

Original article

Risk of developing asthma in young children with atopic eczema: A systematic review

Annelies E. van der Hulst, MD,^a Helen Klip, PhD,^b and Paul L. P. Brand, MD, PhD^a

Zwolle, The Netherlands

Background: It is commonly believed that the majority of infants and young children with early atopic eczema will develop asthma in later childhood. This belief is mainly based on cross-sectional population studies. Recent evidence suggests a more complex relationship between early eczema and asthma. **Objective:** This systematic review was conducted to assess the risk of developing asthma in children with atopic eczema during the first 4 years of life.

Methods: A sensitive search was performed to identify all prospective cohort studies on the topic. By pooling the eligible reports, we calculated the risk of developing asthma at 6 years of age or older in children with atopic eczema in the first 4 years of life.

Results: Thirteen prospective cohort studies were included, with 4 representing birth cohort studies and 9 representing eczema cohort studies. The pooled odds ratio for the risk of asthma after eczema, compared with children without eczema, in birth cohort studies was 2.14 (95% CI, 1.67-2.75). The prevalence of asthma at the age of 6 years in eczema cohort studies was 35.8% (95% CI, 32.2% to 39.9%) for inpatients and 29.5% (95% CI, 28.2% to 32.7%) for a combined group of inpatients and outpatients.

Conclusion: Although there is an increased risk of developing asthma after eczema in early childhood, only 1 in every 3 children with eczema develops asthma during later childhood. This is lower than previously assumed.

Clinical implications: Our results may have important consequences for counseling patients with atopic eczema and their parents. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Atopic eczema, atopic dermatitis, asthma, wheeze, atopic march

Population studies show that allergic diseases peak at different ages in childhood. Atopic eczema (AE) and food allergies have the highest incidence in the first 2 years of life. Sensitization to inhalant allergens is rare during these

Abbreviations used

AE: Atopic eczema

OR: Odds ratio

early years. In later childhood, the prevalence of AE, food allergies, and food allergen sensitization decreases and the prevalence of asthma, allergic rhinitis, and sensitization to inhalant allergens rises.^{1,2} The term *atopic march* is commonly used to describe this typical progression from AE in young children to asthma at school age, not only in population studies but also in individual patients.^{3,4}

Reported risks of asthma in children with AE vary greatly, from 25% in some sources to 80% in others.³⁻⁵ Most of the evidence on which the concept of the atopic march is based comes from cross-sectional population studies at different ages. A recent population-based prospective birth cohort study suggested a more complicated relationship between early AE and asthma later in childhood, with wheezing preceding or coinciding with AE in the majority of children.⁶ As a result, it is unclear whether the concept of the atopic march, with simple progression of AE at early age into asthma at school age, is still valid. This encouraged us to seek an evidence-based answer to the question, "What is the risk of developing asthma at school age in children with AE during the first 4 years of life?" For this purpose, we conducted a systematic review of all published prospective follow-up studies addressing the relationship of early life AE to asthma in later childhood.

METHODS

A sensitive search strategy was designed to retrieve all relevant articles from Medline, Embase (Jan 1, 1950 to August 1, 2006) and the Cochrane library (1966 to August 1, 2006). We searched for ("asthma" OR "wheeze" OR "bronchial hyperresponsiveness") AND ["eczema" OR "atopic dermatitis" OR "atopy"] AND ("prospective study" OR "cohort study" OR "risk factor" OR "epidemiologic study" OR "longitudinal study") as medical subject headings or as main key words in the title or abstract. Potentially eligible reports were selected by 2 independent reviewers and retrieved, and their reference lists were searched for further relevant studies. In addition, reference lists of relevant review articles obtained by the literature search were evaluated. Also, a number of pediatric allergy textbooks were hand-searched.^{3,7,8} Two reviewers (A. H., P. B.)

From ^aPrincess Amalia Children's Clinic and ^bthe Department of Epidemiology and Biostatistics, Isala Academy, Isala Klinieken.

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Reprint requests: Paul L. P. Brand, MD, PhD, Princess Amalia Children's Clinic, Isala Klinieken, Dr Van Heesweg 2, PO Box 10400, 8000 GK Zwolle, The Netherlands. E-mail: p.l.p.brand@isala.nl.

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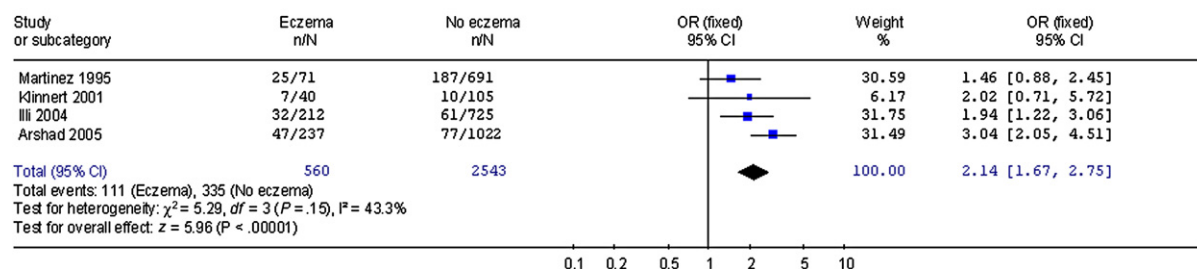
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TABLE I. Eczema and asthma risk: characteristics of birth cohort studies

Author, year, and reference	Year of enrollment	Mean follow-up (y)	Cohort size	Predictor	Outcome	Total no. of asthma cases
Arshad (2005) ²⁸	1989	10	1259	AE 0-1 y	Current wheeze	124
Illi (2004) ⁶	1990	7	937	AE 0-2 y	Current wheeze	93
Klennert (2001) ²⁷	1985-1987	8	145	AE 0-1 y	Doctor's diagnosis	17
Martinez (1995) ⁹	1980-1984	6	762	AE 0-1 y	Current wheeze	212
Total			3103			

Review: Eczema and asthma risk
 Comparison: 01 Birth cohort studies
 Outcome: 01 Asthma

**FIG 1.** Eczema and asthma risk: birth cohort studies.

independently assessed the obtained titles and abstracts for eligibility. Differences were solved by consensus.

Inclusion and exclusion criteria

Articles were included following 2 consecutive sets of inclusion criteria. First, we included all prospective cohort studies in which at least part of the study population presenting with AE was younger than 4 years, and in which follow-up to determine asthma development continued until the age of 6 years or older. The age of 6 years was chosen because it is difficult to separate asthma from episodic viral wheeze in younger children.⁹ Only population-based birth cohorts and cohorts of patients with AE were included. All reports in English, German, or Dutch were included.

A second set of inclusion criteria was used to evaluate study validity. Only studies with a reported follow-up of at least 80% were included. In addition, the outcome "asthma" was only considered valid if it had been diagnosed by a doctor, or when subjects reported "current wheeze" (wheezing in the last 12 months) to a questionnaire.

Statistical analysis

For the birth cohort studies, we calculated odds ratios (ORs) estimating the risk of developing asthma after early AE compared with young children without AE. These ORs were pooled by using a fixed effects model.¹⁰

For the eczema cohort studies, the asthma prevalence rate at follow-up was calculated for each individual study. The eczema cohort studies consisted of 3 types of cohorts: inpatients, outpatients, and a mixed group of inpatients and outpatients. The prevalence rates of cohorts of the same type were pooled in a weighed fashion, taking sample size into account.

To investigate whether the year of enrollment influenced the risk of asthma in patients with AE, a nonparametric correlation coefficient was calculated between study year and risk of asthma.

RESULTS

The search yielded 2668 hits in Medline and 2498 hits in Embase, of which 1609 were duplicate hits. Out of this total of 3557 articles, 23 were eligible according to our first set of criteria. Of these 23, two articles were excluded because they showed duplicate data from a study already included.^{11,12} The full text of 1 report could not be retrieved through library services.¹³ Following the validity criteria, 7 articles were excluded on the basis of insufficient follow-up figures.¹⁴⁻²⁰ No articles were excluded according to the outcome measure of asthma. Although 6 articles did not specify the criteria by which the diagnosis of asthma was made, it was implicitly clear that asthma was doctor-diagnosed.²¹⁻²⁶ Thirteen articles were finally included, 4 representing birth cohort studies and 9 representing eczema cohort studies.^{6,9,21-31}

Birth cohort studies

The 4 birth cohort studies included a total of 3103 subjects (Table I). Two of these reports were general population samples,^{9,28} 1 was a general population sample enriched with high-risk infants,⁶ and 1 was a high-risk birth cohort of mothers with asthma.²⁷ Follow-up periods varied from 6 to 10 years. The diagnostic criteria for eczema in these studies were based on parental reports of recurrent itchy rash,^{6,28} doctor's diagnosis of eczema,⁹ or a combination of the 2.²⁷ The ORs of the risk of developing asthma in young children with AE in these studies are presented in Fig 1. In 2 studies, early childhood eczema was not a significant risk factor for developing asthma in later

TABLE II. Eczema cohort studies: overview

Author, year, and reference	Year of enrollment	Mean follow-up (y)	Total cohort size	Outcome	Predictor
Inpatients					
Burrows (1960) ²⁹	1947-1950	9-12	23	Current wheeze	AE 0-1 y
Linna (1992) ³⁰	1977-1980	10	40	Current wheeze	AE 0-1 y
Pasternak (1965) ²¹	1957-1962	NA	498	Current wheeze	AE
Stifler (1965) ²²	1941	22	40	Doctor's diagnosis	AE infancy*
Total			601		
Inpatients and outpatients					
Kissling (1993) ²³	1967-1970	20	106	Doctor's diagnosis	AE 0-2 y
Queille-Roussel (1985) ²⁴	1978	6	500	Doctor's diagnosis	Early† AE
Rystedt (1985) ²⁵	1952-1956	24	955	Doctor's diagnosis	AE 0-14 y
Wuthrich (2002) ²⁶	1990	8	22	Doctor's diagnosis	AE 2-4 y
Total			1583		
Outpatients					
Gustafsson (2000) ³¹	1990	7	94	Doctor's diagnosis	AE 0-1.5 y

NA, Data not available.

*Infancy: 84% of cohort <2 years.

†Early: mean age at onset of AE, 7.9 months.

childhood.^{9,27} The pooled OR was 2.14 (95% CI, 1.67-2.75; χ^2 test for heterogeneity, 5.29; $P = .15$).

Eczema cohort studies

Of the 9 eczema cohort studies, 4 included only inpatients, 4 included a mixed group of inpatients and outpatients, and 1 cohort included only outpatients (Table II). The follow-up varied from 6 to 22 years. The diagnosis of eczema was made by a specialized doctor in a skin clinic in 8 of the 9 reports. One report did not specify how the diagnosis of eczema was made.²⁶ In the inpatients group, 1 study³⁰ specified that the diagnosis of eczema was made according to the Hanifin and Rajka criteria.³² These criteria were also used for 1 of the studies in the mixed group²⁵ and for the outpatient study.³¹ Prevalence rates of asthma at follow-up ranged from 33.7% to 52.5% in inpatients and from 14.2% to 45.5% in the mixed group (Table III). The weighed prevalence of asthma at follow-up was 35.8% (95% CI, 32.2-39.9) for inpatients, 29.5% (CI 95%, 28.2-32.7) for the mixed group of inpatients and outpatients, and 45.7% (95% CI, 36.9-55.8) for outpatients.

Year of enrollment

The asthma prevalence in the eczema cohort studies showed a very weak and nonsignificant increase with increasing calendar year in which patients were enrolled (Spearman rank correlation, 0.075; $P = .847$).

DISCUSSION

Our study shows that although the risk of developing asthma in young children with AE is elevated (OR, 2.14; 95% CI, 1.76-2.75), the magnitude of this risk is relatively low, with a prevalence of asthma at the age of 6 years or older of 35.8% (95% CI, 32.2% to 39.9%) in inpatients and of 29.5% (95% CI, 28.2% to 32.7%) in a combined group of inpatients and outpatients. These figures, based

TABLE III. Eczema cohort studies: prevalence and 95% CI

Author, year, and reference	Total cohort size	Total no. of asthma cases	Prevalence (%)	95% CI
Inpatients				
Burrows (1960) ²⁹	23	11	47.8	29.2-67.0
Linna (1992) ³⁰	40	21	52.5	37.5-67.1
Pasternak (1965) ²¹	498	168	33.7	29.7-38.0
Stifler (1965) ²²	40	16	40.0	26.3-55.4
Weighted prevalence			35.8	32.2-39.9
Inpatients and outpatients				
Kissling (1993) ²³	106	15	14.2	8.8-22.0
Queille-Roussel (1985) ²⁴	500	150	30.0	26.1-34.2
Rystedt (1985) ²⁵	955	306	32.0	29.2-35.1
Wuthrich (2002) ²⁶	22	10	45.5	26.9-65.3
Weighted prevalence			29.5	28.2-32.7
Outpatients				
Gustafsson (2000) ³¹	94	43	45.7	36.0-55.8

on a systematic review of all studies with more than 80% follow-up until the age of 6 years or older, are considerably lower than the risk estimates provided in many review articles and medical textbooks.^{3,5,7,8} Our systematic review shows that on average, only 1 in 3 young children with AE develops asthma at the age of 6 years or older.

The strength of our study is that it was a systematic review of all published studies. We deliberately designed a highly sensitive search strategy because we did not want to miss any relevant studies. The results of our pooled analyses, however, should be interpreted with caution because of the heterogeneity of the samples studied and the eczema criteria used. Because there is no generally accepted gold standard for diagnosing AE, all cohort studies used different diagnostic criteria. The birth cohort studies used parental report of recurrent itchy rash,^{6,28} doctor's diagnosis of eczema,⁹ or a combination of the 2²⁷ to identify AE. This clinical heterogeneity is the likely explanation for the different ORs observed in these studies (Fig 1), and the pooled OR should be interpreted cautiously. The large majority of eczema cohort studies used a doctor's diagnosis of AE as the inclusion criterion. Although this was not specified in many studies, in our opinion it justified pooling of results.

Given the multifactorial etiology of both AE and asthma, it is likely that genetic and environmental factors and the methods of cohort selection have an effect on the risk of asthma in children with AE. Unfortunately, the published available data of the included studies did not allow any meaningful analysis of these influences in our systematic review. Recently, a large eczema cohort study from Italy, which fell outside our search scope because it was published after August 1, 2006, was the first to examine factors associated with AE outcome and development of asthma. In this study, sensitization to hen's egg and the development of allergic rhinoconjunctivitis were the strongest predictor of the development of asthma in children with AE.³³ The importance of early sensitization to allergens, in particular to hen's egg, in predicting the development of asthma has also been found in the German Multicenter Allergy Study birth cohort study.^{34,35} More studies, however, are needed to address these influences on the risk of developing asthma in children with AE in more detail.

A weakness of our review was that a number of follow-up studies had to be excluded because of incomplete follow-up. This might have reduced the power of our review to detect differences in asthma prevalence between children with mild and more severe AE. A cutoff level of at least 80% follow-up was chosen because this has been used previously in systematic reviews of long-term cohort follow-up studies.³⁶ It is unlikely that this selection of studies influenced the main results of our analysis because the difference in prevalence of asthma between the excluded and included eczema cohorts was only 2% (data not shown).¹⁴⁻²⁰ The difference in weighted prevalences between the inpatient studies and mixed group of inpatient and outpatient studies is small (6.3%), indicating that there appears to be little, if any, influence of AE severity on the risk of developing asthma in later childhood. However, we believe that because of the small number of studies and because of overlap between the inpatient group and the mixed group of inpatients and outpatients, it is not possible to perform a meaningful statistical analysis of the influence of AE severity on the risk of developing

asthma. Curiously, the risk of developing asthma was considerably higher in the only eczema cohort study of outpatients³¹ than in the inpatients studies.^{21,22,29,30} The former study was conducted more recently than the latter ones. This suggests that the risk of developing asthma in patients with AE has changed over time. However, when all studies were pooled, such a relationship could not be confirmed. Thus, more studies on the risk of developing asthma in young outpatients with AE are needed, in particular to assess the influence of AE severity on this risk.

Our results may have important implications for patient and parent counseling. The relatively low risk suggests that the relationship of AE in early childhood to asthma in later childhood is not one of simple linear progression. This supports recent findings from a German birth cohort study in which most children who developed asthma at school age after AE in infancy had already started wheezing before AE became apparent.⁶ Data from recent genetic studies may provide a pathophysiological basis for the complex relationship between early AE and later asthma. Genetic regions found to be associated with AE do not overlap with those associated with asthma. However, the expression of proteins by genetic regions involved in both asthma and AE is mainly located in epithelial tissue. Hypothetically, in atopic disease, epithelial barrier failure results in excess allergen sensitization and IgE production.³⁷ According to this theory, asthma and AE do not have a shared genetic background but do share etiologic factors resulting in epithelial barrier dysfunction. This theory is supported by studies in rodents showing that allergic sensitization is a systemic reaction influencing many organs rather than only a local response.³⁸ These pathophysiological findings may explain why there is an increased risk of asthma in children with AE, but that this risk is only modestly increased.

Conclusion

Although children with AE in the first 4 years of life have an approximately 2-fold increased risk of developing asthma later in childhood compared with children without AE, only 1 in 3 children with AE will actually develop asthma, which is much lower than previously estimated. This is an important finding for counseling patients with AE and their parents. The relationship between asthma and AE seems complex, and both genetic and clinical findings suggest that it is not one of simple progression of AE into asthma as popularly described in the atopic march concept. More studies are needed to unravel the factors associated with the development of asthma in children with AE.

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