

The natural course of eczema from birth to age 7 years and the association with asthma and allergic rhinitis: A population-based birth cohort study

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ABSTRACT

Although “atopic march” is a popular concept, the relationship between eczema and subsequent asthma is far from clear. However, some cohort studies have shown the possibility of two different allergic phenotypes in those who present with early eczema in terms of their persistency. We checked the cohort data from 308,849 children born in 2000 in Taiwan, to evaluate the different courses of eczema and their relationships to subsequent asthma and allergic rhinitis (AR) at age 7 years. We examined the age prevalence of eczema, asthma, and AR up to 7 years of age. We grouped all cases according to their course of eczema, as well as wheezing, and determined the rates of asthma and AR at age 7 years. We checked the adjusted risk factors by multiple logistic regression model. We also examined the distributions of wheezing types in different eczema groups. We found the “atopic march” pattern of allergic diseases based on their age prevalence. Early eczema was associated with asthma and AR at the age of 7 years. Those with eczema symptoms persisting after 36 months of age had a higher risk than those with transient eczema. Early wheeze also contributed to asthma and AR later in childhood. In addition, late-onset eczema had a completely different wheeze distribution compared with other groups and also had a higher risk for asthma and AR than transient eczema. In conclusion, different eczema phenotypes could be found in this population-based cohort. This article emphasizes the special attention to the persistency and late-onset eczema in clinical practice.

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The frequency of allergic diseases, including eczema, asthma, and allergic rhinitis (AR), has increased in recent decades.^{1,2} In general, complex associations between genetic predisposition and environmental factors in early life influence the development of allergies.^{3–5} Although these three conditions tend to cluster in individuals, the exact relationship between early eczema and school-age asthma is far from clear.^{6,7}

According to an asthma prediction index proposed in 2000,^{8,9} eczema before the age of 3 years was a major risk

factor for subsequent asthma among those who were early wheezers. However, one recent German birth cohort study showed that early wheeze and a specific sensitization pattern were significant predictors for wheeze at school age, irrespective of early eczema.¹⁰ This important finding provided a clue that there may be different types of early eczema, which would suggest a more complex scenario than that described by the simple “atopic march” in previous reports.^{11–14}

The National Health Insurance (NHI) system in Taiwan provides a comprehensive, unified, and universal health insurance program for almost all citizens. Approximately 99% of the people in Taiwan participate in the NHI program.¹⁵ Thus, Taiwan’s NHI Research Database (NHIRD) is one of the largest, most comprehensive nationwide population-based data source currently available. This includes a birth cohort of all newborns in 2000. This provides all of their health insurance records, with data available up to the end of 2008.

Therefore, we conducted this study to determine the prevalence by age of the three common allergic disorders (eczema, asthma, and AR) and then to analyze the risk factors of asthma and AR at the age of 7 years in those children with eczema. We attempted to reproduce the patient groupings as was done in the Tucson and German Multicenter Allergy Study cohort conducted, respectively, by Martinez *et al.*¹⁴ and Illi *et al.*⁸ That is, we grouped all newborns in 2000 by their wheezing patterns

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as done by Matinez *et al.*¹⁴ and by their eczema patterns as done by Illi *et al.*⁸ We also added one additional eczema group that was not used in these two studies: late-onset eczema. Next, we analyzed the relationships between school age asthma, AR, and different eczema groups with or without early wheeze. The major aim of this large cohort study was to determine if there were different phenotypes for early eczema.

MATERIALS AND METHODS

Data Sources

Database. The NHI program, which began in 1995, has provided for health care coverage for over 98% of the 23 million people living in Taiwan. The Taiwan NHIRD (TNHIRD), provided by the National Health Research Institutes (NHRI) of Taiwan, was used as the data source for this study. The TNHIRD includes a wide range of information, including the backgrounds of insured individuals (*e.g.*, personal identification number, age, gender, and insured area), health care institutions, all medical advice provided (*e.g.*, diagnosis, orders for examinations, drug prescriptions, and modes of care provided), and the total of applicable medical expenses. The diagnostic code used in the TNHIRD is based on the system used by the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) from 2000.

Study Population. The NHRI provided a database of medical claims up to December 2010 in the TNHIRD for all pediatric cases born in 2000. The total number of cases was 308,849. The data consisted of ambulatory care and inpatient care files and registration records, including demographic data for the insured. For privacy protection, the identities of the patients, physicians, and institutions were scrambled in accordance with the Personal Electronic Data Protection Law.

Study Design. We evaluated the first three diagnostic codes listed in the medical records of all patients' outpatient department visits and admissions. The diagnosis code was at the discretion of the doctors the patients visited. In Taiwan, the pediatricians follow the Global Initiative for Asthma, Allergic Rhinitis and Its Impact on Asthma guideline, and SCORing Atopic Dermatitis system for evaluating bronchiolitis, asthma, AR and eczema. We defined a patient as having eczema if they were given the diagnostic code for atopic dermatitis (ICD-9 code 691) in any of his/her medical records. We also defined patients as having asthma and AR by the diagnostic codes for asthma (ICD-9 code 493) and AR (ICD-9 code 477). The diagnosis of wheeze was based on the ICD-9 code including acute bronchitis and bronchiolitis (ICD-466) and asthma (ICD-9 code 493).

From this cohort, we determined the prevalence of eczema, asthma, and AR by age. We checked each of these cases from their day of birth and the subsequent 12 months for each year. Then, prevalence was determined from the accumulation of all cases that fulfilled the definitions for eczema, asthma, and AR described previously.

This cohort was divided into five groups based on their different courses of eczema, as shown in Fig. 1. We designated all patients who ever had a diagnosis of eczema from birth up to 84 months of age as the "preschool eczema" group. We divided eczema patients into "early eczema" and "late-onset eczema" groups based on their age of onset, either before or after 36 months of age. We further divided the early eczema group into three subgroups: (1) we defined "transient eczema" as only those who had a diagnosis of eczema before 36 months of age, (2) "persistent eczema" included those who had a diagnosis of eczema every year after 36 months of age, and (3) "intermittent eczema" included those who had a diagnosis of eczema after the age of 36 months but not every year. Finally, a "no eczema" group included those who were never diagnosed with eczema from birth up to the age of 84 months. We compared the prevalence of asthma and AR at age 7 years (equal to ages from 85 to 96 months) in these five groups, as well as for the early eczema and preschool eczema groups. Then, we divided the cohort by the presence of early wheeze, *i.e.*, wheeze diagnosed before 36 months old to check the prevalence of asthma and AR at age 7 years in these eczema groups.

We also calculated the odds ratios (ORs) for asthma or AR at the age of 7 years in different eczema groups after adjusting gender and early wheezing by multiple logistic regression models. In accordance with privacy rules, data obtained from the NHIRD that could be used to identify patients or care providers, including medical institutions and physicians, are scrambled before being sent to the NHRI for use in a database and is further scrambled before being released to individual researchers in accordance with the Personal Electronic Data Protection Law regulations. The computer-processed Personal Electronic Data Protection Law of Taiwan was strictly followed. This study was approved by the Institutional Review Board in Taichung Veterans General Hospital.

Statistical Methods

SAS 9.1 (SAS Institute, Inc., Cary, NC) was applied for data retrieval and analysis. The proportions of asthma and AR between groups were compared by χ^2 -tests. The difference was also presented as relative risk (RR) with 95% confidence intervals (CIs). Binary multiple logistic regression models were applied for adjusted OR. The variable selection was by enter method. A value of $p < 0.05$ was regarded as statistically significant.

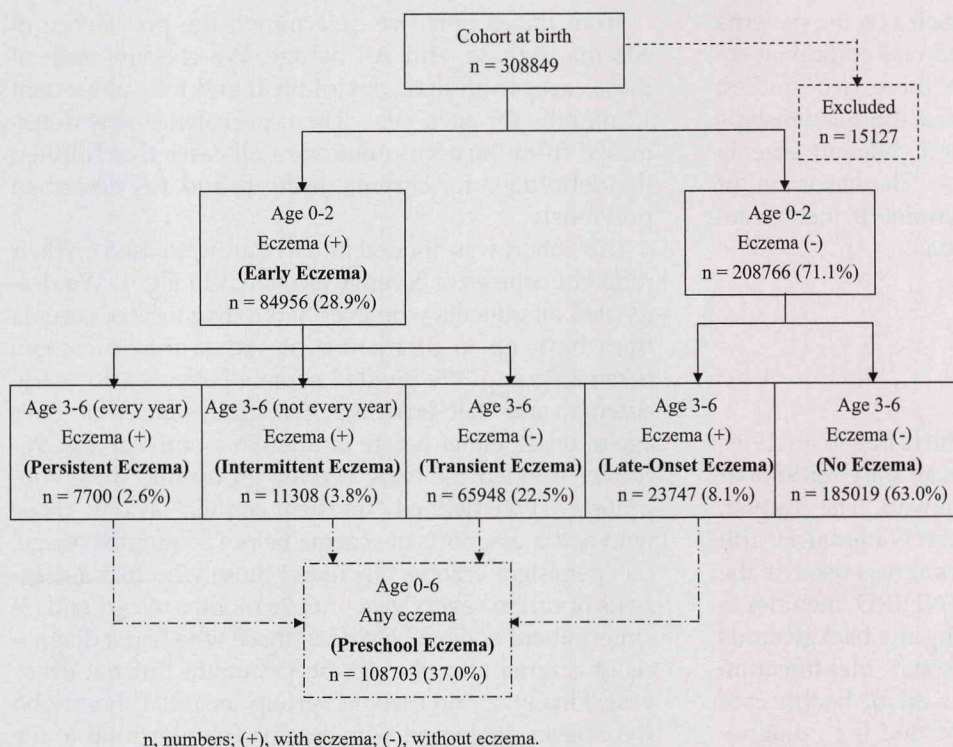


Figure 1. Categorizations of eczema in our enrolled cohort of 293,722 children.

RESULTS

In the birth cohort of 308,849 for the year 2000 in Taiwan, 15,127 were excluded from final analyses for the ages of 85–96 months because of lack of insurance records. The final number of enrolled patients was 293,722, which was ~95% of the initial cohort.

The prevalence of eczema, asthma, and AR from birth up to 7 years of age is shown in Fig. 2. There were 54,095 (18.4%) infants diagnosed with eczema in their 1st year of life, which was the highest rate among all of the ages studied. The trend for having eczema declined with children's age. The percent decline in eczema was 44.9% from age 1 to 2 years, 31.5% from age 2 to 3 years, and diminished to 8.6% from age 3 to 4 years. The asthma prevalence rate increased from 5.5% in the 1st year of life to a peak of 14.6% at 4 years of age, and then decreased to 9.3% by 7 years of age. Regarding AR, this rose from 5.9% in the 1st year of life to a peak of 21.6% at 5 years of age, and then declined to 19.3% at age 7 years. The decline in the prevalence from the age at which a peak occurred to the age of 7 years was more apparent for asthma (~36%) than for AR (~5%).

As shown in Fig. 1, 28.9% of this cohort of children was diagnosed with eczema before 36 months of age. After checking for a diagnosis of eczema between ages 3 and 6 years among this early eczema group, 77.6% had no eczema, 9.1% had eczema in each year, and 13.3% had eczema at some time, but not in every year. In addition, 8.1% of this cohort of children had an initial diagnosis of eczema during ages 3–6 years, and

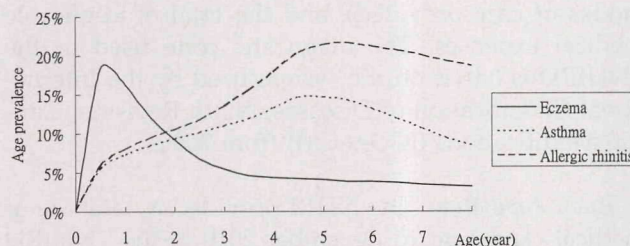


Figure 2. Prevalence of eczema, asthma, and allergic rhinitis (AR) by age from birth to age 7 years.

63.0% never had a diagnosis of eczema before the age of 84 months.

The prevalence of asthma and AR at the age of 7 years based on the different groups of eczema is shown in Table 1. The rate of asthma at age 7 years was 12.72% among those in the preschool eczema group. In comparison with the no eczema group, the RR for asthma at 7 years of age for the preschool eczema' group was 1.74 (95% CI, 1.70–1.78), RR for the early eczema group was 1.62 (95% CI, 1.58–1.66), and RR for the late-onset eczema group was 2.15 (95% CI, 2.08–2.23). Among patients in the early eczema group, those with persistent and intermittent eczema after the age of 36 months had higher RRs for asthma at age 7 years (RR = 2.70, 95% CI, 2.57–2.83, and RR = 2.60, 95% CI, 2.50–2.71, respectively) than for those with transient eczema (RR = 1.33; 95% CI, 1.29–1.37). The RRs for AR at age 7 years showed the same trends in the different eczema groups as for asthma.

As shown in Table 2, we divided patients into two groups based either on the presence of early wheeze

Table 1 The prevalence and RRs of asthma and AR at the age of 7 yr based on the different groups of eczema

Categorizations of Eczema	Numbers	Asthma at Age 7 yr		AR at Age 7 yr	
		<i>n</i> (%)	RR (95% CI)	<i>n</i> (%)	RR (95% CI)
No eczema	185,019	13,533 (7.31)	1	31,330 (16.93)	1
Preschool eczema	108,703	13,826 (12.72)	1.74 (1.70–1.78)	28,013 (25.77)	1.52 (1.50–1.54)
Early eczema	84,956	10,089 (11.88)	1.62 (1.58–1.66)	20,773 (24.45)	1.44 (1.42–1.47)
Persistent eczema	7700	1522 (19.77)	2.70 (2.57–2.83)	2629 (34.14)	2.02 (1.95–2.08)
Intermittent eczema	11,308	2154 (19.05)	2.60 (2.50–2.71)	3973 (35.13)	2.07 (2.02–2.13)
Transient eczema	65,948	6413 (9.72)	1.33 (1.29–1.37)	14,171 (21.49)	1.27 (1.25–1.29)
Late-onset eczema	23,747	3737 (15.74)	2.15 (2.08–2.23)	7240 (30.49)	1.80 (1.76–1.84)

AR = allergic rhinitis; RR = relative risk; CI = confidence interval.

Table 2 The prevalence and RRs of asthma and AR at the age of 7 yr based on the different groups of eczema with or without early wheeze

Categorizations of Eczema and Early Wheeze (%)	Numbers	Asthma at Age 7 yr		AR at Age 7 yr	
		<i>n</i> (%)	RR (95% CI)	<i>n</i> (%)	RR (95% CI)
No early wheeze (<i>n</i> = 246,101; 83.8% of cohort)					
No eczema (66.4%)	163,462	10,975 (6.71)	Ref. 1	26,452 (16.18)	Ref. 2
Early eczema (25.3%)	62,315	6360 (10.21)	1.52 (1.48–1.57)	14,266 (22.89)	1.41 (1.39–1.44)
Persistent eczema (2.1%)	5154	840 (16.30)	2.43 (2.28–2.59)	1648 (31.98)	1.98 (1.90–2.06)
Intermittent eczema (3.3%)	8059	1341 (16.64)	2.48 (2.35–2.61)	2646 (32.83)	2.03 (1.96–2.10)
Transient eczema (19.9%)	49,102	4179 (8.51)	1.27 (1.23–1.31)	9972 (20.31)	1.25 (1.23–1.28)
Late-onset eczema (8.3%)	20,324	2950 (14.51)	2.16 (2.08–2.25)	5936 (29.21)	1.80 (1.76–1.85)
Early wheeze (<i>n</i> = 47,621; 16.2% of cohort)					
No eczema (45.3%)	21,557	2558 (11.87)	1.77 (1.70–1.84)	4878 (22.63)	1.40 (1.36–1.44)
Early eczema (47.5%)	22,641	3729 (16.47)	2.45 (2.37–2.54)	6507 (28.74)	1.78 (1.74–1.82)
Persistent eczema (5.3%)	2546	682 (26.79)	3.99 (3.73–4.26)	981 (38.53)	2.38 (2.26–2.50)
Intermittent eczema (6.8%)	3249	813 (25.02)	3.73 (3.50–3.97)	1327 (40.84)	2.52 (2.42–2.63)
Transient eczema (35.4%)	16,846	2234 (13.26)	1.98 (1.89–2.06)	4199 (24.93)	1.54 (1.50–1.58)
Late-onset eczema (7.2%)	3423	787 (22.99)	3.42 (3.21–3.65)	1304 (38.10)	2.35 (2.25–2.46)

Ref. 1 is the reference group for asthma at the age of 7 yr; Ref. 2 is the reference group for AR at the age of 7 yr.

AR = allergic rhinitis; RR = relative risk; CI = confidence interval.

(*n* = 47,621; 16.2% of cohort) or its absence (*n* = 246,101; 83.8% of cohort). Then, we analyzed the RRs for asthma and AR at age 7 years in the different eczema groups. In the early wheeze group, the rate of early eczema was as high as 47.5%; among those with early eczema and wheeze, 11.2% had persistent eczema and 14.4% had intermittent eczema. The rate of asthma at age 7 years in the reference group—those without eczema or early wheeze—was 6.71%.

Compared with the patients in the reference group, patients with early wheeze and persistent eczema had the highest RR for asthma at age 7 years (RR = 3.99; 95% CI, 3.73–4.26), followed by intermittent eczema (RR = 3.73; 95% CI, 3.50–3.97), late-onset eczema

(RR = 3.42; 95% CI, 3.21–3.65), transient eczema (RR = 1.98; 95% CI, 1.89–2.06), and, finally, no eczema (RR = 1.77; 95% CI, 1.70–1.84). In each eczema group, early wheezers had similar RRs in comparison with those without early wheeze, with RRs ranging from 1.50 to 1.77.

Of particular interest, those who had eczema beyond 36 months of age (persistent, intermittent, and late-onset eczema), even though they were not noted to have early wheeze, still showed higher risks for asthma at age 7 years with RRs of 2.43 (95% CI, 2.28–2.59), 2.48 (95% CI, 2.35–2.61), and 2.16 (95% CI, 2.08–2.25), respectively, than early wheezers with transient eczema (RR = 1.98; 95% CI, 1.89–2.02). Comparing the early

Table 3 The prevalence and RRs of asthma and AR at the age of 7 yr by multivariable logistic regression analysis

Factors	Asthma at Age 7 yr		AR at Age 7 yr	
	OR	95% CI	OR	95% CI
Eczema				
No	1		1	
Transient	1.25	1.21–1.29	1.28	1.25–1.30
Intermittent	2.69	2.56–2.83	2.51	2.41–2.61
Persistent	2.76	2.60–2.93	2.38	2.27–2.50
Late onset	2.34	2.25–2.43	2.14	2.08–2.21
Gender				
Female	1		1	
Male	1.34	1.30–1.37	1.43	1.41–1.46
Early wheeze				
No	1		1	
Yes	1.74	1.69–1.79	1.39	1.36–1.43

AR = allergic rhinitis; RR = relative risk; CI = confidence interval; OR = odds ratio.

eczema groups with early wheeze (RR = 2.45; 95% CI, 2.37–2.54), the persistent and intermittent eczema groups without early wheeze still showed comparable risks for asthma at age 7 years (RR = 2.43, 95% CI, 2.28–2.59, and RR = 2.48, 95% CI, 2.35–2.61, respectively).

Table 3 shows the factors associated with asthma and AR at age 7 years in different groups based on the results from multivariable logistic regression analysis. Adjusted risk for different eczema groups showed similar results as Table 1. Boys had higher risk than girls (OR = 1.34; 95% CI, 1.30–1.37). Early wheezer also had higher risk for future asthma (OR = 1.74; 95% CI, 1.70–1.79) and AR (OR = 1.39; 95% CI, 1.36–1.43) at age 7 years.

DISCUSSION

The results of our study showed that the evolution of three common allergic diseases was similar to the results from other studies.^{11,13,14} The age when the peak prevalence occurred was the youngest for eczema, followed by asthma, and finally AR (Fig. 2). This tendency agreed with the concept of an atopic march up to the age of 7 years.^{16,17} However, on further detailed analysis, we found a more complex scenario than a simple atopic march from eczema to asthma.

From our multiple logistic regression model, we found the presence of eczema, male gender, and early wheeze are all independent risk factors for asthma and AR at the age of 7 years. After adjusting the influence of gender and early wheeze, those who had symptoms that persisted after 36 months old showed higher risk

than the early eczema group. In our study, we found the late-onset eczema group also showed higher risk than the transient eczema group. This finding was not discussed before.

In this population-based cohort, we attempted to reproduce the groupings used in the German Multicenter Allergy Study,¹⁰ and also checked for the presence of asthma at the age of 7 years as in that study. In another report from the German Multicenter Allergy Study,¹⁷ although the prevalence of wheeze among atopic and nonatopic groups appeared to be the same before the age of 5 years, the nonatopic group showed a significant decline in the prevalence of wheeze from ages 5 to 7 years, and the prevalence of wheeze became stable after the age of 7 years.

In the German cohort,¹⁰ no association was found between eczema alone and subsequent asthma at age 7 years. However, they did not show any results after analyzing possible associations with asthma at age 7 years in their three eczema groups (transient, intermittent, and persistent). Nevertheless, they did show that the intermittent and persistent eczema groups had more severe early eczema and higher rates of allergic sensitization. In addition, they found a significantly higher risk for asthma at age 7 years associated with allergic sensitization and early wheeze.

In our study, we did find that eczema was associated with a higher risk for subsequent asthma, and those children with early eczema that persisted after 36 months of age (persistent and intermittent eczema groups) had a higher risk than our transient eczema group. In our study, all eczema cases were diagnosed by physicians, whereas the German study also included cases of parental reporting of eczema symptoms.¹⁰ Another difference was that we defined early eczema during the period from birth to 36 months, whereas it was 24 months in the German study.

As shown in Fig. 2, the peak prevalence of eczema occurred at the 1st year of life, as high as 18.4%. It declined significantly during the subsequent 2 years (prevalence at ages 1 and 2 years were 12.3 and 6.8%, respectively) and then became stable after age 3 years (4.6–3.4%). Thus, based on this trend, we defined early eczema from 0 to 36 months of age. Our study had a much higher percentage of transient eczema cases (*i.e.*, complete recovery) than the German cohort (77.6% versus 43.2%). Thus, we found that defining early eczema from ages 0 to 36 months provided a better grouping of eczema for studies on the subsequent outcomes. In the Tucson cohort,¹⁴ early eczema was also defined as eczema that appeared from birth up to the 3rd year of life. Of course, these differences may be attributed to the databases used. The TNHIRD is a population-based cohort, which included much larger numbers than in the German Multicenter Allergy Study cohort. Eczema has been reported to be more

closely associated with allergic rhinoconjunctivitis than with asthma.¹⁸ In Fig. 2, the prevalence of AR at age 7 years was 19.3% and that for asthma was 9.3%. However, as shown in Table 2, we found that eczema contributed less of a risk to AR than to asthma at age 7 years in all eczema groups, because the reference group—no eczema and no early wheeze—showed that the prevalence of AR at age 7 years was as high as 16.18%. Both eczema and early wheeze contributed less of a risk to AR than to asthma at age 7 years. In addition, the decline in the prevalence of AR from age 5 to 7 years was 10.8%, much less than the 34.8% decline in asthma. This implies that some other factor(s) besides eczema and early wheeze are related to AR but not to asthma at age 7 years.

The major limitation of this study using the TNHIRD database was the unavailability of information regarding allergen sensitization, eosinophil counts, family atopic history, daycare exposures, the presence of xerosis, and environmental factors, such as recording pets or smoking exposure. Thus, we can only partly replicate the information included in some important studies to validate their results in this population-based cohort. The findings from this study need further confirmation from more detailed studies using information not found in the TNHIRD, especially some allergen and daycare exposures, which are still now under debate.^{19,20}

In conclusion, from this population-based health insurance database, we found that different courses of eczema were associated with different risks for asthma and AR at age 7 years. From our results, we suggest that special attention should be given to those children with eczema that persists after 36 months of age, in addition to considering early eczema as a single group. We also emphasize that our late-onset eczema group showed a particularly high association with asthma and AR at age 7 years.

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