

Do boys do the atopic march while girls dawdle?

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Background: The atopic march hypothesis suggests that infants with eczema are at increased risk of asthma. Others argue that eczema is not a risk factor for asthma unless there is also sensitization or early wheezing.

Objective: To examine the role of infantile eczema as a predictor of risk of childhood asthma, while allowing for the effects of early wheeze, sensitization, and sex, both as independent effects and possible effect modifiers.

Methods: A total of 620 infants with a family history of allergic disease was recruited. Eczema and wheeze was prospectively documented to 2 years of age. Sensitization was determined by skin prick tests at 6, 12, and 24 months to 6 common food and inhalant allergens. Interviews were conducted at 6 and 7 years to ascertain current asthma.

Results: Sufficiently complete data were available for 403 children. Eczema within the first 2 years of life was clearly associated with an increased risk of childhood asthma in boys (adjusted odds ratio, 2.45; 95% CI, 1.31-4.46) but not in girls (odds ratio, 0.88; 95% CI, 0.43-1.77; *P* for interaction = .031) even with adjustment for the effects of early allergic sensitization and wheeze. If these relationships are causal, an intervention to prevent eczema in boys might reduce the incidence of childhood asthma by as much as 28%.

Conclusion: Eczema in the first 2 years of life is associated with an increased risk of childhood asthma in boys, but there is no evidence of this in girls. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Atopic march, allergy prevention, eczema, asthma

Eczema affects between 10% and 20% of children in developed countries, and the prevalence of eczema in children is increasing.^{1,2} It is generally believed that infants with eczema are at increased risk of developing asthma,³ which is a key concept in the

Abbreviations used

MACS: Melbourne Atopy Cohort Study

MAS: Multicenter Allergy Study

OR: Odds ratio

SPT: Skin prick test

atopic march hypothesis. This concept has arisen mainly out of cross-sectional studies, which are subject to recall bias. Only a handful of prospective birth cohort studies have examined the progression from eczema in infancy to childhood asthma.⁴ Evidence from one of these prospective cohorts has recently been used to challenge the atopic march hypothesis.⁵

Data from the Multicenter Allergy Study (MAS) has been used to show that eczema in the first 2 years of life is not associated with increased risk of childhood asthma if the effects of early wheezing and sensitization are taken into account.⁵ These observations have been used to argue that eczema is associated with childhood asthma because wheeze and eczema are comanifested in early life, a concept that has already gained support in the literature as evidence countering a “simple atopic march.”⁶ However, the analysis of the MAS data did not assess the temporal sequence of the onset of wheeze, sensitization, and eczema; therefore, it did not rule out that eczema could precede and predict sensitization,⁷ early wheeze, and asthma. Furthermore, the analysis of the MAS data did not consider the effect of sex on the relationship between infantile eczema and asthma, despite male sex having been repeatedly shown to be associated with increased risk of childhood asthma⁸⁻¹⁰ as well as atopic eczema.¹¹

We analyzed data from the Melbourne Atopy Cohort Study (MACS), a birth cohort of 620 infants at high risk of developing atopic conditions, to assess the evidence for both the atopic march and comanifestation hypotheses.

METHODS

Study population

Before birth, the MACS recruited 620 infants born between 1990 and 1994 in Melbourne, Australia. The recruitment process has been described in more detail elsewhere.¹² The study was approved by Mercy Maternity Hospital's Human Research Ethics Committee. Informed consent was obtained from all mothers. Infants were eligible to be enrolled in MACS if 1 or more of their first-degree family members had eczema, asthma, allergic rhinitis, or severe food allergy.

Data collection

Baseline details were recorded during pregnancy. After the birth of the infant, an allergy-trained nurse conducted a telephone survey every 4 weeks until the age of 64 weeks, and then at 78 weeks, 2 years, and annually until 7

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years of age. Each survey documented any illnesses, including eczema, since the previous interview.

Skin prick tests (SPTs) were performed at 6, 12, and 24 months according to a standard technique¹³ by 1 of 3 allergy-trained research nurses. Allergen extracts used were cow's milk, egg white, peanut, house dust mite, rye grass, and cat dander (Bayer, Spokane, Wash), and SPTs were read at 20 minutes.

Definitions

A positive SPT was defined as a wheal of at least 3 mm diameter. Eczema in the first 2 years of life was defined as parental report of either a doctor diagnosis of eczema or any rash that was treated with topical steroid preparation (excluding rash that affected only the scalp or nappy region).⁷ Infants who had eczema and 1 or more positive SPT results were classified as having atopic eczema. Infants who had eczema but had negative SPT results on all 3 occasions were classified as having nonatopic eczema.¹⁴ The average number of days of rash treated with topical steroid preparation, per month, when the infant had rash was used as a marker of severity of eczema. Presence of asthma in the previous 12 months was assessed at 6 and 7 years of age. Asthma was defined as a diagnosis by family physician and 1 or more events of wheezing illness.

Statistical analysis

The associations between presence of eczema in the first 2 years of life and risk of asthma at 6 or 7 years of age were estimated by using logistic regression. Generalized estimating equations were used to enable a single combined analysis with outcome data from 6 and 7 years, with allowance for repeated measures.¹⁵ We did not include outcomes measured between 3 and 5 years, because a significant proportion of reported wheeze during this time would not be asthma.⁹

Initially, unadjusted associations between eczema (including severity and age of onset) and the risk of childhood asthma were estimated. Associations between risk of childhood asthma and the following potential confounders was assessed: early life wheeze, early life sensitization, and infant sex. The following family history factors were also considered: maternal and paternal history of allergic disease, age, years of education, smoking in the past 6 months, gas heating and cooking, and pet exposure (all determined at recruitment during pregnancy). To obtain an analysis that would be comparable with that of Illi et al,⁵ the first multivariate model that we fitted examined the association between eczema and childhood asthma with adjustment for early life sensitization and wheeze. After this, interactions between eczema and sex, sensitization, and early wheeze were assessed by using Wald tests. Variables were included in the final model if the inclusion of each variable caused 15% or greater change in the association between eczema and the outcome childhood asthma or predicted the outcome ($P < .05$ for the confounder effect, or interaction term, in the multivariable model). Results were expressed as odds ratios (ORs) and 95% CIs. Stata (release 9.2; Stata Corp, College Station, Tex) was used for all statistical analysis.

RESULTS

Study population

Of the 620 MACS infants, 544 (88%) were followed to 2 years of age. Of these infants, 110 had missing SPT data, so sensitization status could not be determined. Of the remaining 434 infants, 403 were followed up at either 6 or 7 years of age (Fig 1). Further details of the cohort have been published elsewhere.^{7,12,14}

Eczema in the first 2 years of life

Of the 403 infants with complete follow-up in the first 2 years of life and childhood follow-up (6 and/or 7 years), almost half ($n = 193$; 48%) developed eczema within the first 2 years of life. Almost half of these infants (47%; 90/193) developed eczema

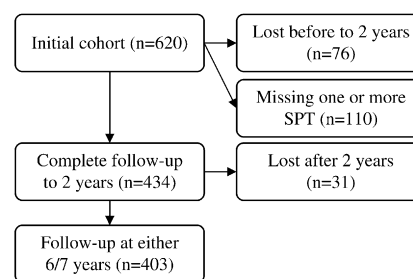


FIG 1. Flow chart of participant loss to follow-up in the MACS cohort.

within the first 6 months of life, with fewer doing so between 6 and 12 months (33%; 65/193) or between 12 and 24 months (20%; 39/193). Eczema was more common in girls (52.0%; 105/198) than in boys (42.9%; 88/205; $P = .042$). The rate of atopic eczema was very similar between boys (27.8%) and girls (28.3%), but girls were more likely to have nonatopic eczema (25.3% vs 14.6%; $P = .008$). However, there was some evidence that boys had more severe eczema during early life (median topical steroid use per month for boys, 1.35 days; interquartile range, 0.49-5.2; vs for girls, median, 0.88; interquartile range, 0.17-2.26; $P = .012$).

Unadjusted early life predictors of childhood asthma

Asthma was assessed in 352 children at both 6 and 7 years, 46 only at 6 years and 5 only at 7 years. Approximately a third of children reported asthma (32%; 130/403). Having eczema in the first 2 years of life doubled the odds of childhood asthma (OR, 2.02; 95% CI, 1.33-3.07; Table I). Infants who had received topical steroid without a recorded diagnosis (117/193) were not at a clearly different risk of asthma (OR, 0.88; 95% CI, 0.50-1.57) compared with infants with a recorded diagnosis. There was a dose-response relationship between increasing severity of eczema and increased risk of asthma (Table I). The increased risk of childhood asthma associated with infantile eczema was greatest for eczema that presented in the first 6 months of life (Table I). Eczema that started from 6 to 12 months, or during the second year of life, was not strongly associated with an increased risk of childhood asthma. Male sex, presence of sensitization and wheezing within the first 2 years of life, and parental history of asthma and allergic rhinitis were also associated with increased risks of childhood asthma (Table I).

Replication of previously reported adjusted associations

When the association between any eczema in the first 2 years and risk of childhood asthma was adjusted for presence of wheeze and sensitization in early life, as per the analysis performed by Illi et al,⁵ the estimated effect of eczema dropped by approximately 28% (OR, 1.45; 95% CI, 0.92-2.31). The effects of early wheeze and sensitization were largely unchanged. Interestingly, adjustment for early life wheeze only (not sensitization as well) resulted in a very small reduction in the association between early eczema and risk of childhood asthma (adjusted OR, 1.83; 95% CI, 1.17-2.85). This suggests comanifestation of early wheeze and eczema does not explain the increased risk of childhood asthma associated with eczema, and that sensitization is the primary confounding factor in this association.

TABLE I. Unadjusted associations between eczema in the first 2 years, and other early-life risk factors, and risk of childhood asthma (n = 403†)

	Proportion with asthma‡	OR (95% CI)	P value
Any eczema	39.9% (77/193)	2.02 (1.33-3.07)	.001
No eczema	25.2% (53/210)		
Severity of eczema*			
First tertile (0-0.5 d/mo)	28.6% (18/63)	1.33 (0.72-2.46)	.364
Second tertile (.5-2 d/mo)	32.8% (21/64)	1.54 (0.85-2.80)	.154
Third tertile (2-17 d/mo)	57.6% (38/66)	3.63 (2.08-6.32)	<.001
Age of eczema onset*			
First 6 mo	50.0% (45/90)	3.01 (1.82-4.99)	<.001
First from 6-12 mo	29.7% (19/64)	1.32 (0.72-2.43)	.376
First from 12-24 mo	33.3% (13/39)	1.47 (0.71-3.04)	.305
Sex: male	40.0% (82/205)	2.07 (1.36-3.16)	.001
Female	24.2% (48/198)		
Sensitization: present	47.4% (90/190)	3.82 (2.46-5.93)	<.001
Absent	18.8% (40/213)		
Early wheeze: present	55.3% (78/141)	5.32 (3.44-8.23)	<.001
Absent	19.8% (52/262)		
Maternal asthma: present	38.1% (67/176)	1.58 (1.03-2.40)	.035
Absent	27.9% (63/226)		
Paternal asthma: present	41.7% (45/108)	2.01 (1.28-3.16)	.002
Absent	29.1% (85/292)		
Maternal allergic rhinitis: present	31.0% (72/232)	0.91 (0.59-1.39)	.650
Absent	36.9% (58/157)		
Paternal allergic rhinitis: present	37.5% (69/184)	1.60 (1.04-2.44)	.031
Absent	30.0% (61/203)		

*Compared with infants who did not have eczema in the first 2 years of life.

†n = 403 Infants excluded because of loss to follow-up in the first 2 years (76) or 6 and 7 years (31), or because of missing SPT data (110).

‡Calculated as the proportion of children with asthma at either the 6-year or 7-year follow-up.

Adjusted early life predictors of asthma

Assessment of interaction effects revealed that association between early life eczema and asthma in childhood varied between male and female subjects. Eczema was associated with a greater increase risk of childhood asthma in boys (OR, 3.05; 95% CI, 1.74-5.35) than in girls (OR, 1.44; 95% CI, 0.74-2.78; *P* for interaction = .088). This sex difference remained evident when adjustment was made for early wheeze and sensitization (OR, 2.45; 95% CI, 1.31-4.46 for boys; and OR, .88; 95% CI, 0.43-1.77 for girls; *P* for interaction = .031). The increased risk of asthma in boys was most marked for eczema that was severe and/or started within the first 6 months of life, whereas neither of these trends was seen in girls (Table II). Because of the strong association between early onset and severe eczema, particularly in boys (Spearman ρ = -0.55; *P* < .001), both severity and age of onset could not be included in the same model, so 2 adjusted models are reported (Table II). Early wheeze remained a strong independent risk factor for the development of asthma (interaction effects with eczema had *P* = .542). The risk of childhood asthma did not differ between infants who had eczema and sensitization compared with infants with eczema without sensitization (*P* for interaction = .811). Having both parents report a history of asthma also increased the risk of childhood asthma. If it is assumed the association between eczema in boys and risk of asthma is causal, the estimated population attributable risk fraction in male infants with a family history of allergic disease is 28%.

Predictive value of eczema on incident asthma

To explore the effect of eczema on incident asthma, we excluded the 141 infants with wheeze in early life. Eczema in

the first 2 years of life conferred a greater risk of childhood asthma in boys than in girls (Table III). These results were similar to those where early wheeze was adjusted for. Boys who had either early-onset or severe eczema were at the greatest risk of having asthma in childhood. There was no evidence that girls with eczema were at increased risk of asthma, regardless of severity and age of onset (Table III). Adjustment for sensitization status reduced the association between eczema in infancy and risk of childhood asthma in boys (Table IV), particularly for eczema that commenced within the first 6 months of life (33% reduction in OR). This suggests that, in boys, some of the association between early eczema and risk of asthma is mediated by increased risk of sensitization. There was no evidence of an interaction between eczema and sensitization in the risk of childhood asthma (*P* = .889).

Sensitivity analysis

A sensitivity analysis was performed to determine whether the definition of asthma that was used influenced the observed relationships. If the outcome was persistent asthma (asthma reported at both the 6-year and 7-year follow-ups), the analysis was limited to 352 children. The observed pattern of associations was largely unchanged: eczema that was either early in onset or severe was a risk factor for persistent asthma in boys, whereas there was no clear evidence that eczema was a risk factor for persistent asthma in girls (data not shown).

DISCUSSION

Our observations in this prospective birth cohort of infants with a family history of allergic disease suggest that eczema in early

TABLE II. Adjusted* associations between any eczema in the first 2 years and risk of childhood asthma (n = 389†)

	Asthma (124/389)		Asthma (124/389)	
	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Any sensitization	2.96 (1.81-4.84)	<.001	2.77 (1.70-4.53)	<.001
Early wheeze	4.30 (2.64-7.02)	<.001	4.07 (2.51-6.57)	<.001
History of asthma in both parents	1.51 (0.90-2.53)	.117	1.66 (1.12-2.45)	.011
Severity of eczema in boys				
First tertile	1.86 (0.68-5.11)	.228		
Second tertile	1.42 (0.55-3.64)	.464		
Third tertile	4.15 (1.80-9.59)	.001		
Severity of eczema in girls				
First tertile	0.62 (0.23-1.68)	.345		
Second tertile	1.24 (0.49-3.11)	.649		
Third tertile	0.87 (0.31-2.44)	.792		
Eczema in boys*				
Commenced from 0-6 mo			3.68 (1.67-8.10)	.001
Commenced from 6-24 mo			1.65 (0.75-3.61)	.211
Eczema in girls*				
Commenced from 0-6 mo			1.08 (0.46-2.55)	.857
Commenced from 6-24 mo			0.72 (0.30-1.70)	.449

Model 1: effect of severity of eczema in boys and girls. Model 2: effect of age of onset of eczema in boys and girls. Both models adjusted for any sensitization, early wheeze, and parental history of asthma.

†An additional 14 children missing data on paternal history of asthma and were excluded.

TABLE III. Unadjusted associations between eczema in the first 2 years and risk of childhood asthma in boys and girls (n = 262†) in infants who did not wheeze within the first 2 years of life

	Boys (n = 117)			Girls (n = 145)			P value for interaction
	Percentage with asthma‡	OR (95% CI)	P value	Percentage with asthma‡	OR (95% CI)	P value	
Any eczema	43.5% (20/46)	5.15 (2.08-12.79)	<.001	17.4% (12/69)	1.09 (0.44-2.67)	.851	.017
No eczema	11.3% (8/71)			15.8% (12/76)			
Severity of eczema							
First tertile (0-0.5 d)*	42.9% (6/14)	5.18 (1.52-17.68)	.009	4.5% (1/22)	0.28 (0.03-2.27)	.232	.018
Second tertile (0.5-2 d)*	17.6% (3/17)	1.62 (0.39-6.66)	.506	20.0% (6/30)	1.39 (0.47-4.11)	.552	.868
Third tertile (2-17 d)*	73.3% (11/15)	13.45 (4.12-43.92)	<.001	29.4% (5/17)	1.82 (0.52-6.41)	.352	.023
Age of eczema onset							
First 6 mo*	55.0% (11/20)	7.46 (2.53-21.96)	<.001	21.4% (6/28)	1.68 (0.57-4.92)	.343	.055
First from 6-24 mo*	34.6% (9/26)	3.78 (1.32-10.85)	.013	14.6% (6/41)	0.74 (0.24-2.31)	.601	.039

*Compared with infants who did not have eczema in the first 2 years of life.

†An additional 141 children who had a wheezing condition within the first 2 years of life were excluded.

‡Asthma present at either 6 or 7 years of age.

life is associated with a clearly increased risk of childhood asthma only in boys. In girls, the evidence for an association between eczema in infancy and childhood asthma was weak. Boys with early-onset and/or severe eczema were at the greatest risk of childhood asthma, whereas there was no apparent increased risk in girls, regardless of age of onset and severity. Sensitization and early wheeze were also strongly associated with risk of childhood asthma, but even after taking these effects into account, there was still a clearly increased risk of asthma in boys with eczema. Collectively, these results support an atopic march or progression from eczema in infancy to asthma in boys, rather than comanifestation of wheeze and eczema.

There are a number of clear differences between the sexes in the development of allergic diseases. It has been repeatedly shown that boys are at great risk of asthma during childhood,⁸⁻¹⁰ although this later reverses, with teenage girls and young women

at greater risk than male subjects.¹⁶ Several parameters of lung development are markedly different between boys and girls.¹⁷ There is a preponderance of nonatopic eczema in girls compared with boys.^{11,18} The skin of girls has a higher surface pH and lower level of stratum corneum hydration than the skin of boys.¹⁸ Given these differences, it is not surprising that eczema could have different effects on risk of asthma in boys and girls. Moreover, it seems unlikely that these are chance observations, because in a cross-sectional population-based sample of German children, eczema that began within the first 2 years of life was a greater risk for childhood wheeze in boys than in girls.¹⁸ It is unclear what mechanisms could cause the difference between boys and girls in the progression from eczema to asthma.

The approximately 2-fold increase in odds of childhood asthma associated with infantile eczema observed in this study is consistent with results from previous prospective birth cohort

TABLE IV. Adjusted* associations between eczema in the first 2 years, and risk of childhood asthma in boys and girls (n = 262†) in infants who did not wheeze within the first 2 years of life

	Boys (n = 117)*		Girls (n = 145)*		P value for interaction
	OR (95% CI)	P value	OR (95% CI)	P value	
Any eczema	3.71 (1.44-9.51)	.006	0.92 (0.37-2.29)	.857	.037
Severity of eczema					
First tertile (0-0.5 d)	4.36 (1.25-15.25)	.021	0.22 (0.03-1.80)	.158	.017
Second tertile (.5- 2 d)	1.25 (0.30-5.21)	.758	1.20 (0.40-3.59)	.745	.963
Third tertile (2-17 d)	9.62 (2.82-32.77)	<.001	1.63 (0.45-5.90)	.459	.049
Age of eczema onset					
First 6 mo	5.00 (1.65-15.14)	.004	1.37 (0.46-4.07)	.567	.100
First from 6-24 mo	3.15 (1.05-9.42)	.040	0.65 (0.20-2.04)	.456	.051

*Adjusted for presence of sensitization and parental history of asthma.

†Excludes 141 children who had a wheezing condition within the first 2 years of life.

studies.⁴ When we used the same analytic techniques as Illi et al,⁵ the findings from our study were similar to theirs. They found that eczema was not an important predictor of childhood asthma when adjustments were made for the effects of early sensitization and wheeze. Given the available evidence for differences between boys and girls in the development of eczema^{11,18} and asthma,¹⁰ we explored this issue further by testing for differential sex effects. What we found is a marked difference in the progression from eczema to asthma between boys and girls. These effects were not explored in the MAS data.

The major strengths of MACS are its prospective design, with multiple measurements of allergic sensitization to a standard battery of common allergens; regular assessment of wheeze and eczema during infancy; and assessment of asthma status at ages 6 and 7 years, when the diagnosis is far more reliable than in earlier life.⁹ A possible weakness of this study is that some of the infants who had eczema may have been sensitized to allergens other than those tested. Sensitization to a number of allergens, including *Alternaria*,¹⁹ has been implicated as a cause for exacerbation of symptoms of asthma. However apart from egg, dust mite, cat, and rye grass (which were tested in this study), only dog hair sensitization in infancy has been shown to be associated with new-onset asthma.²⁰⁻²² Because dog sensitization is unusual, it is unlikely to have influenced our findings.

We have defined eczema in the first 2 years of life as either a doctor diagnosis or use of topical steroids for rash, which is convenient but is yet to be validated. The definition of *eczema* is a limitation of this study. However, none of the current definitions of eczema^{23,24} have been validated in children under the age of 2 years. Although the Scoring Atopic Dermatitis index²⁵ has been examined in infants,²⁶ this tool is primarily for the assessment of eczema severity rather than diagnosis of the presence or absence of eczema. The definition of eczema used in this study probably excludes most cases of seborrheic dermatitis and nappy rash, it may have misclassified some infants whose rash was not a result of eczema. Moreover, we have used convenient definitions of asthma based on parental report of doctor diagnosis. This definition does not divide asthma into atopic and nonatopic or according to the subcategories based on inflammatory markers.²⁷ Any misclassification of both outcome and exposure will have resulted in an underestimate of the true associations between eczema and risk of asthma.

Despite the popularity of the atopic march hypothesis, the mechanisms that might underlie the progression from eczema to asthma have not been clearly elucidated. Three possible

explanations exist to explain this association: (1) a shared environmental factor, (2) a shared genetic association, and (3) a direct effect of eczema increasing risk of asthma, or a combination of these. At this time, it is unclear what the common environmental risk factor might be, although many affected children are sensitized to indoor allergens.

Genetic linkage studies indicate that there is no clear overlap in the chromosomal regions implicated in the development of asthma and eczema,²⁸ suggesting that eczema and asthma are not different expressions of an underlying disease. Possible exceptions are 2 common mutations that cause impaired barrier function as a result of null expression of filaggrin in the skin and oral/nasal mucosa, which has been associated with increased risk of eczema and eczema with concomitant asthma.^{29,30} Interestingly, these polymorphisms are associated with late-onset eczema (after 2 years of age),³⁰ whereas we have found that it is the very-early-onset eczema that is most strongly associated with risk of childhood asthma, and it has been repeatedly demonstrated that eczema onset after the second birthday is less strongly associated with asthma than early-onset eczema.^{18,31}

It seems reasonable to consider that the damaged barrier function associated with eczema may directly result in increased risk of childhood asthma. There is a growing body of evidence that sensitization can occur via damaged skin, which supports sensitization as a mediating factor between eczema and asthma. Murine models have shown that epicutaneous exposure to egg and peanut after the removal of the stratum corneum induces sensitization (raised specific IgE and IgG₁),^{32,33} and that repeated skin exposure to ovalbumin is sufficient to induce not only eczema-like skin lesions but also airway hyperresponsiveness after exposure to ovalbumin as an aerosol.³³ Topical creams that contain peanut oil have been associated with increased risk of peanut allergy.³⁴ Using the same cohort, we have previously demonstrated that eczema within the first 6 months is associated with increased risk of new sensitization,⁷ and it seems likely that the increased risk of childhood asthma associated with eczema is at least partially mediated by sensitization.

These observations suggest possible opportunities to intervene to prevent the progression from eczema in infancy to asthma in childhood. The Early Treatment of the Atopic Child study investigated antihistamine as an intervention of this kind, although it was not successful at reducing the risk of eczematous infants developing asthma.²² It remains to be seen whether other interventions may be more successful.

If the increased risk of asthma is in part mediated by the development of allergic sensitization, it may be possible to improve the barrier function in infants with eczema who are yet to develop sensitization. Despite assisting with the management of eczema, standard emollients do not help restore the barrier function.³⁵ There is evidence that an emollient containing the major lipid components of human skin (ceramides, cholesterol, and free fatty acids) can accelerate the restoration of barrier function in animal and human models.³⁶ If the barrier function in infants with eczema can be repaired before sensitization, the risk of asthma may be reduced.

Conclusion

This study demonstrates that eczema in early infancy is associated with an increased risk of childhood asthma, but only in boys, supporting a sex difference in the atopic march hypothesis. Our findings argue against the comanifestation of early wheeze and eczema for the majority of children. Further interventions that attempt to reduce the progression from eczema to sensitization and asthma are warranted, particularly in boys, and subsequent studies should be sufficiently powered to test for differences in the effect of treatments between boys and girls. Understanding why these sex differences occur may provide novel interventions to prevent the development of asthma.

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Clinical implications: The atopic march may be more relevant in boys, to whom interventions might be targeted.

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