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The temporal sequence of allergic sensitization and onset of infantile eczema

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Clinical and
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Summary

Background Eczema is commonly associated with sensitization in infants, but the causative role of sensitization in the development of eczema has been questioned.**Objective** To determine if allergic sensitization increases the risk of developing eczema, or alternatively, if eczema increases the risk of developing allergic sensitization.**Methods** We used data from the Melbourne Atopy Cohort Study, a prospective birth cohort of 552 infants with a family history of atopic disease. The main outcomes were risk of developing eczema from 6 months to 7 years of age in asymptomatic infants; and risk of developing sensitization, as measured by skin prick tests to milk, egg white, peanut, house dust mite, rye grass pollen and cat extracts, in previously unsensitized infants.**Results** Sensitization to food extracts at 6 months was associated with an increased risk of developing eczema [hazard ratio (HR) 1.63, 95% confidence interval 1.13–2.35] up to 7 years of age, after excluding infants with eczema in the first 6 months. However, eczema in the first 6 months was also associated with increased risk of new sensitization at both 1 year (HR 2.34, 1.38–3.98) and 2 years (HR 3.47, 1.65–7.32).**Conclusion** In some infants, sensitization precedes and predicts the development of eczema, while in others eczema precedes and predicts the development of sensitization. This indicates that there are multiple pathways to atopic eczema.**Keywords** allergy prevention, atopic disease, eczema, skin prick test*Submitted 31 October 2006; revised 15 January 2007; accepted 7 February 2007*

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Introduction

Eczema is often associated with allergic sensitization [either a positive skin prick test (SPT) or allergen-specific serum IgE *in vitro*] particularly in young children [1]. However, it is unclear if allergic sensitization is a cause of eczema or a consequence. There is a growing body of evidence that eczema can induce allergic sensitization. Atopic eczema is associated with dry and damaged skin [2], which may increase allergen absorption through the skin [3], or possibly via an impaired gut mucosal barrier [4, 5], resulting in sensitization to allergens. Murine models have shown that epicutaneous exposure to egg and peanut following the removal of the stratum corneum induces sensitization (raised specific IgE and IgG1) [6, 7], and that repeated skin exposure to chicken egg ovalbumin (OVA) is sufficient to induce atopic dermatitis like skin lesions, and airway hyper-responsiveness following exposure to egg OVA as an aerosol [7]. Recently, two common mutations that cause impaired barrier function of the skin and oral/

nasal mucosa have been shown to result in eczema with allergic sensitization [8, 9]. Use of creams that contain peanut oil have been associated with increased risk of peanut allergy [10]. Collectively, this evidence indicates that sensitization can occur through the skin.

The role of allergic sensitization as a cause of eczema is less clear [11]. As little as a third of 4–5-year-old children with eczema are atopic [12, 13]. A number of studies have demonstrated that sensitization, particularly reactions to hen's egg, in infancy predicts subsequent presence of eczema [12, 14–16] in childhood, but to date no study has reported whether infants already had signs of atopic disease when the SPT or allergen-specific IgE was measured. As such, it is unclear if allergic sensitization is truly predictive, or simply a marker of current disease, which in turn predicts later disease.

In a prospective birth cohort, of 552 infants with a family history of atopic disease, we examined whether allergic sensitization can precede and predict the development of eczema, and conversely whether eczema

can precede and predict the development of allergic sensitization.

Methods and methods

Study population

The Melbourne Atopy Cohort Study (MACS) recruited 620 infants, before birth, born between 1990 and 1994, in Melbourne, Australia.

Data collection

The recruitment process is described in more detail in previous publications [17–19]. This study was approved by the Human Research Ethics Committee of the Mercy Maternity Hospital. Informed consent was obtained from all mothers. Infants were eligible to be enrolled in MACS if their mother attended the Mercy Hospital Antenatal Clinic, and one or more of their first-degree family members had eczema, asthma, hayfever or severe food allergy. Baseline details were recorded during pregnancy. Following 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 years of age. Each survey documented any illnesses since the previous interview.

SPTs were performed at 6, 12 and 24 months according to a standard technique [20], by one of three allergy-research nurses specifically trained in SPT methodology. A single drop of each allergen extract was placed on the infant's back, and pricked using a single-stem blood lancet. Allergen extracts used were cow's milk, egg white, peanut, house dust mite, rye grass and cat dander (Bayer, Spokane, WA, USA). Both negative (saline) and positive (histamine 1 mg/mL) control were used. The SPTs were read at 15–20 min using a ruler. The mean length of the longest weal diameter and the diameter perpendicular to it were recorded. Infants were excluded if they had received any antihistamine within 72 h before the SPT.

Definitions

Eczema was defined as either a doctor diagnosis of eczema or any rash (excluding rash that only affected the nappy region or scalp) that was treated with topical steroid-based preparations [17, 18]. A positive-SPT was defined as a mean diameter of weal 3 mm or greater than a saline control. 'New sensitization' was defined as any positive SPT in infants who had a negative SPT at all previous scheduled time-points (6, 12 and 24 months). The term 'atopic dermatitis' [21] was not used, to avoid the implication that (all) eczema is atopic.

Outcome measures

Primary outcomes were age at development of eczema and risk of developing new sensitization.

Statistical analysis

Risk of developing eczema was analysed using survival analysis methods. To ensure that sensitization preceded the onset of eczema, infants were excluded if they had developed eczema before their 6-month SPT. Cox proportional-hazards regression was used to assess associations between sensitization and risk of developing eczema. Hazard ratios (HRs) > 1 indicate relatively higher rates of developing eczema.

The effects of eczema on risk of developing new sensitization at approximately 1 and 2 years of age was reported as a HR, estimated using a discrete-time survival analysis method. Specifically, a generalized linear model was fitted to the binary outcome, using the complementary log–log link function, and entering log time as an offset variable to allow for differences in length of follow-up intervals [22]. To ensure that eczema preceded sensitization, only infants with all previously scheduled SPT status were included at each time-point.

Variables included, as potential confounders, in all the models were maternal or paternal history of eczema, infant gender and presence of older siblings. Other parental and home environment factors were included in the final model if they altered the point estimate of the primary predictor by 15% or more or were important predictors themselves ($P < 0.05$). Parental factors considered were: smoking (within the past 6 months), age, years of education, history of asthma or allergic rhinitis. Home environment variables considered were: use of gas heating and cooking and pet ownership. The proportional hazards assumption was tested for all associations, using visual inspection of the Kaplan–Meier curves and tests based on Schoenfeld residuals. No evidence was found for violation of this assumption for any co-variate in the analysis. Tests for interactions, using likelihood ratio tests, between SPT results and the following co-variables were performed: infant gender, parental history of atopic disease and wheezing within the first 6 months. Stata (release 9, Stata Corporation, College Station, Texas, USA, 2005) was used for all statistical analysis.

Results

Study population

Of the original cohort of 620 infants, 552 had a valid SPT result at 6 months, and all analyses were limited to this group. The majority of the infants were born into families with married parents who owned their own residence

Table 1. Baseline demographic and clinical characteristics of study cohort (*n* = 552)

	Mothers (<i>n</i> = 552)	Fathers (<i>n</i> = 549)
Mean age (SD)	31.3 (4.3)	33.5 (5.3)
Mean years of education (SD)	13.6 (1.9)	13.5 (2.0)
% born in Australia/NZ (<i>n</i>)	87.5% (483/552)	82.2% (452/550)
% married (<i>n</i>)	91.9% (507/552)	92.2% (506/549)
% owner occupied residence (<i>n</i>)	80.3% (443/552)	81.0 % (442/546)
% current smoker (<i>n</i>)	6.0% (33/552)	16.6% (91/548)
% receiving social security (<i>n</i>)	3.6% (20/552)	3.3% (18/546)
Baseline family history of atopic disease	Mothers (<i>n</i> = 552)	Fathers (<i>n</i> = 547)
Food allergies (%)	39.1	21.6
Eczema (%)	40.7*	20.5
Asthma (%)	42.8*	25.8
Hayfever (%)	60.3*	46.4
Any atopic disease (%)	83.3	62.0

**n* = 551, numbers are not identical because of missing data.

(Table 1). Details of the full cohort have been published elsewhere [19]. Mothers of infants who did not have an SPT performed at 6 months were slightly less educated, and less likely to be married or have eczema. Fathers of infants who did not have an SPT were less likely to be married, and more likely to be a current smoker.

At 6 months 17.2% (*n* = 95) of infants reacted to one or more allergens, with the majority of reactions occurring to egg and the other food allergens (15.9%) (Table 2). Only 3.4% of infants were SPT-positive to an inhalant allergen. Within the first 6 months of life, 20.5% (*n* = 113, Fig. 1) infants had evidence of eczema (57 used topical steroids for rash without a doctor diagnosis). Infants with eczema within the first 6 months of life were more likely to have one or more positive SPTs at 6 months of age (odds ratio (OR) = 2.87, 95% confidence interval (CI) = 1.77–4.66).

Skin prick test as a predictor of eczema

Of the 439 infants who did not have eczema by 6 months, approximately 33% had eczema by 2 years and 48% by 7 years (Fig. 2). A positive SPT reaction to food was associated with risk of subsequently developing eczema (HR = 1.63, 95% CI = 1.13–2.35, Table 3). For example, 44.8% of infants sensitized to food allergens at 6 months had developed eczema by 2 years of age compared with 31.0% of infants who were not sensitized to food allergens at 6 (Fig. 2). Inhalant sensitization at 6 months was not associated with the risk of developing eczema (HR = 0.52, 0.13–2.10, Table 3). Maternal eczema and presence of older siblings were associated with an increased risk of developing eczema from 6 months to 7 years. Adjusting for these and other potential confounding factors (infant

sex, paternal eczema) did not alter the increased risk of eczema in infants sensitized to food allergens (adjusted HR = 1.72, 95% CI = 1.19–2.50).

Infants with the largest SPT weal to *food allergens* at 6 months of age had the greatest risk of developing eczema. Infants with an SPT weal of 6 mm or greater to food allergens were at a clearly increased risk of developing eczema, whereas the evidence was weaker for the smaller weal sizes (Table 4). We were unable to assess if the size of *inhalant allergen* weals predicted the risk of developing atopic diseases, due to the very small numbers of infants sensitized to inhalants at 6 months. Infants who were sensitized to one food allergen were at increased risk of developing eczema, and infants who were sensitized to multiple food allergens were at even greater risk (Table 4). There was no evidence of interaction effects between SPT results and infant sex, parental atopic disease or early onset wheeze on the risk of subsequent development of eczema (*P* > 0.3). There was minimal indication of an association between weal size to histamine control on the 6-month SPT and the risk of developing eczema (data not shown).

The association between SPT at 12 and 24 months and risk of developing eczema after these ages was not as clear. At 12 months of age, a valid SPT was performed on 333 infants who had not previously developed eczema (188 had developed eczema before this age, and 99 were missing SPT data at 6 or 12 months). Only sensitization to cows milk was clearly associated with increased risk of eczema from 1 to 7 years of age (HR = 3.02, 1.47–6.18). Similarly, at 24 months of age, a valid SPT was performed on 229 children who had not previously developed eczema (234 had developed eczema before this age, and 99 were missing SPT data at 6, 12 or 24 months). Only sensitization to rye grass was associated with increased risk of eczema from 2 to 7 years of age (HR = 2.35, 1.01–5.44).

Eczema as a predictor of sensitization

At 1 year, an SPT was performed on 90.8% (415/457) of infants who had a negative SPT at 6 months (Fig. 1). At 2 years, an SPT was performed on 79.3% (275/347) of infants who had a negative SPT at both 6 and 12 months (Fig. 1). A new SPT reaction was observed in 16.4% of infants by 12 months, and in 14.2% between 1 and 2 years (Table 2).

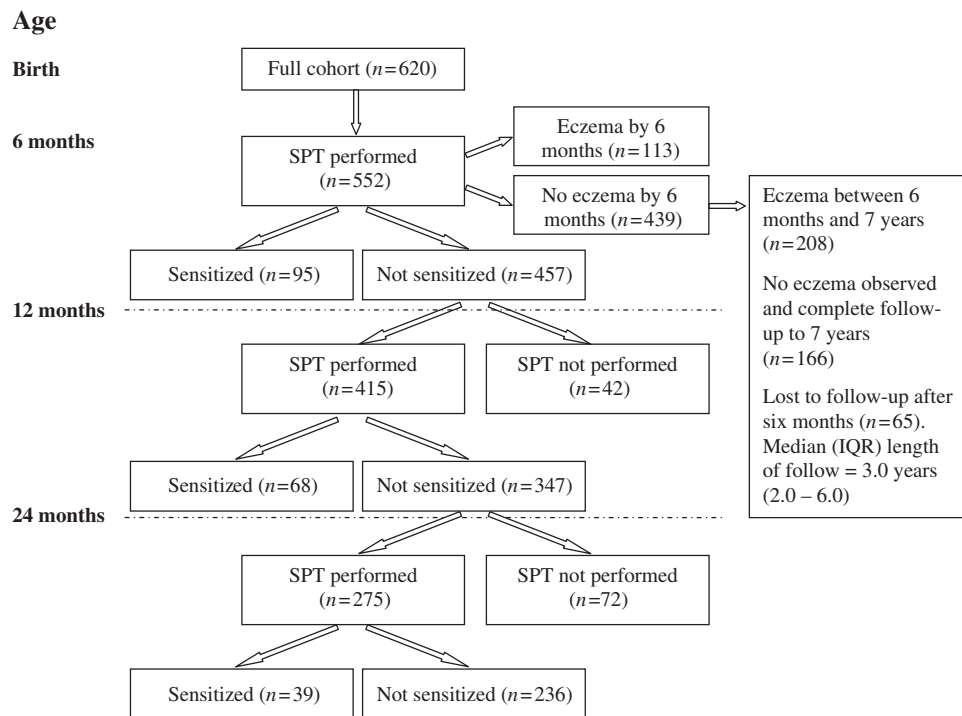
Eczema increased the risk of developing a new positive SPT result. After excluding infants who were sensitized at 6 months, eczema before 6 months was associated with increased risk of having a new sensitization both at 1 year (HR = 2.26, 95% CI = 1.34–3.82, 29.4% vs. 13.8%), where most new sensitizations were due to new food allergens, and at 2 years (HR = 3.19, 95% CI = 1.56–6.55, 29.3% vs. 10.6%) where most new sensitizations were due to new inhalant allergens (Table 2). There was no clear evidence of an association between onset of eczema between 6 and

Table 2. Frequency of SPT reaction at 6 months of age in the whole cohort ($n = 552$), and in infants without eczema ($n = 439$) by 6 months of age, and incidence of new SPT-positive results at 12 and 24 months

Allergen	6-month SPT results		1 and 2 year SPT results	
	Full cohort ($n = 552$)	No eczema by 6 months ($n = 439$)	12 month incidence ($n = 415$)*	24 month incidence ($n = 275$)†
Any food	88 (15.9%)	56 (12.8%)	47 (11.3%)	10 (3.6%)
Milk	23 (4.2%)	15 (3.4%)	6 (1.4%)	0 (0.0%)
Egg	63 (11.4%)	37 (8.4%)	35 (8.4%)	6 (2.2%)
Peanuts	36 (6.5%)	20 (4.6%)	26 (6.3%)	5 (1.8%)
Any inhalant	19 (3.4%)	8 (1.8%)	35 (8.4%)	35 (12.7%)
Mite	10 (1.8%)	4 (0.9%)	22 (5.3%)	21 (7.6%)
Cat	11 (2.0%)	5 (1.1%)	13 (3.1%)	6 (2.2%)
Rye grass	4 (0.7%)	3 (0.7%)	4 (1.0%)	10 (3.6%)
Any allergen	95 (17.2%)	60 (13.7%)	68 (16.4%)	39 (14.2%)

*Excludes any infant with a positive SPT result to any allergen at 6 months test.

†Excludes any infant with a positive SPT result to any allergen at 6 or 12-month tests.
SPT, skin prick test.

**Fig. 1.** Flow chart of participants.

12 months of age and risk of new sensitization by 2 years ($HR = 1.55$, 95% $CI = 0.65-3.69$). Apart from early onset eczema, there were no clear predictors of new sensitization, with the possible exception of paternal hayfever at 12 months ($HR = 1.65$, 95% $CI = 1.00-2.71$). Adjusting for paternal hayfever, parental eczema, infant gender and presence of older siblings did not alter the increased risk of new sensitization in infants with eczema in the first 6 months of life (adjusted $HR = 2.26$, 1.33–3.84, at 12 months, and adjusted $HR = 3.40$, 1.61–7.17, at 24 months).

Discussion

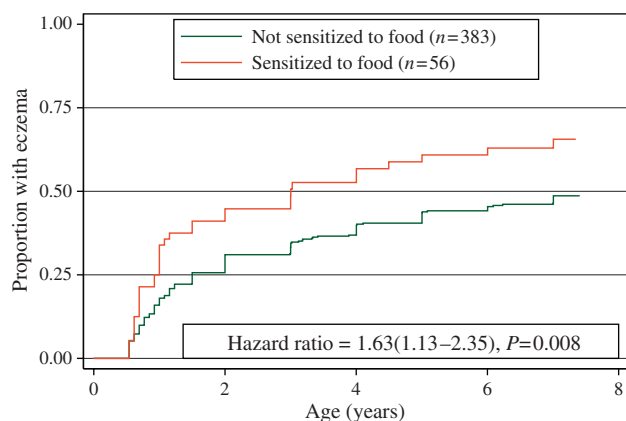
In asymptomatic infants, sensitization to common food allergens at 6 months of age is associated with a clearly increased risk of developing eczema. However, eczema before 6 months is also associated with an increased risk of developing a new positive-SPT response within the first 2 years of life. Thus, *sensitization can precede and predict the development of eczema*, and conversely *eczema can precede and predict the development of new sensitization*. Thus, we have identified at least two pathways to having

Table 3. Univariate associations between 6-month SPT reaction and subsequent incidence of eczema ($n = 439$) expressed as HRs (instantaneous relative risks) and 95% CIs

Allergen	Incidence of eczema*	
	HR (95% CI)	P
Any food	1.63 (1.13–2.35)	0.008
Milk	2.09 (1.17–3.74)	0.013
Egg	1.68 (1.09–2.59)	0.019
Peanuts	1.70 (0.97–2.98)	0.064
Any inhalant	0.52 (0.13–2.10)	0.359
Mite	0.56 (0.08–4.03)	0.568
Cat	0.37 (0.05–2.63)	0.319
Rye grass	0.82 (0.12–5.86)	0.844
Any allergen	1.54 (1.07–2.21)	0.019

*Excludes 113 infants with eczema before 6 months, and 68 infants who did not have a valid SPT performed at 6 months.

SPT, skin prick test; CI, confidence interval; HR, hazard ratio.

**Fig. 2.** Risk of developing eczema from 6 months to 7 years by sensitization to food allergens at 6-month skin prick test.

eczema with sensitization in infancy: either sensitization comes first, or eczema comes first.

When compared with previous research in this area, the current study has a number of strengths. The two possible theories concerning the association between eczema and sensitization have been explored and compared in one cohort, and evidence was found to support both pathways. This study demonstrates not only that infants with non-atopic eczema do have a high risk of subsequent sensitization [23] but also that this risk is greater than that of infants from the same population who do not have eczema. While others have shown that sensitization in early life is associated with greater risk of eczema during follow-up [12, 14–16], this is the first study to explicitly examine the predictive value of SPT on the *incidence* of these diseases in asymptomatic infants. This was possible due to the frequent follow-up of this cohort and repeated use of SPTs to a standard battery of allergens. The association between SPT at 12 and 24 months of age and

Table 4. Relationship between size and number of SPT reactions to *food allergens* at 6 months and incidence of eczema ($n = 439$) expressed as HR (instantaneous relative risk)

	HR (95% CI)
Weal size	
2 mm ($n = 26$)	0.79 (0.42–1.50)
3 mm ($n = 15$)	1.34 (0.69–2.63)
4–5 mm ($n = 20$)	1.30 (0.70–2.39)
≥ 6 mm ($n = 21$)	2.28 (1.34–3.87)
Number of reactions	
1 reaction ($n = 43$)	1.53 (1.10–2.12)
2 reactions ($n = 10$)	2.79 (1.75–4.46)
3 reactions ($n = 3$)	4.73 (2.10–10.66)

SPT, skin prick test; CI, confidence interval; HR, hazard ratio.

development of eczema after these times was not clear. The majority of the associations were in the same direction and magnitude as those seen for the 6-month analysis, but the power to demonstrate a difference was much less. Lack of statistical power may explain why previous studies have not reported the predictive value of allergic sensitization for the development of new onset eczema, as some of the largest previous studies only assessed allergic sensitization for the first time at 12 months of age when a large proportion of eczema was already manifested [24].

These findings support the hypothesis that skin barrier dysfunction associated with eczema is a key mechanism for the establishment of sensitization. It is likely that infants who progressed from eczema to sensitization have primary barrier deficiency that allows for allergen absorption into the skin, resulting in sensitization. This could be due to filaggrin deficiency [8] or other skin defects, but this requires further investigation. It is interesting to note that eczema in the first 6 months is associated with an increased risk of sensitization at 12 months, when new sensitization is predominantly due to *food allergens*, and at 24 months when new sensitization is predominantly due to *inhalant allergens*. Sensitization to food allergens may be induced by ingestion, as well as by dermal contact, as the mucosal barrier has been reported to be impaired in eczema [4, 5].

This study also provides evidence that sensitization is a possible cause for eczema. If all sensitization was simply a consequence of damage to the barrier function due to eczema, we should not have observed that sensitization to food allergens preceded and predicted the clinical manifestation of eczema in some infants. Infants who follow this pathway may be sensitized via the gastro-intestinal tract, or have persistent T helper 2 (Th2) immunity, and eczema is one of its consequences. Infants with the largest weals and the greatest number of reactions on the 6-month SPT were at the greatest risk of developing eczema. We observed that infants with SPT weals of 6 mm or

greater to food allergens had the highest risk of developing eczema. Such large SPT responses have previously been shown to have a high positive predictive value for food allergy, as determined by food challenge [25]. The development of eczema in these infants most likely occurred on subsequent exposure to the offending allergen. It appears unlikely that skin reactivity, rather than allergic sensitization, is the marker for the development of eczema, as we did not find any clear relationship between the size of reaction to the histamine control and the risk of subsequent eczema. We have previously used a 2 mm cut point as defining a positive-SPT result in this cohort [19], but there was no clear increase in risk of subsequent eczema for infants with a weal diameter of 2 mm.

This analysis has some limitations. The present study defined eczema as either a doctor diagnosis of eczema or any rash (excluding rash that only affected the nappy region or scalp) that was treated with topical steroid-based preparations. This is a convenient definition of eczema that should exclude most seborrhoeic dermatitis and nappy rash. However, it is likely that some misclassification of infants occurred using this definition. Infants with very mild eczema may not have been identified. Other infants who did not have eczema may have been misdiagnosed as having eczema or had topical steroid preparations applied to their skin. Unfortunately, we did not examine the infants at the time of the SPT to confirm the diagnosis of eczema or on every occasion that a rash was identified by telephone interview. However, even if we had, we would still have faced two problems: firstly, eczema can be a transient phenomenon, so even if the infant was free of eczema at the time of examination, we could not be sure he/she did not previously have it. Secondly, despite there being a range of definitions of eczema currently in use [26, 27], none have been validated in infants and children under the age of 2 years. Even dermatologists do not universally agree on what constitutes eczema in this age group. As we only used the six most common allergens [28, 29] for SPT, we cannot exclude the possibility that infants were sensitized to other allergens. Misclassification of infants as not being sensitized (false negatives) may have strengthened the observed association between early eczema and risk of new SPT positivity. It is likely that infants with eczema by 6 months were more likely to be sensitized to untested allergens and sensitization to untested allergens increased the risk of becoming sensitized to one of the six tested allergens. However, if this misclassification has occurred, the association between the SPT result at 6 months and the risk of developing eczema is an underestimate, as sensitized infants would have been analysed in the non-sensitized group.

Parents and family doctors of infants were not blinded to the results of 6-month SPT. Therefore, we cannot

exclude the possibility that early sensitization altered the interpretation of possibly atopic symptoms, and therefore altered the likelihood of a diagnosis of eczema or the use of topical steroids. However, given the strength of the association between sensitization and risk of developing these diseases and the biological plausibility, we feel that detection bias cannot fully explain our observation. Also, the research nurses who performed the SPT had knowledge of the clinical manifestations of allergy, making it possible for them to interpret an ambiguous SPT result (e.g. 2.5 mm) as positive in those infants who had already developed eczema. Such infants would have been classified as having both eczema and sensitization, thus excluding them both from the analyses of SPT as a predictor of the incidence of eczema, and of eczema as a predictor of sensitization. This possible misclassification may have led to exclusion of infants and a reduction in statistical power, but cannot explain the observed results. The MACS was a birth cohort of high-risk children due to a family history of allergic disease, making them more likely to develop both allergic sensitization and allergic diseases than a normal-risk birth cohort. Moreover, an attempt was made to modify the early dietary intake of these infants [19], which may have altered the development of allergic sensitization. This limits the generalizability of our findings and further replication in other populations is needed. However, these design issues do not alter the main finding that sensitization can precede and predict the development of eczema, and eczema can precede and predict the development of sensitization.

A final limitation is that it is possible that sensitization and atopic disease are simply two manifestations of the action of the same or related genes, or some other underlying mechanism, and that the associations that we have observed are not causal in nature. Unfortunately, we were not able to address this possibility with the available data.

Conclusions and recommendations

In infants with a family history of atopic disease, early eczema is associated with an increased risk of developing sensitization, but sensitization can also precede and predict the development of eczema. As such, there appears to be at least two pathways to sensitization with eczema in infants. Further research is required to determine if the pathway to eczema with sensitization influences its severity, prognosis or the risk of developing asthma and allergic rhinitis. It is quite likely that these different pathways indicate different underlying genetic and environmental determinants. It remains to be determined if targeted interventions can prevent the progression from eczema to sensitization, such as the use of specialized emollients [30], or the progression from sensitization to atopic disease.

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