Original Article

Asthma Phenotypes in the First Three Years of Life and Correlation with Active Asthma at Six Years of Age: A National Population-Based Study in Taiwan

Yu-Tsun Su[1,2,6,7], Ying-Chun Li[7], Li-Min Chen[2,5], Ching-Chung Tsai[2,3], Yuan-Yi Huang[1], Chen-Kuang Niu[8], Hong-Ren Yu[3,9], Chao-Yu Chuang[6], Yao-Chun Hsu[3,4,10], Jiu-Yao Wang[11], Ming-Chun Yang[2,5,6], Yu-Cheng Tsai[1]

Background: Wheezing phenotypes in young children and their associations with subsequent wheezing in later life have been reported, however, longitudinal data based on physician-diagnosed asthma in early life are scant.

Objective: To identify asthma phenotypes in the first 3 years of life, and to investigate their associations with active asthma at 6 years of age.

Methods: Children with physician-diagnosed asthma in the first 36 months of life were enrolled in this national population-based cohort study. We identified asthma phenotypes using latent class analysis, and analyzed risk factors for subsequent asthma at 6 years of age.

Results: From 2000 to 2011, we identified 5013 children with physician-diagnosed asthma in their first 36 months of life. Three asthma phenotypes were identified: transient early (34.9%), late-onset (45.4%), and persistent (19.8%). Among these phenotypes, gender, age at first asthma visit, number of asthma visits in the 1st, 2nd, and 3rd years, total number of asthma visits, coincidental allergic rhinitis, and atopic dermatitis were all significantly different. The prevalence of active asthma at 6 years of age was 13.6% in the transient early, 24.3% in the late-onset (OR = 2.04, 95% CI, 1.72 – 2.41), and 26.6% in the persistent (OR = 2.30, 95% CI, 1.89 – 2.80) group.

Conclusions: Three asthma phenotypes in the first 3 years of life contributed to the natural course of pediatric asthma. The children with late-onset and persistent asthma phenotypes, which were characteristic of frequent asthma visits at 3 years of age, had an increased risk of subsequent asthma at 6 years of age.

Key words: asthma, phenotype, pediatric, latent class analysis, NHIRD

From the [1]Division of Pediatric Allergy, Immunology, and Pulmonology, and [2]Department of Pediatrics, and [3]Department of Internal Medicine, and [4]Center for Database Research, E-Da Hospital, Kaohsiung, and [5]School of Medicine for International Students, and [6]School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, and [7]Institute of Health Care Management, National Sun Yat-Sen University, Kaohsiung, and [8]Departments of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center, and [9]Graduate Institute of Clinical Medical Science, Chang Gung University College of Medicine, Taoyuan, and [10]Graduate Institute of Clinical Medicine, China Medical University, Taichung; and [11]Department of Pediatrics, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

Received: December 7, 2017 Accepted: February 12, 2018

Address reprint request and correspondence to: [1]Ming-Chun Yang, Department of Pediatrics, and [2]Yu-Cheng Tsai, Division of Pulmonology, Department of Pediatrics, E-Da Hospital, I-Shou University, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan.

[1]Tel: +886-7-615-0011 ext. 251867, Fax: +886-7-615-0950, E-mail: suyutsun@gmail.com; ed100616@edah.org.tw

[2]Tel: +886-7-615-0011 ext. 251730, Fax: +886-7-615-0950, E-mail: b90401107@ntu.edu.tw; ed104872@edah.org.tw

Introduction

Asthma is the most common chronic disease in children and a major socio-economic burden worldwide. The International Study of Asthma and Allergies in Childhood (ISAAC) in 1995 and 2005 reported an average global prevalence rate of asthma of 11 – 12% in preschool children, and continued increases in the prevalence in Africa, Latin America and parts of Asia.[1] This chronic disease causes intermittent inflammation and remodeling of the respiratory system.[2] It is a heterogeneous disease, and influenced by the interaction of genomic and environmental factors. Therefore, asthma presents as multiple phenotypes which contribute to the clinical prognosis.[3]

Early-life is a crucial period for the development of asthma, so it is important to clarify the different phenotypes of asthma during this early period. Clinical features (symptoms, triggers, response to treatment) and pathologic/physiologic findings have been used to categorize asthma phenotypes. Pediatric asthma phenotypes have long been studied because they are associated with different prognoses and can aid in the development of personalized target therapy. The Tucson Children's Respiratory Study (1995) first categorized wheezing phenotypes before 6 years of age as transient wheezing, late-onset wheezing, and persistent wheezing, depending on wheezing in the first 3 years of life and the absence or presence of symptoms at 6 years of age.[4] In addition, these wheezing phenotypes have been reported to be associated with allergy, lung function and clinical presentation.[4,5] Several studies published in 2018 and 2012 used probabilistic classification methods such as latent class analysis (LCA) to distinguish asthma and wheezing phenotypes.[6,7] These studies used subjective data derived from questionnaires completed from the parents' memory. However, data on asthma phenotypes in early childhood based on physician-diagnosed asthma and their relationships with subsequent asthma in school-age children are scant.

Due to the heterogeneous mechanism of asthma, we hypothesized that there may be several asthma phenotypes in toddlers, and that these phenotypes may be correlated to prognosis. We conducted this study to clarify the phenotypes of physician-diagnosed asthma in the first 3 years of life using LCA, and to predict subsequent asthma at 6 years of age in a nationwide population-based cohort study.

Methods

Source of data

The National Health Insurance Research Database (NHIRD) served as the data source for this study. The Taiwan Department of Health initiated the National Health Insurance (NHI) program in 1995 to provide health care for all residents in Taiwan. The National Health Research Institute (NHRI) of Taiwan manages the medical benefit claims of all 22.9 million residents of Taiwan. The NHRI has established several claims data files for research purposes, and in this study we used claims data from the NHIRD from 1997 to 2012. The completeness and accuracy of the NHIRD are guaranteed by the Department of Health and the NHI Bureau of Taiwan. The NHRI releases the insured medical records as de-identified secondary data for research purposes, and thus this study was exempted from an ethics review. In this retrospective population-based cohort study, we used data from the Longitudinal Health Insurance Database 2005 (LHID 2005), which is a subset of the NHIRD containing the complete original claims data of one million insured individuals who were randomly sampled from the NHIRD registry in 2005. All sampled individuals were followed until the end of 2012, and their outcomes were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes.

Study patients

Cases of physician-diagnosed asthma were defined as meeting two criteria: (1) diagnosis of asthma clinical in at least three outpatient visits, and/or at least one hospitalization (1 month was required as a minimum duration between distinct clinical visits); and (2) at least one prescription of an anti-asthma drug (corticosteroid, montelukast, anti-IgE) during these clinical visits.[8,9] These clinical visits were identified in the NHIRD by the diagnosis of asthma (ICD code 493.XX). Each of these asthma clinical visits was defined as an "asthma visit". We used these strict inclusion criteria to ensure that the enrolled children had asthma. The exclusion criteria were cases with ICD codes 748.5 (agenesis, hypoplasia, and dysplasia of lung) or 770.7 (chronic respiratory disease arising in the perinatal period).

Study variants

Active asthma at 6 years of age was defined as a diagnosis of asthma (ICD code 493.XX) in outpatient visits or hospitalizations as well as the prescription of an anti-asthma drug at the same clinical visit. Several covariates were also evaluated, including gender, age at the first asthma visit, the number of asthma visits in the 1st, 2nd, and 3rd years of life, the total number of asthma visits (birth to 36 months), and the incidence rates of coincidental allergic rhinitis and atopic dermatitis in the first 3 years of life. Cases were defined as having allergic rhinitis and atopic dermatitis before 3 years of age if they had a diagnosis of allergic rhinitis or allergic conjunctivitis in at least three outpatient visits, and/or at least one hospitalization (Fig. 1). These criteria were also used to identify cases with allergic rhini-

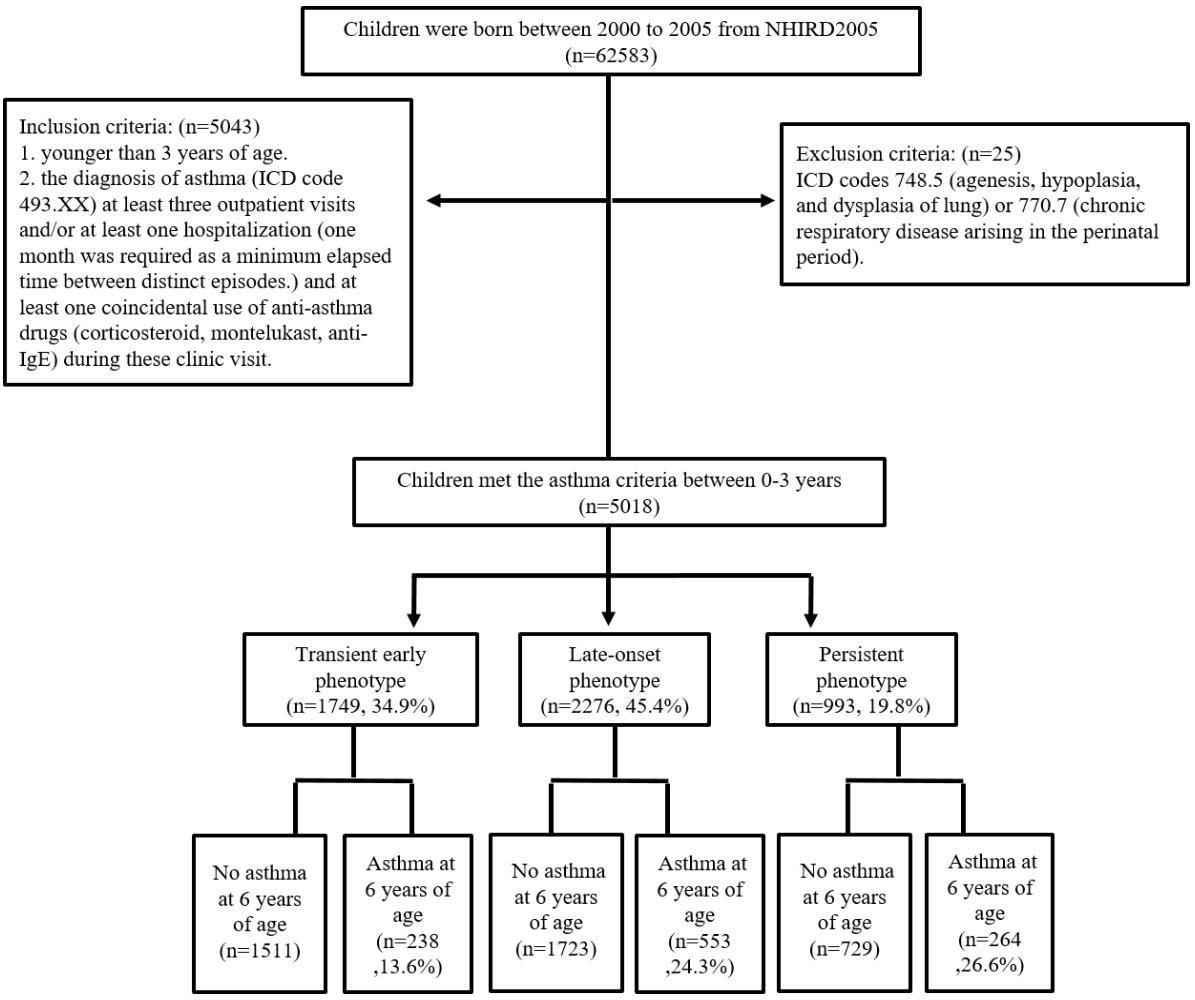

Fig . 1 Flow chart of case enrollment and outcome measurement

tis (ICD code 493.9) and atopic dermatitis (ICD code 691.8) at 6 years of age as diagnosed by a physician.

Data analysis

A latent class is a variable indicating underlying subgroups of individuals based on observed characteristics. In this study, we used LCA Distal SAS Macro to identify asthma phenotypes.[10-12] These phenotypes were categorized according to the probability of any asthma visit occurring in a 3 months period. We investigated the number of latent classes between one and seven using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) together in the selection model. The values of AIC and BIC declined as the number of classes increased, as shown in Table 1. This meant that the more latent classes the better the model. However, it was not possible to increase the number of classes without restriction, since there would be difficulties in applying a large number of classes in clinical practice. In addition, the AIC and BIC values were still quite large when divided into one class and two classes. When the number of classes was divided into three groups, the AIC and BIC values obviously declined. When the number of classes continued to increase, the AIC and BIC values continued to decrease,

Table 1. Latent class analysis, best model selection

Number of clusters	AIC	BIC	Adjusted-BIC	Degrees of freedom
1	8481.92	8560.17	8522.04	4083
2	6396.98	6560.00	6480.56	4070
3	3779.95	4027.74	3906.99	4057
4	3429.40	3761.96	3599.90	4044
5	3270.86	3688.19	3484.82	4031
6	3177.93	3680.03	3435.35	4018
7	3079.83	3666.70	3380.71	4005

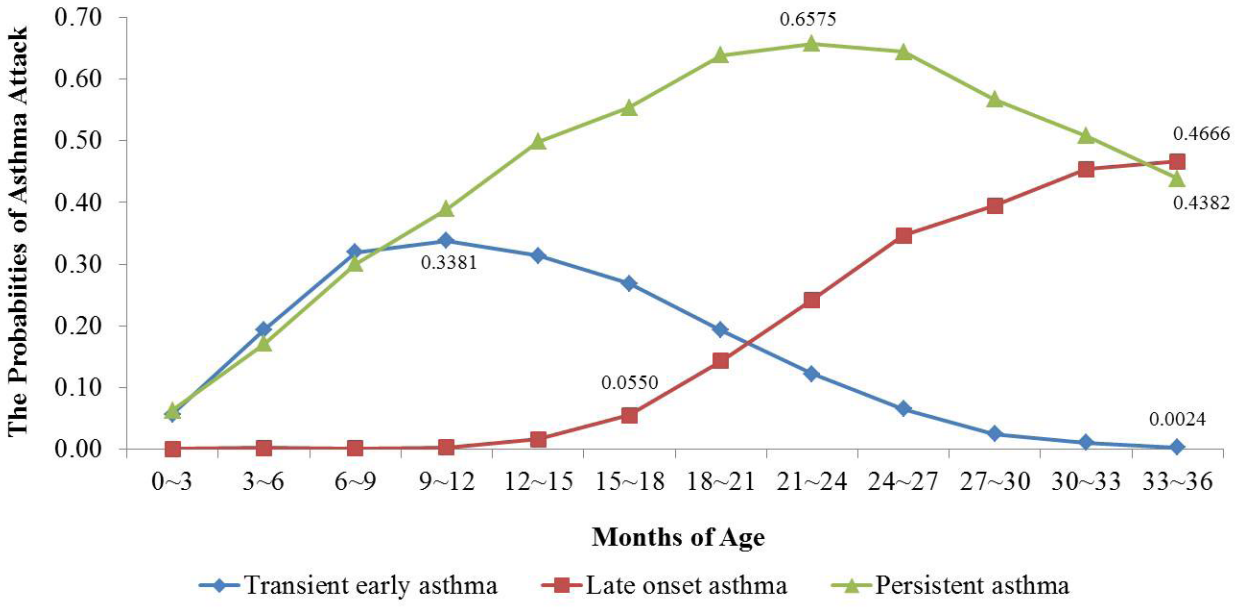

Fig . 2 The pattern of probability of asthma visit in each three-month period from birth to 36 months by latent class analysis

although the rate of decline was not as pronounced. Therefore, taking both the theoretical and practical aspects into consideration, we chose three latent classes for analysis in this study (Fig. 2). Other analyses were performed using Pearson's chi-square test and Fisher Yates continuity correction. We used multivariate logistic regression analysis to analyze the risk factors for outcomes at 6 years of age. Odds ratios (ORs) were listed with corresponding 95% confidence intervals (95% CIs). All *p*-values less than 0.05 were considered to be statistically significant. All data management and calculations were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Asthma cases

Cases of physician-diagnosed asthma in the first 36 months of life and those with asthma morbidity at 6 years of age were identified retrospectively from the LHID 2005. Of 62583 children born between 2000 and 2005, 5018 were diagnosed with asthma between 0 – 3 years of age (Fig. 1). The prevalence rate was 8.0%, and the male to female ratio was 1.65 : 1.

Phenotypes

Asthma in the first 36 months of life could be classified into three discrete phenotypes by LCA according to temporal patterns: transient early asthma (TEA), late-onset asthma (LOA), and persistent asthma (PA). These phenotypes were categorized according to the probability of any asthma visit occurring in a 3-month period (Table 2, Fig. 2).

TEA was characterized by a rapid rise in asthma visits from birth to a peak at 10 – 12 months of age, when 33.8% of the children with this phenotype had had an asthma visit. The occurrence of asthma visits in the children with the TEA phenotype then decreased rapidly to 27 – 30 months of age. The occurrence of asthma visits in the children with the LOA phenotype remained low until 15 – 18 months of age, and then steadily increase to 36 months of age, when 46.7% of the children had had an asthma visit. The PA phenotype was characterized by a rapid rise in asthma visits from birth, and then a steady increase to a peak at 21 – 24 months of age, when 65.8% of the children had had an asthma visit. The incidence then remained high until 36 months of age.

Table 2. The probabilities of asthma visits in each three-month period in the three phenotypes by latent class analysis

	Asthma Phenotypes		
Months	Transient early	Late-onset	Persistent
0~3	0.0565	0.0001	0.0626
3~6	0.1933	0.0019	0.1711
6~9	0.3192	0.0013	0.3003
9~12	0.3381	0.0025	0.3892
12~15	0.3135	0.0157	0.4985
15~18	0.2685	0.0550	0.5541
18~21	0.1930	0.1430	0.6387
21~24	0.1217	0.2423	0.6575
24~27	0.0648	0.3467	0.6443
27~30	0.0242	0.3951	0.5675
30~33	0.0102	0.4542	0.5076
33~36	0.0024	0.4666	0.4382

Several covariates were significantly different among these phenotypes, including gender, age at the first asthma visit, the number of asthma visits in the 1st, 2nd, and 3rd years of life, and the total number of asthma visits (birth to 36 months) ($p < 0.0001$). The incidence rates of coincidental allergic rhinitis and atopic dermatitis in the first 3 years of life were also significantly higher in the LOA and PA phenotypes ($p < 0.0342$) (Table 3).

Subsequent asthma at 6 years of age

The prevalence rates of subsequent asthma at 6 years of age were 13.6% in the TEA, 24.3% in the LOA (OR = 2.04 vs. TEA, 95% CI, 1.72 – 2.41), and 26.6% in the PA (OR

Table 3. Characteristics of the three asthma phenotypes

	Asthma phenotypes			*p* value
	Transient early	Late-onset	Persistent	
Percentage (%)	34.9	45.4	19.8	
Male sex (%)	64.4	68.8	66.7	< 0.0001**[#]
Atopic dermatitis before 3 years (%)	7.7	7.6	10.2	< 0.0342*[#]
Allergic rhinitis before 3 years (%)	22.4	34.4	41.7	< 0.0001**[#]
Age at the first asthma visit (months)	10.50	25.50	10.50	< 0.0001**[^]
≥ 4 asthma visit, birth to 36 months (%)	8.9	11.6	92.5	< 0.0001**[#]
Asthma visit, 1st year (n ± SD)	0.91 ± 0.80	0.00 ± 0.04	0.95 ± 0.95	< 0.0001**[^]
Asthma visit, 2nd year (n ± SD)	0.90 ± 0.86	0.44 ± 0.63	2.44 ± 0.84	< 0.0001**[^]
Asthma visit, 3rd year (n ± SD)	0.07 ± 0.25	1.67 ± 0.93	2.23 ± 1.03	< 0.0001**[^]
Asthma visit, birth to 36 months (n ± SD)	1.88 ± 1.09	2.11 ± 1.05	5.63 ± 1.59	< 0.0001**[^]
Hospitalization times (n ± SD)	0.67 ± 1.01	0.41 ± 0.78	0.85 ± 1.49	< 0.0001**[^]

[#] *p* value by Pearson's chi-square test of variance across the three phenotypes
[^] *p* value for ANOVA test of variance across the three phenotypes
* $p < 0.05$, ** $p < 0.0001$

= 2.30 vs. TEA, 95% CI, 1.89 – 2.80) phenotypes. Asthma, allergic rhinitis and atopic dermatitis are major allergic syndromes in childhood, so we also investigated the prevalence rates of these two diseases at 6 years of age.[13,14] The results showed that children with either the LOA or PA phenotype had higher prevalence rates of allergic rhinitis and atopic dermatitis at 6 years of age than those with the TEA phenotype (OR = 1.91, 95% CI, 1.60 – 2.29, OR = 1.99, 95% CI, 1.61 – 2.45, for allergic rhinitis, and OR = 2.60, 95% CI, 1.45 – 4.64, OR = 2.74, 95% CI, 1.42 – 5.28, for atopic dermatitis, respectively) (Table 4). When we analyzed the cases with asthma at 6 years of age, the risk factors were male sex, allergic rhinitis morbidity (0 – 3 years), atopic dermatitis morbidity (0 – 3 years), and the LOA and PA phenotypes (Table 5).

Table 4. The outcomes at 6 years of age between the three asthma phenotypes

	Asthma phenotypes			*p* value
	Transient early	Late-onset	Persistent	
Active asthma at 6 years (%)	13.6	24.3	26.6	< 0.0001**
Atopic dermatitis at 6 years (%)	0.9	2.2	2.3	0.0019*
Allergic rhinitis at 6 years (%)	11.8	20.3	20.9	< 0.0001**

p value for Pearson's chi-square test of variance across the three phenotypes
* $p < 0.05$, ** $p < 0.0001$

Table 5. The risk factors associated with asthma at 6 years of age

	No asthma at 6 y/o	Asthma at 6 y/o	cOR (95% CI)	aOR (95% CI)
Gender				
female	1527	365	1	1
male	2436	690	1.19 (1.03 – 1.37)*	1.19 (1.03 – 1.38) *
Asthma phenotypes				
Transient early	1511	238	1	1
Late-onset	1723	553	2.04 (1.72 – 2.41)*	1.95 (1.64 – 2.31) *
Persistent	729	264	2.30 (1.89 – 2.80)*	2.06 (1.69 – 2.52) *
Birth season				
Spring	970	258	1	
Summer	1001	234	0.88 (0.72 – 1.07)	
Fall	1037	285	1.03 (0.86 – 1.25)	
Winter	955	278	1.09 (0.90 – 1.33)	
Allergic rhinitis (0 – 3 years)				
No	2827	602	1	1
Yes	1136	453	1.87 (1.63 – 2.15)*	1.65 (1.43 – 1.91)*
Atopic dermatitis (0 – 3 years)				
No	3685	924	1	1
Yes	278	131	1.88 (1.51 – 2.34)*	1.67 (1.33 – 2.10)*

Multivariate logistic regression was used to analyze variance
aOR: adjusted for the influence of gender, group, allergic rhinitis (0 – 3 years), and atopic dermatitis (0 – 3 years)
* significant difference

Discussion

In this study, we identified three asthma phenotypes in children during their first 36 months of life in a longitudinal population-based cohort: transient early asthma, late-onset asthma, and persistent asthma. These phenotypes were correlated with the prevalence of subsequent asthma. Around 25% of the cases with the LOA and PA phenotypes had subsequent asthma at 6 years of age, which was around twice that of the TEA phenotype.

Of 62583 children aged less than 3 years, 5018 had asthma, with a prevalence rate of 8.0% and a male to female ratio of 1.65 : 1. The ISSAC studies in 1995 and 2005 reported mean prevalence rates of asthma symptoms at 6 – 7 years of age of around 11 – 12%. Few studies have reported the prevalence of asthma in children aged less than 3 years of age, since only 40% of wheezing children in the first 3 years of life develop asthma in later life.[4] Therefore, although asthma symptoms usually develop early in life, "wheezing" is usually used to describe respiratory problems in younger children instead of "asthma". However, asthma symptoms usually start in early childhood, and the first 3 years of life are a key stage in the development of lung function and the prognosis of wheezing.[15-17] Therefore, studying asthmatic children less than 3 years of age is important, and an increasing number of studies have revealed good responses to the use of anti-asthmatic medicine in asthmatic or wheezing children less than 3 years of age.[8,18-20] In order to study this critical period of life, we conducted this study focusing on physician-diagnosed asthma in children less than 3 years of age. Alfredo et al. (SLAM study group) surveyed the clinical pattern of younger wheezing children in the first 36 months of life,

and reported that 45.6% experienced at least one episode of wheezing, with 15.8% having frequent wheezing episodes.[21] In comparison, the prevalence rate of asthma was 8.0% in the current study, which may be because we set stricter inclusion criteria when enrolling the asthma cases.

We identified three asthma phenotypes based on the frequency of asthma visits and temporal trajectory: TEA, LOA, and PA. Among these phenotypes, gender, age at the first asthma visit, the number of asthma visits in the 1st, 2nd, and 3rd years of life, the total number of asthma visits (birth to 36 months), coincidental allergic rhinitis and atopic dermatitis were all significantly different ($p < 0.05$). Children with the TEA and PA phenotypes had frequent asthma visits before 1 year of age, which is a period when children commonly suffer from bronchiolitis. The children with the TEA phenotype then had a decreasing incidence of asthma visits with few asthma visits after 1.5 years of age, whereas those with the PA phenotype still had frequent asthma visits over the whole 36 months period. This suggests that it is difficult to predict the prognosis in children with asthma visits during infancy. The Tucson study described three "wheezing" phenotypes before 6 years of age in 1995: transient early, late-onset, and persistent wheezing phenotypes. In addition, Martinez et al. studied correlations between allergens and pulmonary function, and found that the children with the transient early wheezing phenotype had diminished airway function, especially before the age of 1 year.[4] Similar to this finding, diminished airway function in early life may have contributed to wheezing episodes during bronchiolitis, and these wheezing episodes then improved following maturation of the bronchial airway in the children with the TEA phenotype in the present study. In addition, clinical asthma phenotypes have been proposed to be influenced by genetic factors, atopy, viral infection, or the effect of pharmacological treatment.[4,18-20,22] With regards to allergic profiles, the children with the LOA and PA phenotypes had higher rates of allergic rhinitis and atopic dermatitis than those with the TEA phenotype. Since the incidence of asthma visits persisted or increased after 18 months of age, the PA and LOA phenotypes may be related to the progressive development of allergic sensitization.[22,23] Further research is needed to investigate the corresponding heterogeneous etiology of the three asthma phenotypes in the first 3 years of life. The "asthma" phenotypes (transient early, late-onset, persistent) in our study are the same as the "wheezing" phenotypes in the Tucson study in 1995, and similar to the phenotypes in the SLAM study in 2014 and the phenotypes in Depner's study in 2014.[4,21,25] Martinez et al. categorized wheezing phenotypes according to the temporal patterns of wheezing episodes in the first 6 years of life.[4] They treated "wheezing episodes at 6 years of age" as a variable by which to group the phenotypes, whereas we treated "active asthma at 6 years of age" as an outcome of the asthma phenotypes in the current study. With the aim of identifying asthma phenotypes earlier, we focused on the first 3 years of life to predict subsequent asthma at 6 years of age.

Alfredo et al. (SLAM study group) published an important study on clinical wheezing phenotypes in the first 36 months of life. They categorized all children into four phenotypes according to wheezing recorded by physicians at 29 primary health care centers in Spain: never/infrequent wheezing (NIW, 65.4%), transient wheezing (TW, 18.3%), late wheezing (LW, 9.7%), and persistent wheezing (PW, 6.6%). However, in the current study, we focused on cases with frequent asthma visits, since asthma is characterized by recurrent airway inflammation. There are some similarities between the "asthma" phenotypes in our study and the "wheezing" phenotypes in the SLAM study.[21] The TW, LW, and PW phenotypes in the SLAM study were similar

to the TEA, LOA, and PA phenotypes in our study. NIW did not have a counterpart in our study, since we focused on relatively frequent asthma visits. If we extracted the three wheezing phenotypes (total 100%) with frequent wheezing episodes in the SLAM study, the rates of TW, LW and PW were 52.9%, 28.0% and 19.1%, respectively. In our asthma cases, the rates of TEA, LOA and PA were 34.9%, 45.4% and 19.8%, respectively. In addition, the rate of TEA (34.9%) in our study was lower than that of TW (52.9%) in the SLAM study, and the children with the TW phenotype had the fewest wheezing episodes from birth to 36 months in the SLAM study. Some TW cases may not have been included in our study due to different inclusion criteria.

With regards to the prognosis of asthmatic children, 1055 (21.0%) of the 5018 children with asthma in the first 3 years of life subsequently had asthma at 6 years of age. This means that 79.0% of the children who had asthma when they were less than 3 years of age were free of asthma at 6 years of age. However, the prevalence of active asthma at 6 years of age was different in the three phenotypes, at 13.6%, 24.3%, and 26.6% in the TEA, LOA, and PA groups, respectively. Those with TEA had fewer asthma visits after 1.5 years of age, and only 0.2% had asthma visits at 34 – 36 months of age, with 13.6% having asthma at 6 years of age. Those with LOA and PA had a high prevalence of asthma visits at 34 – 36 months of age, and 24.3% and 26.6% had asthma at 6 years of age, respectively, which is around twice that of the TEA phenotype. In addition, there were higher rates of the comorbidities of allergic rhinitis and atopic dermatitis in those with the LOA and PA phenotypes in the first 3 years of life. This finding is similar to that of the asthma predictive index, in which the major criteria include atopic dermatitis, and the minor criteria include allergic rhinitis. When we studied the cases with asthma at 6 years of age, we found that the risk factors were male sex, allergic rhinitis morbidity, atopic dermatitis morbidity, and the LOA and PA phenotypes (Table 5). Compared to TEA, the OR for LOA was 2.04 (95% CI, 1.72 – 2.41) compared to 2.30 (95% CI, 1.89 – 2.80) for PA. The children with the LOA and PA phenotypes had high prevalence rates (24.3%, and 26.6%) of active asthma at 6 years of age, around twice that (13.6%) of those with the TEA phenotype. The first 3 years of life are a key stage for the development of lung function and the prognosis of wheezing,[15] and our results imply that asthma has a heterogeneous mechanism, diverse phenotypes, and different prognoses. Further studies are needed to elucidate the underlying mechanism, which may allow for target therapy to improve the prognosis and prevent on-going airway injury in children with diverse asthma phenotypes such as LOA and PA.

Several aspects of the current study need to be clarified with regards to pediatric asthma phenotypes and published studies on wheezing phenotypes. First, we used LCA to identify the TEA, LOA, and PA phenotypes. LCA is a novel statistical method based on probabilistic classification, and it is increasingly being used to categorize clinical phenotypes in medical data.[24,25] Using LCA analysis, wheezing phenotypes were also identified in four large birth cohort studies: ALSPAC (in the UK), PIAMA (in the Netherlands), PASTURE (in Europe), and SLAC (in Spain).[24-27] Second, our asthma cases under 3 years of age were diagnosed by physicians, and they were enrolled after the application of strict inclusion criteria. In comparison to the physician-diagnosed asthma in the current study, the ASLAC, PIAMA, and PASTURE studies collected data on wheezing episodes through questionnaires filled out according to the parents' subjective memory, which may have incurred recall bias.[25,26] Third, the SLAM study in 2014 recruited children with physician-recorded "wheezing" according to the medical charts in 29 primary care

centers to categorize "wheezing" phenotypes. In comparison, we studied a large nationwide population-based cohort longitudinally to identify asthma phenotypes based on physician-diagnosed asthma.

There are some limitations to the present study. First, the NHIRD is derived from claims data of all physicians in the NHI program. In order to ensure the accuracy of the diagnosis of asthma, we set strict inclusion criteria including a diagnosis of asthma in at least three outpatient visits and/or at least one hospitalization, accompanied with at least one prescription of an anti-asthma drug (corticosteroid, montelukast, anti-IgE) during these clinical visits. This may have excluded cases with relatively mild asthma or asthma-like cases. Second, the cases with asthma may have received different bronchodilators and anti-inflammatory medicine, and a prospective control study is needed to investigate the effects of phenotypes on pharmacology. Third, the NHIRD does not include data on allergy tests, lung function, or environmental factors.[28] Therefore, we could not analyze correlations between phenotypes and atopy, pulmonary function, and other environmental factors.

In conclusion, this nationwide study of 5018 asthmatic children under 3 years of age revealed three asthma phenotypes, which were identified by analyzing asthma visits and temporal patterns. With regards to the prognosis of the asthmatic children in the first 3 years of life, 1055 (21.0%) subsequently had asthma at 6 years of age. This means that 79.0% of the children with asthma when they were less than 3 years of age were free of asthma at 6 years of age. The asthmatic children with fewer asthma visits after 1.5 years of age who had the transient early asthma phenotype remained relatively stable at 6 years of age. In comparison, the children with frequent asthma visits at 3 years of age with late-onset asthma or persistent asthma phenotypes still had an up to 25% increased risk of having active asthma at 6 years of age. In addition, the asthmatic children with co-existing allergic rhinitis and atopic dermatitis had a higher risk of subsequent asthma at 6 years of age.

Acknowledgments

We would like to thank Jhen-Hong Wong, Tzu-Yun Chen, and Chen Yen for data collection and analysis. This work was supported by the Center for Database Research, E-DA HEALTHCARE GROUP (CFDR-B-103-1-8 and CFDR-B-104-2-6) and Grants from E-Da Hospital (Grant no. EDAHP103041 and EDAHP104030).

Author Contributions

Conceived and designed: Yu-Tsun Su, MCY, YCT; Methodology: YTS, YCT, CCT, YCL; Performed the experiments: YTS, HRY, YCT, LMC; Data collection: YTS, YCH; Data analysis: YTS, JYW, YCL; Writing- original draft: YTS, CYC; Writing- review & editing: YTS, CKN, MCY, YYH.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Pearce N, Ait-Khaled N, Beasley R, et al: Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2007; 62:758-66.
2. Illi S, von Mutius E, Lau S, et al: Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet 2006;368: 763-70.
3. Kauffmann F, Demenais F: Gene-environment interactions in asthma and allergic diseases: challenges and perspectives. J Allergy Clin Immunol 2012;130:1229-1240;quiz 1241-22.
4. Martinez FD, Wright AL, Taussig LM, et al: Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133-8.

5. Kulig M, Bergmann R, Klettke U, et al: Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J Allergy Clin Immunol 1999;103:1173-9.
6. Spycher BD, Silverman M, Brooke AM, et al: Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. Eur Respir J 2008;31:974-81.
7. Herr M, Just J, Nikasinovic L, et al: Risk factors and characteristics of respiratory and allergic phenotypes in early childhood. J Allergy Clin Immunol 2012;130:389-96.e4.
8. Szefler SJ, Phillips BR, Martinez FD, et al: Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy and Clin Immunol 2005;115:233-42.
9. Mansbach JM, Espinola JA, Macias CG, et al: Variability in the Diagnostic Labeling of Nonbacterial Lower Respiratory Tract Infections: A Multicenter Study of Children Who Presented to the Emergency Department. Pediatrics 2009;123: e573-81.
10. LCA Distal SAS Macro (Version 3.0) [Software]. The Methodology Center, PennState. 2015. Retrieved from https://methodology.psu.edu/downloads/distal
11. Jeroen KV, Jay M: Latent Class Cluster Analysis. In: Hagenaars JA, McCutcheon AL, eds. Applied latent class analysis. Cambridge University Press, 2009:89-106
12. Dziak JD, Yang J, Tan X, et al: LCA distal SAS macro users' guide (version3). TheMethodology Center, Penn State, 2015:7-11. Retrieved fromhttp://methodology.psu.edu
13. Spergel JM: Atopic march: link to upper airways. Curr Opin Allergy Clin Immunol 2005;5:17-21.
14. Bousquet J, van Cauwenberge P, Khaltaev N, et al: Allergic rhinitis and its impact on asthma. J Allergy Clin Immuno 2001;108:S147-S334.
15. Saglani S, Bush A: The early-life origins of asthma. Curr Opin Allergy Clin Immunol 2007;7:83-90.
16. Yeh KW, Ou LS, Yao TC, et al: Prevalence and risk factors for early presentation of asthma among preschool children in Taiwan. Asian Pac J Allergy Immunol 2011;29:120-6.
17. Park ES, Golding J, Carswell F: Preschool wheezing and prognosis at 10. Arch Dis Child 1986;61:642-6.
18. Guilbert TW: Identifying and managing the infant and toddler at risk for asthma. J Allergy Clin Immunol 2010;126:417-22.
19. Qaqundah PY, Sugerman RW, Ceruti E, et al: Efficacy and safety of fluticasone propionate hydrofluoroalkane inhalation aerosol in pre-school-age children with asthma: A randomized, double-blind, placebo-controlled study. J Pediatr 2006;149:663-70.
20. Kemp JP, Skoner DP, Szefler SJ, et al: Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. Ann Allergy Asthma Immunol 1999;83:231-9.
21. Cano-Garcinuno A, Mora-Gandarillas I, SLAM Study Group: Wheezing phenotypes in young children: an historical cohort study. Prim Care Respir J 2014;23:60-6.
22. Caliskan M, Bochkov YA, Kreiner-Møller E, et al: Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N Engl J Med 2013;368:1398-407.
23. Bisgaard H, Jensen SM, Bønnelykke K: Interaction between Asthma and Lung Function Growth in Early Life. Am J Respir Crit Care Med 2012;185:1183-9.
24. Henderson J, Granell R, Sterne J: The search for new asthma phenotypes. Arch Dis Child 2009;94:333-6.
25. Depner M, Fuchs O, Genuneit J, et al: Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med 2014;189:129-38.
26. Henderson J, Granell R, Heron J, et al: Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax 2008;63:974-80.
27. Savenije OE, Granell R, Caudri D, et al: Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. J Allergy Clin Immunol 2011;127:1505-12.e14.
28. Su YT, Yang YN, Li YC, et al. Age-dependent distribution of the atopic phenotype and allergen sensitization among asthmatic children in southern Taiwan. Asian Pac J Allergy Immunol 2016;34:206-11.