

Does eczema in infancy cause hay fever, asthma, or both in childhood? Insights from a novel regression model of sibling data

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Background: The atopic march hypothesis proposes that eczema precedes the development of asthma and allergic rhinitis.

Objective: We sought to assess the evidence for a causal effect of infantile eczema on childhood hay fever, asthma, or both.

Methods: We used parental reports on infantile eczema and childhood asthma and hay fever for 3778 pairs of 7-year-olds matched to their sibling closest in age within 2 years from the Tasmanian Longitudinal Health Study. We analyzed paired sibling data using a logistic regression model that allowed inference about a causal effect of a familial predictor on a child's outcome by examining the change in association with their cosibling's predictor after adjusting for their own predictor status.

Results: Siblings were concordant for infantile eczema (tetrachoric correlation, 0.40). For having both hay fever and asthma by age 7 years, the association with cosibling's eczema was an odds ratio (OR) of 1.98 (95% CI, 1.37-2.86), which reduced after adjusting for own eczema to an OR of 1.65 (95% CI, 1.17-2.34). For having hay fever only, the association with cosibling's eczema was an OR of 1.68 (95% CI, 1.22-2.31) before and an OR of 1.59 (95% CI, 1.19-2.14) after adjusting for own

eczema. There was no association between having asthma only and cosibling's eczema (OR, 1.00; 95% CI, 0.77-1.30).

Conclusions: Eczema in infancy might have a causal effect on hay fever in children with and perhaps without asthma. The association of infantile eczema on asthma in children without hay fever, which might be early transient wheeze, is unlikely to be causal or familial. These findings have implications for hay fever prevention. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Atopic march, infantile eczema, childhood asthma, childhood hay fever, causation, familial confounding, sibling design

The atopic march hypothesis proposes that eczema in early life precedes, if not causes, the development of hay fever with and without asthma in later life.¹ Another hypothesis is that there is a comanifestation of eczema with hay fever and asthma.² Contrary to the latter hypothesis, several prospective studies, including ours, have demonstrated a temporal association between infantile eczema and asthma in both childhood and adulthood.³⁻⁷ Less is known about the association between eczema and hay fever in childhood. We have previously reported that infants with atopic eczema had a greater risk of allergic rhinitis compared with infants with nonatopic eczema.⁶ Recently, we found an association between infantile eczema and adult atopic asthma (ie, asthma in adults who are atopic).⁸

Asthma, hay fever, and eczema are interrelated in childhood. For example, more than 30% of children with asthma also have hay fever, and over time, about 40% to 60% of children with infantile eczema have hay fever, asthma, or both.⁹ Infantile eczema could be associated with hay fever, asthma, or both in childhood because of factors common to these conditions rather than any causal effect on the other childhood conditions. One such "confounder" could be familial, if not genetic, factors common to these conditions.

Asthma and hay fever in childhood and infantile eczema are all familial in that siblings are more concordant for the condition than would be expected by chance alone. Familial aggregation of a condition could be due to genetic causes, nongenetic causes, or both that are shared by, or correlated within, relatives. Researchers conducting twin studies have claimed evidence that genetic factors explain a large part of the familial aggregation. This conclusion has been made under the assumptions of the classic twin model,¹⁰ which states that the effects of environmental factors shared by twins are the same for monozygotic as for dizygotic twin pairs and that the excess concordance for the

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Abbreviations used

FLG: Filaggrin gene

OR: Odds ratio

TAHS: Tasmania Longitudinal Health Study

condition within pairs is due solely to familial factors common to conditions.¹¹ Therefore an important question arises when trying to understand the atopic march phenomenon: Is there a direct, perhaps causal relationship from eczema to hay fever, asthma, or both, or are the associations between eczema and these childhood conditions explained by overlapping familial, if not genetic, causes?

We have recently developed a regression approach for analyzing the relationship of a predictor on an outcome, both of which are measured for pairs of related subjects.¹² Here we have applied this approach to parent-reported data on infantile eczema as a familial predictor of 3 independent outcomes defined by childhood asthma and childhood hay fever and collected as part of a population-complete study of 7-year-old children and their siblings living in Tasmania in 1968.

METHODS**Tasmania Longitudinal Health Study**

The Tasmania Longitudinal Health Study (TAHS)^{4,8,9} commenced in 1968 when the parents of all Tasmanian schoolchildren (proband) born in 1961 were approached for a research study, the Tasmanian Asthma Study, a collaborative project involving the Asthma Foundation (as it was known then), Tasmanian School Medical Service staff, and researchers from the Universities of Queensland and New South Wales. Parents completed respiratory questionnaires for 8,583 probands (99%) and 21,043 of their siblings, as well as for themselves.

Subjects

Each proband with at least 1 sibling within 2 years of age was matched to the sibling closest in age, resulting in 3778 pairs (we excluded monozygotic twin pairs).

Definitions

- *Childhood asthma* was defined as a “yes” response to the following question: “Has he/she at any time in his/her life suffered from attacks of asthma or wheezy breathing?”
- *Childhood hay fever* was defined as a “yes” response to the following question: “Does he/she get attacks of “hay fever” (that is sneezing, running or blocked nose, sometimes with itchy eyes or nose)?”
- *Infantile eczema* was defined as a “yes” response to the following question: “Did he/she have infantile (baby) eczema?”

Statistical methods

We adapted a recently developed regression model for analyzing twin pair data on a continuously distributed outcome and a familial predictor measured for both the twin and his or her cotwin.¹² The underlying statistical model allows for a direct causal relationship between the predictor and the outcome, as well as for familial factors both specific and common to the outcome and predictor. If the predictor is familial, in that it is correlated in relatives, and there is an association between the outcome of a person (self) with the predictor of his or her relative that reduces after adjusting for the predictor of self, the data are consistent with the existence of a causal relationship between the predictor and

the outcome. If the associations between the outcome of a person and the predictors of both himself or herself and of his or her relative are the same before and after adjusting for each other, then under this model, there is no evidence for the existence of a direct causal relationship between the predictor and the outcome. If at least some cross-trait cross-sibling association is still evident after adjusting for the predictor variable of self, the data are consistent with the existence of common familial factors in addition to any causal component. We call this approach “inference on causation from examination of familial confounding (ICE FALCON).”

We have used it here to analyze binary outcome data using logistic regression; for a detailed description of the approach, see Appendix E1 in this article's Online Repository at www.jacionline.org. Irrespective of whether a subject is the proband or the selected sibling of the proband, he or she can play the role of “self,” and we use the term “cosibling” to refer to the sibling. The correlation in outcomes is taken into account in the statistical analyses by using generalized estimating equations.

We defined 3 childhood outcomes: (1) having hay fever and asthma, (2) having hay fever only, and (3) having asthma only. The predictor was infantile eczema. We also adjusted for parental status for the condition that defined the childhood outcome as a binary variable indicating that 1 or both parents had the condition.

The outcome for each subject was regressed against his or her predictor, the predictor of his or her sibling, or both. The analyses were conducted with and without adjusting for the other covariate. We fitted a series of models, fitting the following: model I, predictor for self only; model II, predictor for the cosibling only; and model III, predictors for both self and cosibling. The results are presented in the tables as logistic regression coefficient (logit) estimates and SEs, from which odds ratios (ORs) and 95% CIs are calculated and presented in the text.

The percentage reduction in the parameter was computed as the difference between the estimated parameters before and after adjustment divided by the estimated parameter before adjustment and then multiplied by 100. We used the bootstrap method to compute an approximate CI for the percentage reduction. This technique involves randomly drawing twin pairs of the same sample size as the original dataset with replacement, fitting models I to III to this new dataset to get new estimated parameters, and then repeating the process a large number of times to yield a sampling distribution of the estimated parameters. In our application we performed 5000 bootstraps. The approximate CI for the percentage reduction was obtained by ranking the bootstrap estimated percentage reductions from smallest to largest and choosing the percentile values according to the CI. To derive the approximate 95% CI based on 5000 bootstraps, we chose the 125th and 4874th bootstrap values.

To calculate the approximate CIs using bootstrapping, we wrote programs in R (<http://www.R-project.org/>). We used the polychoric correlation¹³ and the OR to measure the within-sibship association in infantile eczema. All other analyses were conducted with STATA software, version 8.2 (2004; StataCorp, College Station, Tex).

RESULTS

Table I shows the characteristics of the paired siblings as individuals. It also shows that, within an individual, all 3 childhood conditions were associated with infantile eczema in decreasing order of strength from having hay fever and asthma, having asthma only, to having hay fever only. All conditions were also associated with having a parental history of the same condition. Having childhood asthma, with or without having a history of childhood hay fever, was more common in boys. After adjusting for the parental conditions, the associations between infantile eczema and the childhood conditions reduced by approximately 10% but remained highly significant.

The within-sibling pair tetrachoric correlation for infantile eczema was 0.40, with an SE of 0.04 ($P < .0001$), and the corresponding OR was 4.2 (95% CI, 3.2-5.4).

TABLE I. Crude associations between potential predictors and outcomes based on hay fever and asthma in childhood

	Hay fever and asthma		Asthma only		Hay fever only	
	No. (%)	OR (95% CI)	No. (%)	OR (95%CI)	No. (%)	OR (95%CI)
Infantile eczema						
No	182 (2.67)	4.40 (3.29-5.88)	652 (9.58)	2.39 (1.96-2.92)	299 (4.39)	1.77 (1.31-2.40)
Yes	84 (11.2)		151 (20.2)		59 (7.88)	
Sex						
Male	166 (4.23)	1.61 (1.25-2.08)	497 (12.7)	1.59 (1.37-1.85)	170 (4.33)	0.84 (0.68-1.03)
Female	100 (2.75)		306 (8.42)		188 (5.17)	
Parental hay fever and asthma						
No	162 (2.47)	4.54 (3.46-5.96)	624 (9.52)	2.06 (1.70-2.49)	270 (4.12)	2.23 (1.70-2.91)
Yes	104 (10.4)		179 (17.8)		88 (8.76)	
Parental asthma only						
No	242 (3.44)	1.36 (0.87-2.11)	691 (9.82)	2.49 (1.98-3.14)	338 (4.80)	0.80 (0.51-1.26)
Yes	24 (4.62)		112 (21.5)		20 (3.85)	
Parental hay fever only						
No	199 (3.32)	1.30 (0.96-1.77)	652 (10.9)	0.88 (0.72-1.07)	226 (3.77)	2.34 (1.85-2.96)
Yes	67 (4.29)		151 (9.67)		132 (8.46)	

ORs and their CIs were calculated by using generalized estimating equations.

TABLE II. Logistic regression estimates, SEs, and *P* values from fitting models for having hay fever and asthma in childhood against having eczema in infancy

Covariate(s)	Model I			Model II			Model III			Percentage reduction* (95% CI)
	Estimate (β_{s1})	SE	<i>P</i> value	Estimate (β_{c1})	SE	<i>P</i> value	Estimate (β_{s2} and β_{c2})	SE	<i>P</i> value	
Infantile eczema (a)										
Self	1.482	0.148	<.001				1.420	0.148	<.001	4% (1% to 9%)
Cosibling				0.683	0.191	<.001	0.503	0.177	.005	26% (6% to 140%)
Infantile eczema (b)										
Self	1.358 (8%†)	0.152	<.001				1.312	0.152	<.001	3% (0% to 9%)
Cosibling				0.563 (18%†)	0.190	.003	0.391	0.181	.03	31% (−8% to 280%)

a, No adjustment; b, adjusting for parental hay fever and asthma.

* $\Delta = 100(\beta_{s2} - \beta_{s1})/\beta_{s1}$ or $\Delta = 100(\beta_{c2} - \beta_{c1})/\beta_{c1}$.

†Percentage change of regression estimate after adjusting for parental hay fever and asthma.

Having hay fever and asthma

Table II shows that, within a child, having hay fever and asthma was strongly associated with eczema (OR, 4.41 [95% CI, 3.29-5.88] from model I[a]). This condition was also associated with cosibling's eczema (OR, 1.97 [95% CI, 1.36-2.88] from model II[a]). When fitted simultaneously, there was a 26% (95% CI, 6% to 140%) reduction in the logit estimate of the association with cosibling's eczema (OR, 1.65 [95% CI, 1.17-2.34]; compare model III[a] with model II[a]).

Table II also shows that, after adjusting for parental hay fever and asthma, the logit estimates of associations with infantile eczema of self and the cosibling were reduced by 8% and 18%, respectively (compare model I[b] with model I[a] and model II[b] with model II[a], respectively). After adjusting for parental status, the logit estimate of the association with cosibling's eczema was reduced by 31% (95% CI, −8% to 280%) when fitted simultaneously with eczema of self (compare model III[b] with model II[b]).

Having hay fever only

Table III shows that, within a child, having hay fever only was associated with eczema (OR, 1.77 [95% CI, 1.29-2.42] from model I[a]). This condition was also associated with cosibling's eczema (OR, 1.68 [95% CI, 1.22-2.31] from model II[a]). When fitted simultaneously, there was a 10% (95% CI, 2% to 40%)

reduction in the logit estimate of the association with cosibling's eczema (compare model III[a] with model II[a]).

Table III also shows that, after adjusting for parental hay fever only, the logit estimates of the associations with eczema of self and of the sibling were both reduced by 5% and 11%, respectively (compare model I[b] with model I[a] and model II[b] with model II[a], respectively). After adjusting for parental status, the logit estimate of the association with cosibling's eczema was reduced by 11% (95% CI, 2% to 50%) when fitted simultaneously with eczema of self (compare model III[b] with model II[b]).

Having asthma only

Table IV shows that, within a child, having asthma only was associated with eczema (OR, 2.39 [95% CI, 1.95-2.93] from model I[a]). There was no association between this condition and sibling's eczema (OR, 1.00 [95% CI, 0.77-1.30] from model II [a]). Model III(a) shows that these associations were unchanged when fitted simultaneously.

Table IV also shows that, after adjusting for parental asthma only, the logit estimates of the associations with eczema of self and of the sibling were virtually unchanged (compare model I[b] with model I[a] and model II[b] with model II[a], respectively).

Fig 1 plots the changes in the cosibling coefficient for infantile eczema after adjusting for infantile eczema status of self before

TABLE III. Logistic regression estimates, SEs, and *P* values from fitting models for having hay fever only in childhood against having eczema in infancy

Covariate(s)	Model I			Model II			Model III			Percentage change reduction* (95% CI)
	Estimate (β_{s1})	SE	<i>P</i> value	Estimate (β_{c1})	SE	<i>P</i> value	Estimate (β_{s2} and β_{c2})	SE	<i>P</i> value	
Infantile eczema (a)										
Self	0.572	0.156	<.001				0.524	0.151	.001	8% (1% to 29%)
Cosibling				0.519	0.159	.001	0.466	0.154	.002	10% (2% to 40%)
Infantile eczema (b)										
Self	0.543 (5%†)	0.157	.001				0.495	0.153	.001	9% (1% to 34%)
Cosibling				0.491 (11%†)	0.159	.002	0.436	0.155	.005	11% (2% to 50%)

a, No adjustment; b, adjusting for parental hay fever only.

* $\Delta = 100(\beta_{s2} - \beta_{s1})/\beta_{s1}$ or $\Delta = 100(\beta_{c2} - \beta_{c1})/\beta_{c1}$.

†Percentage change of regression estimate after adjusting for parental hay fever only.

TABLE IV. Logistic regression estimates, SEs, and *P* values from fitting models for asthma only in childhood against having eczema in infancy

Covariate(s)	Model I			Model II			Model III		
	Estimate (β_{s1})	SE	<i>P</i> value	Estimate (β_{c1})	SE	<i>P</i> value	Estimate (β_{s2} and β_{c2})	SE	<i>P</i> value
Infantile eczema (a)									
Self	0.872	0.102	<.001				0.876	0.103	<.001
Cosibling				0.003	0.132	.9	−0.054	0.126	.7
Infantile eczema (b)									
Self	0.881	0.103	<.001				0.886	0.105	<.001
Cosibling				0.004	0.133	.9	−0.061	0.128	.6

a, No adjustment; b, adjusting for parental asthma only.

and after adjusting for parental status for the same condition. Model I in Tables II to IV shows that the strongest cosibling association was between eczema and having hay fever and asthma, and this association is also the one that is most reduced, in absolute and percentage terms, by adjusting for eczema of self.

DISCUSSION

The most important finding of our study was that the relationships between eczema in infancy and having asthma with or without hay fever up to age 7 years seem to have different causes, as evident by Fig 1. Our data are consistent with the following scenarios. Eczema in infancy causes a substantial proportion, perhaps about 30%, of hay fever in children with a history of asthma and perhaps about 10% of hay fever in children without asthma in childhood. The approximate CIs based on bootstrapping indicate that these changes are unlikely to have occurred by chance. On the other hand, although eczema in infancy is associated with asthma in childhood without a history of hay fever, this association is unlikely to be causal. Moreover, although eczema in infancy is correlated in siblings, its association with asthma without a history of hay fever is not consistent with familial factors that influence both infantile eczema and that condition. We describe below how we came to these conclusions.

Eczema in infancy as a predictor of having both hay fever and asthma in childhood

There was a strong association between eczema in infancy and having hay fever and asthma in childhood, both within a child and across siblings. In part, this could be due to the existence of

familial factors that predispose to both outcomes. A proportion of these associations (11% to 19%) was explained by parental hay fever and asthma. These associations were also consistent with a causal component to the atopic march from infantile eczema to having both hay fever and asthma in childhood. This was seen by the reduction in the logit estimate of the association with eczema in the sibling by 26% after adjusting for eczema in oneself and by 31% when allowing for whether the parents ever had both asthma and hay fever, respectively. Therefore there appears to be a role for familial factors not associated with hay fever or asthma that explain why infantile eczema predicts having hay fever and asthma in childhood.

Eczema in infancy as a predictor of having hay fever only in childhood

Our data are consistent with the sibling association between eczema in infancy and having hay fever only in childhood, for the most part because of the existence of familial factors predisposing to both outcomes. A proportion of the familial association between these 2 childhood conditions (24% to 25%) was explained by parental hay fever. It is also possible that there could be a role for a causal relationship of infantile eczema with childhood hay fever without asthma, although the attenuation of regression coefficients with sibling eczema after adjusting for eczema of self was small.

Eczema in infancy as a predictor of having asthma only in childhood

In stark contrast to the above, our data were consistent with a modest association between eczema in infancy and asthma only in

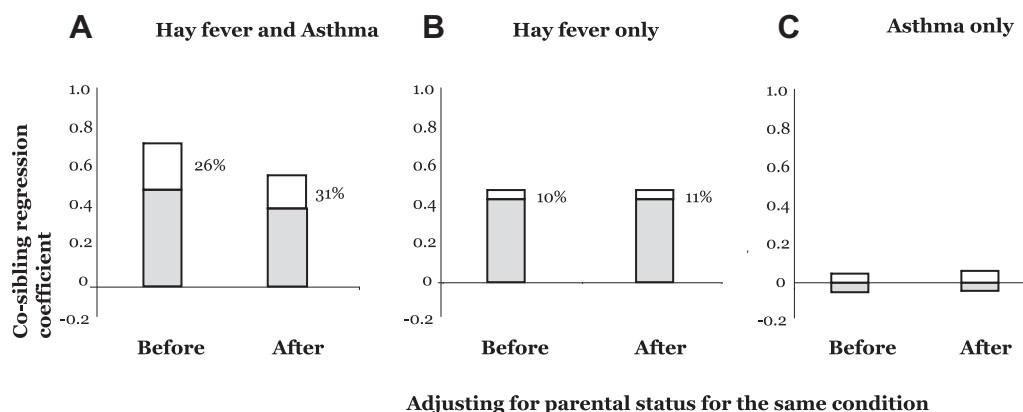


FIG 1. Logistic regression estimates of cosibling association with infantile eczema from fitting models II and III before (shaded and unshaded bars) and after (shaded bars only) adjusting for infantile eczema of self and for having asthma and hay fever (A), hay fever only (B), and asthma only (C) in childhood before and after adjusting for parental status for the same condition. Percentage reduction after adjusting for eczema of self is shown for Fig 1, A and B.

childhood that was (1) not due to the existence of familial factors predisposing to both outcomes (there were no significant associations with sibling infantile eczema) and (2) explained by parental asthma (if any) in only a very small proportion of cases, and (3) not explained by a direct causal relationship between infantile eczema and this outcome in later childhood. Had there been a causal relationship, then given that infantile eczema is correlated within siblings, this would have generated a sibling association between infantile eczema and childhood asthma without hay fever. Therefore it would appear that individual-specific covariates, such as respiratory tract infections,¹⁴ must explain this association.

The familial component of the above associations could be genetic, shared environmental, or both in origin. Recent studies of mutations in the filaggrin gene (*FLG*) support the existence of a genetic component on the pathway from eczema to allergic asthma. Filaggrin is a key protein required to form the cornified cell envelope, which is the primary form of the skin barrier.¹⁵ Approximately 10% of white persons carry mutations in *FLG* that result in null expression of filaggrin,¹⁶ and these “null mutations” have been shown to be associated with an increased risk of eczema.¹⁷ Despite these *FLG* null mutations having no known immunologic function, they are also associated with an increased risk of asthma, although only for persons with previous eczema.¹⁷ This suggests that the defect in the skin barrier caused by *FLG* null mutations predispose some persons to the development of asthma. It has been suggested that this is due to increased penetration of allergens through the skin, exposing Langerhans cells to these allergens and leading to cutaneous and systemic allergies.⁹

It is difficult to compare our findings on the lack of familial associations between infantile eczema and asthma only with those genetic studies reported by others.^{18–20} None of those studies reported the presence of allergic rhinitis among asthma cases or divided asthma cases by hay fever status as we did in this study when trying to identify genetic variants associated with eczema, asthma, or both. Not partitioning asthma into separate phenotypes might have obscured true genetic associations.

Some studies have found varying risk patterns when asthma was separated into different phenotypes. For example, our recent study of adult-onset and persistent asthma from childhood found that childhood eczema and rhinitis were associated with atopic

asthma in later life (with atopic asthma defined as sensitization to ≥ 1 aeroallergen), whereas childhood eczema and rhinitis were not risk factors for nonatopic asthma in adulthood.⁸

Few studies have examined the role of eczema on hay fever from a familial perspective. To our knowledge, only 2 twin studies have been published, and they made the “equal shared environments” assumption of the classic twin model referred to above without allowing for causation as we have and concluded that genetic factors explain the cross-pair correlations between the conditions.^{19,20} In both of those studies, the samples of children were of a similar age group to the participants in our study. Our findings are consistent with a small causal role in the atopic march from eczema in infancy to hay fever in childhood and contribute to the epidemiologic literature on this issue. In a cohort study of 94 children with atopic dermatitis, 45% had allergic rhinitis by age 7 years.⁵

Strengths of this study

There are novel aspects in the analytic approach we have developed and applied here. In traditional variance components modeling of paired data, the variances and covariances are partitioned into genetic, shared, and nonshared environmental components both specific and common to the variables. In contrast, the regression model adopted in this study allows for a causal association between a specified predictor and a specified outcome. By including a parameter for the sibling’s predictor, we can test whether the data are consistent with there being a causal component by seeing whether the association of one’s outcome with the predictor of a sibling is attenuated after adjusting for one’s own predictor status. These models rely on the fact that the predictor of interest is familial. They have the potential to identify associations that have a causal component in addition to a familial component and might therefore provide further insights into the natural history of common diseases. These are major methodological improvements to current methods on analyzing twin data, as has already been demonstrated for a continuous outcome.¹²

Another strength is the large sample of population-based and unselected pairs of siblings. Few twin/sibling studies conducting a bivariate trait analysis of eczema, hay fever, and asthma in children of a similar age group have included such large numbers,^{19,20} and none of these have used the analytic approach

used here, let alone divided the hay fever and asthma outcomes into 3 mutually exclusive categories.

Limitations of this study

The data used here are cross-sectional, and therefore we are unable to know definitively whether eczema occurred before asthma or allergic rhinitis. However, eczema in this study was defined as infantile or baby eczema, implying it occurred in the first 12 months of life, and most cases of asthma and hay fever in childhood develop after this age. Because our study did not collect data on family history of eczema, we might have overestimated the magnitude of the associations between infantile eczema and the outcome variables. Because the questions asked of the parents were broad, there is the potential for misclassified reporting. Although this would have attenuated the model estimates toward the null, if it was at random, it would not have produced misleading conclusions about the potential for causation, except perhaps negating evidence of true causation. The definition of asthma used in this study, in combination with asking about having attacks in the last 12 months, has been found to have high validity against physician diagnosis and bronchial hyperreactivity.²¹

Because our asthma definition was related to both ever asthma and wheezy breathing, the group of children with asthma would have included children who had any wheezing in the first 7 years of life. A substantial (40% to 50%) proportion of children with wheeze in early life have “transient early wheeze” in that they do not wheeze after age 3 to 4 years.²²⁻²⁵ Transient early wheezers are less likely to be atopic than children with persistent or late-onset wheeze.^{22,25} Consequently, the majority of transient early wheezers would have been classified as having “asthma only,” whereas late-onset or persistent wheezers would have been classified as having both hay fever and asthma. Therefore our findings suggest that infantile eczema might be causally related to late-onset/persistent wheeze but not to transient early wheeze.

In summary, we believe our findings are of considerable importance because, to the best of our knowledge, this is the first study to show that the contribution of eczema to hay fever and asthma in childhood varies for different phenotypes. Our findings could have important implications for understanding these conditions and suggest that it might be possible to prevent hay fever in children with eczema, especially those who are asthmatic, for example by conducting trials of emollients to improve skin barrier function, antihistamines,²⁶ and preventive immunotherapy.²⁷

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Clinical implications: Eczema in infancy could be a cause of hay fever in childhood, especially for asthmatic children, raising the possibility of prevention for a proportion of childhood hay fever.

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APPENDIX E1.

Let Y_{ij} denote a binary outcome measured for sibships of size 2, with $j = 1, 2$ (the order is arbitrary) and $i = 1, \dots, m$, where m is the number of sibling pairs. Let X_{ij} denote a p -covariate vector of potential predictors that have a unique value associated with each individual within each pair and Z_i denote a q -covariate vector of potential predictors that have an identical value for both members of the pair, such as parental characteristics.

Let $\pi_{ij} = P(Y_{ij} = 1 | X_{ij}, Z_i)$ be the probability of having the outcome conditional on the measured X_{ij} and Z_i . This probability is also equal to the expected value of Y_{ij} , $\pi_{ij} = E(Y_{ij})$. The logistic regression model expresses the relationship between a binary trait and a linear combination of the covariates through the function

$$\text{logit}(\pi_{ij}) = \log\left(\frac{\pi_{ij}}{1 - \pi_{ij}}\right) = \alpha + \beta X_{ij} + \gamma Z_i,$$

where α is an intercept, and β and γ are the regression coefficient vectors that correspond to cluster-varying and cluster-constant covariates, respectively. Each regression coefficient represents the change in log odds associated with a unit increase in the corresponding covariate while holding all other covariates constant.

For simplicity, suppose we only consider a single covariate, X_{ij} . Following the approach of Dite et al,^{E1} we wish to estimate the association between both the individual's and the sibling's value or values of the covariate. The first model expressed the relationship between an individual's Y_{ij} value and their his or her covariate.

$$\text{logit}(\pi_{i1}) = \alpha + \beta_{s1} X_{i1} \text{ and } \text{logit}(\pi_{i2}) = \alpha + \beta_{s1} X_{i2} \quad \text{Model I}$$

where $\pi_{i1} = \Pr(Y_{i1} = 1 | X_{i1})$ and $\pi_{i2} = \Pr(Y_{i2} = 1 | X_{i2})$, and β_{s1} is the regression coefficient representing the association with a sibling's own X covariate value. The subscript "s" refers to "self."

The relationship between Y_{ij} and the covariate of the sibling is as follows:

$$\begin{aligned} \text{logit}(\pi_{i1}^*) &= \alpha + \beta_{c1} X_{i2} \\ \text{and } \text{logit}(\pi_{i2}^*) &= \alpha + \beta_{c1} X_{i1} \end{aligned} \quad \text{Model II}$$

where $\pi_{i1}^* = \Pr(Y_{i1} = 1 | X_{i2})$ and $\pi_{i2}^* = \Pr(Y_{i2} = 1 | X_{i1})$, and β_{c1} is the regression coefficient representing the association with the cosibling's X covariate value. The subscript "c" refers to the "cosibling."

The logistic regression model for considering both self and cosibling variates concurrently is as follows:

$$\begin{aligned} \text{logit}(\pi_{i1}^+) &= \alpha + \beta_{s2} X_{i1} + \beta_{c2} X_{i2} \\ \text{and } \text{logit}(\pi_{i2}^+) &= \alpha + \beta_{s2} X_{i2} + \beta_{c2} X_{i1} \end{aligned} \quad \text{Model III}$$

where $\pi_{i1}^+ = \Pr(Y_{i1} = 1 | X_{i1}, X_{i2})$ and $\pi_{i2}^+ = \Pr(Y_{i2} = 1 | X_{i1}, X_{i2})$.

The 3 models above can be extended by adding other sibling-varying and sibling-constant covariates.

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