

## ORIGINAL PAPER

# Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis

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## Clinical and Experimental Allergy

### Summary

**Background** Assessment of allergic sensitization is not routinely performed in infants and young children with eczema.

**Objective** To determine whether infants who have atopic eczema (with sensitization) are at a greater risk of developing asthma and allergic rhinitis (AR) than those with non-atopic eczema (without concurrent sensitization).

**Methods** The presence of eczema was prospectively documented until 2 years of age in a birth cohort of 620 infants with a family history of atopic disease. Sensitization status was determined by skin prick tests (SPTs) at 6, 12, and 24 months using six common allergens. Interviews were conducted at 6 and 7 years to determine the presence of asthma and AR.

**Results** Within the first 2 years of life, 28.7% of the 443 children who could be classified had atopic eczema: 20.5% had non-atopic eczema, 19.0% were asymptomatic but sensitized and 31.8% were asymptomatic and not sensitized. When compared with children with non-atopic eczema in the first 2 years of life, children with atopic eczema had a substantially greater risk of asthma [odds ratio (OR) = 3.52, 95% confidence interval = 1.88–6.59] and AR (OR = 2.91, 1.48–5.71). The increased risk of asthma was even greater if the infant had a large SPT (OR = 4.61, 2.34–9.09) indicative of food allergy. There was no strong evidence that children with non-atopic eczema had an increased risk of asthma or AR compared with asymptomatic children.

**Conclusion** In children with eczema within the first 2 years of life, SPT can provide valuable information on the risk of childhood asthma and AR.

**Keywords** allergy prevention, asthma, atopic disease, eczema, skin prick test

*Submitted 9 May 2007; revised 23 July 2007; accepted 30 July 2007*

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### Introduction

Eczema is a burdensome condition, for both the child and their family, and can be associated with a substantial reduction in quality of life [1]. Eczema affects between 10% and 20% of children in developed countries [2], and symptoms occur within the first year of life in approximately 60% of cases [3]. Eczema is commonly, although not always, associated with allergic sensitization, as measured by either a skin prick test (SPT) or specific serum IgE [4]. Food [5] and inhalant [6] allergens can cause exacerbations of eczema and avoidance can reduce the severity of disease. Despite this, testing for allergic sensi-

tization in infants and children with eczema is not routinely performed, and current guidelines on the management of eczema do not explicitly recommend testing for allergic sensitization [7, 8]. The majority of cases of childhood eczema are managed in the primary care setting where a range of effective treatments are available (emollients and topical corticosteroids). As assessment of allergic sensitization is limited outside of specialist allergy centres, which generally requires a referral and a long waiting period for an appointment; it is not surprising that children with eczema are rarely allergy tested.

A major concern is that children with eczema are at an increased risk of developing asthma [9]. It has been

suggested that atopic eczema (with sensitization) is associated with a greater risk for development of asthma than non-atopic eczema (without sensitization). Atopic and non-atopic eczema cannot be distinguished by physical examination alone. Previous studies have suggested that distinguishing between them using SPT may provide a better estimate of the subsequent risk of an infant developing asthma and allergic rhinitis (AR) [10–13]. However, it is difficult to draw firm conclusions from the past studies due to the methods used: assessment of allergic sensitization was performed at various ages, comparison of children with atopic and non-atopic eczema groups has been made with a third poorly defined group rather than directly against each other, lack of adjustment for possible confounders including severity of eczema, and lack of statistical power [14].

We aimed to determine whether SPT infants and children with eczema can aid in determining their risk of childhood asthma and AR.

## 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 has been described in more detail elsewhere [15, 16]. Informed consent was obtained from all mothers. Mercy Maternity Hospital's Human Research Ethics Committee approved this research. Infants were eligible to be enrolled in MACS if one or more of their first-degree family members had eczema, asthma, AR, or severe food allergy. An allergy-trained nurse conducted a telephone survey every 4 weeks until the infant was 64 weeks of age, and then at 78 weeks, 2 years, and annually until 7 years of age.

SPT were performed at 6, 12, and 24 months according to a standard technique [17]. A single drop of each allergen extract was placed on the infant's back, and the skin was pricked using a lancet. Allergen extracts used were cow's milk, egg white, peanut, house dust-mite, rye grass and cat dander (Bayer, Spokane, WA, USA). Both a negative (saline) and a positive (histamine 1 mg/mL) control were used. The SPTs were read at 15–20 min.

### *Definitions*

For the purpose of this study, infants were defined as children under the age of 2 years. A positive SPT was defined as a weal of at least 3 mm (mean) diameter greater than the negative saline control. Eczema in the first 2

years of life was defined as a parental report of 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 [18, 19].

Infants were allocated into four exclusive groups based on their SPT results and the presence of eczema in the first 2 years of life. Infants who had eczema and one or more positive SPT results were classified as having 'atopic eczema'. Infants who had eczema but had negative SPT results on all three occasions were classified as having 'non-atopic eczema'. Infants who had one or more positive SPTs but did not have eczema were classified as being 'asymptomatic-sensitized'. Finally, infants who did not develop eczema or sensitization were classified as 'asymptomatic'.

### *Outcome measures*

The primary outcomes were the presence of asthma, and AR in the previous 12 months was measured at 6 and 7 years of age. Asthma was defined as one or more events of wheezing illness attributed to asthma by the family physician. AR was defined as one or more episodes of nasal discharge and/or congestion, in the absence of an upper respiratory tract infection, which either the family physician or parent attributed to hayfever and required treatment with an anti-histamine and/or nasal steroid. A secondary analysis was performed to examine the risk of asthma and AR in the previous 12 months from 3 to 7 years in those infants with complete follow-up.

### *Statistical analysis*

The association between group (asymptomatic, atopic eczema, non-atopic eczema and asymptomatic sensitized) and a range of baseline demographic factors was assessed using  $\chi^2$  tests for nominal data, and by a Kruskal–Wallis test for ordinal data. The risks of having asthma and AR in the previous year at 6 and 7 years of age were each analysed using generalized estimating equations in order to allow for repeated measures on the same subject at the two time-points [20]. Results are reported as odds ratios (ORs) from logistic regression models. We did not include outcomes measured between 3 and 5 years, as a significant proportion of reported wheeze during this time would not be asthma [21]. As our aim was to determine whether the use of SPT for infants with eczema could aid in determining their risk of childhood asthma and AR, the primary comparison was between infants with atopic eczema and those with non-atopic eczema (reference group). Outcomes for asymptomatic and asymptomatic-sensitized infants were included as secondary comparisons. Infants were excluded from the analysis if it was not possible to determine group due to missing SPT data or follow-up data.

Adjustments for the following variables were made for all models: presence of atopic diseases in either parent, infant gender, presence of older siblings, parental smoking within the last 6 months at the time of recruitment (during pregnancy), and severity of eczema (measured by total number of days of topical steroid use for rash in the first 2 years of life, excluding rash only on the scalp or nappy region). The following variables were included in the final model if they caused significant confounding (15% or greater change in the association between the eczema type and the outcome) or predicted the outcome ( $P < 0.05$  for the confounder effect in the multivariable model): maternal and paternal age and years of education, use of gas heating and cooking in the home and pet exposure.

Tests for interactions between type of eczema and the following baseline factors were performed: infant gender, presence of a wheezing condition in the first 2 years of life and parental history of atopic disease. Stata (release 9.2, Stata Corporation, College Station, TX, USA) was used for all statistical analysis.

## Results

### Study population

Most infants (470/620) enrolled in MACS had two or more family members with an atopic disease, and a minority of mothers (39/620) and fathers (112/615) were current smokers at the time of gestation. Further details of the cohort have been published elsewhere [15, 16, 19].

We were able to classify 71.5% ( $n = 443/620$ ) children into one of the four predefined groups, while the remain-

ing children did not have sufficient data to determine whether they had eczema or sensitization (50 had insufficient data to determine whether they had eczema during the first 2 years of life, and 127 more children (60 with and 67 without eczema) missed one or more scheduled SPT and had negative results at all sessions when they were tested). Of the children who could be classified, approximately a third (31.8%,  $n = 141$ ) were asymptomatic. Half the children had eczema (49.2%,  $n = 218$ ), and of these there were slightly more cases of atopic eczema (58.3%,  $n = 127$ ) than non-atopic eczema (41.7%,  $n = 91$ ). The remaining 84 children (19.0%) were asymptomatic but sensitized.

### Characteristics of type of eczema

Children with atopic eczema were more likely to have their eczema manifest in the first 6 months of life than children with non-atopic eczema [55.1% vs. 31.9%, 95% confidence interval (CI) for difference 10.3 to 36.1%] (Table 1). There were no clear differences between the groups on breastfeeding, child care use, or environmental tobacco smoke exposure, and most of the parents reported atopic diseases. However, infants with atopic eczema were somewhat more likely to be male and to have a father with a history of eczema, compared with those with non-atopic eczema.

### Outcomes at 6 and 7 years

A childhood follow-up at 6 or 7 years of age was completed on 91.0% (403/443) of children who could be classified into a group, and 65% (403/620) of the total

Table 1. Description of infants with atopic and non-atopic eczema, as well as asymptomatic and asymptomatic sensitized infants, in the first 2 years of life

|                                               | Group                             |                                |                               |                                         |
|-----------------------------------------------|-----------------------------------|--------------------------------|-------------------------------|-----------------------------------------|
|                                               | Non-atopic eczema<br>( $n = 91$ ) | Atopic eczema<br>( $n = 127$ ) | Asymptomatic<br>( $n = 141$ ) | Asymptomatic-sensitized<br>( $n = 84$ ) |
| % males                                       | 39.6                              | 52.0                           | 54.6                          | 57.1                                    |
| % with eczema in first 6 months               | 31.9                              | 55.1                           | –                             | –                                       |
| Median (IQR) weeks of exclusive breastfeeding | 12 (1–22)                         | 16 (3–20)                      | 14 (3–19)                     | 15.5 (2–20)                             |
| Median (IQR) weeks of any breastfeeding       | 49 (28–64)                        | 44 (27.5–64)                   | 44 (24–60)                    | 47 (24–60)                              |
| % attended child care in first year           | 46.9                              | 48.3                           | 48.2                          | 50.6                                    |
| % any ETS exposure in the first 2 years       | 13.2                              | 15.8                           | 16.3                          | 16.7                                    |
| % antenatal ETS exposure                      | 17.6                              | 20.5                           | 19.2                          | 17.9                                    |
| % maternal asthma                             | 41.1                              | 41.7                           | 41.1                          | 48.8                                    |
| % paternal asthma                             | 31.5                              | 32.5                           | 17.0                          | 27.7                                    |
| % maternal eczema                             | 47.8                              | 45.7                           | 36.2                          | 32.1                                    |
| % paternal eczema                             | 18.0                              | 27.8                           | 17.7                          | 24.1                                    |
| % maternal allergic rhinitis                  | 55.6                              | 62.2                           | 56.7                          | 61.9                                    |
| % paternal allergic rhinitis                  | 49.4                              | 54.8                           | 34.0                          | 51.8                                    |

IQR, inter-quartile range; ETS, environmental smoke exposure.

cohort. Children who contributed to the final analysis did not clearly differ from those who did not, in terms of the presence of eczema within the first 6 months (OR = 1.40, 95% CI = 0.90–2.18), sex (OR = 0.96, 95% CI = 0.68–1.34), or presence of any parental history of allergic diseases. Asthma was present in 28.1% and 28.6% of the children at 6 and 7 years, while AR was present in 17.3% and 21.0% of the children at these ages. A total of 58 children had both asthma and AR during childhood (44.6% of all children with asthma, and 56.9% of all children with AR). Owing to the substantial overlap between these conditions, there are some similarities between the findings of the two analyses.

#### *Association between eczema type in early childhood and the risk of childhood asthma and allergic rhinitis*

Infants with atopic eczema had a greater risk of having childhood asthma (OR = 3.52, 95% CI = 1.88–6.59) and AR (OR = 2.91, 95% CI = 1.48–5.71) than infants with non-atopic eczema (Tables 2 and 3). Having both asthma and AR was much more common in children who had experienced infantile atopic eczema (OR = 6.30, 95% CI = 2.35–16.88) than children who had had non-atopic eczema. The increased risk of asthma associated with atopic eczema was clear at all follow-up times, while the increased risk of AR was only apparent from the age of 5 years (data not shown). Infants with non-atopic eczema did not have a clearly different risk of asthma and AR in childhood than asymptomatic infants (Tables 2 and 3). When compared with asymptomatic-sensitized infants,

infants with non-atopic eczema had a lower risk of having asthma and possibly AR. The increased risk associated with atopic eczema remained clear for asthma (aOR = 2.60, 95% CI = 1.32–5.14) and AR (aOR = 2.61, 1.28–5.30), after adjustment for a range of possible confounders, including the severity of eczema during the first 2 years (Tables 2 and 3). Adjustment for severity did somewhat attenuate the associations, particularly for childhood asthma, where there was a 26% decline in the OR. Infants with atopic eczema who had large SPT weals, indicative of food allergy [22], had a greater risk of asthma (OR = 2.13, 1.01–4.50), but not AR (OR = 0.92, 0.45–1.91) when compared with infants with atopic eczema with smaller SPT weals. Infants with large SPT weals had approximately a 4.5-fold increased risk of childhood asthma (OR = 4.61, 2.34–9.09) when compared with infants with non-atopic eczema. Also, of the children with atopic eczema, those whose eczema commenced within the first 6 months were marginally more likely to have asthma in childhood than those whose eczema commenced from 6 to 24 months of age (OR = 1.76, 0.86–3.59). There were no clear interaction effects between the type of eczema and sex, early-onset wheeze, or a parental history of atopic disease, in models for the risk of childhood asthma and AR (all *P* values > 0.1).

The temporal sequence of onset of the sensitization and eczema could be determined in 48% (62/127) of the atopic eczema group. Slightly more infants developed eczema before sensitization (*n* = 37) rather than sensitization before eczema (*n* = 25). The sequence of sensitization and eczema was not clearly associated with the risk of

**Table 2.** Risk of childhood asthma by sensitization and eczema group in the first 2 years of life

|                                                                           | Group             |                  |                  |                         |
|---------------------------------------------------------------------------|-------------------|------------------|------------------|-------------------------|
|                                                                           | Non-atopic eczema | Atopic eczema    | Asymptomatic     | Asymptomatic-sensitized |
| <b>Unadjusted associations</b>                                            |                   |                  |                  |                         |
| 6 years % ( <i>n</i> )                                                    | 21.8 (17/78)      | 47.8 (53/111)    | 14.3 (19/133)    | 30.3 (23/76)            |
| 7 years % ( <i>n</i> )                                                    | 17.4 (12/69)      | 44.6 (45/101)    | 13.6 (16/118)    | 42.0 (29/69)            |
| OR (95% CI)*                                                              | 1                 | 3.52 (1.88–6.59) | 0.63 (0.31–1.27) | 2.19 (1.11–4.32)        |
| <i>P</i>                                                                  | –                 | < 0.001          | 0.201            | 0.025                   |
| <b>Adjusted associations†</b>                                             |                   |                  |                  |                         |
| OR (95% CI)*                                                              | 1                 | 2.60 (1.32–5.14) | 0.73 (0.35–1.54) | 2.36 (1.14–4.90)        |
| <i>P</i>                                                                  | –                 | 0.006            | 0.410            | 0.021                   |
| <b>Unadjusted associations after excluding infants with early wheeze‡</b> |                   |                  |                  |                         |
| 6 years % ( <i>n</i> )                                                    | 14.8 (8/54)       | 31.0 (18/58)     | 8.2 (8/97)       | 16.0 (8/50)             |
| 7 years % ( <i>n</i> )                                                    | 12.2 (6/49)       | 30.8 (16/52)     | 5.8 (5/86)       | 23.3 (10/43)            |
| OR (95% CI)*                                                              | 1                 | 2.92 (1.22–7.00) | 0.50 (0.18–1.36) | 1.52 (0.58–3.99)        |
| <i>P</i>                                                                  | –                 | 0.016            | 0.174            | 0.395                   |

\*Repeated measures analysis.

†Variables adjusted for were: severity of eczema in the first 2 years as measured by the number of days of topical steroid treatment used, sex, maternal and paternal history of asthma and eczema, and parental smoking within the last 6 months at the time of recruitment. Data missing on confounders for three children who have been excluded.

‡Unadjusted association after excluding infants diagnosed with an asthma-like condition before 2 years of age.

CI, confidence interval; OR, odds ratio.

Table 3. Risk of childhood allergic rhinitis by sensitization and eczema group in the first 2 years of life

|                                                                                | Group             |                  |                  |                         |
|--------------------------------------------------------------------------------|-------------------|------------------|------------------|-------------------------|
|                                                                                | Non-atopic eczema | Atopic eczema    | Asymptomatic     | Asymptomatic-sensitized |
| Unadjusted associations                                                        |                   |                  |                  |                         |
| 6 years % (n)                                                                  | 10.3 (8/78)       | 27.0 (30/111)    | 11.3 (15/133)    | 21.1 (16/76)            |
| 7 years % (n)                                                                  | 15.9 (11/69)      | 34.7 (35/101)    | 9.3 (11/118)     | 26.1 (18/69)            |
| OR (95% CI)*                                                                   | 1                 | 2.91 (1.48–5.71) | 0.79 (0.38–1.68) | 2.04 (0.98–4.27)        |
| P                                                                              | –                 | 0.002            | 0.548            | 0.058                   |
| Adjusted associations <sup>†</sup>                                             |                   |                  |                  |                         |
| OR (95% CI)*                                                                   | 1                 | 2.61 (1.28–5.30) | 0.70 (0.32–1.52) | 1.61 (0.75–3.47)        |
| P                                                                              | –                 | 0.008            | 0.365            | 0.225                   |
| Unadjusted associations after excluding infants with early wheeze <sup>‡</sup> |                   |                  |                  |                         |
| 6 years % (n)                                                                  | 9.3 (5/54)        | 24.1 (14/58)     | 8.2 (8/97)       | 16.0 (8/50)             |
| 7 years % (n)                                                                  | 12.2 (6/49)       | 28.8 (15/52)     | 8.1 (7/86)       | 18.6 (8/43)             |
| OR (95% CI)*                                                                   | 1                 | 2.75 (1.14–6.64) | 0.74 (0.29–1.91) | 1.71 (0.66–4.44)        |
| P                                                                              | –                 | 0.024            | 0.532            | 0.273                   |

\*Repeated measures analysis.

<sup>†</sup>Variables adjusted for were: severity of eczema in the first 2 years as measured by the number of days of topical steroid treatment used, sex, maternal and paternal history of asthma and eczema, and parental smoking within the last 6 months at the time of recruitment. Data missing on confounders for three children who have been excluded.

<sup>‡</sup>Unadjusted association after excluding infants diagnosed with an asthma-like condition before 2 years of age.

CI, confidence interval; OR, odds ratio.

childhood asthma (OR = 1.43, 0.50–4.09) or AR (OR = 1.12, 0.43–3.34).

#### *Effect of excluding infants with early wheeze*

Infants with atopic eczema were more likely to wheeze in the first 2 years of life (47.8%) than infants with non-atopic eczema (30.0%, 95% CI of difference = 4.2–31.4%). To ensure that the observed increased risk of asthma and AR associated with atopic eczema was not due to concomitant early wheeze, we excluded all infants who were diagnosed with an asthma-like condition in the first 2 years (Tables 2 and 3). Atopic eczema remained a risk factor for asthma and AR after excluding infants with early wheeze, but removing them did attenuate the association with asthma.

#### *Sensitivity analysis*

Two forms of sensitivity analysis were undertaken. The first was to modify the definition of eczema in infancy to be a doctor diagnosis only rather than a doctor diagnosis or use of topic steroid treatment for rash. The results remained largely unchanged, with a possible increase in the magnitude of difference between infants with atopic vs. non-atopic eczema, if this stricter definition of eczema was used (data not shown).

The second sensitivity analysis assessed the effect of different assumptions about missing SPT data. The difference between the groups was increased if it was assumed that all the infants with missing SPT data were not

sensitized, and decreased if it was assumed that all these infants were sensitized (data not shown). However, the overall conclusion that atopic eczema in infancy conferred a greater risk of asthma and AR than non-atopic eczema was not altered by these 'extreme-case' assumptions concerning the missing SPT results.

#### **Discussion**

Eczema is a very common clinical presentation and parents are often concerned that their child will develop asthma and 'hayfever'. Our results show that infants with atopic eczema in the first 2 years of life have a greater risk of childhood asthma and AR than infants with non-atopic eczema. Infants with non-atopic eczema did not have a clearly increased risk of childhood allergic respiratory conditions when compared with asymptomatic infants. These findings suggest that in infants with eczema, SPT is useful in determining the risk of childhood asthma and AR.

These findings are largely in agreement with previous literature [10, 11, 13], which has found that atopic eczema is associated with an increased risk of asthma and AR when compared with non-atopic eczema. However, unlike previous studies that have made indirect comparisons by way of a third group [13], we have directly compared atopic and non-atopic eczema groups in a large cohort, both in terms of their predictors and their association with childhood asthma and AR. This has allowed us to draw stronger conclusions concerning differences between the types of eczema. By adjusting for the severity of eczema, we also have evidence that the effect of atopic eczema is

not simply due to a positive SPT result being more common in infants with severe eczema [18, 23, 24]. Moreover, by excluding infants with a wheezing condition within the first 2 years of life, we have confirmed that the association between atopic eczema and increased risk of asthma and AR was not simply due to co-manifestation of eczema with wheeze. As all the children in this cohort had a family history of allergic disease, we were not able to see any interactions between eczema type and a parental history of atopic disease, due to a lack of a reference group without a family history. Given the findings that the effect of breastfeeding on risk of asthma varies between children with and without a family history [25], the possibility of such an interaction effect should be further explored using population-based cohorts.

There are a number of benefits associated with performing SPTs on eczematous infants. If a young child is currently consuming, and apparently tolerating, a particular food but has a positive SPT to that food, it may indicate a previously unidentified cause for the eczema. Constant low-dose exposure to the food can induce mild non-specific symptoms that are difficult to associate with the exposure. However, elimination of the food can result in clearing of the eczema, and severe reactions on re-exposure [26]. Where a positive SPT to a food allergen is detected to a food that is currently being consumed, a diagnostic elimination diet should be considered. A therapeutic elimination diet should only be suggested after a positive response to an oral food challenge. If these measures fail to reveal a specific response to the food, then the positive SPT should be ignored and treated as clinically unimportant.

Our observations indicate that the main risk factor for childhood asthma and AR is not eczema *per se*, but sensitization in early life. We have previously noted in this cohort that eczema can precede and predict allergic sensitization, while allergic sensitization can precede and predict new-onset eczema [19]. We argued that this may represent two groups of children with atopic eczema: one where there is a primary barrier dysfunction, such as filaggrin deficiency [27], which results in eczema, followed by allergic sensitization due to allergen absorption via damaged skin. The second group in whom sensitization precedes the development of eczema may be sensitized via the gastro-intestinal tract, or may have persistent T helper type 2 (Th2) immunity, and eczema is one of its consequences. The risk of asthma and AR was similar between infants whose eczema preceded allergic sensitization and those infants who developed allergic sensitization before eczema. Moreover, we have shown that the risk in those infants who were sensitized but did not have eczema approached that of the atopic eczema group, while the non-atopic eczema group showed no clear increased risk compared with the asymptomatic group (no eczema or sensitization). As such, atopy in early life is the risk

factor for childhood asthma and AR, independent of its association with eczema.

Having said that atopy is the main risk factor for allergic respiratory conditions in childhood rather than eczema, it is currently not feasible to perform SPT on all infants as a population-wide screening programme. Performing opportunistic SPT on infants with eczema who present to primary care physicians may be a useful tool in identifying sensitized infants, particularly in those with a family history of allergic disease, who are therefore at a much greater risk of asthma and AR.

If it is assumed that there is a causal association between atopic eczema and childhood allergic respiratory conditions; SPT eczematous infants would allow for targeted interventions to prevent high-risk children from developing these conditions. However, this causal role has recently been questioned, with some arguing that there may be a co-manifestation of wheeze and eczema in early life, rather than a simple atopic march from eczema to asthma and AR [28]. Given our observation that the increased risk of asthma associated with atopic eczema groups persists even after excluding infants with an early wheezing syndrome, it remains reasonable to consider possible interventions to prevent the progression from eczema to childhood asthma. Reduction in allergen exposure is one such approach, as it has been observed that children sensitized under the age of 3 have a more rapid loss of lung function if exposed to high levels of perennial allergen (house dust mite, cat, and dog) [29]. There is good evidence that allergen immunotherapy is an effective treatment of asthma [30], and can reduce the progression from seasonal rhino-conjunctivitis to asthma [31], but it has not yet been established whether such a treatment could prevent the progression from atopic eczema to asthma.

This study has a number of limitations. SPT was performed using six of the most common allergens for the region [32]. We cannot be sure that infants were not sensitized to untested allergens. Cross-reactivity between the tested allergens with untested allergens [33, 34] may have partially reduced the number of missed cases. The definition of eczema used in this study (doctor diagnosis or use of topical steroid treatment) is a convenient one, but it has not been validated. The conclusions of this work could have been strengthened if the infants' skin was examined for objective evidence of eczema. However, even if this was done, despite there being a range of definitions of eczema currently in use (such as the Hanifin and Rajka [35] and UK working party definition [36]), none have been validated in children under the age of 2 years. Most cases of seborrhoeic dermatitis and nappy rash would have been excluded using this definition of eczema, but it may have incorrectly labelled some infants who had non-eczematous rashes. The sensitivity analysis that used a doctor diagnosis of eczema to define infant

eczema showed that using this stricter definition (more specific but less sensitive) provided very similar results. Also, a convenient definition of asthma and AR was used, based on parental report of a doctor diagnosis. This definition does not divide asthma into atopic and non-atopic or according to the sub-categories based on inflammatory markers [37]. These possible misclassifications will have resulted in an underestimate of the true associations between atopic eczema and the risk of asthma and AR. However, we are not able to exclude the possibility that the parents', or child's doctor's, knowledge of the SPT results may have influenced the subsequent diagnosis of asthma and AR, which would have led to us overestimating the association between atopic eczema and the risk of these outcomes.

The sampling frame and loss to follow-up of this study may limit the generalisability of these findings. All infants enrolled in this cohort had a family history of allergic disease, and as such, the presence of both genetic and environmental risk factors for allergic diseases will have been greater than that found in a general population. This will have resulted in higher rates of allergic diseases being expressed in this cohort, but it is unclear how this could have influenced the association between atopic eczema and the risk of childhood asthma and AR. The analysis was performed on approximately 65% of the cohort. We were not able to identify any evidence of selective attrition, as there were no clear differences found between the children who contributed to this analysis and those who did not. Furthermore, a sensitivity analysis confirmed the conclusion that atopic eczema is a substantial risk factor for asthma, regardless of the assumptions made about missing SPT data.

### Conclusions and recommendations

Assessment of allergic sensitization in infants with eczema to determine whether it is atopic or non-atopic provides valuable information on the risk of childhood asthma and AR. Identification of high-risk infants will allow for preventive strategies to be explored. Future research on predictors and outcomes of eczema should avoid combining infants with these two types of eczema as it is possible that any effects will be obscured due to differences between the two phenotypes.

### Acknowledgements

We wish to thank Dr John Thorburn, FRACP, for assistance in patient recruitment and administrative assistance, the Mercy Hospital Department of Obstetrics for participant recruitment, Christine Axelrad for assistance with data collection, and Anne Balloch for data management. Adrian Lowe is supported by Dairy Australia, CRC for Asthma and VicHealth. Initial development of MACS was

supported by Nestlé Australia, while the Asthma Foundation of Victoria supported the 10-year follow-up.

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