

Received Date : 26-Sep-2012

Revised Date : 10-Dec-2012

Accepted Date : 11-Jan-2013

Article type : Original Article-Epidemiology of Allergic Disease

Title page

The prevalence and socio-demographic risk factors of clinical eczema in infancy: A population-based observational study

Running title:

The prevalence and socio-demographic predictors of infantile eczema

Pamela E. Martin^{1,2}, Jennifer J. Koplin¹, Jana K. Eckert¹, Adrian J. Lowe^{1,3}, Anne-Louise Ponsonby^{1,2}, Nicholas J. Osborne^{1,4}, Lyle C. Gurrin^{1,3}, Marnie N. Robinson⁵, David J. Hill¹, Mimi L.K. Tang^{1,2,5}, Shyamali C. Dharmage^{1,3}, Katrina J. Allen^{1,2,5} for the HealthNuts Study Investigators*

1. Murdoch Childrens Research Institute, Parkville
2. The Department of Paediatrics, The University of Melbourne
3. Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne

This article has been accepted for publication and 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/cea.12092

4. European Centre for Environment and Human Health, Peninsula College of Medicine and Dentistry, University of Exeter, United Kingdom

5. Department of Allergy and Immunology, Royal Children's Hospital, Parkville

Corresponding author:

Katrina J. Allen MBBS, FRACP, AAAAI, PhD

Department of Allergy and Immunology

Royal Children's Hospital

Flemington Rd

Parkville

Victoria 3052

Phone: +61 3 9345 4870

Fax: +61 3 9345 4848

Email: Katie.Allen@rch.org.au

Abstract

Background

Socio-demographic predictors for the development of clinically-observed, infantile eczema have not been formally examined in a large population-based study. Few studies of eczema risk factors have included current, objective eczema outcomes as well as parent-reported history.

Objectives

We aimed to measure the population prevalence of infantile eczema using novel sampling methodology, and identify socio-demographic risk factors for eczema in the first year of life.

Methods

A population-based cross-sectional study of infantile allergy (the HealthNuts study, n= 4972, response rate 74.1%) was conducted from 2008-2011 in Melbourne, Australia. Infants were examined for current eczema at age 12 months (mean 12.7, SD 0.7). Parents provided information about the infants' history of eczema and demographic factors. Factors associated with eczema were modelled using multinomial logistic regression.

Results

The population prevalence of observed eczema at 12 months was 20.3% (95% CI 19.0, 21.5), while cumulative prevalence for parent-reported eczema was 28.0% (95% CI 26.7, 29.4). The strongest predictors of eczema were maternal eczema and asthma (multinomial (M)-OR 1.7, $p<0.001$, and M-OR 1.4, $p=0.007$), male sex (M-OR 1.4, $p<0.001$), and East Asian ethnicity (M-OR 1.4, $p<0.001$) with over 80% of infants with all risk factors exhibiting eczema. East Asian parents, particularly recent migrants, reported fewer allergies than other parents.

Conclusions and Clinical Relevance

Approximately one in three infants developed eczema by 12 months of age. East Asian infants are at increased risk of eczema despite their parents having lower rates of allergy than non-Asian parents. Gene-environment interactions may explain the differential effect seen in this minority group.

Key words:

Eczema, infancy, prevalence, severity, risk factors, epidemiology, ethnicity, parental allergy.

Abbreviations:

M-OR: Multinomial odds ratio.

SEIFA: Socio-Economic Indexes for Areas.

Introduction

Eczema is a chronic inflammatory skin disorder that can occur at any age but is common in childhood. Daily treatment, pruritus, sleep loss, recurrent skin infections, parental stress and school absence all contribute to a decreased quality of life [1, 2] and significant costs to families and the healthcare system [3-6].

Eczema in early childhood is a strong predictor for the development of other allergic conditions including food allergy, allergic rhinitis and asthma. We have previously shown in a clinic-based population that 80% of infants with moderately-severe eczema in the first 6 months of life developed food allergy [7, 8] and that participants in a longitudinal cohort who had parent-reported childhood eczema were 9 times more likely to develop persistent atopic asthma at age 42 years [9].

Knowledge of socio-demographic risk factors for eczema may help identify a high-risk group to target strategies in early life not only for the prevention and improved management of eczema, but also with the potential to ameliorate the development of other co-existent allergic disease including asthma and the progression of the *atopic march*. Suggested

Accepted Article

predictors of children at increased risk of eczema include family history of allergy, maternal education levels and socio-economic status [10-12]. Few studies have examined the effect of these factors on clinically-observed eczema separately from parent-reported measures.

The prevalence of eczema is also suspected to vary between ethnic groups living in multicultural cities [11, 13-16]. Furthermore the rise in allergic disease has been postulated to be due to factors associated with the modern lifestyle since the change in prevalence has occurred more rapidly than changes to the genome could occur [17].

Within the HealthNuts study- a large, population-based study of allergy in infants conducted in Melbourne, Australia- we sought to determine the population prevalence of clinical eczema at 12 months of age, describe the spectrum of eczema severity, and identify socio-demographic risk factors for infantile eczema.

Methods

Design and recruitment

The HealthNuts study methodology has been described [18]. In brief, unselected infants (aged 11-15 months) were recruited at council-led immunization sessions. Parents or guardians completed a questionnaire about their infant's history of diagnosed eczema and itchy rashes (excluding napkin rash), age at diagnosis and treatment history (for itchy rash), including topical steroid use (Table E1, online repository). Infants were examined for signs of eczema at recruitment by nurse-researchers.

Between July 15th, 2008, and August 10th, 2011, 6714 families were approached at community immunization clinics. A response rate of 74.1% (n= 4972) was achieved (Figure 1). The mean age of participating infants was 12.7 months (standard deviation, 0.7 months). An additional 310 participants recruited in the pilot stages of the study before July 15th, 2008, were excluded due to differences in the eczema-related data collected.

Parents and guardians who did not wish to participate in the study were asked a brief set of questions about allergic disease in the family and infantile diagnosed eczema. The participant group was found to be population-representative in most demographic aspects, however were more likely to have eczema, older siblings or a family history of allergy, and less likely to have eaten and tolerated peanut [18].

Parents or guardians of infants provided written, informed consent. Ethics approval was obtained for the HealthNuts study from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no. 10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047).

Measures of eczema

A history of eczema was defined as parent-reported diagnosed eczema, or parent-reported itchy rash that had been treated with topical steroids (excluding nappy (diaper) rash).

Current eczema was measured objectively at recruitment by clinical staff. In our eczema observation the nurses were asked to look for the cardinal signs of eczema – erythema, excoriation, oedema/papulation, lichenification and vesiculation- and use their clinical judgement (e.g. erythema on the cheeks from crying). All range of severity of eczema was captured by the 'current eczema'

Accepted Article

measure. The nurses were referred to online SCORAD training photo tutorials, which cover the issue of different skin pigmentation and appearance of eczema. The presence or absence of eczema in the elbow flexures, the face and the back was recorded for each participant. For a random sample of 43 infants, two researchers examined the same infant for eczema in the elbow flexures and on the face and back, blinded to patient history or questionnaire responses. Each researcher completed their assessment unaware of the other researcher's conclusions. There was 97.6% concordance for elbow flexure examination, 95.0% for back examination but only 83.3% concordance for the face examination.

Current flexural eczema was defined as only those infants with signs of eczema affecting their elbow flexures. This group was a sub-group of all current eczema cases.

Collection of demographic information

Information on a range of demographic and environmental factors were collected in the parent (or guardian)-administered questionnaire at recruitment (see Table E1, online repository).

Ethnicity of each infant was assigned according to their parents' countries of birth, classified into ten broad regions (see Table E2 in the online repository). The second most common region of birth, after Australia, was 'East Asia', consisting of Brunei, Burma, Cambodia, China, Hong Kong, Indonesia, Japan, Korea, Laos, Macau, Malaysia, Papua New Guinea, Philippines, Singapore, Taiwan, Thailand and Vietnam.

Socioeconomic status was assigned to each participant based on the local government area in which they were recruited using SEIFA (Socio-Economic Indexes For Areas) measures,

which assess relative socio-economic advantage and disadvantage, economic resources (income, assets and expenditure) and educational and occupational characteristics [19].

Statistical Analysis

Participants with a 'not sure' response for eczema diagnosis or itchy rash were excluded from the analyses.

Age at eczema diagnosis (in completed months) was compared between groups using a Kruskal-Wallis test. Topical steroid treatments were categorized as mild (available without prescription) and strong (requiring a prescription within Australia; see Table E3, online repository, for medications used). Pearson's χ^2 tests were used to identify statistical differences in the frequency of these factors between infants with and without eczema.

Adjustment for population prevalence was made using the propensity weighting method described by Little and Rubin [20]. Weights were calculated as the inverse of the probability of participation. The probability was derived from information available for both participants and non-responders: sex, socioeconomic status, family history of allergy, a previous diagnosis of eczema, the child's number of siblings and whether the child was eating and tolerating peanut.

Factors that were associated with eczema in univariate analyses (where $p < 0.05$) were selected for inclusion in a multinomial regression model. Two mutually exclusive definitions of eczema (current eczema, or a history of eczema (with no current eczema)) were compared to the reference group infants who did not have any eczema. For each socio-demographic exposure in the model, the Wald χ^2 test was computed to test the hypothesis that the effect of the exposure was the same for both eczema outcomes. None of the

excluded potential confounders altered the final estimates by 10% or greater. Exposures included in the model were checked for interactions using likelihood ratio tests for improvement of the model when interaction terms were included.

The absolute risk of eczema (history or current) was modelled using a logistic regression including all socio-demographic factors identified in the multinomial regression, after propensity weighting to adjust for factors associated with participation in the study. From changes in the risk of eczema when a single risk factor was present, an aggregate risk increase (averaged for males and females) was derived and placed in a risk prediction algorithm.

To examine risk factors for current flexural eczema in particular, a logistic regression model was formed to look at the association between socio-demographic factors and this type of eczema (a sub-group of current eczema), compared to no eczema.

STATA release 11.0 and 12.0 (StataCorp, College Station, Tex) were used for all analyses.

Results

Data available on infantile eczema

Of 4972 infants who were recruited to the HealthNuts Study, 4485 had data for all of itchy rash, diagnosed eczema and current eczema after excluding 'not sure' responses for eczema diagnosis (n= 206) and were included in the analysis. An additional 70 infants were included in the analysis that had clear information for current eczema but unclear information for a history of eczema. 47.5% (n= 2129) were affirmative for at least one of the measures. Itchy rash was reported most

frequently (37.3%), followed by diagnosed eczema (25.9%), then current eczema (21.1%).

There was considerable overlap between the three measures of eczema (Figure 2a).

Of infants with current eczema and a complete examination of all three sites (n=731), there was overlap in the anatomical sites affected (face, back and elbow flexures) (Figure 2b).

Eczema on the face alone or back alone occurred most frequently.

Population prevalence of eczema

The proportion of participants with eczema and corresponding adjusted prevalence estimates are summarized in Table 1. Prevalence estimates based on parent-report were reduced following adjustment for participation-related factors, whilst estimates based on current clinical eczema changed little.

Severity of infantile eczema among HealthNuts participants

Many infants had current eczema or a history of itchy rash, but were not diagnosed with eczema (Table 2). Infants with all three measures- diagnosed eczema, itchy rash and current eczema- were most likely to have prescription-only treatment and have current eczema affecting all three examined sites. The mean age at eczema diagnosis was between 4 and 5 months. Among infants with diagnosed eczema, the age at which they were diagnosed did not vary according to whether they also had current eczema or itchy rash ($p=0.17$).

Socio-demographic predictors of eczema

A wide range of socio-demographic factors were considered a priori to our analysis (see Table E4 online repository for full list). There was no association between socio-economic status, annual household income or parental age, and the infant's risk of eczema (Table E4 online

repository). Male sex was associated with both current eczema and a history of eczema (Table E4 online repository).

Infants of East Asian ethnicity had a higher prevalence of eczema than infants of Australian-born parents (Table E4 online repository). Numbers of parents born in other regions were small. Most sets of parents were both born in Australia (n= 2908 couples, 59.2% of parent sets), following by both born in East Asia (n= 311, 6.3% of parent sets). An infant whose parents had migrated to Australia were also at increased risk of current eczema, however this association was not observed among parents migrating from regions other than East Asia (compared to Australian-born parents, p= 0.25). The proportion of East Asian infants with any eczema was slightly lower where parents had migrated to Australia recently (within 5 years) compared to over 5 years prior to recruitment (48.0% versus 61.7% respectively, p= 0.03). The proportion with infantile eczema, stratified by specific East Asian countries is summarized in Table E5 (online repository).

There was a parental history of allergic rhinitis, asthma or eczema for 48.8%, 26.7% and 20.9% of infants, respectively. Parental allergic rhinitis, asthma and eczema were associated with infantile eczema (Table E4 online repository). Parental food allergy, reported for 8.8% of infants, was not associated with infantile eczema.

An association was found between parental history of allergy and ethnicity. Compared to mothers born in other regions, mothers born in East Asia were less likely to report having eczema (10.3% versus 14.7% respectively, p= 0.008), asthma (8.7% versus 15.7% respectively, p<0.001) and allergic rhinitis (25.8% versus 31.1%, p=0.014). Compared to fathers born in other regions, fathers born in East Asia were less likely to report asthma (7.4% versus 14.2% respectively, p<0.001) but more likely to report allergic rhinitis (33.4%

versus 27.0% respectively, $p=0.006$). East Asian mothers who were non-recent migrants (in Australia >5 years) were more likely to report an allergy (eczema, allergic rhinitis, asthma or food allergy) than recent migrants (70.13% versus 55.3% respectively, $p=0.005$).

Following adjustment for multiple factors, male sex, East Asian ethnicity and maternal eczema were the strongest predictors of eczema (Table 3). There was a linear increase in the odds of eczema for each parent born in East Asia, combining to a multinomial-OR of 2.6 in cases where both parents were born in East Asia. Parental allergies also remained associated with infantile eczema. The effect sizes of each factor did not vary for the two measures of eczema. In order to assess the role of change in environmental exposure and potential impact on the increased predisposition to eczema in East Asian infants, we explored migration factors such as change in diet, pet ownership and prevalence of smoking that might be expected to impact on the hygiene hypotheses [21]. We compared East Asian migrants to UK/European migrants, which is the other large group of immigrants in our HealthNuts cohort. East Asian migrants were more likely to change their diet (59.29% versus UK/European 20.74%, $p<0.001$), (Note question asked: "Has your diet changed significantly since moving to Australia?"). Furthermore East Asian migrants were less likely to have any pets (16.17% versus 44.9% UK/European, $p<0.001$). History of maternal smoking was also different between East Asian mothers (10.65% versus 32.18% UK/European, $p<0.001$), while the prevalence for current maternal smoking was similar (1.49% East Asian versus 1.79% UK/European).

An interaction was detected between maternal allergic rhinitis and East Asian ethnicity, with the odds of a history of eczema increased by an extra 2.1-fold (95% CI 1.0, 4.4, $p=0.04$) for each parent from East Asia, and odds of current eczema increased by an extra 2.4-fold (95% CI 1.3, 4.4, $p=0.008$), where infants had both risk factors.

Sensitivity analysis to address potential participation bias

Some of the 10.1% of non-responders with insufficient English for participation may have been recent migrants from non-English speaking countries, including the East Asia region. If all these non-responders (n=136) were assumed to be East Asian migrants (one or both parents), and their infants negative for eczema, the overall proportion with infantile eczema remained higher for East Asian infants than infants of other ethnicities (40.7% versus 36.0%, $p=0.023$).

The distribution of current eczema, stratified by socio-demographic risk factors

The distribution of current eczema was stratified by sex, parental allergy and ethnicity (see Table E6, online repository). East Asian infants (one or both parents born in East Asia) differed notably in eczema distribution with a greater proportion having flexural involvement compared to infants of other ethnicities (10.4% versus 4.5%, respectively, $p<0.001$) and a greater proportion having all three examined sites affected (3.5% versus 1.6%, $p=0.008$).

Differences between current flexural eczema and other measures of eczema

Compared to infants with no eczema, having current flexural eczema was associated with a history of parental migration to Australia (34.4% of cases, $p=0.001$), East Asian ethnicity (23.8% of cases, $p<0.001$), maternal eczema (23.2% of cases, $p<0.001$), maternal asthma (22.1% of cases, $p=0.003$), maternal allergic rhinitis (35.3% of cases, $p=0.046$), paternal asthma (17.4% of cases, $p=0.046$), paternal allergic rhinitis (32.6% of cases, $p=0.039$), and male sex (56.6% of cases were male, $p=0.015$). Paternal eczema was not associated with current flexural eczema.

In an adjusted regression model, the only factors associated with current flexural eczema were maternal eczema (OR 2.0, 95% CI 1.3, 3.1, $p=0.002$), maternal asthma (OR 2.1, 95% CI 1.4, 3.2, $p=0.001$), and East Asian ethnicity (OR 2.0 for each parent born in East Asia, 95% CI 1.5, 2.7, $p<0.001$). No interactions were detected between the factors associated with flexural eczema.

Absolute risk of eczema in the first year of life among high risk infants

The estimated risk of eczema (measured by history or examination at 12 months of age) for infants in the first year of life ranged from 25% for females of non-East Asian ethnicity and with no parental eczema, asthma or allergic rhinitis, to over 80% for East Asian infants with parental eczema and maternal allergic rhinitis or asthma (Figure 3). There was strong evidence for an interaction between maternal allergic rhinitis or asthma and East Asian ethnicity on the risk of any eczema ($p=0.006$), with infants at higher risk of eczema if their mother had either condition. Risk estimates from the algorithm and from the original participant data can be compared in Table E7 (online repository).

Discussion

In one of the largest population-based studies of infantile allergy to date, we confirmed that eczema, including current, observed eczema, is a highly prevalent pediatric health problem with up to 1 in 3 infants having a history of eczema by age 12 months or current, clinically-observed eczema. Parental allergy, East Asian ethnicity and male sex conveyed an increased risk of eczema development, with over 80% of infants with all three factors developing eczema in the first year of life. Despite East Asian ethnicity being a predictor of infantile

Accepted Article
eczema, East Asian parents were less likely to have a history of eczema than non-Asian parents.

The strengths of this analysis include a sample size large enough to enable precision in our prevalence estimates, a breadth of socio-demographic information that can identify individuals at high risk of eczema, and a range of eczema measures including objective eczema examination and definitions by history that are comparable to other studies.

Limitations of our analysis include missing information about the use of topical steroids among cases of eczema that did not also have a history of itchy rash, and a bias towards families with allergy (including infants with eczema) agreeing to participate in the study.

However the participation bias was attenuated in part by prospective use of a non-responder questionnaire during recruitment, allowing adjustment of our prevalence estimates for many factors associated with participation. Recent (<5 years) non-English speaking migrants may have been underrepresented in our sample where they had insufficient English to participate, however we estimate that there would still be a significantly higher rate of eczema among East Asian infants if we were able to include all non-English speaking families approached, assuming their infants did not have eczema.

The high prevalence of early onset infantile eczema in our study confirms previous reports of eczema as a common childhood condition. The prevalence of eczema among Australian 6-7 year-olds estimated in the ISAAC study was high: 32.3% had eczema-ever and 17.1% had recent eczema [22]. Longitudinal follow-up sampling of the HealthNuts cohort, currently underway, will investigate the natural history of eczema and whether there is a change of prevalence among 6-7 year-old children between 2002 and a decade later. We also

confirmed a moderate rate of current flexural eczema at 12 months of age. Flexural involvement, as with the presence of itch, are hallmarks of atopic eczema in particular [23]. Prevalence studies outside of Australia found the prevalence of (parent reported) eczema to be highly variable in our age group. A European birth cohort found eczema in 15% under 1 year old infants [24]. A study from Spain [25] reported 12.2% in the same age group. In Japan a study with infants under 2 years found 18.6% participants with eczema [26], while China reported eczema to be prevalent in 13.58%, 31.05% and 42.86% of participating infants under 1 year [27]. The differences in prevalence within China are from 3 different major cities. Unfortunately the reasons for variations in disease prevalence among the three cities were not further investigated.

East Asian ethnicity was a strong predictor of eczema in this study, a link previously suspected by clinicians [14] and explored in small community studies [13, 15, 16]. Higher rates of eczema were found among young East Asian migrants to Sweden. The younger the child was when they arrived in Sweden, the higher the risk of allergic disease [28]. A study among East Asian immigrants (Chinese origin) in Melbourne observed rates of atopy increasing with the duration since arrival to Australia [29]. In light of lower rates of allergy among parents born in East Asia, the high rates of eczema among their infants may be the result of interactions between genes and the Australian environment suggesting that environmental factors associated with increased allergy work differentially on different genotypes. Furthermore, allergy rates were higher among East Asian mothers who had been in Australia for a longer period of time (>5 years), and their infants' eczema rates slightly higher than for recent migrants. A study of eczema rates within East Asia suggests that environmental factors might affect the prevalence of eczema since prevalence was higher in Hong Kong and Malaysia than in mainland China [30]. The authors postulated risk factors included

susceptibility to certain viral infections, indoor microclimate and dietary factors. In our HealthNuts study we found the prevalence of change in dietary choices was higher, pet ownership and history of maternal smoking was lower in East Asian migrants versus migrants from UK/Europe suggesting a possible role for these factors in increasing the risk of infantile eczema.

In conclusion, eczema in infancy is a common pediatric health problem, particularly among male infants, of East Asian decent and with a parental history of allergy. More research is needed to examine environmental drivers and mechanisms for the high incidence of infantile eczema, and the possible programming trigger for eczema in East Asian migrant populations.

Additional authorship acknowledgement

* The HealthNuts Study Investigators include Melissa Wake, Melanie C Matheson, Leone Thiele, Dean Tey, Thanh Dang, Tina Tan, Deborah Anderson, Rima Mograby, Margaret Sutherland, Helen Czech and John Zurzolo.

Acknowledgements

We thank the children and parents who participated in the HealthNuts Study as well as the staff of Melbourne's Local Government Areas for access to community Immunization Clinics.

We thank ALK Abello, S.A. Madrid, Spain for supplying the skin prick testing reagents and the HealthNuts safety committee: Associate Professor Noel Cranswick (Australian Paediatric Pharmacology Research Unit/Murdoch Childrens Research Institute), Dr Jo Smart (Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia), and Associate Professor Jo Douglass (Head of Allergy, Alfred Hospital, Melbourne, Australia).

We also thank the additional members of the HealthNuts team: Jeeva Sanjeevan, Marjolein Slaa, Lucy Miles, Mark Nethercote, Kelley Mancer.

Sources of Funding

The HealthNuts Study is funded by the Australian National Health & Medical Research Council, the Ilhan Food Allergy Foundation and AnaphylaxiStop. K.J.A. is a Viertel Senior Medical Research Fellow which included funding for N.J.O for this work. P.E.M. and J.J.K. are recipients of Australian Postgraduate Awards and David Danks Memorial Scholarships (MCRI). S.C.D., L.C.G., A.J.L. and A-L.P. hold National Health and Medical Research Council awards. The Murdoch Childrens Research Institute is supported by funding from the Victorian Government's Operational Infrastructure Support Program.

Conflict of Interests

N.J.O. has received research funding from the Australian Egg Corporation. K.J.A. has received honoraria as a speaker from Abbott, Nutricia, and Pfizer. The other authors declare no conflicts of interests.

References:

1. Kiebert G, Sorensen SV, Revicki D, Fagan SC, Doyle JJ, Cohen J, Fivenson D, Atopic dermatitis is associated with a decrement in health-related quality of life. *Int J Dermatol* 2002;41: 151-8.
2. Darsow U, Wollenberg A, Simon D, Taieb A, Werfel T, Oranje A, Gelmetti C, Svensson A, Deleuran M, Calza AM, Giusti F, Lubbe J, Seidenari S, Ring J, ETFAD/EADV eczema task force

- 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol*;24: 317-28.
3. Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR, Lebwohl M, Stevens SR, Whitaker-Worth DL, Cheng JW, Tong KB, Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol* 2002;46: 361-70.
 4. Emerson RM, Williams HC, Allen BR, What is the cost of atopic dermatitis in preschool children? *Br J Dermatol* 2001;144: 514-22.
 5. Kemp AS, Cost of illness of atopic dermatitis in children: a societal perspective. *Pharmacoeconomics* 2003;21: 105-13.
 6. AccessEconomics, The economic impact of allergic disease in Australia: not to be sneezed at. In: *Allergy ASocla ed.*, 2007.
 7. Hill DJ, Heine RG, Hosking CS, Brown J, Thiele L, Allen KJ, Su J, Varigos G, Carlin JB, IgE food sensitization in infants with eczema attending a dermatology department. *J Pediatr* 2007;151: 359-63.
 8. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V, Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy* 2008;38: 161-8.
 9. Martin PE, Matheson MC, Gurrin L, Burgess JA, Osborne N, Lowe AJ, Morrison S, Meszaros D, Giles GG, Abramson MJ, Walters EH, Allen KJ, Dharmage SC, Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: A prospective cohort study over 4 decades. *J Allergy Clin Immunol* 2011;127: 1473-79 e1.
 10. Dom S, Droste JH, Sariachvili MA, Hagendorens MM, Bridts CH, Stevens WJ, Desager KN, Wieringa MH, Weyler JJ, The influence of parental educational level on the development of atopic sensitization, wheezing and eczema during the first year of life. *Pediatr Allergy Immunol* 2009;20: 438-47.

11. Moore MM, Rifas-Shiman SL, Rich-Edwards JW, Kleinman KP, Camargo CA, Jr., Gold DR, Weiss ST, Gillman MW, Perinatal predictors of atopic dermatitis occurring in the first six months of life. *Pediatrics* 2004;113: 468-74.
12. Suarez-Varela MM, Gonzalez AL, Martinez Selva MI, Socioeconomic risk factors in the prevalence of asthma and other atopic diseases in children 6 to 7 years old in Valencia Spain. *Eur J Epidemiol* 1999;15: 35-40.
13. George S, Berth-Jones J, Graham-Brown RA, A possible explanation for the increased referral of atopic dermatitis from the Asian community in Leicester. *Br J Dermatol* 1997;136: 494-7.
14. Lee CS, Lim HW, Cutaneous diseases in Asians. *Dermatol Clin* 2003;21: 669-77.
15. Mar A, Tam M, Jolley D, Marks R, The cumulative incidence of atopic dermatitis in the first 12 months among Chinese, Vietnamese, and Caucasian infants born in Melbourne, Australia. *J Am Acad Dermatol* 1999;40: 597-602.
16. Sladden MJ, Dure-Smith B, Berth-Jones J, Graham-Brown RA, Ethnic differences in the pattern of skin disease seen in a dermatology department--atopic dermatitis is more common among Asian referrals in Leicestershire. *Clin Exp Dermatol* 1991;16: 348-9.
17. Prescott S, Allen KJ, Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol*;22: 155-60.
18. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang ML, Ponsonby AL, Dharmage SC, Allen KJ, The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010;40: 1516-22.
19. Pink B, An introduction to Socio-Economic Indexes for Areas (SEIFA). Canberra: Australian Bureau of Statistics 2006.
20. Little RJAaR, D.B, Statistical analysis with missing data, 2nd ed. NY: Wiley, 2002.
21. Koplin JJ, Dharmage SC, Ponsonby AL, Tang ML, Lowe AJ, Gurrin LC, Osborne NJ, Martin PE, Robinson MN, Wake M, Hill DJ, Allen KJ, Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 2012;67: 1415-22.

- Accepted Article
22. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR, Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008;121: 947-54 e15.
 23. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, Bingham EA, Finlay AY, Pembroke AC, Graham-Brown RA, et al., The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131: 383-96.
 24. McBride D, Keil T, Grabenhenrich L, Dubakiene R, Drasutiene G, Fiocchi A, Dahdah L, Sprickelman AB, Schoemaker AA, Roberts G, Grimshaw K, Kowalski ML, Stanczyk-Przyluska A, Sigurdardottir S, Clausen M, Papadopoulos NG, Mitsias D, Rosenfeld L, Reche M, Pascual C, Reich A, Hourihane J, Wahn U, Mills EN, Mackie A, Beyer K, The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol* 2012;23: 230-9.
 25. Pellegrini-Belinchon J, Miguel-Miguel G, De Dios-Martin B, Vicente-Galindo E, Lorente-Toledano F, Garcia-Marcos L, Study of wheezing and its risk factors in the first year of life in the Province of Salamanca, Spain. The EISL Study. *Allergol Immunopathol (Madr)* 2012;40: 164-71.
 26. Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W, Yokoyama T, Hirota Y, Breastfeeding and atopic eczema in Japanese infants: The Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2009;20: 234-41.
 27. Zhao J, Bai J, Shen K, Xiang L, Huang S, Chen A, Huang Y, Wang J, Ye R, Self-reported prevalence of childhood allergic diseases in three cities of China: a multicenter study. *BMC Public Health* 2010;10: 551.
 28. Hjern A, Rasmussen F, Hedlin G, Age at adoption, ethnicity and atopic disorder: a study of internationally adopted young men in Sweden. *Pediatr Allergy Immunol* 1999;10: 101-6.
 29. Leung R, Asthma, allergy and atopy in South-east Asian immigrants in Australia. *Aust N Z J Med* 1994;24: 255-7.

30. Leung R, Ho P, Asthma, allergy, and atopy in three south-east Asian populations. *Thorax* 1994;49: 1205-10.

Figure Legends

Figure 1: Overview of participant recruitment and eczema measures in the HealthNuts study. An eczema-related question was added to the non-responder questionnaire part-way through the study (response rate 1259/1357, 92.8%).

Figure 2a: The overlap in measures of current eczema, diagnosed eczema and itchy rash. The diagram includes all infants who were positive to at least one measure (n= 2129, 47.5% of the 4485 infants with complete information on all measures).

Figure 2b: The distribution of sites affected by eczema at 12 months of age. Infants were examined on their face, back and elbow flexures for signs of eczema. Percentages represent the frequency of one or more sites being affected in the same infant, among the infants who were positive for current eczema and had data for all three sites (n= 731), a sub-sample of all infants with current eczema (n= 1000).

Figure 3: Calculation of approximate risk of any eczema (steroid-treated itchy rash, diagnosed eczema or current eczema) in the first year of life, based on the strongest demographic risk factors. Baseline risk of eczema is measured among infants of non-East Asian ethnicity, without a parental history of eczema and asthma/allergic rhinitis, and averaged among males and females.

Table 1: Population prevalence of infantile eczema, by various measures

Measure of eczema	Number affirmative for the eczema measure†	Proportion in participant fraction		Population prevalence*	
		%	95% CI	%	95% CI
<i>During the first year of life</i>					
Diagnosis of eczema	1223/4719	25.9%	24.7, 27.2	23.7%	22.5, 25.0
History of itchy rash (any)	1849/4955	37.3%	36.0, 38.7	35.3%	33.9, 36.8
History of itchy rash, treated with topical steroids	931/4889	19.0%	17.9, 20.1	17.5%	16.3, 18.6
<i>Current eczema at 12 months of age</i>					
Any current eczema (face, back or elbow flexures)	1000/4730	21.1%	20.0, 22.3	20.3%	19.0, 21.5
Eczema on the face	582/4771	12.2%	11.3, 13.1	11.8%	10.9, 12.9
Eczema on the back	594/4719	12.6%	11.6, 13.5	11.9%	10.9, 12.9
Eczema in the elbow flexures	190/3656	5.2%	4.5, 5.9	5.0%	4.3, 5.8
Eczema on back, face and in elbow flexures	68/3638	1.9%	1.4, 2.3	1.9%	1.5, 2.4
<i>Combined estimates</i>					
Diagnosis &/or Itchy rash, treated with steroids	1466/4735	31.0%	29.6, 32.3	28.0%	26.7, 29.4
Current, Diagnosis, &/or Itchy rash, treated with steroids	1690/4486	37.7%	36.3, 39.1	35.9%	34.5, 37.4

†The denominator for each measure represents that number of participants who responded to the corresponding question, or the number of infants examined for eczema at each site at 12 months of age. *Prevalence estimates were calculated by weighting the proportion of the participants with each eczema measure using sampling weights, calculated using the probability that a family participated in the study based on family history of food allergy and other allergy, infantile eczema, family size, socioeconomic status, and whether the infant was tolerating peanut in their diet.

Table 2: The prevalence and clinical features of eczema and itchy rash in the first year of life.

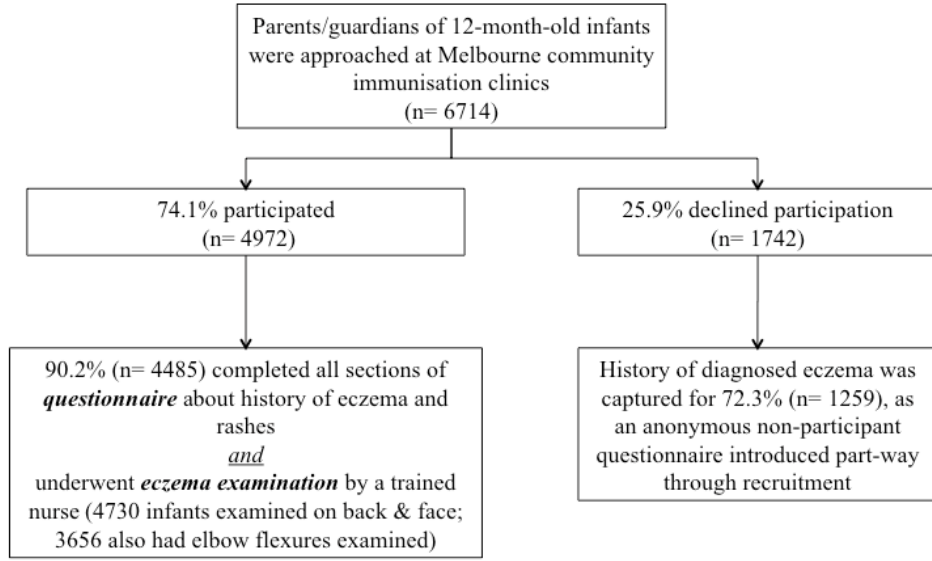
Eczema measures			Weighted prevalence [‡]			Treatment history for presumed eczema*					Extent of current eczema at 12 months*				Age at diagnosis* (completed months): Mean (SD)
Current eczema	Itchy rash	Diagnosed eczema	N	%	95% CI	% No treatment	% Using moisturisers only	% Using mild steroids [†]	% Using strong steroids [†]	% Needing steroids ≥10 days	% Visible flexural involvement	% 1 site affected	% 2 sites affected	% 3 sites affected	
-	-	-	23	54.0%	52.4, 55.6										
+	-	-	24	5.6%	4.9, 6.4	N/A*					8.6%	91.3%	8.2%	0.5%	N/A*
-	+	-	58	13.2%	11.1, 14.3	25.1%	51.6%	18.9%	4.4%	1.4%	N/A*				N/A*
+	+	-	18	4.3%	3.7, 5.0	15.3%	53.1%	25.4%	6.2%	1.6%	18.1%	77.3%	15.9%	6.8%	N/A*
-	-	+	19	4.1%	3.6, 4.8	N/A*					N/A*				4.4 (3.0)
+	-	+	86	1.8%	1.5, 2.3	N/A*					15.7%	76.5%	17.7%	5.9%	4.2 (3.1)
-	+	+	41	8.4%	6.9, 9.3	1.7%	24.9%	50.3%	23.1%	13.4%	N/A*				4.6 (2.9)
+	+	+	41	8.5%	7.9, 9.4	2.0%	20.2%	48.4%	29.4%	19.1%	42.0%	53.7%	28.9%	17.5%	4.7 (3.1)

'+/-' Indicates the presence/absence (respectively) of each measure of eczema. *Prevalence estimates were calculated to represent the greater Melbourne population. Weighting the proportion of the participants with each eczema measure using sampling weights, calculated using the probability that a family participated in the study based on family history of food allergy and other allergy, infantile eczema, family size, socioeconomic status, and whether the infant was tolerating peanut in their diet. *Treatment history available for infants who were positive for itchy rash; age at diagnosis available for infants with a diagnosis of eczema; and details of sites affected (of elbow flexures, face and back) for infants with visible eczema at 12 months of age. † 'Mild steroids' refers to topical preparations that are available without a doctor's prescription in Australia (e.g. 0.5% hydrocortisone), whilst 'strong steroids' refer to preparations only available with a prescription.

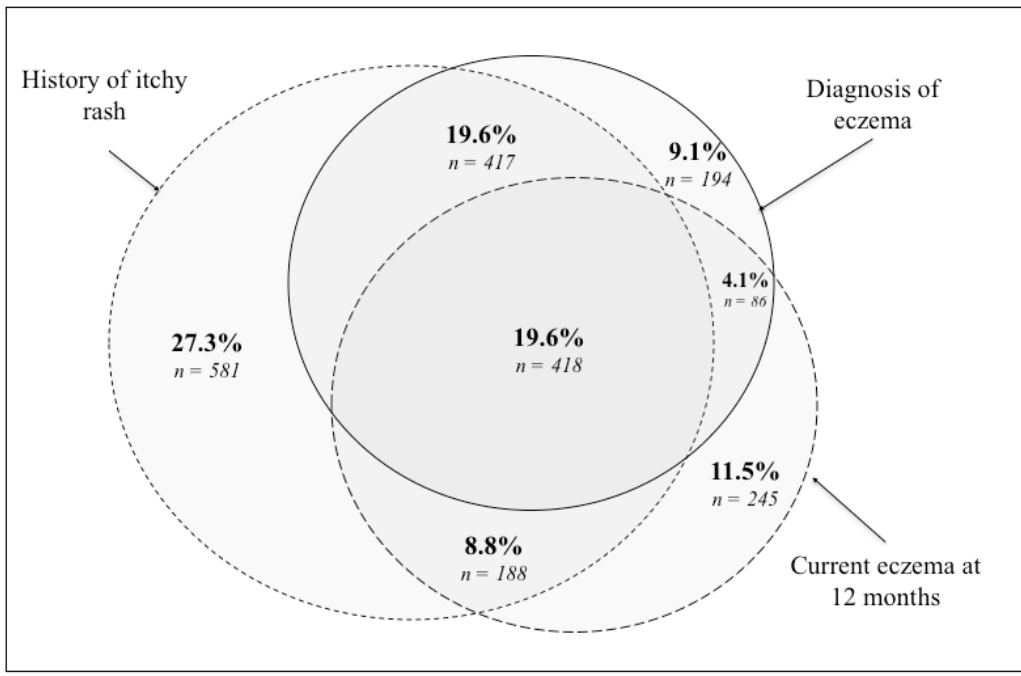
Table 3: Multinomial logistic regression of demographic and family allergy-related predictors of eczema in infancy

	History of eczema**, but no current eczema			Any current eczema			<i>p</i> value for difference
	aM-OR†	95% CI	<i>p</i>	aM-OR†	95% CI	<i>p</i>	
Male sex	1.4	1.2, 1.8	<0.001	1.4	1.1, 1.6	<0.001	0.60
# Parents of East Asian decent*	1.3	1.0, 1.6	0.022	1.6	1.3, 1.9	<0.001	0.11
Migrated to Australia	1.1	0.8, 1.4	0.61	1.0	0.7, 1.2	0.76	0.51
Increasing socio-economic status***	1.0	0.0, 1.1	0.89	1.0	0.9, 1.1	0.69	0.67
Maternal eczema	2.2	1.7, 2.8	<0.001	1.7	1.3, 2.1	<0.001	0.07
Paternal eczema	1.7	1.2, 2.4	0.002	1.5	1.1, 2.1	0.008	0.54
Maternal asthma	1.2	0.9, 1.6	0.18	1.4	1.1, 1.8	0.007	0.33
Paternal asthma	1.0	0.8, 1.4	0.87	1.1	0.9, 1.5	0.30	0.50
Maternal allergic rhinitis	1.2	1.0, 1.5	0.13	1.1	0.9, 1.3	0.35	0.57
Paternal allergic rhinitis	1.3	1.0, 1.6	0.036	1.2	1.0, 1.4	0.13	0.53

*East Asia region includes Brunei, Burma, Cambodia, China, Hong Kong, Indonesia, Japan, Korea, Laos, Macau, Malaysia, Papua New Guinea, Philippines, Singapore, Taiwan, Thailand and Vietnam. †Multinomial logistic regression model includes adjustment for all other factors in the table, M-OR = multinomial odds ratio. Control group for each eczema groups are infants with no current eczema, itchy rash or diagnosed eczema **History of eczema defined by a previous diagnosis of eczema, or a history of itchy rash that was treated with topical steroids. ***OR is for each increase in SEIFA quintile, from baseline (least advantaged quintile) to each quintile of increasing advantage. SEIFA was developed by the Australian Bureau of Statistics to compare relative socio-economic advantage and disadvantage, economic resources (income, assets and expenditure) and educational and occupational characteristics.



A



B

