

The natural course of early-onset atopic dermatitis in Taiwan: a population-based cohort study*

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Summary

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Conflicts of interest

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Background Atopic dermatitis (AD) often manifests in early childhood and has variable disease course among individual patients. Previous studies regarding the natural course of AD have usually been of small sample size and were not based on nationwide populations.

Objectives We aimed to find out the disease duration and remission rate of children with early-onset AD (onset in the first 2 years of life) in Taiwan, and to determine whether the presence of allergic rhinitis (AR) or asthma affects the disease course.

Methods The patients with early-onset AD in a nationally representative cohort were selected using the National Health Insurance Research Database of Taiwan and were followed from birth to 10 years of age. Kaplan–Meier survival analysis was carried out to analyse the disease duration and remission of AD. Between-group analysis using the log-rank test was carried out to analyse the influence of risk factors on the disease course.

Results Of the 1404 children with early-onset AD, 19.4% had disease duration < 1 year and 48.7% had disease duration < 4 years. During the follow-up, 69.8% of the patients went into remission. Sex, onset age, presence of AR, presence of asthma and presence of respiratory atopy (either AR or asthma) did not show statistically significant influence on disease course.

Conclusions Children in Taiwan with early-onset AD had disease of variable natural course, and the median disease duration was 4.2 years. About 70% of the patients went into remission eventually. The presence of AR or asthma did not affect the disease course of AD.

What's already known about this topic?

- Atopic dermatitis (AD) commonly affects infants and children.
- The natural course of AD varies among individual patients.
- Spontaneous resolution occurs in some children as they grow older.

What does this study add?

- The probability of children with early-onset AD healing in a given time is calculated using nationwide population-based data.
- About 70% of the patients with early-onset AD went into remission eventually.
- Presence of allergic rhinitis or asthma did not affect the course of AD.

Atopic dermatitis (AD) is a common inflammatory skin disease affecting mainly infants and children. Patients with AD show increased risk of allergic rhinitis (AR) and asthma.¹ There are many published reports describing the prevalence of AD, and the prevalence usually decreases with increasing age.^{2–4} The prevalence of AD, and its association with AR and asthma in Taiwan, have been determined using a nationally representative cohort in a previous study.⁵

The natural history of AD is not completely known. Studies have shown that the disease is generally more severe and persistent in young children, and periods of remission appear as the patients grow older. Spontaneous resolution also occurs in some patients.^{6–10} However, previous studies regarding the natural course of AD have drawbacks in terms of inadequate sample size, selection bias in the initial cohort, inadequate length of follow-up and excessive loss to follow-up. To our knowledge, nationwide claims-based studies of the disease course of AD are limited.

In our study, a cohort of patients with early-onset AD (onset in the first 2 years of life) was followed from birth to 10 years of age using the National Health Insurance Research Database (NHIRD). The aims of our study were to investigate the disease duration of patients with early-onset AD and the rate of remission, and to determine the relationships between the disease course and AR and asthma.

The study protocol was reviewed and approved by the institutional review board of Taipei Veterans General Hospital (2012-10-014B).

Materials and methods

Data source

The Department of Health and the National Health Research Institutes of Taiwan maintain the Taiwan NHIRD claims database. The National Health Insurance (NHI) programme was started in Taiwan on 1 March 1995. It covered 96.2% of the total population in 2000, and by the end of 2010, 23.07 million (99.6%) of Taiwan's 23.16 million people had been enrolled in the programme.^{11,12} In 1999, the NHI bureau began to release all claims data in electronic format under the NHIRD project. The NHIRD is one of the largest insurance databases in the world, and its data have been used in many epidemiological studies, including those associated with AD.^{5,13,14}

The database provides scrambled patient identification number, date of birth, sex, diagnostic codes in the format of the International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM) code, and date of visit to medical institutes. In our study, 1 million people (about 5% of Taiwan's population) were randomly selected from the Taiwan NHIRD. All the enrolled subjects were followed up from 1996 to 2010. All medical services that they sought in the NHI programme were collected in the database, including those provided by medical centres, local hospitals and private clinics.

Patient selection

Both ambulatory and inpatient databases were used for patient selection. In the present study, to be designated as having a certain disease, the patient had to have two consecutive corresponding ICD-9-CM codes in the diagnosis field in the ambulatory database, or one in the inpatient database. The ICD-9-CM code used for AD in our study was 691.8; the codes used for AR were 477.0, 477.1, 477.2, 477.8 and 477.9; and the code used for asthma was 493.

Among the patients with AD, those who were born between 1996 and 2000 with first diagnosis before the age of 2 years were included in our study cohort. All enrolled study subjects were followed until the age of 10 years. Disease duration was calculated as the time span from diagnosis to the last time the subject possessed the ICD-9-CM code of AD. 'Remission' was defined as having no diagnosis of AD for > 2 years until the end of follow-up. Because AD is a chronic dermatitis, subjects with disease duration < 90 days were excluded.

Statistical analysis

Kaplan–Meier survival analysis was carried out to analyse the disease duration and remission of AD. Log-rank tests were performed for between-group comparison. A *P*-value < 0.05 was considered statistically significant. PASW Statistics 18 (IBM, Armonk, NY, U.S.A.) was used to analyse the data in this study.

Results

Demographic data and the disease course of atopic dermatitis

The number of children in the database born between 1996 and 2000 was 63 427. In total 1404 children fulfilled the inclusion criteria of our study. Among them, 794 (56.6%) were boys and 610 (43.4%) were girls. At the time of first diagnosis of AD, 463 children (33.0%) were younger than 6 months of age, 351 (25.0%) were aged 6–12 months and

Table 1 The disease duration in children with early-onset atopic dermatitis who went into remission

Disease duration (years)	No. of patients	Cumulative no. of patients	Cumulative remission rate, %
< 1	273	273	19.4
1–2	196	469	33.4
2–3	118	587	41.8
3–4	97	684	48.7
4–5	103	787	56.1
5–6	107	894	63.7
6–7	66	960	68.4
7–8	20	980	69.8

590 (42.0%) were aged 12–24 months. In total, 147 children (10.5%) had been diagnosed with AR at the time of first diagnosis of AD, and 117 children (8.3%) had been diagnosed with asthma at the first diagnosis of AD. Overall, 225 children (16.0%) had been diagnosed with either AR or asthma, regarded as 'respiratory atopy', at the time of first diagnosis of AD.

We also calculated what specialties these children sought medical help for. Among the total 250 604 times of ICD-9-CM coding of AD in the 1404 children, 94 569 (37.7%) were under the service of dermatologists. Physicians of family medicine accounted for 40 929 visits (16.3%) and paediatricians accounted for 29 623 (11.8%). Other specialties with large numbers of coding included internal medicine (7.8%) and traditional Chinese medicine (4.0%).

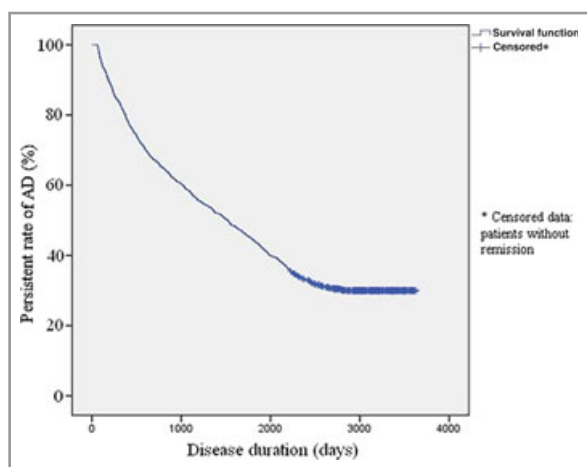


Fig 1. Kaplan–Meier survival analysis of persistence of atopic dermatitis (AD) in the whole study group.

In the whole study group, 273 children (19.4%) had disease duration < 1 year, 587 (41.8%) had disease duration < 3 years and 787 (56.1%) had disease duration < 5 years (Table 1). In total 980 children (69.8%) went into remission during our follow-up period, meaning that the other 424 (30.2%) still sought medical help for AD after the age of 8 years. The expected disease duration in the whole study group was estimated by survival analysis (Fig. 1). The median duration of AD was 1523 days (4.2 years).

Risk factors associated with the duration and remission rate of atopic dermatitis

We carried out between-group analysis using the log-rank test to analyse the influence of risk factors on the disease duration and remission rate of AD (Table 2). Trends could be seen in the survival curves showing that boys have a longer disease course and lower remission rate than girls (Fig. 2). When dividing the patients according to the onset age, the 1–2-year-old group had a longer disease course and a lower remission rate than the 0–1-year-old group (remission rates 67.6% and 71.4%, respectively). The remission rates of patient with AR (66.0%) or asthma (63.2%) were lower than in those without AR (70.2%) or without asthma (70.4%). The remission rate of children with 'respiratory atopy' (65.8%) was also lower than in those without it (70.6%). However, none of the differences in the between-group analysis were statistically significant.

Discussion

In a retrospective manner, we observed a large, population-based birth cohort. Those with early-onset AD (onset of disease in the first 2 years of life) were followed from birth until 10 years of age. Among this cohort, about half of the patients

Variable	No. of patients	No. of patients in remission	Remission rate (%)	Median (IQR) disease duration (days)	P-value ^a
Sex					
Male	794	549	69.1	1545 (475–NA)	0.522
Female	610	431	70.7	1442 (478–NA)	
Age of onset					
< 1 year	814	581	71.4	1383 (460–NA)	0.157
1–2 years	590	399	67.6	1632 (503–NA)	
AR					
No	1257	883	70.2	1523 (478–NA)	0.592
Yes	147	97	66.0	1526 (426–NA)	
Asthma					
No	1287	906	70.4	1525 (500–NA)	0.487
Yes	117	74	63.2	1523 (396–NA)	
AR or asthma					
No	1179	832	70.6	1504 (500–NA)	0.477
Yes	225	148	65.8	1527 (415–NA)	

IQR, interquartile range; NA, not available because of censored information on survival analysis; AR, allergic rhinitis. ^aThe P-values are from between-group analysis using log-rank tests.

Table 2 Influences of variables on disease duration and remission rate

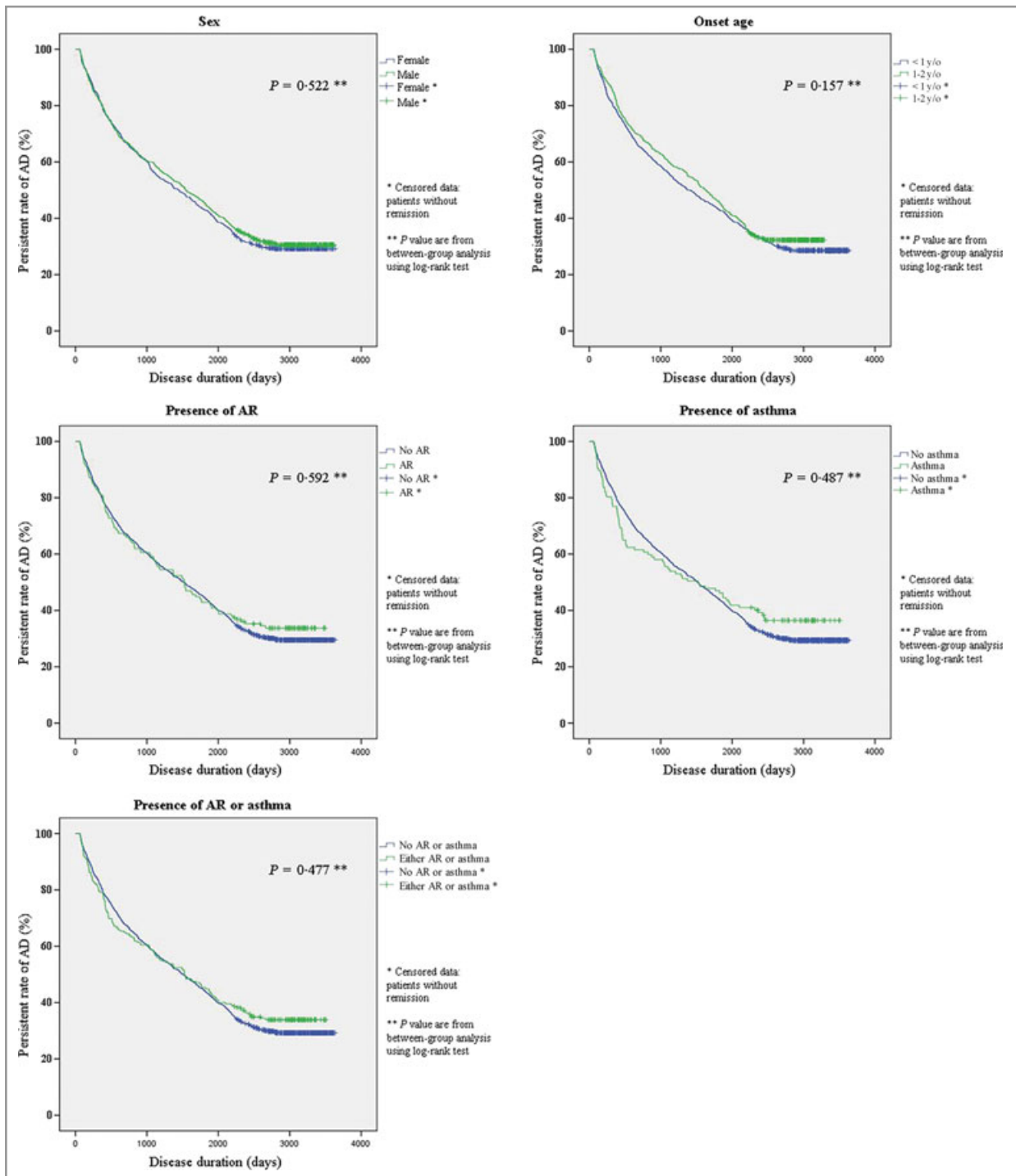


Fig 2. Kaplan–Meier curves showing the disease duration with different variables. AD, atopic dermatitis; AR, allergic rhinitis; y/o, years old.

(48.7%) had disease duration < 4 years. That is, about half of the children with early-onset AD went into complete remission before school age. However, there were also another 30.2% of patients still seeking medical help for AD after 8 years of age, given that the remission rate in our study was 69.8%.

The remission rate and disease duration of our study fell between the values from previous reports. Illi *et al.*⁷ followed

192 children with early-onset AD and found that 43.2% went into complete remission by the age of 3 years. In another retrospective follow-up study,⁸ AD had completely resolved in 60.5% of patients first diagnosed between 6 and 36 months of age. A recent study in Korea had results similar to ours.¹⁰ They analysed 597 children with AD who manifested skin symptoms in the first year of life, and found that 70.6% became disease free after a mean duration of 60 months of follow-up.

Several factors may explain the differences in remission rate and disease duration. In the first study, by Illi *et al.*,⁷ complete remission after age 2 years was calculated, but we were unable to discern the percentage of children who went into remission in the later years of life in this cohort. Both the study by Ricci *et al.*⁸ and that of Chung *et al.*¹⁰ were retrospective analyses at a single centre. The longer follow-up time (mean 16.9 years) of the study by Ricci *et al.* may explain the lower remission rate because of detection of late relapses.

Compared with previous studies, our study better reflected the population data because the initial cohort was nationwide and claims based, the follow-up time was long, and almost all medical services in the nation are included in this database. The presence of AD was defined as either ambulatory or inpatient visits under the diagnosis of AD made by clinicians. The reliability is better compared with the phone calls or questionnaires used in previous studies.^{7,8,10}

Although the data were not statistically significant, our study suggests that boys may have longer disease course and lower remission rates than girls among patients with early-onset AD. Previous studies, including both cohort and cross-sectional studies, showed that the prevalence of AD in girls was lower than that in boys in infancy, but exceeded male patients in preschool children.^{5,9,15,16} Considering the results of our study, it could be assumed that the shifting was due to later onset in girls.

When comparing according to the onset age, the 1–2-year-old group had a longer disease course and a lower remission rate than the 0–1-year-old group. However, it did not reach statistical significance. There have been some natural history surveys underlining that earlier age at onset is associated with lower frequency of healing of AD.^{17,18} This may be explained by patients with earlier onset of AD having higher SCORAD (Scoring of Atopic Dermatitis) indexes and thus more severe clinical disease.¹⁹ However, if we focus on patients with early-onset AD, previous studies showed that those with a manifestation of disease in the first year of life did not have a poorer prognosis than those whose onset was later.^{7,20} Our study had the same finding.

In this study, the presence of AR, asthma or 'respiratory atopy' (either AR or asthma) at the first diagnosis of AD failed to show any influence on AD disease course. It is considered that AD is one of the first steps in the 'atopic march'.^{21,22} Therefore, patients with AD may develop AR or asthma in their later years of life. Our study helps to clarify only that patients with other atopic comorbidities do not have more protracted disease duration of AD.

Understanding the natural history of AD helps to provide accurate information for prognosis and to establish an appropriate management strategy for each patient. Although it is impossible to guarantee, we can give parents the probability that children with early-onset AD will recover in a given time. This helps them to understand the disease better and to cooperate with physicians in the care of these children. Educational intervention with the patient and family has proven to be of use in the care of AD, and was included in recent guidelines

for AD management.^{23,24} The results of our study provide important information and can be incorporated into educational programmes for AD.

There were some limitations to our study. Firstly, because the recognition of AD depended on diagnosis by a physician, subclinical disease might be missed. The disease duration may be better interpreted as the 'disease duration requiring medical intervention'. However, the result was still of great value, as not requiring medical treatment meant the disease went into remission to an extent. Secondly, our data did not show the disease severity, the given treatment, or other factors that may have effects on the course of AD. Thirdly, although the follow-up to 10 years of age was longer than most previous similar studies, it failed to capture the relapses after 10 years. The remission rate of AD may be overestimated.

In conclusion, about 70% of children in Taiwan with early-onset AD went into remission eventually, and the median disease duration was 4.2 years. The between-group analysis did not show significant influence of sex, age and presence of AR or asthma on disease duration.

References

- 1 Akdis CA, Akdis M, Bieber T *et al.* Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol* 2006; **118**:152–69.
- 2 Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994; **30**:35–9.
- 3 Saeki H, Iizuka H, Mori Y *et al.* Prevalence of atopic dermatitis in Japanese elementary schoolchildren. *Br J Dermatol* 2005; **152**:110–14.
- 4 Williams H, Robertson C, Stewart A *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999; **103**:125–38.
- 5 Hwang CY, Chen YJ, Lin MW *et al.* Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. *Acta Derm Venereol* 2010; **90**:589–94.
- 6 Kissling S, Wuthrich B. Follow-up of atopic dermatitis after early childhood. *Hautarzt* 1993; **44**:569–73.
- 7 Illi S, von Mutius E, Lau S *et al.* The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; **113**:925–31.
- 8 Ricci G, Patrizi A, Baldi E *et al.* Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; **55**:765–71.
- 9 Eller E, Kjaer HF, Host A *et al.* Development of atopic dermatitis in the DARC birth cohort. *Pediatr Allergy Immunol* 2010; **21**:307–14.
- 10 Chung Y, Kwon JH, Kim J *et al.* Retrospective analysis of the natural history of atopic dermatitis occurring in the first year of life in Korean children. *J Korean Med Sci* 2012; **27**:723–8.
- 11 Bureau of National Health Insurance. National Health Insurance in Taiwan. Available at: <http://www.nhi.gov.tw/english/> (last accessed 9 October 2013).
- 12 Chang YJ, Yeh ML, Li YC *et al.* Potential drug interactions in dermatologic outpatient prescriptions – experience from nationwide

- population-based study in Taiwan. *Dermatologica Sinica* 2011; **29**:81–5.
- 13 Chung SD, Keller JJ, Lin HC. Association of erectile dysfunction with atopic dermatitis: a population-based case–control study. *J Sex Med* 2012; **9**:679–85.
 - 14 Hwang CY, Chen YJ, Lin MW *et al.* Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: a nationwide cohort study in Taiwan. *Int J Cancer* 2012; **130**:1160–7.
 - 15 Smidesang I, Saunes M, Storro O *et al.* Atopic dermatitis among 2-year olds; high prevalence, but predominantly mild disease – the PACT study Norway. *Pediatr Dermatol* 2008; **25**:13–18.
 - 16 Saval P, Fuglsang G, Madsen C, Osterballe O. Prevalence of atopic disease among Danish school children. *Pediatr Allergy Immunol* 1993; **4**:117–22.
 - 17 Rystedt I. Long term follow-up in atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1985; **114**:117–20.
 - 18 Rystedt I. Prognostic factors in atopic dermatitis. *Acta Derm Venereol* 1985; **65**:206–13.
 - 19 Ingordo V, D'Andria G, D'Andria C. Adult-onset atopic dermatitis in a patch test population. *Dermatology* 2003; **206**:197–203.
 - 20 Horwitz AA, Hossain J, Yousef E. Correlates of outcome for atopic dermatitis. *Ann Allergy Asthma Immunol* 2009; **103**:146–51.
 - 21 Barnetson RS, Rogers M. Childhood atopic eczema. *BMJ* 2002; **324**:1376–9.
 - 22 Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. *Immunol Allergy Clin North Am* 2010; **30**:269–80.
 - 23 Baron SE, Cohen SN, Archer CB. Guidance on the diagnosis and clinical management of atopic eczema. *Clin Exp Dermatol* 2012; **37** (Suppl. 1):7–12.
 - 24 Ring J, Alomar A, Bieber T *et al.* Guidelines for treatment of atopic eczema (atopic dermatitis). Part II. *J Eur Acad Dermatol Venereol* 2012; **26**:1176–93.