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Lowe, AJ;Angelica, B;Su, J;Lodge, CJ;Hill, DJ;Erbas, B;Bennett, CM;Gurrin, LC;Axelrad, C;Abramson, MJ;Allen, KJ;Dharmage, SC

Title:
Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age

Date:
2017-06-01

Citation:
Lowe, A. J., Angelica, B., Su, J., Lodge, C. J., Hill, D. J., Erbas, B., Bennett, C. M., Gurrin, L. C., Axelrad, C., Abramson, M. J., Allen, K. J. & Dharmage, S. C. (2017). Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age. Pediatric Allergy and Immunology, 28 (4), pp.384-390. https://doi.org/10.1111/pai.12714.

Persistent Link:
https://hdl.handle.net/11343/292861

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Received Date : 03-Oct-2016

Revised Date : 22-Feb-2017

Accepted Date : 13-Mar-2017

Article type : Original

Title: Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age

Running title: Eczema and allergic airways disease

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12714

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Word count: 2500

Number of tables: 5

Number of figures: 1

Abstract

Background: Few studies have simultaneously addressed the importance of age of onset and persistence of eczema for the subsequent development of asthma and hay fever, particularly into early adulthood.

Methods: A high risk birth cohort was recruited comprising 620 infants, who were then followed up frequently until two years of age, annually from age 3 to 7, then at 12 and 18 years, to document any episodes of eczema, current asthma and hay fever. The generalised estimation equation technique was used to examine asthma and hay fever outcomes at 6 (n=325), 12 (n=248) and 18 (n=240) years, when there was consistency of associations across the follow-ups.

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Results: Very early-onset persistent (onset <6 months, still present from 2 to 5 years) eczema was related to current asthma (adjusted OR=3.2 [95%CI=1.7-6.1]), as was very early onset remitting eczema (onset <6 months but not present from 2-5 years, OR=2.7, 95%CI=1.0-7.2) and early onset persistent eczema (onset from 6-24 months, OR=2.3, 95%CI=1.2-4.7). Late onset eczema (commenced from 2-5 years) was associated with increased risk of asthma at 12 years (OR=3.0, 95%CI=1.1-8.2) but not at age six years. Only very early onset persistent eczema was associated with increased risk of hay fever (aOR=2.4, 95%CI=1.4-4.1).

Conclusion & Clinical relevance: Eczema which commences in early infancy and persists into toddler years is strongly associated with asthma, and to a lesser extent hay fever, in high risk children. If these associations are causal, prevention of early life eczema might reduce the risk of respiratory allergy.

Key words

Eczema

Asthma

Allergic rhinitis

Epidemiology

Risk factors

Natural history

Abbreviations

aOR: adjusted odds ratio

MACS: Melbourne Atopy Cohort Study

OR: odds ratio

SPT: skin prick test

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INTRODUCTION

Eczema is an increasingly prevalent skin condition[1], that frequently, but not always, starts early in life and remits before adolescence[2]. Children with eczema tend to develop food allergy, asthma and allergic rhinitis at later ages; an aspect of the atopic march hypothesis[3], which suggests a possible causal role of eczema in the development of allergic airways disease.

There is emerging evidence that the development of early life eczema may be prevented by regular use of emollients[4] [5]. Whilst early life interventions, such as daily emollient application, may be feasible in the first months of life, it is likely that it will not be possible to continue such preventive treatments indefinitely. Better understanding of the long term prognosis of early life eczema, based on age of onset and persistence, and its relationship with allergic airways disease, may help inform optimal duration of early life preventive interventions.

Relatively few studies have examined the differential associations between age of onset and persistence of eczema and later development of asthma and allergic rhinitis[6-8]. We have previously demonstrated that early onset (particularly under six months) and more severe eczema is associated with increased risk of asthma at age 6-7 years, especially in boys[9]. Here, we extend on our previous work by using the same prospective birth cohort to examine the role of age of eczema onset and persistence of eczema symptoms in the development of hay fever and asthma up to age 18 years.

METHODS

Study population

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The Melbourne Atopy Cohort Study (MACS)[10, 11] is a prospective birth cohort of 620 babies recruited prenatally in Melbourne, Australia, between 1990 and 1994, on the basis of eczema, hay fever, asthma, or severe food allergy in at least one first-degree relative, and followed to 18 years of age. The study started as a randomised controlled trial of three infant formulas at weaning[10]. The project was approved by the Human Research Ethics Committee of the Mercy Hospital for Women. All mothers gave written informed consent.

Data collection

Baseline information was collected with questionnaires during pregnancy. Following birth, standardised telephone questionnaires were administered by an allergy-trained nurse 18 times in first two years, annually up to 7 years, and at 12 and 18 years. Each survey documented any episodes of illness since the previous interview.

Skin prick testing (SPT) was performed at 6, 12, 24 months, and 12 and 18 years, according to a standard technique[12] with the following allergens: cow's milk, egg white, peanut, house dust-mite, rye grass and cat dander (Bayer, Spokane, WA, USA). A positive (histamine 1 mg/mL) control was used. Wheals were measured and recorded at 15-20 minutes.

Definitions

Eczema in the first two years of life was defined as parental report of either a doctor diagnosis of eczema or any rash (excluding scalp or nappy rashes) which was treated with topical steroid[13]. Eczema from age three to 12 was defined as parental report of one or more episodes of eczema or rash treated with topical steroid or episodes of eczema which required a visit to the doctor, in the past 12 months.

Early-onset eczema was defined as eczema which commenced before age two years, and ***very early-onset eczema*** was defined as eczema that commenced in the first six months.

"Early-onset persistent eczema" was defined as early-onset eczema which was still present between ages 2 and 5, while "**early-onset remitting eczema**" defined eczema which only manifested in the first two years, but not between ages 2 and 5.

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"Late-onset eczema" described eczema first arising between ages two and seven. From ages 6 to 18 years, asthma and hay fever were defined as parental report of one or more episodes of asthma and hay fever in the past 12 months, respectively. A skin prick test of 2mm or greater in the first two years of life was defined as positive, while a 3mm cut point was used at 12 and 18 years.

Statistical analysis

Logistic regression models were used to examine the associations between age of eczema onset and persistence up to 5 years of age and the risk of eczema, asthma and hay fever and sensitisation to food and inhalant allergens. Generalised Estimating Equations (GEE) were used to accommodate repeated measurements for these outcomes. To test if these associations changed over time, interactions between age of onset and persistence of eczema symptoms and age of follow-up were tested. If there was possible evidence that the associations varied over time ($p<0.1$ for interaction with time) a pooled result was not reported. Regression models were adjusted for both a priori confounders (weight at four weeks, gender, parental history of atopic conditions, duration of breastfeeding in weeks, and group of randomisaiton) and the following potential confounders: number of siblings, carpets in home environment, pet ownership, parental smoking during pregnancy and socio-economic status if they caused a 10% or greater change in the odds ratio were included in the final multiple regression models. Stata release 13.0 (College Station, Texas) was used for all statistical analyses. Results are presented as OR with 95% Confidence intervals.**RESULTS**

Study population

Of the 620 infants recruited, 92.7% were followed-up at age two, 79.8% were assessed at least once at 6 or 7 years, and 58.9% and 67.4% at the 12 and 18 year follow-ups respectively (Figure 1). Children of parents with proxy markers for lower socio-economic status were more likely to be lost to follow-up[11]. Early signs of atopy or eczema in the child, were not associated with loss to follow-up[11]. Participants who could not be included in the analysis due to missing data, but who had outcome data at during the follow-up periods, had similar prevlences of allergic disease as those who were included (Supplementary Table 1)."

Prevalence of eczema

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Of the 325 children with complete data up to 7 years of age, by six months of life, 21.5% (n=70) had developed eczema, while 47.4% (n=154) had developed eczema by age 2 years. The prevalence of current eczema declined with age, and was 21.3% at age18 years. Of the children who had not developed eczema by two years, 34.5% (59/171) developed late-onset eczema between 2 and 7 years, but relatively few children first developed symptoms between 7 and 12 years (8.4%, 7/83) or from 12 to 18 years (6.7%, 4/60).

Risk of current eczema

Children with a history of eczema within the first 5 years had an increased risk of current eczema at 6, 12 and 18 years, but the strongest association was for children who had eczema that commenced by 1 year (table I). The strength of these associations was greatest at 6/7 years, and declined by the 18 year follow-up (p values for interaction < 0.05), so pooled estimates were not reported.

Risk of asthma

Very early-onset persistent eczema was strongly associated with asthma (aOR=3.2, 95%CI=1.7-6.1, table II]. This association was observed even when children who had early wheeze (35.3%, 203/575) were excluded (aOR=3.8, 95%CI=1.6-9.3). Early onset (6-24 months) persistent eczema was also associated with an increased risk of asthma. There was a trend towards increased risk of asthma for early-onset remitting eczema and asthma at each time point, and the pooled estimate indicated an increased risk (OR=2.7, 1.0-7.2). Late onset eczema was associated with an increased risk only at 12 years of age (p for interaction =0.01, Table II). More years of having eczema was associated with an increased risk of asthma at all ages (p for trend<0.01 at all ages).

At ages 6 and 7, the association between early-onset persistent eczema and asthma was seen in boys (aOR= 6.9; 95% CI=2.7-17.9) but not in girls (aOR=1.7; 95% CI=0.55-5.3; p for interaction=0.05) [9]. This gender difference was not seen at the 12 or 18-year follow-ups (all p for interactions>0.2).

Risk of hay fever

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Very early onset persistent eczema was related to increased risk of hay fever (Table III). There was no evidence of an association between eczema that commenced later, regardless of persistence.

Risk of sensitisation

Very early onset persistent eczema was associated with an increased risk of food sensitisation at all time points (table IV). These associations varied over time, and were particularly strong at 12 months and 12 years. The only other eczema group to be associated with food sensitisation and then only at 12 years, was eczema that commenced from 6 to 24 months and was persistent (aOR=4.3, 95%CI=1.4-12.4). Very early onset persistent eczema was again associated with increased risk of inhalant sensitisaiton at all time points (repeated measures aOR= 2.4, 95%CI=2.2-5.2, table V). Both late onset eczema and early onset persistent eczema, were associated with increased risk of inhalant sensitisation at 18 years only.

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DISCUSSION

In this birth cohort of children with family history of allergic diseases followed prospectively until 18 years, very early-onset (<6 months) *persistent* eczema (up to age 5) was associated with increased risk of both asthma and hay fever and sensitisation. The association between early onset-persistent eczema and increased risk of asthma, and hay fever, was still evident even when children with early onset wheeze, were excluded. This study is the first to clearly demonstrate that the strongest and most consistent associations between eczema and allergic airways disease are for the very early onset (<6 months) and persistent eczema, highlighting this as a period where interventions to prevent the atopic march may be effective."

Broadly, the results from this study are comparable to previously published findings. Direct comparisons between studies are difficult due to differences in definitions used when defining "early onset" eczema. Less than 6 months[9], 1 year[6], 2 years[14] [8] and 3 years[7] have been used in various papers. Consistent patterns of our findings with these studies are that persistent eczema, and earlier onset eczema, are more strongly related to asthma, allergic rhinitis and allergic sensitisation than remitting and late onset eczema. Some studies have failed to show an association between late onset eczema and increased risk of asthma or allergic rhinitis[8, 14] up to the ages of 7 and 12 years, while a very large, data linkage, study found an increased risk of both conditions with late onset eczema. Interestingly, we found that late onset eczema was not related to atopy, asthma or allergic rhinitis up to 7 years of age, but that there was evidence of increased risk of asthma at 12 years and inhalant sensitisation at 18 years. When coupled with our observation that greater years of symptoms of eczema is associated with increased risk of asthma and allergic rhinitis, this observation may indicate that there is a cumulative effect of eczema and that even late onset eczema, if persistent, is associated with increased risk of these conditions with increasing age.

The mechanism of these associations has not been clearly elucidated and may be due to shared genetic or environmental risk factors, or due to a causal mechanism. At this time, there are few known shared environmental risk factors for the development of both eczema and allergic airways disease, except possibly for early life exposure to pets[15, 16] and indoor mould [17]. The strongest evidence for a shared genetic risk factor comes from filaggrin (FLG) null mutations[18], which have been shown to be strongly associated with early-onset [19] and

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persistent eczema[20], and risk of asthma, but only in children who have also developed eczema[21]. Sensitisation to inhalant allergens is an important risk factor for asthma[22] and allergic rhinitis[23], and early-onset eczema can predict new onset sensitisation[24, 25]. It is possible that the association between early-onset eczema and later respiratory allergic disease may be due to an increased risk of aero-allergen sensitisation, mediated by impaired skin barrier function. Alternatively, chronic eczema lesions may express thymic stromal lymphopoietin (TSLP), and other pro-inflammatory mediators, which then increases the risk of developing allergic inflammation and sensitisation in the lungs[26]. This is consistent with our observation that greater numbers of years with eczema symptoms were associated with increased risk of both asthma and hay fever.

Previously some authors have argued that the association between early life eczema and childhood asthma is due to confounding by sensitisation, and that eczema is not a true independent risk factor for asthma[27]. Whilst we had data on allergic senstisation in this cohort, for many participants, it was unclear if sensitisation or eczema came first, so we did not have sufficient sample size to tease out independent effects of eczema and sensitisation. We recommend investigation of this issue in future studies

Key strengths of this study include its prospective design, regular assessments of eczema from birth to age 18, multiple measurements of sensitisation to common allergens, and assessments up to 18 years, when the nature of wheeze and rhinitis is much easier to determine than in early life. The prospective design of this study reduces possible recall bias, and also allowed for an analysis of the persistence or remission of symptoms.

The definition of eczema used within this study is a limitation. Eczema in the first two years of life was defined as a doctor-diagnosed eczema or parental report of rash (excluding those on the scalp or nappy area) treated with topical steroid. This definition of eczema has been validated, and shown reasonable sensitivity (85%) and specificity (81%)[28]. Another possible weakness was the minor variations between questionnaires administered at different follow-ups, resulting in a very slight difference in the definition of eczema before and after age two.

A further limitation of these results is that only 38.7% of the cohort had complete follow-up at all time points. This restriction allowed us to define age of onset and persistence of eczema.

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Although this reduced our statistical power to observe associations, it appears unlikely to have introduced bias. We elected to report results as odds ratios, which are larger than risk ratios when the outcome is common as seen in this study, for computational reasons. Finally, these results may not be applicable children without a family history of allergic disease.

Observations from the current study suggest that appropriate interventions in early life could potentially reduce the progression of eczema to asthma and hay fever, especially in children with very early onset disease. Restoration of skin barrier function in infants and patients with eczema, before sensitisation occurs, may be beneficial. Evidence from recent small scale trials suggest that such preventive strategies may reduce the incidence of early onset eczema [4, 5]. Hence, further work is urgently required to confirm if this may also lead to reduce rates of sensitisation and allergic airways disease. Proactive management of early-onset eczema, including skin hydration and regular use of emollients, antiseptics and topical anti-inflammatory agents, might be practical secondary preventive measures to reduce the risk of the atopic march progressing.

Conclusions

Our findings show that very early-onset persistent eczema is strongly associated with asthma and hay fever later in life in children with a family history of allergic disease. If these associations are causal, effective intervention in early-life eczema may reduce the risk of asthma and hay fever. The first six months of life appears to be the most important period where eczema prevention may reduce risk of asthma and allergic rhinitis.

Acknowledgments

We thank Dr John Thorburn for assistance in patient recruitment and administrative assistance and the Mercy Maternity Hospital Department of Obstetrics for participant recruitment, and Dr Cliff Hosking for study leadership from 1989 to 2005. We thank Anne Balloch for assistance with data management, Rida Khalafzai, Carlie Dunford and Jeeva Sanjeevan for coordinating the 18-year follow up. We acknowledge the following investigators of the 18 year follow-up: Paul Thomas, Melanie C Matheson, Sharon Goldfeld, Vijaya Sundararajan, Christopher Barton, John

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Hopper, Cecilie Svanes. Finally, we thank all of the MACS children and parents for their participation and ongoing support for this study.

Declaration of all sources of funding: Nestec Ltd, a subsidiary of Nestle Australia, provided staff funding for the first 6 years of the study, Asthma Foundation of Victoria supported the 12-year follow-up, while the National Health and Medical Research Council of Australia (NHMRC) funded the 18 year follow-up (APP454856). A.J.L., C. J. L., K.J.A. and S.C.D. are supported by the National Health and Medical Research Council of Australia.

Conflict of interest statement: A Lowe declares he has received in kind research support (donation of EpiCeram emollient) from PuraCap pharmaceuticals for use in an eczema prevention trial (see ACTRN12613000472774). All authors declare they have not conflicts of interest in relation to this manuscript.

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Table I. Risk of **eczema** by age of eczema onset

	6-7 year outcome † (n=325)		12 year outcome (n=241)**		18 year outcome (n=240)		Repeated measures aOR†
	% with eczema‡ (n/N)	Adjusted OR* (95% CI)	% with eczema (n/N)	% with eczema‡ (n/N)	% with eczema (n/N)	Adjusted OR* (95% CI)	
0-6 months	50.0 (35/70)	9.5 (4.5-19.9)	39.5 (17/43)	6.4 (2.4-17.5)	35.6% (16/45)	5.7 (2.2-15.0)	^
6-12 months	53.1 (26/49)	10.1 (4.5-22.4)	41.5 (17/41)	7.5 (2.7-21.2)	29.3% (12/41)	4.0 (1.5-11.2)	^
12-24 months	40.0 (14/35)	5.6 (2.3-14.0)	35.7 (10/28)	5.7 (1.8-17.7)	34.5% (10/29)	4.3 (1.4-13.2)	5.7 (2.7-11.9)
2-5 years	42.6 (20/47)	5.5 (2.4-12.8)	18.9 (7/37)	2.1 (0.6-6.8)	10.0% (3/30)	0.8 (0.1-3.9)	^
No eczema ≤5 y	9.7 (12/124)	1	9.8 (9/92)	1	10.5% (10/95)	1	1

† Odds ratios (OR) were estimated using repeated measures (generalised estimation equation)

* Adjusted for weight at four weeks, gender, parental history of eczema, duration of breastfeeding and randomisation

^ Indicates one or more significant difference in associations between the follow-up periods, so no pooled estimate is provided.

** 7 participants had missing eczema outcome data at age 12 years

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372 **Table II**. Risk of **asthma** at age 6 and 7, 12 and 18 years by age of onset and persistence of eczema symptoms

Pattern of eczema†	6 – 7 years (n=325) † % with asthma (n/N)	aOR* (95%CI)	12 years (n=240)** % with asthma (n/N)	aOR* (95%CI)	18 years (n=240) % with asthma‡ (n/N)	aOR* (95%CI)	Repeated measures aOR†
0-6 m persistent	47.1 (24/51)	**3.2 (1.6-6.5)**	48.5 (16/33)	**6.5 (2.5-17.1)**	28.6% (10/35)	**2.9 (1.0-8.1)**	**3.2 (1.7-6.1)**
0-6 m remitting	31.6 (6/19)	2.0 (0.7-5.8)	33.3 (3/9)	**5.8 (1.0-33.3)**	27.3% (3/11)	4.0 (0.8-19.3)	**2.7 (1.0-7.2)**
6-24 m persistent	32.0 (16/50)	1.9 (0.9-4.2)	32.5 (13/40)	**3.7 (1.3-10.1)**	22.7% (10/44)	**3.1 (1.1-8.5)**	**2.3 (1.2-4.7)**
6-24 m remitting	23.5 (8/34)	1.4 (0.5-3.6)	20.7 (6/29)	2.0 (0.6-7.0)	19.2% (5/26)	1.7 (0.4-6.5)	1.5 (0.6-3.6)
Late-onset	29.8 (14/47)	1.4 (0.6-3.1)	32.4 (12/37)	**3.0 (1.1-8.2)**	33.3% (10/30)	2.8 (1.0-8.4)	^
No eczema^	21.8 (27/124)	1	13.0 (12/92)	1	10.6% (10/94)	1	1

373 † Odds ratios (OR) estimated using repeated measures (generalised estimation equation) for any episode of asthma in the previous 12 months at
374 each follow-up point

375 * Adjusted for weight at four weeks, gender, parental history of asthma, duration of breastfeeding and randomisation

376 ^ Indicates one or more significant difference in associations between the follow-up periods, so no pooled estimate is provided.

377 ** 8 participants had missing asthma outcome data at age 12 years

378 **Table III**. Risk of **hay fever** at age 6 & 7, 12 and 18 years by age of onset and persistence of eczema symptoms

379

Pattern of eczema†	6 – 7 years (n=325) † % with hay fever (n/N)	aOR* (95%CI)	12 years (n=241)** % with hay fever (n/N)	aOR* (95%CI)	18 years (n=239)** % with hay fever‡ (n/N)	aOR* (95%CI)	Repeated measures aOR†
0-6 m persistent	41.2 (21/51)	**2.5 (1.2-5.2)**	64.7 (22/34)	**5.5 (2.2-13.3)**	61.8% (21/35)	**2.7 (1.2-6.4)**	**2.4 (1.4-4.1)**
0-6 m remitting	26.3 (5/19)	1.3 (0.4-4.3)	33.3 (3/9)	2.4 (0.5-13.1)	54.6% (6/11)	1.6 (0.4-6.3)	1.4 (0.6-3.3)
6-24 m persistent	26.0 (13/50)	1.6 (0.7-3.7)	37.5 (15/40)	2.0 (0.8-4.7)	36.4% (16/44)	0.8 (0.4-1.8)	1.4 (0.8-2.5)

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6-24 m remitting	29.4 (10/34)	1.2 (0.5-3.3)	27.6 (8/29)	1.3 (0.5-3.7)	40.0% (10/25)	1.3 (0.5-3.4)	1.3 (0.7-2.6)
Late-onset	25.5 (12/47)	1.4 (0.6-3.3)	43.2 (16/37)	2.3 (1.0-5.5)	33.3% (10/30)	0.8 (0.3-1.9)	1.4 (0.8-2.6)
No eczema	18.6 (23/124)	1	26.1 (24/92)	1	36.8% (35/94)	1	1

† Odds ratios (OR) estimated using repeated measures (generalised estimation equation) for any episode of hay fever in the previous 12 months at each follow-up point

* Adjusted for weight at four weeks, gender, and parental history of hay fever.

** 7 participants had missing hay fever outcome data at age 12 years and 1 participant had missing data at 18 years.

Table IV. Risk of **food sensitisation‡** at age 6,12 and 24 months and, 12 and 18 years by age of onset and persistence of eczema symptoms

Pattern of eczema†	**6 months (n=313) †**		**12 months (n=313)****		**24 months (n=287)****		**12 years (n=243)**		**18 years (n=223)**		**Repeated measures**
	% (n/N)	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**aOR†**
0-6 m persistent	38.0% (19/50)	**3.3 (1.5-7.0)**	59.2% (29/49)	**7.1 (3.3-15.2)**	37.8% (17/45)	**3.8 (1.6-8.7)**	44.1% (15/34)	**8.8 (3.1-25.0)**	25.7% (9/35)	**5.2 (1.5-17.9)**	^
0-6 m remitting	27.8% (5/18)	2.0 (0.6-6.6)	26.3% (5/19)	1.8 (0.5-5.9)	20.0% (3/15)	1.5 (0.4-6.6)	11.1% (1/9)	2.0 (0.2-21.1)	10.0% (1/10)	1.9 (0.2-19.0)	1.9 (0.8-4.7)
6-24 m persistent	14.3% (7/49)	0.8 (0.3-2.1)	26.0% (13/50)	1.6 (0.7-3.8)	23.9% (11/46)	2.1 (0.8-5.4)	27.5% (11/40)	**4.1 (1.4-12.4)**	12.5% (5/40)	2.1 (0.5-8.7)	^
6-24 m remitting	19.4% (6/31)	1.2 (0.4-3.7)	22.6% (7/31)	1.9 (0.7-5.1)	16.1% (5/31)	1.5 (0.5-4.8)	20.0% (6/30)	2.7 (0.8-9.5)	4.2% (1/24)	0.8 (0.1-7.9)	1.5 (0.7-3.3)
Late-onset	13.0% (6/46)	0.9 (0.3-2.3)	6.5% (3/46)	0.4 (0.1-1.3)	10.3% (4/39)	0.8 (0.2-2.5)	15.8% (6/38)	2.1 (0.7-7.0)	0.0% (0/29)	-	^

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No eczema	16.8% (20/119)	1	16.9% (20/118)	1	15.3% (17/111)	1	9.8% (9/92)	1	7.1% (6/85)	1	1

† Odds ratios (OR) estimated using repeated measures (generalised estimation equation)

‡ Food sensitization: sensitisation to one or more of milk, egg or peanut

* Adjusted for weight at four weeks, gender, parental history of eczema, duration of breastfeeding and randomisation

** 7 participants had missing hay fever outcome data at age 12 years and 1 participant had missing data at 18 years.

Table V. Risk of **inhalant sensitisation** at age 6,12 and 24 months and, 12 and 18 years by age of onset and persistence of eczema symptoms

	6 months (n=313) †		**12 months (n=313)**		**24 months (n=287)**		**12 years (n=243)**		**18 years (n=225)**		**Repeated measures aOR†**
Pattern of eczema†	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	**% (n/N)**	**aOR* (95%CI)**	
0-6 m persistent	20.0% (10/50)	**3.9 (1.4-11.0)**	44.9% (22/49)	**6.3 (2.8-14.3)**	53.3% (24/45)	**4.0 (1.9-8.6)**	76.5% (26/34)	**5.0 (2.0-12.6)**	85.3% (29/34)	**5.8 (2.0-16.9)**	**3.4 (2.2-5.2)**
0-6 m remitting	0.0% (0/18)	-	31.6% (6/19)	3.1 (0.9-9.9)	46.7% (7/15)	3.1 (1.0-9.9)	44.4% (4/9)	2.2 (0.4-11.3)	80.0% (8/10)	3.4 (0.6-17.9)	1.7 (0.8-3.4)
6-24 m persistent	4.1% (2/49)	0.6 (0.1-3.2)	14.0% (7/50)	1.2 (0.5-3.3)	26.1% (12/46)	1.3 (0.6-3.0)	57.5% (23/40)	1.9 (0.8-4.3)	75.6% (31/41)	**3.2 (1.3-7.5)**	^
6-24 m	6.5%	1.1	12.9%	1.2	25.8%	1.4	50.0%	1.6	64.0%	1.9	1.5

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remitting	(2/31)	(0.2-5.8)	(4/31)	(0.3-3.9)	(8/31)	(0.6-3.8)	(15/30)	(0.6-3.9)	(16/25)	(0.7-5.2)	(0.9-2.6)
Late-onset	4.3% (2/46)	0.8 (0.2-3.8)	15.2% (7/46)	1.3 (0.5-3.5)	23.1% (9/39)	0.9 (0.4-2.2)	57.9% (22/38)	1.9 (0.8-4.1)	73.3% (22/30)	**2.8 (1.1-7.1)**	^
No eczema	6.7% (8/119)	1	12.7% (15/118)	1	23.4% (26/111)	1	41.3% (38/92)	1	49.4% (42/85)	1	1

† Odds ratios (OR) estimated using repeated measures (generalised estimation equation)

‡ Inhalant sensitization: sensitisation to one or more of dust mite, rye grass or cat dander

* Adjusted for weight at four weeks, gender, parental history of eczema, duration of breastfeeding and randomisation

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406 **Figure legends**

407 **Figure 1.** Follow-up rate of participants in the first eighteen years

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