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Original Article

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Longitudinal Trajectories of Asthma and Allergic Comorbidities in the Korean Childhood Asthma Study

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ABSTRACT

Purpose: Studies on the longitudinal clinical features of asthma or allergic comorbidities in children are limited. We aimed to examine the trajectories of asthma and allergic comorbidities and determine whether these trajectories differ according to clinical asthma phenotypes from birth to adolescence.
Methods: We enrolled 958 children with physician-diagnosed asthma from the Korean childhood Asthma Study (KAS) cohort. Children with asthma were classified using

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hierarchical cluster analysis. Information on the diagnosis and treatment of allergic diseases before cohort entry was collected through linkage with national claims data from the Health Insurance Review and Assessment Service.

Results: In the KAS cohort, approximately half had a history of atopic dermatitis (AD) before infancy, with its prevalence gradually decreasing during adolescence. The prevalence of allergic rhinitis (AR) increased with age. The prevalence of asthma increased during early childhood and decreased during adolescence. According to the natural progression of asthma, AD, and AR trajectories, 4 distinctive phenotypes were identified using latent class analysis: "almost controlled," "early-onset asthma with AD and late-onset AR," "early-onset asthma only," and "intermediate-onset asthma and late-onset AR." Four distinct clinical trajectory patterns of asthma, AD, and AR were identified among the 4 cluster phenotypes based on baseline characteristics. Cluster 1 comprised male-dominant, atopic asthma with early-onset AD and late-onset AR. Cluster 2 included early-onset, atopic asthma with AD" persistent into adolescence. Cluster 3 encompassed "puberty-onset, female-dominant atopic asthma" with early-onset and low remission rates. Cluster 4 comprised "early-onset asthma with less atopic features" and the lowest comorbidities of AD and AR.

Conclusions: The longitudinal trajectories of asthma and allergic comorbidities in Korean children can be classified into distinct clusters. Most phenotypes exhibited early-onset asthma with a varying prevalence of comorbidities. The persistence of AD, rather than its onset age, determines the phenotype.

Keywords: Asthma; dermatitis, atopic; rhinitis, allergic; phenotype; cohort studies; cluster analysis; child; adolescent

INTRODUCTION

Asthma is a heterogeneous, chronic airway disease characterized by recurrent and reversible bronchial obstruction.[1] Childhood asthma presents diverse clinical phenotypes and follows varied natural trajectories from early childhood to adulthood depending on its endotypes and functional and/or pathophysiological mechanisms.[2,3] Clearly differentiating these clinical phenotypes and endotypes is essential for improving and personalizing asthma treatment.[4,5] Understanding the allergic comorbidities associated with different childhood asthma phenotypes is also crucial, as these comorbidities can affect asthma symptoms and progression.

In South Korea, the Health Insurance Review and Assessment service (HIRA) database, also known as National Health Insurance data, serves as a repository for claims data collected during the reimbursement process for healthcare providers.[6] Operating under a universal coverage system that includes all South Korean citizens, the HIRA database contains extensive, detailed information on healthcare services, including treatments, pharmaceuticals, procedures, and diagnoses, for nearly 50 million beneficiaries.[6,7] This claims data can be reviewed retrospectively with the patient's consent. Although this study is retrospective, it has the advantage of monitoring the patient's disease diagnosis, treatment, and progression, including the identification of comorbidities. Integrating these data into prospective cohort studies enables assessment of the natural course of patients' diseases, including evaluation of their previous disease patterns before recruitment.

Studies investigating the longitudinal clinical features of asthma and allergic comorbidities in Korean children remain scarce. The Korean childhood Asthma Study (KAS) is the first

nationwide prospective cohort study to identify asthma phenotypes in Korean children.[3] Using this cohort, we aimed to examine trajectories of asthma and allergic comorbidities and investigate whether these trajectories differ according to clinical asthma phenotypes, using longitudinal HIRA data from birth to adolescence.

MATERIALS AND METHODS

Study participants

The KAS, a nationwide, prospective, multicenter cohort study, was conducted in 19 tertiary hospitals between August 2016 and December 2018. Pediatric allergists and pulmonologists diagnosed asthma in the study participants. A total of 958 children, aged 5 to 15 years, with physician-diagnosed asthma, were included in the KAS. Details of the study design, including initial and follow-up evaluations of participants, are provided elsewhere.[8]

Data from the HIRA were merged with the KAS data for each patient to obtain information on healthcare utilization. Medical prescription records and the 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes for diagnosing asthma and other allergic comorbidities were surveyed from birth to age 13 (**Fig. 1**).

The study was approved by the following Institutional Review Boards (IRBs): Asan Medical Center (IRB No. 2016-0914); Seoul National University Hospital (IRB No. 1607-165-779); Pusan National University Yangsan Hospital (IRB No. 05-2016-121); Inha University Hospital (IRB No. 2016-07-016-008); Seoul National University Bundang Hospital (IRB No. 10-2017-036); Chonnam National University Hospital (IRB No. 2017-201); Korea University Anam Hospital (IRB No. 2015 AN 0310); Soonchunhyang University Hospital in Seoul (IRB No. 2017-01-011-002); Bucheon St. Mary's Hospital (IRB No. HC16SNMI0056); Sungkyunkwan University Samsung Changwon Hospital (IRB No. 2017-02-006-001); Kangdong Sacred Heart Hospital (IRB No. 2016-12-007-001); Catholic University of Korea, Uijeongbu St. Mary's Hospital (IRB No. UC16ONMI0113); Chungbuk National University Hospital (IRB No. 2016-09-003); Dankook University Hospital (IRB No. 2017-02-013); Korea University Guro Hospital (IRB No. 2016GR0336); Inje University Seoul Paik Hospital (IRB No. 2016-314); CHA Gangnam Medical Center (IRB No. GCI-16-37); National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2017-02-008); and Soonchunhyang University School of Medicine

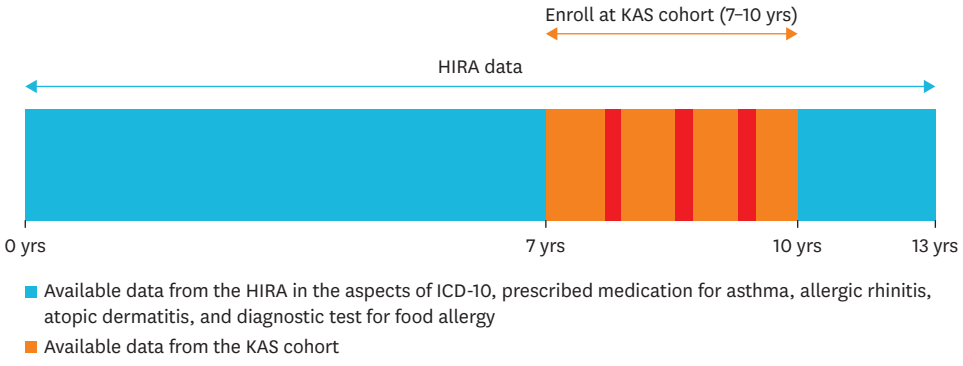

Fig. 1. Structure of data used in the present study.
KAS, Korean childhood asthma study; HIRA, Health Insurance and Review Assessment; ICD-10, the 10th International Statistical Classification of Diseases and Related Health Problems.

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in Bucheon (IRB No. 2016-08-007-009). Written informed consent was obtained from the parents and guardians of all patients after a comprehensive explanation of the study.

Assessment of asthma and other allergic comorbidities

The participants' previous medical records, including diagnoses and treatments for asthma, allergic rhinitis (AR), and atopic dermatitis (AD), were acquired from the HIRA database. Asthma was confirmed by the presence of asthma diagnosis codes J45 and J46 and at least one annual prescription of any of the followings: inhaled corticosteroids (ICS), ICS combined with inhaled long-acting β2-agonists (ICS/LABAs), inhaled short-acting β2-agonists (SABAs), LABAs, oral leukotriene receptor antagonists (LTRAs), xanthine derivatives, and systemic corticosteroids. AD was defined by the diagnosis code J20, along with at least one annual prescription of either topical corticosteroids or topical calcineurin inhibitors. AR was defined by diagnosis code J30, along with at least one annual prescription of intranasal corticosteroids. Food allergy was defined by the diagnosis code T781 with at least one annual measurement of allergen-specific immunoglobulin E (IgE) antibody levels using ImmunoCAP or multiple allergen simultaneous test. Anaphylaxis was defined by the diagnosis code T782 with at least one occurrence, enabling the extraction of the participants' allergic comorbidities from birth to age 13.

Cluster analysis of asthma phenotypes

Eleven clinical baseline variables were selected for a cluster analysis to define the asthma phenotypes. The variables included: 1) sex; 2) age; 3) current diagnosis of AR defined as AR symptoms within the last 12 months and a physician's diagnosis at baseline; 4) current diagnosis of AD defined as AD symptoms within the last 12 months and a physician's diagnosis at baseline); 5) a lifetime history of AD diagnosis; 6) a history of acute bronchiolitis; 7) puberty stage[9]; 8) age at asthma onset; 9) atopy defined as a positive response to at least one allergen in allergen-specific IgE antibody tests; 10) baseline predicted forced expiratory volume in 1 second (FEV1) (%); and 11) frequency of asthma symptoms. These variables were collected and evaluated during the recruitment of the KAS cohort from 2016 to 2018.[8] Asthma remission was defined as the absence of asthma medication prescriptions, including ICS, LTRAs, SABAs, and LABAs, along with the absence of medical visits due to asthma exacerbation in the past 12 months, based on the HIRA data.

Statistical analysis

A cluster analysis of the cross-sectional variables was performed at baseline using a hierarchical clustering algorithm following the Ward minimum variance method, to minimize the total within-cluster variance.[10] Differences among clusters were compared using analysis of variance (ANOVA) for continuous variables and chi-square (χ^2) tests for categorical variables, with Bonferroni correction adjustment for multiple comparisons. Variables showing significant differences among clusters ($P < 0.05$) were considered potential distinguishing features.

Longitudinal asthma clusters with allergic comorbidities were classified using a method that identifies clusters of longitudinal trajectories. This method determines various longitudinal patterns of changes in quantitative health indicators using HIRA data.[11] Prevalence rates of asthma, AD, AR, food allergies, and anaphylaxis from birth to age 13 were collected. Subsequently, these selected measures were analyzed to identify subgroups of patients with similar longitudinal trajectories using factor analysis. This analysis determined the longitudinal changing patterns, including stable–unstable, increasing–decreasing, linear–nonlinear, and monotonic–nonmonotonic.

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Subsequently, latent class analysis (LCA) was used to identify distinct individual changes in the diagnoses of asthma, AD, and AR. Using HIRA data and the definitions of asthma, AD, and AR from birth to age 13, models of 1–7 latent classes were repeatedly fitted with the number of latent classes in a stepwise fashion. The best-fit model was assessed using log-likelihood and Akaike's information criterion, adjusted Bayesian information criterion, entropy, the Lo-Mendell-Rubin adjusted ratio test, and clinical judgment.[12]

Data management and statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), respectively. All reported *P* values were 2-sided, and a *P* value of < 0.05 was considered significant.

RESULTS

Participant's baseline characteristics

The baseline characteristics of 958 patients are presented in **Table 1**. The mean age of the study population was 9 years, and the proportion of boys was higher (64.7%) than that of girls (35.3%). The age of asthma symptom onset was mostly below 6 years, and approximately one-third of the patients had a history of bronchiolitis. Mild persistent asthma was the most common (38.0%), followed by mild intermittent asthma (36.2%), moderate persistent asthma (25.1%), and severe persistent asthma (0.01%). The mean values of the pulmonary function tests were as follows: forced volume vital capacity (FVC) at 97.1% ± 15.1% predicted, FEV1 at 90.2% ± 16.4% predicted, and FEV1/FVC at 79.1 ± 18.4.

Longitudinal trajectories of allergic comorbidities among children with asthma

This study is based on the HIRA dataset, which allows for long-term prospective monitoring of allergic disease diagnosis and progression from birth to age 13 before asthma diagnosis. In this analysis, patients aged > 13 years were excluded owing to the small number of follow-up participants identified as outliers, affecting the overall outcome flow (**Fig. 2**).

Chronological analysis of asthma progression in the KAS cohort revealed that more than half of the participants exhibited symptoms indicative of asthma during early infancy. Although defining asthma in early infancy based on the claimed diagnostic ICD-10 codes and related asthma treatment transcription codes from HIRA data has limitations, recurrent wheezing in early childhood often progresses to childhood asthma. Childhood asthma was most prevalent among school-aged children, with a tendency of its prevalence decreasing during adolescence.

Among the study population, the highest rate of allergic comorbidities was observed in patients with AD. Specifically, about 50% of the participants were diagnosed with AD at age one. The prevalence of AD gradually decreased with age, dropping to < 15% by age 13. In contrast, AR showed its highest incidence around ages 8 to 9 years, with a slight decline during mid-adolescence. It remains the most prevalent comorbid allergic disease in school-aged children. Owing to the extremely low frequencies of diagnoses, analyzing trends in food allergies and anaphylaxis was challenging.

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Table 1. Baseline characteristics of the study participants

Characteristics	Patients (n = 958)
Age (yr)	9.0 ± 2.6
Male	620/958 (64.7)
Current AR diagnosis	729/952 (76.6)
Current AD diagnosis	192/761 (25.2)
Lifetime history of AD	370/944 (38.6)
History of acute bronchiolitis	339/930 (36.5)
Anthropomorphic features Tanner stage	
I	673/940 (71.6)
II	154/940 (16.4)
III	70/940 (7.4)
IV	30/940 (3.2)
V	13/940 (1.4)
BMI (kg/m^2)	19.5 ± 3.4
Age at asthma symptom onset (yr)	
< 3	153/941 (16.3)
≥ 3 to < 6	294/941 (31.2)
≥ 6 to < 9	271/941 (28.8)
≥ 9 to < 12	153/941 (16.3)
≥ 12	70/941 (7.4)
Asthma severity	
Mild intermittent	344/951 (36.2)
Mild persistent	361/951 (38.0)
Moderate persistent	239/951 (25.1)
Severe persistent	7/951 (0.01)
Frequency of asthma symptoms	
None	220/915 (24.0)
< 1/month	270/915 (29.5)
≥ 1/month to < 1/week	195/915 (21.3)
≥ 1/week to < 2/week	87/915 (9.5)
≥ 2/week to < 1/day	90/915 (9.8)
≥ 1/day	53/915 (5.8)
Methacholine (PC20, mg/mL), mean (1 SD range)	6.7 (0.1–44.1)
Baseline FVC (% predicted)	97.1 ± 15.1
Baseline FEV1 (% predicted)	90.2 ± 16.4
Baseline FEV1/FVC (% predicted)	79.1 ± 18.4
Positive skin test response, atopy (%)	703/957 (73.5)

Data are presented as the number (%) or mean ± SD, unless otherwise indicated.
AR, allergic rhinitis; AD, atopic dermatitis; BMI, body mass index; PC20, provocative methacholine concentration causing a 20% reduction in FEV1; FVC, forced volume vital capacity; SD, standard deviation; FEV1, forced expiratory volume in 1 second.

Phenotype-specific trajectories of childhood asthma, AD, and AR based on LCA

We investigated the natural progression of asthma and allergic comorbidities in the KAS cohort and classified them into distinct phenotypes. Through LCA of 958 participants, we identified 4 distinct groups characterized by notable traits (**Fig. 3**). The demographic characteristics of the population included in the LCA are presented in **Supplementary Table S1**.

Group 1 had the lowest asthma prevalence rate when monitored up to the age of 13, even among the asthma population, and exhibited low prevalence of AD and AR from birth to age 13, similar to the control group (n = 13, 1.4%; control). Group 2, the largest group, comprised patients who had AD during infancy and exhibited a high prevalence of asthma from an early age, and developed AR around school age (n = 602, 62.9%; early-onset asthma with AD and late-onset AR). This cluster pattern resembled allergic march, though it was distinguished by a high prevalence of asthma in early childhood. Group 3 had the highest prevalence rate of asthma when tracked up to the age of 13, which developed in early childhood and persisted beyond teenage years. However, this group exhibited the lowest rates of comorbid AD and

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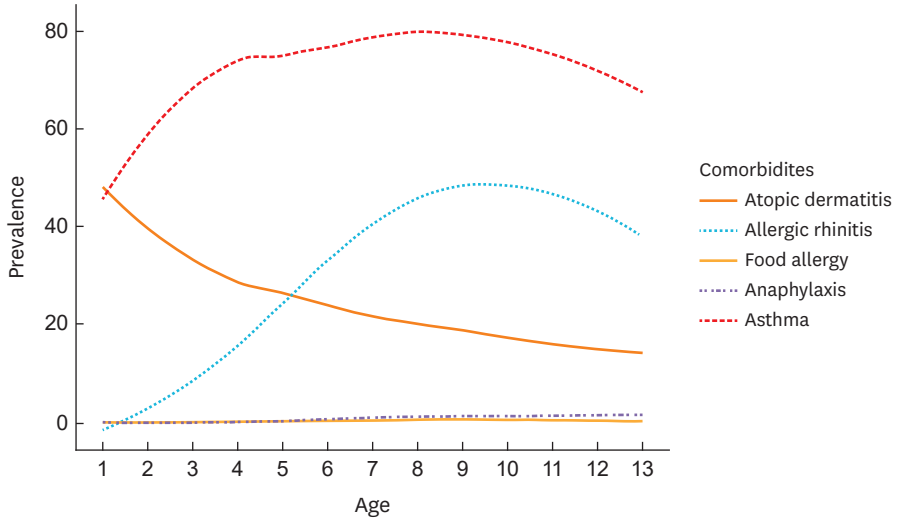

Fig. 2. Longitudinal trajectories of allergic comorbidities among childhood asthma.

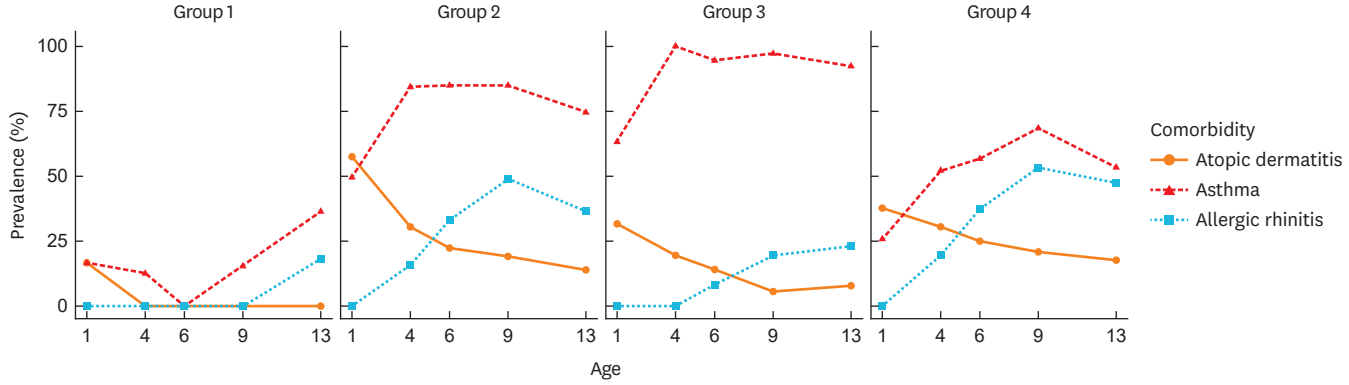

Fig. 3. Phenotype-specific trajectories of childhood asthma, atopic dermatitis, and allergic rhinitis based on the results of latent class analysis.

AR, reflecting an "early-onset asthma only" phenotype (n = 36, 3.8%). Lastly, Group 4 showed a relatively low prevalence of AD and asthma during early childhood, but peaked in asthma and AR prevalence at age 8 (n = 306, 32.0%; late-onset asthma with AR).

Four asthma phenotypes by cluster analysis at baseline

Cluster analysis using 11 clinical baseline variables was conducted in the KAS cohort, recruited between 2016 and 2018, to define asthma phenotypes. Participants with missing data on any cluster variables were excluded, resulting in 794 out of 958 patients eligible for analysis. All variables showed significant differences among the 4 clusters. Baseline characteristics of the 4 asthma phenotypes are described in **Table 2**.

Cluster 1 (n = 396, 49.9%) was characterized by male-dominant, atopic asthma. Cluster 2 (n = 145, 18.3%) featured early-onset, atopic asthma with AD. Cluster 3 (n = 127, 16%) consisted of predominantly female adolescents with the lowest pulmonary function and was classified as puberty-onset, female-dominant, atopic asthma. Finally, cluster 4 (n = 126, 15.9%) was characterized by early-onset asthma, with a low tendency for atopic features. Based on the HIRA data, the rate of asthma remission in the previous 12 months at age 13 was lowest in cluster 3, followed by clusters 1, 2, and 4, with significant differences among these 4 groups

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Table 2. Clinical characteristics of the 4 clusters

Variables	Cluster 1 (n = 396)	Cluster 2 (n = 145)	Cluster 3 (n = 127)	Cluster 4 (n = 126)	*P* value	Bonferroni
Age (yr)	8.3 ± 2.0	8.9 ± 2.2	12.5 ± 2.2	7.7 ± 2.0	< 0.001	3 > 1 = 2 ≥ 4
Male	307 (77.5)	98 (67.6)	34 (26.8)	77 (61.1)	< 0.001	2 = 3 ≥ 4 > 1
Age of asthma onset (yr)					< 0.001	1 vs. 2, 3, and 4
< 3	68 (17.2)	29 (20.0)	9 (7.1)	26 (20.6)		
≥ 3 to < 6	139 (35.1)	53 (36.6)	16 (12.6)	50 (39.7)		
≥ 6 to < 9	128 (32.3)	40 (27.6)	18 (14.2)	33 (26.2)		
≥ 9 to < 12	56 (14.1)	22 (15.2)	33 (26.0)	15 (11.9)		
≥ 12 year	5 (1.3)	1 (0.7)	51 (40.2)	2 (1.6)		
History of acute bronchiolitis	159 (40.2)	52 (35.9)	30 (23.6)	46 (36.5)	0.01	2 = 4 = 1 ≥ 3
Atopic features						
Current AR diagnosis	396 (100.0)	123 (84.8)	98 (77.2)	0 (0.0)	< 0.001	1 > 2 = 3 > 4
Current AD diagnosis	0 (0.0)	143 (98.6)	14 (11.0)	0 (0.0)	< 0.001	2 > 3 > 1 = 4
Lifetime history of AD diagnosis	103 (26.0)	136 (93.8)	57 (44.9)	19 (15.1)	< 0.001	2 > 3 > 1 ≥ 4
Positive skin test response, atopy (%)	271 (68.4)	101 (69.7)	85 (66.9)	57 (45.2)	< 0.001	3 = 2 = 1 ≥ 4
Total serum IgE levels, geometric mean (1 SD range) (KU/L)	553.0 (3.22–5,000)	751.0 (13.2–5,001)	631.0 (1.34–5,001)	405.0 (2–3,620)	0.001	3 = 2 = 1 ≥ 4
Anthropomorphic features						
Tanner stage					< 0.001	1 vs. 2, 3, and 4
I	345 (87.1)	116 (80.0)	13 (10.2)	104 (82.5)		
II	47 (11.9)	21 (14.5)	40 (31.5)	20 (15.9)		
III	4 (1.0)	7 (4.8)	37 (29.1)	2 (1.6)		
IV	0 (0.0)	1 (0.7)	24 (18.9)	0 (0.0)		
V	0 (0.0)	0 (0.0)	13 (10.2)	0 (0.0)		
BMI (kg/m^2)	18.2 ± 3.29	18.7 ± 3.6	21.2 ± 4.3	17.5 ± 2.6	< 0.001	1 > 2 = 3 = 4
Asthma remission in the previous 12 months at age 13	98 (24.8)	36 (24.8)	13 (10.2)	34 (27.0)	< 0.001	2 = 4 = 1 > 3

Data are presented as number (%) or mean ± SD, unless otherwise indicated.
AR, allergic rhinitis; AD, atopic dermatitis; IgE, immunoglobulin E; BMI, body mass index; SD, standard deviation.

(P < 0.001). The study participants were classified according to the characteristics of the 4 phenotypes previously reported in 472 KAS participants.[3] Despite the increased sample size with the HIRA data, the features of these phenotypes remained consistent.

Longitudinal trajectories of allergic comorbidities by asthma phenotype determined at baseline

We analyzed the longitudinal trajectories of asthma and allergic comorbidities using the 4 asthma phenotypes determined at baseline (**Fig. 4**). Clusters 1 and 2 exhibited relatively similar patterns, with the highest diagnosis rates of AD during infancy, which gradually decreased with age, particularly after the school-age period. Cluster 2 had the highest prevalence of AD throughout the study, particularly among teenagers, despite a similar trend across clusters. The prevalence of AR in clusters 1 and 2 followed a similar longitudinal course, peaking during the school-age period and slightly declining thereafter. Asthma in clusters 1 and 2 typically began in early childhood, peaked at age 7, and declined during adolescence. Asthma trajectory of cluster 4 was similar to that of clusters 1 and 2, with similar longitudinal patterns of AD and AR, but cluster 4 had the lowest prevalence of these allergic comorbidities.

In contrast, cluster 3 showed distinct trends in allergic comorbidities and asthma progression compared to the other clusters. Although the course of AD in cluster 3 was similar to other clusters, its co-occurrence rate of AR was relatively low (<30%). Their asthma trajectory was also unique This group, characterized by puberty-onset at baseline, showed that nearly half had a prior history of asthma diagnosis according to HIRA data records. This suggests that this group likely experienced persistent asthma from early childhood through puberty. This cluster exhibited a continuous increase in asthma and AR from school age through adolescence.

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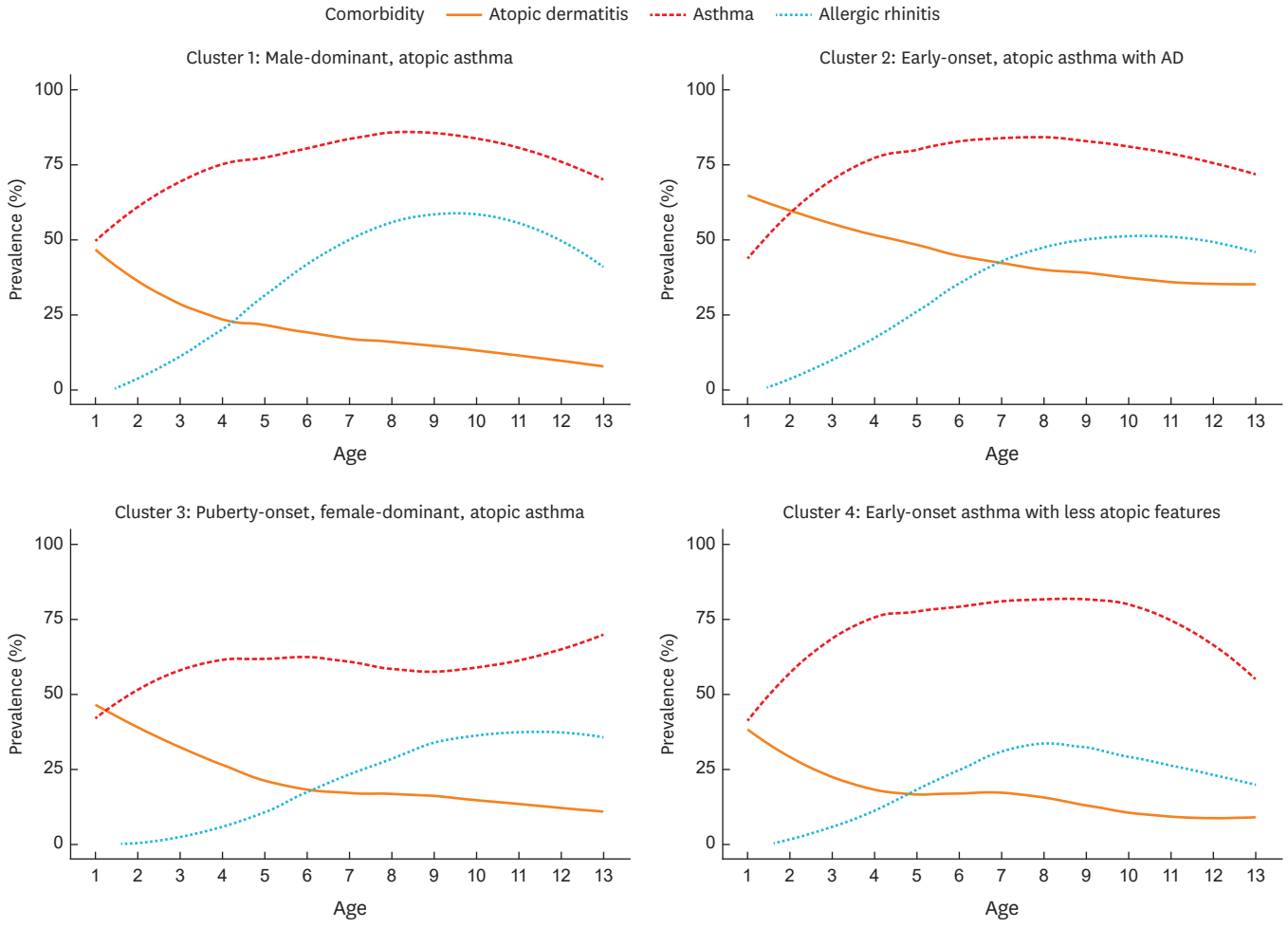

Fig. 4. Longitudinal trajectories of atopic dermatitis and allergic rhinitis among the 4 clusters of childhood asthma.

DISCUSSION

To the best of our knowledge, this nationwide study is the first one in Korea to show longitudinal asthma trajectories and allergic comorbidities in an entire cohort population as well as across distinct asthma phenotypes, by combining the HIRA data for each participant. Approximately half of the patients had a history of AD during infancy, with prevalence gradually decreasing toward adolescence. As expected, the prevalence of AR increased with age. The prevalence of asthma increased during early childhood and decreased during adolescence. Based on the natural progression of asthma, AD, and AR trajectories in the entire KAS cohort, 4 distinct phenotypes were identified according to the LCA results: "almost controlled," "early-onset asthma with AD and late-onset AR," "early-onset asthma only," and intermediate-onset asthma with late-onset AR." When examining the clinical trajectories of asthma and allergic comorbidities across the 4 clusters identified at cohort recruitment, cluster 1, characterized by "male-dominant, atopic asthma," displayed trajectory patterns similar to those of the entire cohort. Cluster 2, characterized by "early-onset, atopic asthma with AD," maintained a relatively high prevalence of AD into adolescence, peaking in AR prevalence observed during the school-age period. Cluster 3, characterized by "puberty-onset, female-dominant, atopic asthma," showed distinctive patterns of asthma and allergic

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comorbidities, demonstrating a low pulmonary function, a low asthma remission rate, and a history of asthma diagnosis during the preschool age with a continuous increase in asthma and AR prevalence until adolescence. Finally, cluster 4, characterized by "early-onset asthma with less atopic features," showed the lowest comorbidities of AD and AR.

Only a few cohort studies have investigated childhood asthma and allergic comorbidities. The Mechanisms of the Development of Allergy project, involving 7 European population-based birth cohorts, identified 2 clusters: a reference group with low frequencies of asthma, rhinitis, and eczema symptoms (70% at 4 years and 78.5% at 8 years) and a symptomatic group with high frequencies of the aforementioned symptoms and more prevalent IgE sensitization (30.0% at 4 years and 21.5% at 8 years). This classification was based on multiple variables, including questionnaires on allergic diseases and IgE sensitization to assess the co-occurrence of asthma, rhinitis, and eczema in over 17,000 patients.[13] Despite its prospective design and large sample size, the study is limited by its cross-sectional nature and the assessment at only 2 time points (4 and 8 years) using questionnaire-based symptom evaluation. Similar trajectories of asthma and allergies were also observed in Tasmanian Longitudinal Health Study in Australia.[14] This longitudinal study identified 5 asthma and allergy trajectories from childhood to adult periods (minimal asthma and allergies; late-onset hay fever, no asthma; early-onset remitted asthma and allergies; late-onset asthma and allergies; and early-onset persistent asthma and allergies). These trajectories highlight diverse longitudinal trajectories of asthma and comorbidity profiles, including varying risk of chronic obstructive pulmonary disease in adulthood.[14] However, this study also showed allergic states at limited time points (7 and 53 years), rather than providing continuous longitudinal tracking of outcomes. Compared to previous studies, our study benefited from the inclusion of individual HIRA data to assess participants' allergic diseases, offering a more comprehensive observation of allergic comorbidities associated with asthma. Furthermore, analyzing annual patterns based on the participants' diseases provided a more precise yearly tracking compared to a few time points assessed in other studies. Given the genetic and ethnic diversity of asthma and allergic comorbidities, the lack of longitudinal trajectories reported among Asians underscores the novelty and significance of our findings.

Similar to our study, European studies have reported the results of serial yearly longitudinal monitoring of allergic diseases. Using 2 population-based birth cohorts, the Manchester Asthma and Allergy Study and Avon Longitudinal Study of Parents and Children, 8 different latent classes were distinguished using Bayesian machine learning methods to describe the natural history of eczema, wheeze, and rhinitis from 1 to 11 years.[15] This study indicated that allergy march did not adequately describe the natural progression of allergic diseases during childhood. Only a small proportion of children followed the patterns consistent with the allergic march. They underscored the importance of recognizing the diverse longitudinal trajectories of eczema, wheezing, and rhinitis among young children.[16] While our study's focus on childhood asthma may affect interpretation, it provides insights into the varied natural progression of allergic diseases. In our study based on LCA, Group 2 was the largest, developing early-onset asthma with persistent AD into adolescence and increased AR onset after the school-age period. Although some patients in this group may exhibit aspects of the allergic march, they are not entirely representative, as asthma developed early rather than sequentially following AD. Our findings are consistent with those of a previous study demonstrating that AD alone is not a significant risk factor for asthma. Instead, a subgroup of children with AD who already exhibit signs of wheezing are at a higher risk of developing asthma.[17] Therefore, in

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Korean children and teenagers, the course of allergic diseases can be classified into 4 groups that are distinctly different from the traditional concept of the allergic march.

The 4 clusters werederived from the baseline clinical information at initial recruitmen. After integrating the HIRA data to track the course of asthma, AD, and AR, we analyzed the chronological courses of the 4 clusters from birth to age 13. The longitudinal trajectories of the characteristics across the 4 groups remained consistent throughout the study period. Cluster 3, classified as puberty onset, showed records from HIRA data indicating that approximately half of them had been diagnosed and treated for asthma. This group appeared to have persistent asthma from early childhood through puberty. Clusters 1 (male-dominant, atopic asthma) and 2 (early-onset, atopic asthma with AD) showed similar patterns of allergic comorbidities; AD prevalence was higher in infancy and gradually decreased over time, while AR increased as the children approached school age. Patients were categorized based on the prevalence trends of each disease. Cluster 4 had lower levels of allergic comorbidities throughout the study. In a British cohort study, 27% of participants aged 7–33 years had persistent asthma in the long-term, while complete remission was observed in 35% of patients. The factors contributing to their persistent asthma were smoking and atopy.[18] Results from the Childhood Asthma Management Program study, which monitored mild-to-moderate persistent asthma in adolescents over 4 years, showed a 6% remission rate and a 55% persistence rate. Patients with higher levels of atopy, low lung function, and airway hyperresponsiveness showed lower asthma remission rates.[19] In our results, the remission rate was the lowest in cluster 3 (puberty-onset, female-dominant, atopic asthma) among the 4 clusters. To explore the relationship between allergic comorbidities and asthma remission, cluster 1 had a high comorbidity of AR, while cluster 2 had a high comorbidity of AD. Cluster 4 exhibited lower levels of allergic comorbidities, similar to cluster 3. This suggests no significant relationship between allergic comorbidity patterns and asthma remission. Additionally, baseline assessments revealed higher rates of atopy in clusters 1, 2, and 3 than in cluster 4, indicating that the lower asthma remission rate in cluster 3 was also unrelated to atopy. However, since this study considered the remission rate only within 1 year, further long-term follow-up studies of the KAS cohort are warranted to gain additional insights.

Our study has several strengths. The KAS is the only nationwide prospective study of childhood asthma in Korea. The HIRA data contain healthcare service records from infancy to adolescence across various healthcare settings, providing detailed information on healthcare utilization, procedures, diagnoses, and treatments. This enables researchers to continuously track the patients' medical records in the database over time.[6] Therefore, integrating participants' individual HIRA data is crucial, enabling the examination of the longitudinal natural course of pediatric asthma, as well as AD and AR, both prospectively after recruitment and retrospectively from early infancy to adolescence. Furthermore, our findings revealed that the natural course of allergic diseases may exhibit diverse trajectories beyond the traditional concept of the allergic march in the Asian population. This observation suggests the potential utility of predicting the course of allergic comorbidities based on asthma phenotypes and offers valuable insights for future predictive analyses.

Despite its strengths, this study has some limitations. Although our current study included a larger number of children with asthma nationwide using HIRA data than the previously reported KAS,[3] it may not entirely represent the childhood asthma population in South Korea. Moreover, HIRA data, inherently designed for reimbursement claims, are not specifically intended for clinical research. As a result, discrepancies may occur between

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the recorded diagnoses and the patients' actual medical conditions. For example, some patients may not have the medical conditions that correspond to their diagnoses, potentially introducing bias and undermining the validity of the research. However, these limitations are common not only in HIRA data but also in other claims data collected primarily for administrative purposes.[20] To mitigate these limitations, it is essential to incorporate the physicians' clinical expertise to refine the operational definitions rigorously. Our study, focusing on participants diagnosed with asthma, facilitated more precise observation of trajectories compared to studies targeting the general population. However, we could not examine the trajectory of allergic comorbidities in participants without asthma. Lastly, our study collected baseline data from individuals diagnosed with asthma aged 5–15 years. As a result, cluster names were assigned based on baseline data, which did not accurately reflect the annual patterns for individuals aged 0–12 years. Nontheless, the trajectory phenotypes in this study closely resembled the initial clusters of important phenotypes.

In conclusion, the longitudinal trajectories of asthma and allergic comorbidities in Korean children can be classified into 4 distinct phenotypes based on the LCA from birth to age 12. In addition, 4 representative clusters that combine clinical trajectories of asthma and allergic comorbidities with clinical variables were identified. Most phenotypes showed early-onset asthma with a varying prevalence of comorbidities. For comorbidities involving AD, it is the persistence of AD, rather than its onset, that determines the phenotype. These results may help predict the future course and prognosis of asthma, AD, and AR. This study provides the only epidemiological data on the natural course of childhood asthma and allergic diseases from a nationwide prospective cohort in Korea. These findings enhance our understanding of the courses of asthma and its allergic comorbidities.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1

Demographic characteristics of the study participants in LCA clusters (n = 958)

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