0.03	[-0.05~-0.01]	-0.02	[-0.04~0.00]
EOCA vs IOCA	0.05	[0.03~0.06]	0.05	[0.03~0.07]	0.06	[0.04~0.08]	0.09	[0.06~0.11]	0.09	[0.07~0.12]	0.09	[0.07~0.11]
EOCA vs LOTA	0.06	[0.05~0.07]	0.06	[0.05~0.07]	0.08	[0.06~0.09]	0.11	[0.09~0.13]	0.12	[0.10~0.14]	0.11	[0.09~0.13]

Girl vs Boy	<i>-0.01 [-0.01~0.00]</i>	<i>-0.01 [-0.02~0.00]</i>	<i>-0.01 [-0.02~0.00]</i>	-0.01 [-0.02~0.00]	<i>-0.01 [-0.02~0.00]</i>	<i>-0.02 [-0.03~-0.01]</i>
6~10 vs 0~5 yr	<i>0.00 [-0.01~0.00]</i>	<i>0.00 [-0.01~0.00]</i>	<i>-0.01 [-0.01~0.00]</i>	0.00 [-0.01~0.00]	0.00 [0.00~0.01]	0.00 [-0.01~0.00]
11-15 vs 0~5 yr	<i>-0.01 [-0.01~-0.01]</i>	<i>-0.01 [-0.01~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>
11~15 vs 6~10 yr	<i>-0.01 [-0.01~0.00]</i>	<i>-0.01 [-0.01~0.00]</i>	<i>-0.01 [-0.01~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>	<i>-0.02 [-0.02~-0.01]</i>

EOTA: Early-onset transient asthma; IOCA: intermediate-onset chronic asthma; LOTA: late-onset transient asthma;

EOCA: early-onset chronic asthma

Statistically significant values (p <0.05) are in bold and italics.

Table S4. Proportions of number of emergency department (ED) visits by month for each asthma trajectory phenotype

	No. of ED visits	Early-onset transient asthma (EOTA) (n = 2,906)	Intermediate-onset chronic asthma (IOCA) (n = 1,202)	Late-onset transient asthma (LOTA) (n = 2,641)	Early-onset chronic asthma (EOCA) (n = 1,078)
Jan	351	24.7%	14.2%	20.6%	40.5%
Feb	343	24.4%	15.1%	21.1%	39.4%
Mar	354	18.9%	18.5%	21.1%	41.5%
Apr	316	22.2%	15.0%	22.1%	40.8%
May	254	18.0%	13.8%	27.9%	40.4%
Jun	226	21.7%	14.2%	23.5%	40.7%
Jul	199	21.5%	17.1%	20.1%	41.3%
Aug	208	19.1%	15.9%	24.1%	40.9%
Sep	299	21.6%	16.5%	24.7%	37.2%
Oct	351	21.4%	16.7%	20.7%	41.2%
Nov	380	20.2%	17.6%	20.2%	41.9%
Dec	382	21.7%	16.1%	22.4%	39.9%

Data are shown in row %.