

Childhood eczema and asthma incidence and persistence: A cohort study from childhood to middle age

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Background: The association between eczema and asthma is well documented, but the temporal sequence of this association has not been closely examined.

Objectives: To examine the association between childhood eczema and asthma incidence from preadolescence to middle age, and between childhood eczema and asthma persisting to middle age. A further aim was to examine any effect modification by nonallergic childhood exposures on the association between childhood eczema and both childhood asthma and later life incident asthma.

Methods: Data were gathered from the 1968, 1974, and 2004 surveys of the Tasmanian Longitudinal Health Study. Multivariable logistic regression examined the association between childhood eczema and childhood asthma. Cox regression examined the association between childhood eczema and asthma incidence in preadolescence, adolescence, and adult life. Binomial regression examined the association between childhood eczema and childhood asthma persisting to age 44 years.

Results: Childhood eczema was significantly associated with childhood asthma and with incident asthma in preadolescence (hazard ratio [HR], 1.70; 95% CI, 1.05-2.75), adolescence (HR, 2.14; 95% CI, 1.33-3.46), and adult life (HR, 1.63; 95% CI, 1.28-

2.09). Although childhood eczema was significantly associated with asthma persisting from childhood to middle age (relative risk, 1.54; 95% CI, 1.17-2.04), this association was no longer evident when adjusted for allergic rhinitis.

Conclusion: Childhood eczema increased the likelihood of childhood asthma, of new-onset asthma in later life and of asthma persisting into middle age. (J Allergy Clin Immunol 2008;122:122-130.)

Key words: Childhood eczema, incident asthma, persisting asthma

Childhood eczema carries a heavy burden for the affected child and the family.¹⁻³ It is a disease with a high and variable prevalence,⁴⁻¹¹ and there is evidence that the prevalence has increased in recent decades.^{12,13} An association between childhood atopic eczema and asthma has been shown in at least 1 cross-sectional study¹⁴ and in several longitudinal studies.¹⁵⁻¹⁷ A recent systematic review indicated that about 1/3 of children with atopic eczema before age 4 years will develop asthma by age 6 years or older.¹⁸ The eczema/asthma association has been explained by invoking the atopic march¹⁹⁻²¹ whereby children with eczema have a high risk of progression to asthma and/or allergic rhinitis later in childhood. Epicutaneous sensitization of the bronchus-associated lymphoid tissue has been proposed as a causal pathway.²² Alternatively, eczema, allergic rhinitis, and childhood asthma may be manifestations of diseases with a common atopic background.²³

Whereas the association between childhood eczema and childhood asthma is well described, less is known²⁴ of the relationship between childhood eczema and incident asthma in later life. Demonstrating such an association would strengthen a case for causality.²⁵ We used data from the Tasmanian Longitudinal Health Study (TAHS) to examine the associations between childhood eczema and childhood asthma and between childhood eczema and incident asthma in later life. We also examined whether other childhood exposures modified these associations. We then examined the association between childhood eczema and childhood asthma that persisted to the age of 44 years.

METHODS

Study population and data collection

The TAHS began in 1968 when a cohort (n = 8583) of 7-year-old children attending school in Tasmania was surveyed. A questionnaire completed by parents detailed each child's history of asthma, hay fever, eczema, food or medicine allergy, and urticaria. At a medical examination, FEV₁, forced vita-

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Abbreviations used

AD: Atopic dermatitis

OR: Odds ratio

TAHS: Tasmanian Longitudinal Health Study

capacity, and forced expiratory flow from 25% to 75% of the forced vital capacity were measured with a wedge-bellows spirometer (Vitalograph Ltd, Buckinghamshire, United Kingdom). These measurements were expressed as percent predicted values.²⁶

Another survey was performed in 1974. The parents of the 7383 children (86% of the original cohort) who could be traced completed another respiratory questionnaire in which data were gathered on the participants' "asthma ever" status and age at asthma onset.

The current survey started in 2004 when 6998 participants (81.5%) from the original survey were traced to an address and sent a detailed respiratory questionnaire.²⁷ Of these, 5729 (81.9%) completed the questionnaire that gathered data on having asthma ever, age at asthma onset, eczema and hay fever history, smoking history, exposure to others' tobacco smoke, and allergies to grasses, dust, animals, food, and medicines.

Definitions

Infantile eczema and flexural eczema. These were defined in the 1968 questionnaire by affirmative responses to the questions, "Did he/she have infantile (baby) eczema?" and "Has he/she ever had eczema in the creases (bends) of the elbows, wrists or knees?"

Eczema "ever." This was participant-defined in the 2004 questionnaire by an affirmative response to the question, "Have you ever had eczema or any kind of skin allergy?"

These responses were grouped as a 3-level variable: (1) childhood eczema (infantile eczema, flexural eczema, or both), (2) later-onset eczema (no infantile or flexural eczema but eczema ever documented in the 2004 questionnaire), and (3) never eczema.

Conjoint eczema. This was a variable generated to describe those participants in 1968 with both infantile and flexural eczema.

Asthma ever. Asthma by ages 7 or 13 years was defined in the 1968 or 1974 questionnaires by an affirmative response to the question, "Has your child ever suffered from attacks of asthma or wheezy breathing?" Asthma by age 44 years was defined by an affirmative answer to the question in the 2004 questionnaire, "Have you ever in your life suffered from attacks of asthma or wheezy breathing?"

Age at onset of asthma. This was self-reported in the 2004 questionnaire. The participants' responses in the 2004 questionnaire were compared with their parents' prospectively gathered responses in 1968 and 1974. Where there was disagreement, the parents' responses were taken to be correct.²⁸

Persisting and remitting asthma. Remitting asthma was defined as asthma ever in the 2004 survey, and no attack within the previous 2 years. Those with asthma ever in the 2004 survey and an attack within the previous 2 years were regarded as having persisting asthma.

Covariates

Allergic rhinitis was defined in the 1968 questionnaire by an affirmative answer to the question, "Does he/she get attacks of 'hay fever' (that is, sneezing, running or blocked nose, sometimes with itchy eyes or nose)?" and in the 2004 questionnaire by an affirmative answer to the question, "Have you ever had hay fever (that is, sneezing, running or blocked nose when you do not have a cold or the flu)?"

Lung infection in childhood was defined in the 1968 questionnaire by an affirmative response to the question, "Have you ever been told by a doctor that he/she has pneumonia or pleurisy?"

Impaired lung function at age seven years was defined as an FEV₁ less than 80% of predicted.^{26,29}

Food/medicine allergy or urticaria (hives) in the child were defined in the 1968 questionnaire by an affirmative response to the questions, "Have you ever been told by a doctor that he/she is allergic to any foods or medicines?" and "Does he/she get hives?"

Smoking at age 44 years was a 5-level variable classified as (1) daily smoking, (2) at least weekly smoking, (3) less than weekly smoking, (4) former smoking, and (5) never smoking.

Passive smoking at age 44 years was defined as being exposed currently to other peoples' tobacco smoke for at least 1 hour per day.

Socioeconomic status in 1968 was classified by the occupation of the father of the participant, and divided into 5 categories according to the Australian Standard Classification of Occupations.³⁰

Socioeconomic status in 2004 was classified by the occupation of the participant and divided into the same 5 categories as in 1968.

Analytic methods

Categorical data were expressed as counts and proportions and compared using the Pearson χ^2 test. Asthma incidence to age 44 years was computed, dependent on childhood eczema. Multivariable logistic regression was used to examine the association between childhood eczema and asthma beginning by the age of 7 years (childhood asthma). Effect modification of this association by other childhood allergic disorders, childhood lung infection, or impaired lung function at age 7 years was examined with a parsimonious logistic model developed by using methods outlined by Hosmer and Lemeshow.³¹ Cox proportional hazards regression was used to estimate the association between childhood eczema and asthma developing between the ages of 8 and 12 years (preadolescence), 13 and 20 years (adolescence), and after the age of 20 years (adult life). The effect of childhood eczema on the overall asthma risk from age 8 to 44 years was computed by fitting a single Cox model with smoking and passive smoking as time-dependent covariates and also by performing a meta-analysis of the estimates for each life stage. Binomial regression with the log link function examined childhood eczema and asthma persisting from childhood to middle age. A 2-sided *P* value $\leq .05$ was taken to indicate statistical significance for all estimates. The analysis was performed using Stata statistical software version 9.1 (Stata Corp, College Station, Tex).

RESULTS**Prevalence of eczema and other allergic disorders**

In the cohort at the age of 7 years (*n* = 8583), a response to both eczema questions was obtained for 8237 (96.0%). Of these, 520 (6.3%; 95% CI, 5.8% to 6.9%) were reported as having both infantile and flexural eczema (conjoint eczema), 301 (3.7%; 95% CI, 3.3% to 4.1%) had infantile eczema only, and 279 (3.4%; 95% CI, 3.0% to 3.8%) had flexural eczema only.

A response to the infantile eczema question was obtained for 8311 (96.8%). Of these, 821 (9.9%; 95% CI, 9.2% to 10.5%) were identified as having infantile eczema, which was significantly more common in boys (11.0% vs 8.8%; $\chi^2_1 = 11.2$; *P* = .001). In these 821, allergic rhinitis was present in 233 (28.4%; 95% CI, 25.3% to 31.6%), food or medicine allergy in 160 (19.5%; 95% CI, 16.8% to 22.4%), and urticaria in 202 (24.6%; 95% CI, 21.7% to 27.7%). Among those with infantile eczema, whereas 24 (2.9%; 95% CI, 1.9% to 4.3%) had a history of all these allergic disorders, 367 (44.7%; 95% CI, 41.3% to 48.2%) had no history of any other allergic disorder.

A response to the flexural eczema question was obtained for 96.4% (*n* = 8260). Of these, 799 (9.7%; 95% CI 9.0% to 10.3%) were reported as having flexural eczema, which was also significantly more common in boys (10.4% vs 9.0%; $\chi^2_1 = 4.7$; *P* = .03). In these 799, allergic rhinitis was present in 233 (29.2%; 95% CI, 26.0% to 32.4%), allergy to food or medicine in 146

TABLE I. Childhood eczema and asthma incidence after age 7 to age 44 years

Eczema phenotype*	Person-years at risk	Asthma with onset after age 7 y, n (%)	Incidence per 1000 person-years at risk (95% CI)	Rate ratio (95% CI)	Population attributable fraction
Childhood eczema (n = 796)	18,905	140 (24.0)	7.41 (6.27-8.74)	1.98 (1.63-2.40)	0.12
Never eczema (n = 3346)	116,084	435 (76.0)	3.74 (3.40-4.11)	1.00	—
Total	134,989	575 (100.0)	4.37 (4.01-4.75)	—	—

*Of the 5729 respondents to the 2004 questionnaire, 1587 had eczema that began after the age of 7 years.

TABLE II. Risk of incident asthma at different life stages dependent on childhood eczema

Eczema phenotype†	Age (y) at asthma onset*			From age 8-44 y	
	8-12 Preadolescence (n = 162) HR (95% CI)	13-20 Adolescence (n = 130) HR (95% CI)	21-44‡ Adult life (n = 629) HR (95% CI)	HR (95% CI)§	Pooled HR (95% CI)
Childhood eczema (n = 796)	1.70 (1.05-2.75) P = .03	2.14 (1.33-3.46) P = .002	1.63 (1.28-2.09) P = .001	1.69 (1.39-2.07) P = .001	1.73 (1.42-2.12) Homogeneity test P = .63
Never (n = 3346)	1.00	1.00	1.00	1.00	

HR, Hazard ratio.

*Of the 2196 persons with asthma ever, 26 had no recorded age at asthma onset, and another 1249 had asthma that began at or before the age of 7 years.

†Additionally adjusted for socioeconomic status, smoking, and passive smoking at the age of 44 years.

‡There were 1587 persons from the 5729 participants who had later-onset eczema.

§Model included smoking and passive smoking as time-dependent covariates.

||Fixed effects estimate.

(18.3%; 95% CI, 15.7% to 21.1%), and urticaria in 193 (24.2%; 95% CI, 21.2% to 27.3%). Of those with flexural eczema, whereas 22 (2.8%; 95% CI, 1.7% to 4.1%) had a history of all these allergic disorders, 364 (45.6%; 95% CI, 42.1% to 49.1%) had no history of any other allergic disorder.

Of the 5729 who responded to the 2004 survey, 2383 (41.6%; 95% CI, 40.3% to 42.9%) had a lifetime history of eczema or skin allergy, either self-reported in 2004 or parent-reported in 1968. A significant difference by sex (females, 48.4%; males, 35.9%; $\chi^2_1 = 91.1$; $P < .001$) was the reverse of that seen at the age of 7 years. There was no significant difference in infantile or flexural eczema rates between the responders and nonresponders to the 2004 survey ($\chi^2_1 \leq 2.90$; $P \geq .09$ for all comparisons).

Childhood eczema and childhood asthma

Infantile eczema only (odds ratio [OR], 1.74; 95% CI, 1.30-2.34), flexural eczema only (OR, 1.71; 95% CI, 1.25-2.33), and conjoint eczema (OR, 2.46; 95% CI, 1.98-3.05), each compared with no childhood eczema, were significantly associated with childhood asthma. The estimates were from models adjusted for allergic rhinitis, food allergy, urticaria, sex, childhood lung infection, and impaired lung function at age 7 years. However, there was significant effect modification of the association between infantile eczema only and childhood asthma by childhood lung infection (interaction term, $P < .001$) and also by impaired lung function at age 7 years (interaction term, $P = .01$). These effect modifications were also seen for conjoint eczema but not for flexural eczema only.

The inclusion of an interaction term in each model increased the estimates. The risk of childhood asthma from infantile eczema only was modestly increased by a history of childhood lung infection (OR, 2.39; 95% CI, 1.28-4.44), whereas the presence of impaired lung function at age 7 years substantially increased that

same baseline risk (OR, 14.64; 95% CI, 4.21-50.97). Participants with infantile eczema only and both childhood lung infection and impaired lung function at age 7 years were too few for a useful estimate of an OR.

For those participants with conjoint eczema, baseline childhood asthma risk was more than doubled (OR, 5.75; 95% CI, 3.79-8.73) by a history of childhood lung infection, whereas the presence of impaired lung function at age 7 years increased that baseline risk more than 4-fold (OR, 10.98; 95% CI, 4.61-26.11). There was no effect modification by the other childhood allergic disorders; parental asthma; parental smoking; exclusive breast-feeding for the first 3 months of life; immunization with diphtheria, pertussis, and tetanus vaccines; or having at least 1 older sibling (data not shown).

Childhood eczema and asthma incidence

Over time from age 8 to age 44 years, asthma incidence was nearly twice as high in those with childhood eczema, compared to those with no history of eczema (Table I).

Asthma risk dependent on childhood eczema for each of the life stages from age 8 to age 44 years, as well as the pooled estimate of risk over that time, are shown in Table II. The estimates are from mutually adjusted models that included allergic rhinitis, food or medicine allergy, and urticaria, all by age 7 years; impaired lung function at age 7 years; and sex. The model that examined adult-onset asthma was additionally adjusted for active and passive smoking and for socioeconomic status in adult life. Childhood eczema was associated with a significantly increased risk of incident asthma in preadolescence, adolescence, and adult life. The pooled estimate and the estimate from a model that included smoking and passive smoking as time-dependent covariates both indicated that the risk of incident asthma over time from age 8 to age 44 years, dependent on childhood eczema,

TABLE III. Eczema and childhood-onset asthma persisting and remitting by middle age

Eczema phenotype	Onset before age 7 years	
	Persisting asthma (n = 232), n (%)	Remitting asthma (n = 762), n (%)
Childhood eczema (n = 796)	73 (31.5)	193 (25.3)
Later-onset eczema (n = 1587)	77 (33.2)	190 (25.0)
Never eczema (n = 3346)	82 (35.3)	379 (49.7)
Total (n = 5729)	232 (100.0)	762 (100.0)

was significantly increased. No interaction was found between nonallergic exposures and childhood eczema in terms of incident asthma (data not shown).

Childhood eczema and persisting asthma to middle age

The distribution of childhood eczema and persisting or remitting asthma to age 44 years that began before age 7 years is shown in Table III. Childhood eczema was associated with asthma persisting from childhood to middle age compared with childhood asthma that remitted by middle age (crude relative risk, 1.54; 95% CI, 1.17-2.04). However, the association was no longer significant when allergic rhinitis was added to the model (adjusted relative risk, 1.29; 95% CI, 0.97-1.70). The addition of allergy to food or medicine and urticaria, both by age 7 years; impaired lung function at age 7 years; active and passive smoking; and socioeconomic status in adult life as covariates to the model that included allergic rhinitis made little further difference to the estimate (adjusted relative risk, 1.26; 95% CI, 0.94-1.68).

DISCUSSION

To our knowledge, this is the first study that examines the association between childhood eczema and asthma development and persistence from childhood to middle age. The results suggest that the effect of childhood eczema on asthma risk continues well past childhood, extending what is already known about this subject. Although the majority of children with eczema will not develop childhood asthma,¹⁸ our results suggest that childhood eczema may progress to incident asthma in preadolescence, adolescence, and adult life. Lifetime asthma risk from childhood eczema may be greater than previously realized.

The prevalence of asthma by age 7 years (32.8%) in subjects with childhood eczema in our study was almost identical to that described in the systematic review by van der Hulst et al,¹⁸ supporting their view that the majority of children with eczema will not develop childhood asthma. Flexural involvement is considered a marker of atopy,³² in turn a predictor of childhood asthma.³³ However, our study found no difference in the odds of childhood asthma between the flexural eczema only, infantile eczema only, and conjoint eczema groups, suggesting that nonatopic skin factors such as the extent of skin involvement or age at eczema onset might also contribute to asthma risk.

Childhood eczema clearly preceded, and was associated with, incident asthma in each later life stage, supporting a possible causal relationship.³⁴ The term *atopic march* has been coined to explain the sequential development of eczema, allergic rhinitis,

and asthma. Recently, the existence of the atopic march has been both supported¹⁹ and disputed.²³ The findings from our study support the concept of the atopic march continuing past childhood.

A mechanism that explains the association between childhood eczema and asthma is not established. There is evidence supporting both genetic and environmental factors as links between eczema and asthma. Beyer et al³⁵ found evidence for linkage and allelic association with atopic dermatitis (AD) on chromosomes 13q12-14 and 5q31-33. The marker D5S436 on chromosome 5q31-33, which showed evidence for association with AD in the study by Beyer et al,³⁵ was the same marker associated with bronchial hyperresponsiveness and atopy in a study by Postma et al.³⁶

Spergel and Paller¹⁹ postulated that epicutaneous sensitization in AD arises from exposure of the damaged skin to potential allergens. They suggested that such sensitization is followed by migration of T_H2 memory cells from the skin to the bronchus-associated lymphoid tissue and that subsequent inhalation of the sensitizing allergen causes a cellular and humoral response in the airways, resulting in asthma. That epicutaneous sensitization might occur in human beings is supported by the observation that exposing atopic children to topical emollients containing peanut protein led to an increased risk of airway peanut sensitization.³⁷

Previous studies have suggested associations between early-life lower respiratory infection and childhood asthma³⁸ and between impaired lung function and childhood asthma.³⁹ Our study found that the association between childhood eczema and childhood asthma was stronger if the child developed a serious lung infection before the age of 7 years or had impaired lung function at that age. It is possible that immature airways that were smaller or damaged by early-life lower respiratory infection might be more susceptible to allergen sensitization introduced via the skin, and hence might be at greater risk of asthma. Our findings suggest that the effect of childhood eczema on asthma risk is better understood when the interplay between childhood eczema and concomitant nonallergic exposures is taken into account.

Our study found that for incident asthma, the population attributable risk from childhood eczema was 12%. The disease burden from incident asthma after childhood might be reduced by using more aggressive treatments such as topical calcineurin inhibitors for poorly responsive childhood eczema. Using the TAHS cohort, we have previously calculated a population attributable risk of 22% for incident asthma after the age of 7 from childhood allergic rhinitis.⁴⁰ Our estimate of a combined population attributable risk from childhood allergic rhinitis and childhood eczema for later-life incident asthma is 29%, indicating the importance of childhood allergic disorders in the development of later-life asthma, if the associations reflect causality.

Childhood eczema predicted asthma that persisted to middle age, but the association was confounded by allergic rhinitis. This result is similar to that from another Australian population-based cohort followed from childhood to early adulthood⁴¹ in which childhood eczema predicted "troublesome asthma" in adulthood. However, the association was confounded by hay fever, atopy, impaired lung function in childhood, and female sex. We have previously demonstrated an association between childhood allergic rhinitis and both incident and persisting asthma.⁴⁰ Taken together, our results suggest that among the childhood allergic disorders, allergic rhinitis is a more potent risk factor for later-life incident and persisting asthma than is eczema.

The major strengths of our study are the longitudinal nature of the data collected from a large population-based cohort over a 37-year period, modest loss to follow-up, measurement of lung function in childhood, and the availability of parent-reported data on asthma in early life against which participant-reported data could be checked. The prevalence of childhood eczema in the responders and nonresponders to the 2004 survey did not differ significantly, indicating that response bias related to this was unlikely.

Our study also has limitations. Childhood eczema was parent-defined, and parents could have misclassified other skin disorders as eczema. Childhood asthma defined by the parent would have included nonasthmatic wheeze. We and others have found that parent-defined childhood asthma compares well with the definition including bronchial hyperresponsiveness,^{42,43} and a looser definition would shift estimates toward the null.⁴⁴ The use of "doctor-diagnosed asthma" may result in underdiagnosis.^{45,46} In any case, the asthma question in the 1968 TAHS questionnaire has been validated against a respiratory physician's diagnosis.⁴² Our study did not include objective assessment of childhood atopy, which would have been useful in assessing the nature of the relationship between childhood eczema and asthma. Finally, we acknowledge the possibility of there being unknown or unmeasured confounders that might alter our results.

In conclusion, our study provides novel evidence for an association between childhood eczema and incident asthma risk at different life stages to middle age. We suggest that trials of aggressive therapy directed at childhood eczema might lessen the burden of asthma in later life.

The Archives Office of Tasmania provided archived data from the 1968 and 1974 Tasmanian Longitudinal Health Study questionnaires.

Clinical implications: The effect of childhood eczema on asthma risk persists well past childhood, and aggressive treatment of childhood eczema might provide an opportunity for asthma prevention.

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