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Title Page

**Asian children living in Australia have a different profile of allergy
and anaphylaxis than Australian-born children: a State-wide survey**

Running title:

Allergy profile of Asian children living in Australia

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Abstract

Background

Asian children born in Australia have higher rates of eczema and nut allergy than non-Asian children. However, it is not known whether this country of birth differential exists for other allergies or anaphylaxis risk.

Objective

We investigated the influence of maternal and child's country of birth on the prevalence of parent-reported eczema, asthma, food allergy, and being diagnosed by a doctor as being "at risk of anaphylaxis".

Methods

We assessed the relationship between mother and child country of birth and allergies using the 2010 School Entrant Health Questionnaire, completed for 57,005 5-year old children (85.8% response rate) in Victoria, Australia. Analyses were conducted using logistic regression with results presented as odds ratios (OR) with 95% confidence intervals (CIs).

Results

Children born in Australia to Asian-born mothers were more likely to have parent-reported food allergy (OR 2.33, 95%CI 1.96-2.77) and eczema (OR 2.04, 95%CI 1.73-2.41), but not more likely to have asthma (OR 0.87, 95% CI 0.74-1.02) than non-Asian children. By contrast, children born in Asia who subsequently migrated to Australia had a lower risk of food allergy (OR 0.33, 95%CI 0.20-0.55), eczema (OR 0.37, 95%CI 0.24-0.57) and asthma (OR 0.29, 95% CI 0.21-0.40).

Patterns of anaphylaxis risk differed depending on the trigger. Compared with Australian-born non-Asian children, Australian-born Asian children were more likely to be diagnosed as being at risk of both food-induced and non-food induced anaphylaxis. For children born in Asia, risk was lower for anaphylaxis to milk, peanut and tree nuts compared to non-Asian children, but higher for soy, wheat and non-food triggers.

Conclusions & Clinical Relevance

Patterns of allergy/anaphylaxis risk and their triggers differed according to both ethnicity and country of birth, suggesting a gene-environment factor is in play. The difference in

patterns for asthma compared with other atopic diseases is surprising and warrants further exploration.

Keywords:

Anaphylaxis, food allergy, paediatrics, Asian, ethnicity, country of birth

Abbreviations:

FIA: food-induced anaphylaxis; Non-FIA: non-food induced anaphylaxis; VLBW: very low birth weight; SEIFA: Socio-economic Indexes for Areas; OR: odds ratios; CIs: confidence intervals.

Introduction

The burden of food allergy in children is increasing in terms of prevalence and hospitalizations in both developed and developing countries [1]. We recently reported that 10% of infants in Melbourne, Australia had challenge-proven food allergy, the highest food allergy population prevalence yet reported [2]. An increasing trend of anaphylaxis incidence has been consistently reported in various countries [3, 4]. Most studies confirmed food as the major trigger for anaphylaxis in children [4-6] and food allergy, in particular, drove the rapid increase in anaphylaxis admissions in Australian children reported between 1998 to 2012 [3].

Australia has a high proportion of residents that are of Asian descent and our studies have shown that Australian-born infants with Asian ethnicity were more likely to have nut allergy and eczema compared to Caucasian ethnicity [7] while children born in Asia living in Australia at age 5 years had a lower prevalence of nut allergy compared with Australian-born non-Asian children [8]. This indicates that both genetic and environmental factors likely alter the development of nut allergy. However, less is known about other allergies and anaphylaxis among these groups. Seafood (fish and shellfish) and wheat have been reported to be the main triggers of food allergy and anaphylaxis in some Asian countries [9-13], but little is known about the prevalence of these allergies in Asian children living in other countries.

By using data from the state-wide compulsory School Entrant Health Questionnaire (SEHQ) completed for nearly 60,000 children in 2010 at the time of school entry, we aimed to investigate the influence of maternal and child's country of birth on the prevalence of parent-reported eczema, asthma, food allergy to a range of foods and risk of anaphylaxis by comparing children born in Asia (the largest non-Caucasian immigrant group in Victoria [14]), Australian-born Asian children and Australian-born non-Asian children. We also investigated other demographic and environmental factors associated with the prevalence of food-induced and non-food induced anaphylaxis risk.

99 **Methods**

100 ***Study design and population***

101 This study utilised data from the School Entrant Health Questionnaire (SEHQ), which is a
102 state level questionnaire completed by the parent or guardian of all children entering
103 primary school (preparatory grade students). Children commence school in Victoria at
104 approximately 5 years of age. The survey has been distributed annually to children enrolled
105 in primary schools in Victoria, Australia since mid-1997 [15]. In 2010, the survey included
106 questions on allergy and anaphylaxis which are used in the present analysis.

107 ***Demographic, environmental exposures and confounders***

108 The following variables from the questionnaire were considered in our analysis: mother's
109 country of birth (father's country of birth was not asked in the questionnaire), children's age
110 and gender, child's country of birth (age of migration was not available for children born
111 overseas), whether the child had very low birth weight (less than 1500g) (VLBW), whether
112 the child lives with siblings, postcode of residence, mother's education level, father's
113 education level and region of residence.

114 The socio-economic status for children in our study was calculated using Socio-Economic
115 Indexes for Areas (SEIFA) by matching postcodes of residence with SEIFA data from the
116 Australian Bureau of Statistics. SEIFA takes into account economic and social conditions of
117 people and households within an area, including both relative advantage and disadvantage
118 measures [8].

119 ***Definitions of allergic outcomes***

120 The following food allergy and anaphylaxis questions were asked in the survey:

- 121 1) Has your child ever been told by a doctor that your child has an allergy problem? If
122 yes, parents were instructed to check boxes indicating which food or substance the
123 child was allergic to. Options provided in checkboxes were: milk, eggs, peanuts, tree
124 nuts, soy, wheat, fish/shellfish, bee/insect stings, other.
- 125 2) Have you ever been told by a doctor that your child's allergy may result in
126 anaphylaxis? Parents were also instructed to check boxes indicating which food or
127 substance the child was anaphylactic to (options as defined above).

Parent-reported food allergy (hereafter referred to as “food allergy”) was defined as a report of allergy caused by any of the eight listed foods/food groups (milk, eggs, peanuts, tree nuts, soy, wheat, fish, shellfish). These foods collectively account for more than 90% of IgE-mediated food allergies in children [16].

A student was defined as being at risk of anaphylaxis if the parent reported being told by a doctor that their child’s allergy may result in anaphylaxis for any of the listed foods or substances. If a food trigger was selected, children were classified as being at risk of food-induced anaphylaxis (FIA). Those at risk of anaphylaxis are likely to be those with IgE-mediated food allergy rather than non-IgE mediated food allergy or intolerances. Non-food-induced anaphylaxis (Non-FIA) was defined as any other trigger (bee/insect sting or other trigger, details of “other” triggers were not available). Separate categories were created for risk of anaphylaxis to bee/insect stings and other triggers.

Asthma: An affirmative response to “Have you ever been told by a doctor that your child has asthma”.

Eczema: An affirmative response to “Does your child have ongoing eczema (with daily effects)?”

No additional information on symptoms of allergy or method of diagnosis was collected. The survey did not collect information on allergic rhinitis or hay fever.

Definitions of maternal and child country of birth and ethnicity

Parents were asked to indicate where the child was born and where the child’s mother was born. Checkboxes were provided for the following countries: Australia, New Zealand, England, South Africa, China, Philippines, India, USA, South Korea, Hong Kong (SAR of China) and “other”, with answers for other countries recorded in a free text field. Answers recorded in this free text field were not available and individuals who answered “other” were therefore excluded from the analysis.

We further classified country of birth as “East Asia” if the mother/child was born in China, the Philippines, South Korea or Hong Kong (SAR of China).

For the primary analysis, we combined East Asia and India into a single category ("Asia"). We also conducted a sensitivity analysis which considered East Asia and India as separate categories.

The term "children born in Asia" was applied if the children were born in Asia to Asian-born mothers. "Australian-born Asian children" refers to children born in Australia with Asian-born mothers. "Australian-born non-Asian children" refers to children born in Australia with Australian-born mothers. A combined variable with the categories Australia-Australia, Asia-Australia, Asia-Asia referring to maternal-child country of birth was generated for the analysis.

Statistical analysis

We described the prevalence of allergic outcomes (food allergy, asthma, eczema, food-induced anaphylaxis, non-food anaphylaxis) within categories of maternal and child's country of birth (Australia-Australia; Asia-Australia; Asia-Asia) as the observed proportion with 95% confidence intervals (95% CIs) for the population prevalence calculated by using the normal approximation to the binomial distribution.

Adjusted logistic regression models were used to examine the association between maternal or child country of birth and allergic outcomes, with results presented as odds ratios (OR) with 95% CIs. Potential confounders considered in our analysis were factors that have been reported to be associated with allergic disease in previous studies [7, 8]. Potential confounders considered in the models were children's age and gender, region of residence, whether child had very low birth weight (less than 1500g) (VLBW), whether child lives with any siblings, mother's education level, father's education level and SEIFA. Each model was adjusted for the potential confounder only if its inclusion in the model altered an OR by greater than 10%.

Separate adjusted logistic regression models examined the association between other demographic factors (child's sex, presence of siblings, region, parental education and socioeconomic status) and allergic outcomes.

All data were analysed using Stata version 15.0 (StataCorp, College Station, TX, USA).

Ethics approval

Ethics approval was granted by the human research ethics committees of the Royal Children's Hospital (HREC# 34168) and the Victorian Department of Education and Early Childhood Development.

Results

In 2010, 57,005 of 66,444 (85.8%) eligible children returned the questionnaire and were therefore included in this study. The demographics of these children have been reported elsewhere [8] and are summarized in online repository Table S1. Among participants, the number of Australian-born non-Asian children was 39,585, Australian-born Asian children was 1,657 (representing the largest non-Caucasian ethnic group) and children born in Asia was 1,005. The mean age of participating children was 4.9 years (range 4-7 years).

Patterns of food allergy, eczema and asthma according to ethnicity and country of birth

The prevalence of food allergy, eczema and asthma by maternal and child country of birth is illustrated in **Figure 1**. Australian-born Asian children were more likely to have food allergy (aOR 2.33, 95%CI 1.96-2.77, $P<0.001$) and eczema (aOR 2.04, 95%CI 1.73-2.41, $P<0.001$), but were not more likely to have asthma (aOR 0.87, 95%CI 0.74-1.02, $P=0.08$) compared to Australian-born non-Asian children (**online repository Table S2**). By contrast, children born in Asia who subsequently migrated to Australia had a lower risk of food allergy (aOR 0.33, 95%CI 0.20-0.55, $P<0.001$), eczema (aOR 0.41, 95%CI 0.28-0.62, $P<0.001$) and asthma (aOR 0.29, 95%CI 0.21-0.40, $P<0.001$) compared to Australian-born non-Asian children.

Among children with Asian-born mothers, those born in Australia had a greatly increased risk of food allergy (aOR 6.97, 95%CI 4.14-11.74, $P<0.001$), eczema (aOR 5.50, 95%CI 3.50-8.66, $P<0.001$) and asthma (aOR 2.99, 95%CI 2.12-4.22, $P<0.001$) compared to those who were born in Asia.

Patterns of anaphylaxis risk and its triggers according to ethnicity and country of birth

The prevalence of FIA and non-FIA risk by maternal and child country of birth is shown in **Figure 2**. The overall prevalence of FIA, bee/insect stings anaphylaxis and other anaphylaxis risk in our study was 2.81% (95%CI 2.67-2.94), 0.23% (95%CI 0.26-0.35) and 1.31% (95%CI 1.21-1.40), respectively. Compared to Australian-born non-Asian children, Asian children

were more likely to be diagnosed as at risk of FIA (aOR 1.50, 95%CI 1.16-1.94, P=0.002) if they were born in Australia but they had a lower risk (aOR 0.28, 95%CI 0.14-0.56, P<0.001) if they were born in Asia (**Figure 2, online repository Table S2**). Interestingly, Asian children were more likely than Australian-born non-Asian children to be diagnosed as at risk of anaphylaxis with a non-food trigger regardless of where they were born.

In **online repository Figure S1**, we show the results with Asia further divided into East Asia and India. Both showed similar patterns although the numbers in some groups were small.

Patterns of FIA risk among ethnicity groups differed depending on the food trigger (**Figure 3, online repository Table S3**). Australian-born Asian children were more likely to be at risk of anaphylaxis to peanut and tree nuts compared to Australian-born non-Asian children. By contrast, children born in Asia who migrated to Australia were less likely to be at risk of anaphylaxis to peanut, tree nuts and milk compared to Australian-born non-Asian children. Interestingly, Asian children had a higher risk of anaphylaxis to soy, wheat and seafood (fish/shellfish) compared to Australian-born non-Asian children regardless of where they were born.

Among Asian children, those born in Australia were more likely to be at risk of anaphylaxis to milk (aOR 3.06, 95%CI 1.17-8.04, P=0.023), peanut (aOR 14.14, 95%CI 3.42-58.46, P<0.001) and tree nuts (aOR 9.43, 95%CI 2.25-39.59, P=0.002) compared to those who were born in Asia.

The association between demographic factors and anaphylaxis risk

The association between various demographic factors and risk of anaphylaxis (food induced and non-food induced) are summarized in **Table 1**.

Boys were more likely to be at risk of FIA than girls, but there was less evidence of a difference in non-FIA between genders (**Table 1**). Children born with very low birth weight (VLBW) were less likely to be at risk of FIA, while there was little evidence of a difference in non-FIA. Living with siblings was associated with less risk of non-FIA while there was no association for FIA. There was little difference between regions, except for a slightly lower rate of FIA risk in Gippsland. Children whose mothers had a higher education level were more likely to be at risk of FIA reported by parents, but less likely to be at risk of non-FIA.

Discussion

In a large state-wide survey of more than 57,000 children entering school (age 5 years), we found children with Asian-born mothers who were themselves born in Australia had a higher prevalence of most food allergies, anaphylaxis risk and eczema compared with Australian-born non-Asian children, whilst children born in Asia had a lower risk. In addition, we found that the patterns of anaphylaxis risk in ethnicity groups differed depending on the trigger. Asian children were more likely than non-Asian children to be at risk of anaphylaxis elicited by soy, wheat, seafood and non-food triggers regardless of whether the Asian child was born in Australia or Asia.

The strengths of this study are the large sample size and population-based data set collecting information from 86% of school entrant children in Victoria in a single year. This dataset provides a range of valuable demographics and health status for children across the whole state. Limitations include the use of parent-reported allergy outcomes. The questionnaire captured information on whether the child was ever considered as at potential risk of anaphylaxis, rather than acute anaphylaxis onset. As expected, the prevalence of anaphylaxis in our study is therefore higher than the reported hospital admission rates for anaphylaxis in Australia [3] and in European countries [17]. In a previous study, Loke et al. reported that 1.6% of Victorian government school students in the first year of school were currently at risk of anaphylaxis (from any trigger) in 2010 [18]. In that study, students at risk of anaphylaxis were defined as those prescribed an adrenaline auto-injectors by their doctors and with a current Australasian Society of Clinical Immunology and Allergy Anaphylaxis Management Plan. Factors that may have contributed to the higher prevalence reported by us in comparison to Loke et al. include that our criteria captured past history of anaphylaxis risk as well as current cases and therefore will include a proportion of children who may have outgrown their food allergies early in life. In addition, our questionnaire did not record whether the child carried a current adrenaline auto-injector and over-reporting of anaphylaxis risk in our study is also possible. The relatively high prevalence of “other anaphylaxis” risk in our study might be because this group combined all other triggers together, including medications/drug, serum, latex and other potential triggers. It is also possible that some rare food triggers were misclassified as “other” triggers, although we think this is unlikely to be a large contributor to this group, since the

most common foods responsible for IgE-mediated food allergy and anaphylaxis were captured in the food-induced anaphylaxis group. Another potential limitation is that there might be differences in health care utilisation according to maternal country of birth and length of time spent in Australia that could contribute to the differences observed (e.g. families recently migrated from Asia may be less likely to seek medical diagnosis of asthma), but this also seems unlikely to completely explain our findings since the patterns were not the same for all allergic diseases. Another limitation is the use of maternal country of birth as an indirect marker of ethnicity since other information on ethnicity was not collected. However in our previous population-based study in Victoria we found that parental country of birth was highly correlated (more than 93.0%) with genetically-determined Asian or Caucasian ancestry [19].

In our study, children born in Asia who subsequently migrated to Australia had a lower risk of food allergy and eczema compared with Australian-born both Asian and non-Asian children. Similar findings have been reported in previous studies from America and the International Study of Asthma and Allergies in Childhood (ISAAC), which found that immigrants had lower risk of eczema and food allergy [20, 21], although no information was provided on the immigrant's country of origin. This could be explained by the hygiene hypothesis that either infections or microbial exposures in early childhood may protect against atopic diseases [20]. Alternatively, higher relative humidity and higher UV exposure in some Asian regions such as Philippines and Hong Kong compared with Victoria, Australia, could have contributed to lower rates of eczema in early life. Subsequently, this may have reduced the likelihood of food sensitisation occurring through the skin and thus reduce the risk of food allergy [22, 23]. Differences in Vitamin D exposure might also contribute to differences in allergy rates between growing up in Asia and those growing up in Australia [24].

While both eczema and food allergy were around twice as common in Australian-born Asian children as in non-Asian children, the prevalence of asthma was not similarly increased, suggesting a different pathogenesis between asthma and other allergic diseases. This is consistent with previous study by Buka et al. reporting that rates of asthma were similar between children of South Asian origin and white British populations living in Britain [25].

In addition, children born in Asia who migrated to Australia subsequently had a much lower risk of asthma compared with both Australian-born Asian and non-Asian children. Previous studies have suggested that the asthma prevalence of migrants tends to become more similar to the prevalence in the native population over time [21, 26]. Unfortunately, there was no information on the duration of residence time in Australia for the Asian children in our questionnaire although it had to be less than their age which ranged from 4 to 7 years. Therefore, we are unable to comment on the impact of length of stay of the children and/or their adaptation of lifestyle and dietary habits [27]. The difference in asthma prevalence observed in our study may change over time, as the children age and spend a longer time in the Australian environment.

Our finding of a higher prevalence of food-induced anaphylaxis risk in Australian-born Asian children is consistent with recently published studies in the US and New Zealand that reported that Asian children had higher rates of hospital presentations for food-induced anaphylaxis [28, 29]. However, these studies did not capture information on place of birth, which we found to be important in determining risk of food-induced anaphylaxis in the Asian population. Previous studies reported wheat and seafood as the most common food to elicit anaphylaxis in Asian countries [12, 13]. In our study, children with Asian ancestry more often reported risk of anaphylaxis triggered by soy, wheat and seafood regardless of where they were born. Reasons for this higher prevalence of anaphylaxis risk to soy, wheat and seafood require further study, but may reflect differences in dietary patterns in the Asian population, including potentially differences in timing of introduction of these foods into the infant diet [30].

Conclusions

In conclusion, we found different profiles of allergy and anaphylaxis risk between children born in Asia, Australian-born Asian children and Australian-born non-Asian children. The observed patterns might be explained by a gene-environment interaction, whereby a risk factor present in the Australian environment has a greater effect on allergy risk among those with an Asian ancestry who are exposed to this risk factor early in life. The different pattern of asthma (lower in Asian children born in Australia) compared with other allergic diseases is surprising and warrants further exploration, while bearing in mind the potential for cultural differences in health seeking behaviour.

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Conflict of Interest

The authors have no conflict of interest to declare.

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Legends to figures

Figure 1. Prevalence (%; 95%CI) of food allergy, eczema and asthma categorized by mother's versus child's country of birth.

Figure 2. Prevalence (%; 95%CI) of food-induced anaphylaxis and non-food anaphylaxis risk by mother's versus child's country of birth.

Figure 3. Prevalence (%; 95%CI) of individual food triggers for anaphylaxis risk by mother's versus child's country of birth.

Tables

Table 1. Association between demographic variables and risk of food-induced and non-food induced anaphylaxis

Variable category	FIA		Non-FIA	
	Adjusted OR* (95%CI)	P-value [†]	Adjusted OR* (95%CI)	P-value [†]
Sex of child				
Female	reference		reference	
Male	1.31 (1.17, 1.48)	<0.001	1.14 (0.96, 1.34)	0.127
VLBW				
No	reference		reference	
Yes	0.41 (0.20, 0.83)	0.013	0.68 (0.32, 1.45)	0.321
Live with sibling				
No	reference		reference	
Yes	1.02 (0.89, 1.15)	0.83	0.69 (0.56, 0.85)	0.001
Region of residence[‡]				
North	reference		reference	
West	1.01 (0.81, 1.25)	0.939	1.12 (0.84, 1.49)	0.444
South	0.93 (0.77, 1.12)	0.426	0.98 (0.76, 1.27)	0.898
East	0.99 (0.82, 1.20)	0.839	1.11 (0.83, 1.48)	0.492
Barwon South West	0.90 (0.69, 1.17)	0.509	0.85 (0.57, 1.26)	0.425
Gippsland	0.67 (0.47, 0.97)	0.033	1.04 (0.67, 1.61)	0.871
Grampians	1.09 (0.80, 1.48)	0.572	0.76 (0.45, 1.26)	0.281

Hume	0.86 (0.64, 1.20)	0.413	0.78 (0.49, 1.23)	0.280
Loddon Mallee	0.86 (0.64, 1.15)	0.312	0.97 (0.64, 1.46)	0.887
Mother's education				
Some high school	reference		reference	
Completed high school	1.28 (1.02, 1.60)	0.034	1.00 (0.78, 1.29)	0.997
TAFE trade certificate or	1.42 (1.13, 1.79)	0.003	0.86 (0.65, 1.14)	0.285
University/tertiary	1.64 (1.31, 2.05)	<0.001	0.69 (0.52, 0.91)	0.010
Father's education				
Some high school	reference		reference	
Completed high school	1.14 (0.92, 1.41)	0.245	0.98 (0.75, 1.27)	0.885
TAFE trade certificate or	1.30 (1.07, 1.58)	0.010	0.90 (0.70, 1.16)	0.406
University/tertiary	1.20 (0.97, 1.48)	0.096	0.78 (0.59, 1.04)	0.088
SEIFA quintile[^]				
1 (most advantage)	reference		reference	
2	1.03 (0.86, 1.25)	0.732	0.86 (0.67, 1.10)	0.231
3	1.06 (0.86, 1.30)	0.583	1.04 (0.79, 1.35)	0.801
4	1.16 (0.96, 1.39)	0.119	0.89 (0.69, 1.15)	0.373
5 (least advantage)	1.24 (0.97, 1.58)	0.084	0.90 (0.62, 1.31)	0.593

456 *All factors were included in the model simultaneously and models were additionally
457 adjusted for mother and child country of birth and child's age.

458 †P-values <0.05 are highlighted in bold font.

459 ^SEIFA: Socio-economic Indexes for Areas: most disadvantaged = 1, least disadvantaged = 5.

460 ‡ "North" was the baseline category to compare with other regions of residence.

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