European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 01, 2023

Original Research Article

A prospective cohort study to estimate the association between eczema in early childhood and the onset of asthma and rhinitis later in life in children

[1]Dr. Perumalla Nataraj, [2]Dr. Haritha Komaravelli

[1] Associate Professor, RVM Institute of Medical Sciences & Research Centre, Laxmakkapally, Telangana, India

[2] Assistant Professor, RVM Institute of Medical Sciences & Research Centre, Laxmakkapally, Telangana, India

Corresponding Author:
Dr. Haritha Komaravelli (nrajperumalla@gmail.com)

Date of acceptance: 11-01-2023

Abstract

Aim: This study aimed to estimate the association between eczema in early childhood and the onset of asthma and rhinitis later in life in children.
Methods: The present study was conducted in the department of dermatology and 2000 children were included in the study. A questionnaire based on an International Study of Asthma and Allergies in Childhood (ISAAC) protocol[18] was given to parents of all children aged 1 to 5 years.
Results: There were no differences in background (age and sex) and health factors (prevalence of eczema, asthma, wheezing and rhinitis, and parents with history of allergic disease) measured at baseline between the children participating in both surveys compared with the "drop-outs" (p>0.05). However, there was a higher prevalence of parental smoking (30.5% vs. 22.2%; p<0.001). In adjusted analysis, children with persistence of eczema, early onset of eczema, or moderate to severe eczema had even higher odds of developing asthma and rhinitis than children with eczema in general. The odds of developing asthma and rhinitis was 5-fold in children with persistence of eczema compared with the absence of eczema (aOR, 5.16; 2.62–10.18 and aOR, 4.00; 2.53-6.22, respectively). Early onset of eczema was a strong risk factor for the incidence of asthma (aOR, 3.44; 95% CI, 1.94-6.09) and the incidence of rhinitis (aOR, 4.05; 95% CI, 2.82-5.81) compared with children without eczema, whereas there was no significant association between the late onset of eczema and the incidence of asthma (aOR, 2.07; 0.78-5.49) and rhinitis (aOR, 0.96; 0.45-2.03).
Conclusion: Eczema in infancy is associated with development of asthma and rhinitis during the following 5-year period, and eczema is one of the strongest risk factors. Early identification is valuable for prediction of the atopic march.

Keywords: Eczema, asthma, rhinitis

Introduction

Eczema, rhinitis and asthma are diseases of high prevalence in developed countries [1, 2]. Although childhood eczema often improves during childhood [3], rhinitis and asthma often persist through adulthood, with a substantial increase in asthma associated mortality observed

ISSN 2515-8260 Volume 10, Issue 01, 2023

for those aged more than 60 years [4, 5].

Earlier studies have shown that immunological development and maturation starts during pregnancy and continues during early childhood [6]. Health risks from exposures at birth may serve as a surrogate indicator of exposures throughout pregnancy. Exposures during the first 3 years of life represent a critical period of immune development that may modify immune responses and cells, and thus influence the risk of allergies and other immune diseases later in life. Recent systematic reviews by KHREIS *et al*. [7] and BOWATTE *et al*. [8] suggested that childhood exposure to traffic-related air pollution (TRAP) contributes to the development of asthma. Assessing exposures both at birth and during early life is therefore important.

As the most frequent inflammatory condition in childhood, eczema affects physiological and psychological wellbeing of affected children and results in substantial costs [9, 10]. It has been suggested that early life eczema is a risk factor for the development of asthma later in life [11]. However, evidence for the progression to asthma comes mainly from cross-sectional studies [12]. There are only a few prospective cohort studies that have investigated the association between early life eczema and later onset of asthma and rhinitis. Some of the existing longitudinal studies found no association between eczema and later onset of asthma [13, 14] and other prospective studies found an eczema/asthma relationship much weaker than expected [15]. This overall weak association might be partly explained by a different effect across eczema subgroups on allergic airway diseases. The severity of eczema has been found to be more closely associated with the risk of developing asthma than the timing of onset, or duration of eczema symptoms [16, 17].

We examined whether eczema in early childhood predicts the later onset of asthma and rhinitis in children and determined the importance of severity, time of onset and persistency of the childhood eczema by analysing data from a large prospective population-based cohort with a follow-up period of 5 years.

Methods

The present study was conducted in the department of dermatology and 2000 children were included in the study. A questionnaire based on an International Study of Asthma and Allergies in Childhood (ISAAC) protocol [18] was given to parents of all children aged 1 to 5 years.

Inclusion criteria of the baseline survey were all children aged 1-5 years whose parents gave consent to participate and who answered a postal questionnaire. The study was approved by the regional ethical committee.

The original ISAAC questions were used. In addition, questions on doctor-diagnosed asthma and doctor diagnosed rhinitis were included. The additional questions were: “Has your child been diagnosed with asthma by a physician?” and “Has your child been diagnosed with rhinitis by a physician?” The main outcomes were “5-year cumulative incidence of asthma” and “5-year cumulative incidence of rhinitis”.

The main explanatory variable was eczema. Eczema in early childhood was defined by affirmative responses to the question “Has your child had an itchy rash at any time in the last 12 months?” in the baseline questionnaire, Secondary analysis was performed for subgroups of eczema, persistent eczema, severe eczema and early onset of eczema, and their association with later development of allergic airway diseases. Persistent eczema was assumed when children reported signs of eczema both at baseline and at follow-up; the questions asked were: “Has your child ever had an itchy rash (eczema) which was coming and going for at least 6 months” and “Has your child had this itchy rash at any time in the last 12 months?” and “Has your child had this itchy rash at any time in the last 12 months?”

The onset of eczema was determined form the question “At what age did this itchy rash first occur?” and it was categorised into “early onset” if symptoms occurred before the age of 1 year. The question “In the last 12 months, how often, on average, has your child been kept awake at night by eczema?” was included in the ISAAC eczema questionnaire as a measure

ISSN 2515-8260 Volume 10, Issue 01, 2023

of the severity of eczema, where sleep loss several times per week was considered to be severe eczema [17, 18]. To simplify analysis, the severity of eczema was re-categorized, by using "any awakening at night" as an identifier for moderate to severe eczema, and "no awakening" was considered to be mild eczema. Information on single parenthood was obtained via the question "How many adults are currently living with the child"; two adults caring for the child could be any two adults.

Statistical analysis

All analyses were carried out using STATA, version 11 (STATA Corp., College Station, TX). The association between eczema in early childhood and the development of asthma and rhinitis was estimated by using univariable logistic regression and expressed as odds ratios (ORs) with confidence intervals (CIs). Statistical significance was assessed using the likelihood ratio test (LRT; $p<0.05$). Characteristics of participants and non-participants were compared in drop-out analysis using the chi-square test ($p<0.05$). Crude analysis of the association between all other risk factors, and asthma and rhinitis were performed. Linear trends of variables with several categories were evaluated. In multivariable logistic regression analysis, the ORs were adjusted for sex, age of the child, socioeconomic variables (parental smoking, number of adults living with the child, and type of house), and potential confounding variables, which included all other factors. The potential confounding variables were added in descending order of strength of crude association (smallest p-value first). Factors still associated with asthma and rhinitis were kept in the model. The interaction between eczema and sex was explored. The effect of different subgroups of eczema on asthma and rhinitis was examined. Because of the strong association between persistence, early onset and severe eczema, three adjusted models for these groups are reported.

Results

Table 1: Crude association between risk factors at baseline and the incidence of asthma and rhinitis

Risk factor at baseline	Total number in category n (%)	Number with asthma n	Asthma OR (95% CI)	P-value	Number with rhinitis n	Rhinitis OR (95% CI)	P-value
Eczema							
No	1600 (80)	101	1.0	<0.001	107	1.0	<0.001
Yes	400 (20)	49	2.85 (1.72-4.71)		65	3.14 (2.27-4.36)	
Onset of eczema							
No	1600 (80)	46	1.0	<0.001	98		<0.001
Age ≥ one year	160 (8)	6	1.87 (0.7-4.45)		8	0.96 (0.46-2.00)	
Age < one year	240 (12)	21	3.63 (2.12-6.22)		66	5.02 (3.58-7.05)	
Gender							
Female	1000 (50)	25	1.0	0.002	65	1.0	0.001
Male	1000 (50)	48	2.16 (1.32-3.54)		107	1.67 (1.21-2.29)	
Age of the child							
12-23 months	900 (45)	41	1.0	0.325	88	1.0	0.720
24-35 months	1100 (55)	32	0.79 (0.49-1.27)		84	0.95 (0.70-1.29)	
Asthma in the child							
No	1800 (90)	-	-	-	147	1.0	<0.001

Yes	200 (10)	-	-	-	25	4.10 (2.57-6.54)	
Parental smoking							
No	1600 (80)	56	1.0	0.691	139	1.0	0.350
Yes	400 (20)	17	1.12 (0.64-1.94)		33	0.83 (0.56-1.23)	

There were no differences in background (age and sex) and health factors (prevalence of eczema, asthma, wheezing and rhinitis, and parents with history of allergic disease) measured at baseline between the children participating in both surveys compared with the "drop-outs" (p>0.05). However, there was a higher prevalence of parental smoking (30.5% vs. 22.2%; p<0.001).

Table 2: Subgroups of eczema in children and the 5-year cumulative incidence of asthma and rhinitis

Eczema group	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Incidence of asthma				
Duration of eczema				
Never eczema	1.0	<0.001	1.0	<0.001
Eczema	1.94 (0.93-4.06)		2.17 (1.01-4.65)	
Persistence of eczema	4.95 (2.65-9.25)		5.16 (2.62-10.18)	
Onset of eczema				
Late onset of eczema	1.87 (0.78-4.45)	<0.001	2.07 (0.78-5.49)	<0.001
Early onset of eczema	3.63 (2.12-6.22)		3.44 (1.94-6.09)	
Severity of eczema				
Mild eczema	2.42 (1.36-4.29)	<0.001	2.85 (1.57-5.19)	<0.001
Moderate to severe eczema	4.55 (2.27-9.11)		3.56 (1.62-7.83)	
Incidence of rhinitis				
Duration of eczema				
Never eczema	1.0	<0.001	1.0	<0.001
Eczema	2.52 (1.61-3.94)		2.25 (1.40-3.61)	
Persistence of eczema	4.91 (3.23-7.46)		4.00 (2.53-6.22)	
Onset of eczema				
Late onset of eczema	0.96 (0.46-2.00)	<0.001	0.96 (0.45-2.03)	<0.001
Early onset of eczema	5.02 (3.58-7.05)		4.05 (2.82-5.81)	
Severity of eczema				
Mild eczema	2.74 (1.90-3.95)	<0.001	2.37 (1.60-3.51)	<0.001
Moderate to severe eczema	4.74 (2.98-7.55)		3.87 (2.37-6.33)	

In adjusted analysis, children with persistence of eczema, early onset of eczema, or moderate to severe eczema had even higher odds of developing asthma and rhinitis than children with eczema in general. The odds of developing asthma and rhinitis was 5-fold in children with persistence of eczema compared with the absence of eczema (aOR, 5.16; 2.62-10.18 and aOR, 4.00; 2.53-6.22, respectively). Early onset of eczema was a strong risk factor for the incidence of asthma (aOR, 3.44; 95% CI, 1.94-6.09) and the incidence of rhinitis (aOR, 4.05; 95% CI, 2.82-5.81) compared with children without eczema, whereas there was no significant association between the late onset of eczema and the incidence of asthma (aOR, 2.07; 0.78-5.49) and rhinitis (aOR, 0.96; 0.45-2.03). Both mild and moderate to severe eczema were associated with the incidence of asthma and rhinitis compared with children without eczema, with a higher odds of developing asthma and rhinitis in moderate to severe eczema (aOR, 3.56; 1.62-7.83 and aOR, 3.87; 2.37-6.33, respectively) than mild eczema compared with children without eczema (aOR, 2.85; 1.57-5.19 and aOR, 2.37; 1.60-3.51, respectively).

ISSN 2515-8260 Volume 10, Issue 01, 2023

Discussion

The increased risk of asthma at ages 6 to 7 years for those with eczema in infancy, a sequence known as the atopic march, has been characterized in prospective studies [19, 20]. We have observed this effect to be more pronounced for boys than girls [21]. Rather than being independent consequences of a genetic predisposition or a shared environmental factor to allergic disease, there is growing evidence for a potentially causal link between eczema and asthma. Skin-derived thymic stromal lymphopoietin has been implicated as a cause of airway inflammation in murine models [23]. Mutations in the filaggrin gene, which is important to skin barrier integrity, have been linked to both eczema and asthma with eczema [24], suggesting that an impaired skin barrier might promote sensitization to environmental allergens and eventually allergic airways disease [22]. Eczema was one of the strongest independent risk factors. Interestingly, when eczema was divided into subgroups, children with early onset of eczema, moderate to severe eczema, and persistence of eczema had the highest odds of developing asthma and rhinitis.

Although some previous prospective studies were not able to show an association between early childhood eczema and later development of asthma and rhinitis [25, 26], our findings are robust and in line with the study by Arshad *et al*. [27] In addition, similar results regarding severity have been found in both Gustavsson's and Ricci's eczema cohorts [19, 28], which reported that eczematous children with high severity scores were at increased risk of developing asthma. To the best of our knowledge, our study is the first prospective cohort to show that early onset of eczema or persistent eczema increases the odds of later onset of asthma in both boys and girls, which is in contrast to a previous study that only showed a relationship in boys [21]. Definitions of asthma and rhinitis are important for the interpretation of results [29]. Our sensitivity analysis confirmed that the association between eczema and asthma/rhinitis remained when symptom-based criteria for asthma and rhinitis were used.

Evidence from several experimental studies has suggested that impaired epithelial function results in increased sensitization and IgE production [30]. In humans, the theory of epicutaneous sensitization is supported by the observation that exposing atopic children to topical emollients containing peanut protein leads to an increased risk of airway peanut sensitization [31]. Genetic factors, such as the common loss of function mutations within the filaggrin gene, are a risk factor for incident eczema and account for skin barrier dysfunction [32, 33]. Recently, it has been shown that filaggrin mutations affect asthma, which supports the hypothesis that impaired skin function acts as a gateway for allergens, increasing the risk of atopic airways diseases [34].

Currently, there is no clear definition of persistence of eczema, which is consistent as reported by Williams [35] Illi [20] and Möhrenschlager [36] considered eczema as persistent when signs of the disease were present at different points of time. In our study, persistence of eczema was defined as having had eczema at least three times. Therefore, the risk of including children with "short-term rashes only" might be low, but we cannot exclude the possibility that some children classified as having persistent eczema had longer symptom-free intervals. It would have been advantageous to assess the prevalence of eczema more often during the study period.

Based on the results of our study, further evidence is required to unravel the underlying mechanisms of eczema in early childhood leading to asthma. Although we confirmed a relationship between childhood eczema and incident asthma and rhinitis, the association between childhood eczema and later asthma and rhinitis might still be separate and sequential, but are otherwise unrelated in the background of an atopic phenotype. Because the relationship between childhood eczema and incident asthma and rhinitis was temporal, strong, and linear, our findings suggest that the relationship might be causal. In this regard, impaired skin function might hypothetically be one explanatory factor [37].

Further, it might be beneficial to estimate if objective measured sensitization (IgE) modifies or confounds the eczema/asthma relationship in future studies. Our study results have important implications for patient management since asthma can lead to high impairment and

ISSN 2515-8260 Volume 10, Issue 01, 2023

costs.

Conclusion

Eczema in infancy independently increases the odds of developing asthma and rhinitis during the following 5- year period. This association is present for children with eczema at baseline; however when they are divided into subgroups (severe eczema, early onset of eczema and persistence of eczema) the odds of the incidence of asthma and rhinitis further increases. Identifying risk groups is important for healthcare planning.

References

1. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351:1225-32.
2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, *et al*. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multi-country cross-sectional surveys. The Lancet. 2006 Aug;368(9537):733-43.
3. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis-a prospective follow- up to 7 years of age. Allergy. 2000 Mar;55(3):240-5.
4. Australian Institute of Health and Welfare. Asthma among older people in Australia. Canberra (Australia): Australian Institute of Health and Welfare; Catalog no. ACM 19; c2010.
5. Stupka E, De Shazo R. Asthma in seniors: Part 1. Evidence for under diagnosis, under treatment and increasing morbidity and mortality. The American journal of medicine. 2009 Jan;122(1):6-11.
6. Martikainen MV, Rönkkö TJ, Schaub B, Täubel M, Gu C, Wong GW, *et al*. Integrating farm and air pollution studies in search for immuno-regulatory mechanisms operating in protective and high- risk environments. Pediatric Allergy and Immunology. 2018 Dec;29(8):815-22.
7. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environment international. 2017 Mar;100:1-31.
8. Bowatte G, Lodge CJ, Knibbs LD, Lowe AJ, Erbas B, Dennekamp M, *et al*. Traffic-related air pollution exposure is associated with allergic sensitization, asthma and poor lung function in middle age. Journal of Allergy and Clinical Immunology. 2017 Jan;139(1):122-9.
9. LEWIS- JONES S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. International journal of clinical practice. 2006 Aug;60(8):984-92.
10. Carroll CL, Balkrishnan R, Feldman SR, Fleischer Jr AB, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. Pediatric dermatology. 2005 May;22(3):192-9.
11. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. Journal of Allergy and Clinical Immunology. 2003 Dec;112(6):S118-27.
12. Beasley R, Asthma TI. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The Lancet. 1998 Apr;351(9111):1225-32.
13. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, Group Health Medical Associates. Asthma and wheezing in the first six years of life. New England Journal of Medicine. 1995 Jan;332(3):133-8.

14. Klinnert MD, Nelson HS, Price MR, Adinoff AD, Leung DY, Mrazek DA. Onset and persistence of childhood asthma: predictors from infancy. Pediatrics. 2001 Oct;108(4):e69.
15. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyper responsiveness at 10 years of age. Chest. 2005 Feb;127(2):502-8.
16. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. Journal of the American Academy of Dermatology. 2006 Nov;55(5):765-71.
17. Queille-Roussel C, Raynaud F, Saurat JH. A prospective computerized study of 500 cases of atopic dermatitis in childhood. I. Initial analysis of 250 parameters. Acta dermato-venereologica. Supplementum. 1985 Jan;114:87-92.
18. Asher ME, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, *et al*. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. European respiratory journal. 1995 Mar;8(3):483-91.
19. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis-a prospective follow- up to 7 years of age. Allergy. 2000 Mar;55(3):240-5.
20. Illi S, Von Mutius E, Lau S, Nickel R, Grüber C, Niggemann B, *et al*. Multicenter Allergy Study Group. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. Journal of Allergy and Clinical Immunology. 2004 May;113(5):925-31.
21. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Abramson MJ, Hill DJ, *et al*. Do boys do the atopic march while girls dawdle?. Journal of Allergy and Clinical Immunology. 2008 May;121(5):1190-5.
22. Burgess JA, Lowe AJ, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? Journal of Asthma. 2009 Jan;46(5):429-36.
23. Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. PLoS biology. 2009 May;7(5):e100-0067.
24. Van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitization and allergic disorders: systematic review and meta-analysis. BMJ, 2009 Jul, 339.
25. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Group Health Medical Associates. Asthma and wheezing in the first six years of life. New England Journal of Medicine. 1995 Jan;332(3):133-8.
26. Klinnert MD, Nelson HS, Price MR, Adinoff AD, Leung DY, Mrazek DA. Onset and persistence of childhood asthma: predictors from infancy. Pediatrics. 2001 Oct;108(4):e69.
27. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyper responsiveness at 10 years of age. Chest. 2005 Feb;127(2):502-8.
28. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. Journal of the American Academy of Dermatology. 2006 Nov;55(5):765-71.
29. Larsson M, Hagerhed-Engman L, Sigsgaard T, Janson S, Sundell J, Bornehag CG. Incidence rates of asthma, rhinitis and eczema symptoms and influential factors in young children in Sweden. Acta Paediatr. 2008;97:1210-1215.

ISSN 2515-8260 Volume 10, Issue 01, 2023

30. Kolarik B, Naydenov K, Larsson M, Bornehag CG, Sundell J. The association between phthalates in dust and allergic diseases among Bulgarian children. Environmental health perspectives. 2008 Jan;116(1):98-103.
31. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. Nature Reviews Immunology. 2004 Dec;4(12):978-88.
32. Weidinger S, Illig T, Baurecht H. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. J Allergy Clin. Immunol. 2006;118:214-219.
33. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, *et al*. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. Journal of Allergy and Clinical Immunology. 2008 May;121(5):1203-9.
34. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. New England Journal of Medicine. 2003 Mar;348(11):977-85.
35. Williams HC. Editor. Atopic dermatitis: the epidemiology, causes and prevention of atopic eczema. Cambridge University Press; c2000 Feb.
36. Möhrenschlager M, Schäfer T, Huss- Marp J, Eberlein- König B, Weidinger S, Ring J, *et al*. The course of eczema in children aged 5-7 years and its relation to atopy: differences between boys and girls. British Journal of Dermatology. 2006 Mar;154(3):505-13.
37. Kolarik B, Naydenov K, Larsson M, Bornehag CG, Sundell J. The association between phthalates in dust and allergic diseases among Bulgarian children. Environmental health perspectives. 2008 Jan;116(1):98-103.