

Title Page

## **Children of Asian ethnicity in Australia have higher risk of food allergy and early onset eczema than those in Singapore**

Running title: Risk factors for food allergy in Australia & Singapore

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## **Abstract**

**Background:** In Western countries, Asian children have higher food allergy risk than Caucasian children. The early life environmental exposures for this discrepancy are unclear. We aimed to compare prevalence of food allergy and associated risk factors between Asian children in Singapore and Australia.

**Methods:** We studied children in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort (n=878) and children of Asian ancestry in the HealthNuts cohort (n=314). Food allergy was defined as a positive SPT  $\geq 3$  mm to egg or peanut AND either a convincing history of IgE-mediated reaction at 18 months (GUSTO) or a positive oral food challenge at 14-18 months (HealthNuts). Eczema was defined as parent-reported doctor diagnosis.

**Results:** Food allergy prevalence was 1.1% in Singapore and 15.0% in Australia ( $p < 0.001$ ). Egg introduction was more often delayed ( $> 10$  months) in Singapore (63.5%) than Australia (16.3%;  $p < 0.001$ ). Prevalence of early onset eczema ( $< 6$  months) was lower in Singapore (8.4%) than Australia (30.5%) ( $p < 0.001$ ). Children with early onset eczema were more likely to have food allergy than those without eczema in Australia [aOR 5.11 (2.34-11.14);  $p < 0.001$ ] and Singapore [aOR 4.00 (0.62-25.8);  $p = 0.145$ ].

**Conclusions:** Among Asian children, prevalence of early onset eczema and food allergy was higher in Australia than Singapore. Further research with larger sample sizes and harmonized definitions of food allergy between cohorts is required to confirm and extend these findings. Research on environmental factors influencing eczema onset in Australia and Singapore may aid understanding of food allergy pathogenesis in different parts of the world.

### **Key words:**

Asian children, eczema, food allergy, GUSTO, HealthNuts

### **Abbreviations:**

GUSTO: Growing Up in Singapore Towards healthy Outcomes

ISAAC: International Study of Asthma and Allergies in Childhood

SACC: Standard Australian Classification of Countries

SPT: Skin Prick Test

OFC: Oral Food Challenge

## Introduction

Food allergy rates are rising rapidly worldwide but this phenomenon seems to be observed mainly in Western populations<sup>1</sup> whereas food allergy prevalence in children living in Asia remains relatively low.<sup>2</sup> The prevalence of peanut allergy, for example, is as high as 1-3% in children in the USA, UK and Australia,<sup>3-5</sup> but is <1% in most Asian countries.<sup>2</sup> The Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study found that the prevalence of parental reported peanut allergy was only 0.1-0.3% in children up to 4 years of age.<sup>6</sup> In contrast, the prevalence of peanut allergy in a longitudinal food allergy cohort in Melbourne, Australia (HealthNuts) was 3.1% at 1 year of age and 1.9% at 4 years of age.<sup>3</sup> In the same study, egg allergy prevalence was 9.5% and this dropped to 1.2% by age 4 years.

The combined effects of migration, ethnicity and country of birth appear to influence the burden of allergic diseases,<sup>7</sup> particularly in children of Asian ancestry living in Western countries. Previous work in the HealthNuts cohort has shown that Australian-born infants of Asian ancestry were more likely to be food allergic than Australian-born non-Asians. The prevalence of peanut allergy was 3 times higher in infants with at least one East Asian parent compared to those with two Australian-born parents.<sup>8</sup> Up to 50% of infants with two East Asian parents developed eczema and 25% had challenge-proven food allergy by age 1 year. Paradoxically, the parents of these East Asian infants themselves had lower rates of allergic diseases compared with Australian-born parents. Further, in a separate study, children who had migrated postnatally from Asia to Australia had a lower risk of peanut allergy<sup>9</sup>, any food allergy and asthma compared to Australian-born non-Asian children.<sup>10</sup> Among those of Asian ethnicity, being born in Australia conferred significantly higher risks of food allergy [aOR 6.96 (4.14 – 11.74); p<0.001], eczema [aOR 5.50 (3.50-8.66); p<0.001] and asthma [aOR 2.99 (2.12-4.22); p<0.001] than being born in Asia<sup>10</sup>.



The ethnic differences appear to extend to other allergic disorders as well. At age 6 years, children of Asian descent living in Australia had a higher prevalence of allergic rhinitis and aeroallergen sensitization compared with Caucasian children.<sup>11</sup> These observations suggest that both genetic and early life environmental factors play a vital role in driving the development of allergies in individuals of Asian ancestry. However, no direct comparison of the prevalence and risk factors for food allergy between Asians living in different geographical locations has been performed before.

Using data from the GUSTO cohort in Singapore and the HealthNuts cohort in Australia, we compared the prevalence of food allergy and evaluated risk factors such as eczema, environmental exposures and dietary factors in modulating food allergy risk in Asian children living in Singapore and Australia.

## **Methods**

### **Singapore GUSTO cohort**

The GUSTO cohort is a population based birth cohort study in Singapore comprising extensive longitudinal assessments of mother-infant dyads from pregnancy and through childhood. The GUSTO study methodology has been previously described in detail.<sup>12</sup> Briefly, a total of 1247 women of Chinese, Malay and Indian ethnicity who were in their first trimester of pregnancy from the two major public obstetric hospitals in Singapore – the National University Hospital (NUH) and the KK Women’s and Children’s Hospital (KKH) – were included between June 2009 and September 2010.

Ethics approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group and the Centralised Institutional Review Board of SingHealth. Written informed consent was taken from all participants.

Parental demographic data inclusive of age, ethnicity, education level and socio-economic status as well as family history of atopy (self-reported diagnosis of asthma, allergic rhinitis or eczema in the mother, father or sibling) were captured using interviewer-administered questionnaires. Maternal dietary intake during pregnancy was captured using food diaries administered in the third trimester. Information on birth and delivery, child health, pet ownership, childcare attendance, feeding practices in early life and allergic outcomes were obtained from interviewer-administered questionnaires, including the modified ISAAC questionnaire<sup>13-15</sup> at 3-monthly time-points from birth until 18 months of age and 6-monthly thereafter. Skin prick tests (SPT) were offered to all children at age 18, 36 and 60 months, while food reaction data was obtained via questionnaires at ages 6, 12, 18, 36, 48 and 60 months.

## **Australia HealthNuts cohort**

The HealthNuts study is a population-based longitudinal study of food allergy that recruited 11-15 month old children (mean age 12.7 months) recruited at community immunisation centres in Melbourne, Australia (N=5,276). The HealthNuts study methodology has previously been described in detail <sup>16</sup>. In summary, all children underwent skin prick testing to four common allergens (egg, peanut, sesame and either shrimp or cow's milk) at the immunisation centres. Children with a detectable wheal size  $\geq 1$  mm to any of the foods were invited to the HealthNuts clinic at the Royal Children's Hospital, Melbourne for an oral food challenge (OFC) to ascertain their food allergy status (generally between 14-18 months of age). During the clinic visit, children underwent repeat SPT and a blood test to determine their food specific IgE levels. The children's mean age at the first clinic visit was  $13.9 \pm 1.3$  months (standard deviation). OFCs were carried out using a pre-determined protocol described previously. <sup>17,18</sup> The following objective criteria were used to define a positive OFC: three or more concurrent, non-contact urticaria persisting for at least 5 minutes, perioral or periorbital angioedema, vomiting or evidence of circulatory or respiratory compromise, occurring within 2 hours of ingestion of a dose during food challenge. The food challenge was deemed negative if the child was able to complete the challenge with no reaction. <sup>18</sup>

Ethics approval was obtained from the Human Research Ethics Committee (HREC) of the Victorian State Government Office for Children (reference no. CDF/07/492) and Department of Human Services (reference no. 10/07) as well as the Royal Children's Hospital HREC (reference no. 27047). Parents gave written consent for child's participation in the study.

## **Definitions**

### ***Ethnicity Definitions***

*Asians in GUSTO* were made up of children born in Singapore whose parents and grandparents were of homogenous Chinese, Malay or Indian ethnicity, which are the three main ethnic groups in Singapore.

*Asians in HealthNuts* consisted of children born in Australia with both parents born in North East Asia region (China, Hong Kong, Japan, Taiwan, Macau, North Korea, South Korea), South East Asia region (Vietnam, Philippines, Singapore, Thailand, Indonesia, Malaysia, Cambodia, Laos) or South Asia region (India and Sri Lanka). These countries were grouped based on the Standard Australian Classification of Countries (SACC) which were developed to be relevant to Australia's multicultural society for use in analysing Australian-based country of origin data<sup>19</sup>. Groups in the SACC comprise geographically proximate countries which have broadly similar social, cultural, economic and political characteristics. The parent's country of birth act as proxy for ancestry background in HealthNuts. It was shown previously that parent's country of birth information correlated well with genetically inferred ancestry in this cohort<sup>20</sup>. All analyses in the HealthNuts cohort were restricted to this Asian population.

### ***Outcome Definitions – Food Allergy***

In GUSTO, food allergy was defined by a positive SPT of  $\geq 3$  mm to egg or peanut at 18 months **AND** a convincing history of an IgE-mediated reaction upon exposure to egg or peanut.

In HealthNuts, food allergy was defined as a positive SPT  $\geq 3$  mm to egg or peanut at the clinic visit at 14-18 months of age **AND** a positive OFC to egg or peanut. Previous definitions using the HealthNuts data was based on a positive SPT  $\geq 2$  mm to relevant foods. This was modified in the current study in order to have a harmonised definition that is in line with GUSTO.

### ***Exposure definitions***

We also used harmonised exposure definitions to ensure they are comparable between the two studies. Definitions for all exposure variables included in the analysis are summarized in Table S1. For eczema, the following definitions were used in each cohort:

In GUSTO, eczema was defined as a parent-reported doctor's diagnosis of eczema at any time point up until 18 months. A categorical variable was also created with the following categories: “No eczema, Eczema that started before 6 months” and “Eczema that started after 6 months”.

Similarly, in HealthNuts, eczema was defined as a parent-reported diagnosis of eczema based on an affirmative response to the question “Has your child ever been diagnosed with eczema?” In conjunction with responses to the question “Age when eczema was first diagnosed”, a categorical variable with the following categories were created “No eczema”, “Eczema that started before 6 months” and “Eczema that started after 6 months”.

### **Statistical Analysis**

The prevalence of food allergy in each study was estimated as the observed proportion with 95% confidence intervals generated using the normal approximation to the binomial distribution.

Baseline characteristics of each study were reported and compared using chi-square tests. Student’s t-test was carried out to compare continuous variables (e.g birthweight).

Adjusted logistic regression models were used to analyse the association between exposure variables and food allergy in each of the two Asian populations separately, to obtain odds ratios (OR) and 95% confidence intervals. For this, three sets of hypothesis-driven analyses were carried out:

- i. Association between eczema and food allergy (adjusted for maternal history of self-reported atopy, child’s sex and pet ownership)

- ii. Association between household exposure to tobacco smoke and proxy markers of hygiene hypothesis (use of antibiotics, dog ownership, cat ownership, childcare attendance, any siblings and caesarean delivery) with food allergy (adjusted for maternal history of self-reported atopy and child's sex)
- iii. Association between infant diet and food allergy (adjusted for child's sex, maternal history of atopy and child history of eczema)

Interaction analyses were carried out to assess whether the relationship between each potential risk factor and food allergy differed between the two cohorts. Regression models were fitted to the combined group of Singapore and Australian children, with product terms added to test for interactions between the study cohort and each risk factor. Models with and without interaction terms were compared using the likelihood ratio test.

## **Results**

### **Prevalence of food allergy**

The prevalence of food allergy among 18 month old Asian children in Singapore was 1.1% (n=10/878) (95% CI 0.6 - 2.1%) compared to 15.0% (n=47/314) (95% CI 11.4-19.4%) in 14-18 month old Asian children in Australia (p<0.001).

### **Demographics of Asian participants in each study cohort**

The demographics of participants in each study are shown in Table S2. In the Australian cohort this analysis was restricted to children with two Asian-born parents (n=314) whereas the Singapore cohort consisted of 878 Asian children (Table S2). More Singapore children had siblings (58.2% vs 45.5%, p<0.001) while fewer mothers had completed tertiary education (34.1% vs 76.9%). Paternal history of allergy was more common in Australia.

### **Environmental Exposures**

Maternal smoking during pregnancy and household exposure to tobacco smoke were more prevalent in Singapore (Table 1). Childcare attendance in the first 12 months of life was more common in Australia compared with Singapore (p<0.001). Among those attending childcare, a larger proportion of Singaporean children started childcare before 6 months whereas more Australian children started childcare after 6 months. Rates of pet ownership and use of antibiotics in infancy were similar between the two studies.

## **Eczema**

**Error! Reference source not found.** Eczema diagnosis was more common in Australian children than Singaporean children. In particular, the percentage of children with early onset eczema (before 6 months) was higher in Australia at 30.5% compared to 8.4% in GUSTO,  $p < 0.001$ , while the percentage of children with later onset eczema was similar between the two cohorts (Table 1).

Of those with eczema, a higher proportion of Australian children (84.2%) required topical steroids compared to Singaporean children (61.9%),  $p = 0.001$ .

## **Infant's Diet**

Delayed introduction of solids ( $> 6$  months) and egg into the infant's diet was more common in Singapore compared with Australia (Table 1). A significantly larger proportion of Singaporean children had not been introduced to egg by 12 months of age compared to only 3.9% of Australian children. Peanut introduction was delayed in both cohorts, with only 10.6% of Singaporean children and 13.8% of Australian children introducing peanut before 10 months of age. By age 12 months, the majority of Singaporean children and Australian children had still not been introduced to peanut.

We investigated whether the timing of introduction of food in the two cohorts differed by eczema status, since pre-existing eczema can influence food introduction practices. Regardless of eczema status, a higher proportion of Singapore children were introduced to egg after 10 months compared to Australian children (Table S3). Among those with eczema, 17.9% of Singapore children were introduced to egg between 10 – 12 months and 59.0% still had not been introduced to egg by age 12 months. This is compared to in Australia where 14.4% had been introduced between 10-12 months and 7.2% were still not introduced by 12 months ( $p < 0.001$  for both). For peanut introduction, 23.8% of Singapore children with eczema were introduced to peanut between 10-12 months of age compared to only 5.8% of Australian



children with eczema ( $p=0.022$ ). However, the percentage of children not introduced to peanut by 12 months was higher in Australia compared to Singapore, regardless of eczema status .

When we examined within group comparisons, we found that among Australian children, a higher percentage of children with eczema (85.4%) were not introduced to peanut by 12 months compared to those without eczema (76.0%);  $p=0.031$  (Table S4). In the Singapore cohort, there was no difference in proportion of children introduced to peanut by 12 months stratified by eczema status.

In both Singapore and Australia, more children with eczema had delayed egg introduction compared to those without eczema. 7.2% of Australian children with eczema were still not introduced to egg by 12 months compared to only 1.8% who had no eczema ( $p=0.021$ ). Similarly in Singapore, 59% of children with eczema were not introduced to egg while 43.8% with no eczema were already introduced to egg by 12 months ( $p<0.001$ ).

Additionally, duration of breastfeeding was shorter among Singapore children. 87.5% of Singaporean children were already on mixed feeding in the first 6 months of life compared to 63% in Australia (Table 1).

### **Maternal diet**

Maternal dietary practices during pregnancy varied between the two studies for all investigated foods (Table 1). Fewer mothers of Singaporean children consumed nuts, peanuts, shellfish, egg and soy during pregnancy compared to mothers of Australian children (all  $p<0.001$ ).

### **Association between food allergy and potential risk factors**

In the unadjusted model, family history of allergic disease, particularly maternal and paternal history, were associated with an increased risk of food allergy in the Australian cohort but only maternal history was associated with food allergy in the Singapore cohort (Table 2). We therefore, adjusted for maternal atopic history in our model when examining the association between eczema and food allergy risk. Early onset eczema was associated with an increased risk of food allergy in both Australia and Singapore (Table 3). Children in Australia with early onset eczema (<6 months) were 5 times more likely to also have food allergy compared to those with later onset. The magnitude of association was similar for GUSTO but lacked precision and included the null [aOR 4.00 (0.62-25.8);  $p=0.145$ ]. However, of those with early onset eczema, only 5.7% of Singaporean children also had food allergy compared to 32.6% of Australian children ( $p<0.001$ ).

Eczema with use of topical steroids were strongly associated with an increased risk of food allergy in the Australian cohort ( $p<0.001$ ) (Table S6). There was weak evidence of a similar association between eczema with use of topical steroids and food allergy in the Singapore cohort ( $p=0.074$ ). Conversely, children in Singapore with eczema not requiring use of topical steroids had greater odds of developing food allergy compared to those without eczema ( $p=0.021$ ). Weak evidence for a similar association was observed in the Australian cohort ( $p=0.075$ ) (Table S6). When comparing the use of topical steroids among those with eczema, there was no evidence of an association between eczema and steroid use with risk of food allergy in both cohorts (data not shown).

In the adjusted models assessing environmental factors and infant diet, there was no evidence of an association between any of the factors examined and food allergy (Table 3). There was also no strong evidence that the association between any of the examined factors

and food allergy differed between cohorts (all interaction  $P > 0.05$ ), apart from paternal history of atopy and type of milk feeding (Table S5). In the Singapore cohort, those who were fully breastfed had increased odds of food allergy compared to those who received mixed feeding [OR 9.89 (2.59-37.87)].

## Discussion

This is the first study directly comparing the prevalence of food allergy and identifying whether known risk factors for food allergy are different in Asian children living in two different geographical locations, utilizing combined data from two cohorts – HealthNuts (Australia) and GUSTO (Singapore). Despite the ethnic similarities between both cohorts, the prevalence of food allergy in Singapore (1.1%) was substantially lower than in Asians living in Australia (15%) ( $p < 0.001$ ). Prevalence of eczema was also lower in Singapore. We also showed that early onset eczema was associated with food allergy in Australia; the magnitude of association was similar in Singapore but lacked precision with 95% CIs including the null. These findings suggest that early life environmental factors and gene-environment interactions are likely to play a significant role in modulating food allergy development in ethnic Asians.

We found that the prevalence of several risk factors and environmental exposures differed between the cohorts, namely higher maternal and household exposure to tobacco smoke and larger families in Singapore as well as a higher proportion of children with delayed introduction of solids and egg and shorter duration of exclusive breastfeeding. More Asian children in Australia had a family history of atopy, more mothers reported intake of allergenic foods during pregnancy and more mothers had completed tertiary education. The differences in these factors may be due to cultural and societal influences, as well as maternal educational background and awareness of prevailing infant feeding guidelines. Despite the observed differences, these risk factors were not strongly associated with food allergy in the respective cohorts. There was also little evidence that the relationship between individual risk factors and food allergy differed between the two cohorts.

Previous allergy guidelines internationally recommended avoidance of allergenic foods during pregnancy and in early life for the prevention of food allergy in infants.<sup>21,22</sup> However, as the evidence base for this recommendation was weak, this guideline was later revoked.<sup>23</sup>

More recently, clinical trials, systematic reviews and meta-analyses have shown early introduction of peanut and egg into the infant diet to be protective against food allergy<sup>24,25</sup>. Many mothers in Singapore, however, still do not routinely consume allergenic foods during pregnancy and more mothers in Singapore also delayed the introduction of eggs into their children's diets compared to Asian mothers in Australia. Peanut introduction mostly occurred after 12 months in both cohorts. There was no evidence of an association between timing of egg or peanut introduction in the Asian population in Singapore or Australia in adjusted models, perhaps due to limited power to detect associations. However, we have previously shown that Singaporean children have a low prevalence of food allergy despite delayed introduction of allergenic food<sup>6</sup>. Collectively, timing of introduction of allergenic foods into the infant diet is therefore unlikely to explain the higher prevalence of food allergy among Asian children in Australia. It may also be that early introduction of certain foods is beneficial only in groups at high risk of developing food allergy and given that the prevalence of allergy was generally lower in Singapore, the delay in food introduction seems unlikely to contribute a detrimental effect on the development of food allergy.

We found a much higher prevalence of early onset eczema in Australia, while the association between early onset eczema and food allergy was similar in Australian and Singaporean children. The strong association between early onset eczema and food allergy is consistent with other cohort and mechanistic studies which implicate epicutaneous sensitization to food allergens through an impaired skin barrier as the primary trigger driving the development of food allergy.<sup>26-28</sup> Notably, the prevalence of early onset eczema with increased severity was also higher in Australian-born Asian children than in children in Singapore. However, guidelines for the management of eczema and use of topical steroids are similar in the two countries. Use of moisturisers are recommended regardless of severity of eczema and topical steroids are recommended in the presence of eczema flares. It is possible

that parental attitudes to treatment may differ between these two populations, but parents from both countries typically do seek medical attention for eczema that is severe and not responding to moisturizers alone. It is thus likely that the difference in the use of topical steroids between the two studies reflects a difference in eczema severity of infants in the two countries. Early risk factors for eczema may also differ in Australia compared to Singapore.

Predisposition to eczema among Asians may be compounded by the weaker skin barrier of the East Asian skin, compared to Caucasians and African Americans <sup>29</sup>. A relatively weaker skin barrier of East Asians living in Australia may be further compromised by exposure to environmental risk factors such as a dry climate in Melbourne, further aggravating severity of eczema. The prevalence of eczema has previously been shown to be inversely related to relative ambient humidity in US children.<sup>30</sup> Other studies have shown that low humidity and low temperature decrease skin barrier function, making the skin more reactive towards irritants and allergens <sup>31</sup>. Therefore, an environment with high humidity, such as that in Singapore, may moderate the adverse consequences of eczema on epicutaneous food allergen sensitization, contributing to the lower prevalence of eczema and food allergy observed compared to that in Australia.

A combination of factors, such as environmental food allergen exposures and eczema severity, may also modulate a child's risk of developing food allergy. We have shown here that maternal allergen consumption during pregnancy was significantly lower in Singapore. This may in turn be a surrogate indicator of household allergen consumption, which has been linked with increased risks of allergen sensitization in high-risk children with eczema, in a series of studies by Brough et al. <sup>32-35</sup> Exposure to airborne peanut protein was associated with peanut sensitization and peanut allergy in children with eczema. It could thus be speculated that a combination of lower household food allergen exposures in the homes of children in Singapore, along with a lower prevalence of eczema compared to Asian children in Australia, could

contribute to the lower prevalence of food allergy in the former. In this study, we were not able to test this hypothesis as environmental allergen exposures, including household consumption of peanut or/and egg were not directly measured in both cohorts, but this is an important research question to be addressed in future studies. Other factors such as vitamin D levels and childhood vaccinations schedules, which have been shown to influence food allergy risk, were also not directly measured in this study. However, we speculate that differential effect of these factors between the two countries could contribute to the difference in prevalence observed.

Data obtained from the World Health Organisation (WHO) showed a stark difference in UVR exposure between Singapore and Melbourne. In any given year, Singapore's UVR is in the extreme high range (UV index 10-13) throughout the year whereas Melbourne's UVR fluctuates according to the different seasons, (UV index 2 in winter and 9 in summer)<sup>36</sup>. A lower UV-B exposure during fall and winter in Australia, along with reduced vitamin D synthesis, might play a role in the pathogenesis of food allergy.<sup>38</sup> In addition, childhood vaccinations can exert an important immunologic effect on the infant's immune system. Tuberculosis is endemic in Singapore, thus the Bacille-Calmette-Guerin (BCG) vaccine is part of the compulsory immunization schedule and is routinely given to all infants at birth. It is, however, not compulsory in Australia, where the incidence of tuberculosis is low. As a potent immune modulator, there has been much interest in the role of the BCG vaccine as a primary preventative strategy against childhood atopic disorders.<sup>39</sup> Furthermore, perturbations in the gut microbiome have also been linked to food allergy. There was a significant reduction in biodiversity of gut microbiota in self-reported food allergic adults in the Human Gut Project.<sup>40</sup> Gut microbiota comparisons were however not possible in this study and remains a research gap that could be filled in future inter-geographic studies.

A limitation of this study is the difference in food allergy definitions between the two cohorts. Food allergy in the Singapore cohort was defined as a parental report of a suggestive history of reaction to the food with a positive SPT, while in the Australia cohort, it was defined as a positive OFC. However, self-reported prevalence tends to overestimate the true prevalence, thus the true prevalence of food allergy may be even lower in Singaporean children, which would further increase the magnitude of difference between the two cohorts rather than nullifying it. The low food allergy prevalence in Singaporean children is also consistent with previous published studies.<sup>42,43</sup> Furthermore, the magnitude of differences in sensitisation to egg and peanut (based on SPT) between the two studies is consistent with the differences in food allergy prevalence. Additionally, eczema definition and eczema severity in both cohorts was not based on an objective measure or a validated severity score, but instead on parent-reported doctor diagnosis and topical steroid use as a proxy measure obtained from questionnaires. The analysis of risk factors for food allergy in the individual cohorts has limited statistical power due to the relatively small sample size of the Asian population in the Australian cohort study and small number of food allergic subjects in Singapore cohort study. We may be insufficiently powered to detect an association for some of the key epidemiological risk factors such as that with topical steroids use as the Singapore cohort were made up of infants with predominantly mild eczema and few severe cases.

Despite these limitations, the GUSTO and HealthNuts cohorts are two of the largest, well-phenotyped and comprehensive population-based childhood cohorts in the Asia Pacific region, which are unselected for allergy risk and have been shown to be reflective of the characteristics of the general population<sup>16</sup>. This is also the first inter-geographical comparison of food allergy and its risk factors in Asian children residing in two different geographical locations. The statistical comparisons made possible through raw data sharing between the cohorts is also unparalleled. These findings highlight the children of East Asian-born parents



living in Western countries as a high-risk allergic group. This group of children therefore might benefit from more frequent monitoring clinically. These findings are also important clinically with regards to targeted implementation of nutritional strategies as a prevention and management strategy.

## **Conclusion**

The prevalence of food allergy and early onset eczema is much higher in Australian children of Asian ancestry compared to Asian children in Singapore. Genetically predisposed children of Asian ancestry may have an increased risk of food allergy upon exposure to environmental risk factors. Eczema appears to be more severe in Australia, whereas the high humidity in Singapore may abrogate the impact of skin barrier deficits on epicutaneous food allergen sensitization and food allergy, contributing to the lower prevalence of food allergy in Singapore. This calls into question the role of epigenetics and other yet to be identified risk factors such as diet, microbiome and meteorological influences.

**Table 1** Comparison of hygiene hypothesis-associated variables, eczema status, infant and maternal dietary intake between Australia (N=314) and Singapore (N=878).

<b>Exposure</b>	<b>Australia N (%)</b>	<b>Singapore N (%)</b>	<b>P-value*</b>
<b>Hygiene hypothesis variables</b>			
<b>Maternal smoking during pregnancy</b>	1 (0.3)	21 (2.4)	<b>0.018</b>
<b>Household exposure to tobacco smoke</b>	62 (19.8)	276 (38.2)	<b>&lt; 0.001</b>
<b>Age started childcare</b>			
None (ref)	254 (81.7)	651 (90.4)	
< 6 months	11 (3.5)	44 (6.1)	
≥ 6 months	46 (14.8)	25 (3.5)	<b>&lt; 0.001</b>
<b>Cat ownership</b>	10 (3.2)	26 (3.1)	0.956
<b>Dog ownership</b>	24 (7.6)	39 (5.5)	0.176
<b>Infant antibiotic use (ever)</b>	124 (40.9)	351 (45.9)	0.137
<b>Eczema</b>			
<b>Infant eczema</b>			
None (ref)	168 (59.6)	691 (83.2)	
< 6 months	86 (30.5)	70 (8.4)	<b>&lt; 0.001</b>
≥ 6 months	28 (9.9)	70 (8.4)	<b>0.036</b>
<b>Use of topical steroids to treat eczema</b>			
No eczema (ref)	168 (67.2)	635 (85.8)	
Eczema + steroids	69 (27.6)	65 (8.8)	<b>&lt; 0.001</b>
Eczema + no steroids	13 (5.2)	40 (5.4)	0.533
<b>Infant diet</b>			
<b>Age at solid introduction</b>			
≤ 6 months	273 (91.6)	664 (84.1)	
> 6 months	25 (8.4)	126 (16.0)	<b>0.001</b>
<b>Age at egg introduction</b>			
≤ 10 months	257 (83.7)	295 (36.5)	
> 10 months	38 (12.4)	140 (17.3)	<b>&lt;0.001</b>
Not yet given by 12 months	12 (3.9)	373 (46.2)	<b>&lt;0.001</b>
<b>Age at peanut introduction</b>			

<b>Exposure</b>	<b>Australia N (%)</b>	<b>Singapore N (%)</b>	<b>P-value*</b>
≤ 10 months	40 (13.8)	82 (10.6)	
10-12 months	18 (6.2)	177 (22.9)	<b>&lt;0.001</b>
Not yet given by 12 months	232 (80.0)	516 (66.6)	0.696
<b>Type of milk feeding in the first 6 months of life</b>			
Mixed feeding	194 (63.0)	710 (87.6)	
Fully formula fed	12 (3.9)	40 (4.9)	0.783
Fully breastfed	102 (33.1)	61 (7.5)	<b>&lt; 0.001</b>
<b>Duration of breastfeeding</b>			
< 1 month	21 (6.9)	208 (24.6)	<b>&lt; 0.001</b>
1 - 2 months	25 (8.2)	157 (18.6)	<b>&lt; 0.001</b>
3 - 5 months	56 (18.4)	149 (17.6)	<b>0.004</b>
6-11 months	82 (27.0)	151 (17.9)	0.269
≥ 12 months	120 (39.5)	181 (21.4)	
<b>Maternal diet during pregnancy</b>			
<b>Any peanut consumption</b>	244 (85.6)	121 (14.0)	<b>&lt; 0.001</b>
<b>Any egg consumption</b>	277 (94.5)	486 (56.4)	<b>&lt; 0.001</b>
<b>Any tree nut consumption</b>	215 (83.0)	67 (7.8)	<b>&lt; 0.001</b>
<b>Any shellfish/crustacean consumption</b>	189 (69.2)	256 (29.7)	<b>&lt; 0.001</b>
<b>Any soy consumption</b>	243 (87.4)	343 (39.8)	<b>&lt; 0.001</b>

\*For variables with more than 2 categories, P-values shown are pairwise P-values obtained from comparison of the relevant category against reference category.

**Table 2** Univariate analyses of key associations (p<0.05) between environmental exposure and food allergy in Australia and Singapore

	Australia (N=314)		Singapore (N=878)		Australia (N=314)		Singapore (N=878)		P interaction
	Non Food-Allergic N (%)	Food Allergic N (%)	Non Food-Allergic N (%)	Food Allergic N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value	
<b>Demographics and environmental factors</b>									
<b>Gender</b>									
Male	134 (51)	35 (74.5)	451 (52)	7 (70)	1	-	1	-	-
Female	129 (49)	12 (25.5)	417 (48)	3 (30)	0.36 (0.18-0.72)	<b>0.004</b>	0.46 (0.12-1.80)	0.267	0.735
<b>Cat Ownership</b>									
No	261 (97.8)	43 (91.5)	797 (96.8)	10 (100)	1	-	1	-	-
Yes	6 (2.2)	4 (8.5)	26 (3.2)	0 (0)	4.04 (1.1-14.93)	<b>0.036</b>	NA	NA	NA
<b>Family and personal history of atopy</b>									
<b>Paternal Atopy</b>									
No	184 (68.9)	18 (38.3)	612 (71.7)	8 (80)	1	-	1	-	-
Yes	83 (31.1)	29 (61.7)	242 (28.3)	2 (20)	3.57 (1.88-6.79)	<b>&lt;0.001</b>	0.63 (0.13-3.00)	0.564	<b>0.044</b>
<b>Maternal Atopy</b>									
No	200 (74.9)	24 (51.1)	601 (70.4)	3 (30.0)	1	-	1	-	-
Yes	67 (25.1)	23 (48.9)	253 (29.6)	7 (70.0)	2.86 (1.52-5.40)	<b>0.001</b>	5.54 (1.42-21.6)	<b>0.014</b>	0.388
<b>Family History Atopy</b>									
No	129 (48.3)	11 (23.4)	387 (45.2)	2 (20)	1	-	1	-	-
Yes	138 (51.7)	36 (76.6)	469 (54.8)	8 (80)	3.06 (1.49-6.26)	<b>0.002</b>	3.30 (0.70-15.6)	0.132	0.931
<b>Eczema Diagnosis</b>									
No eczema	155 (92.3)	13 (7.7)	687 (99.4)	4 (0.6)	1	-	1	-	-

	Australia (N=314)		Singapore (N=878)		Australia (N=314)		Singapore (N=878)		P interaction
	Non Food-Allergic N (%)	Food Allergic N (%)	Non Food-Allergic N (%)	Food Allergic N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value	
Before 6 months	58 (67.4)	28 (32.6)	66 (94.3)	4 (5.7)	5.76 (2.79-11.87)	<0.001	10.41 (2.54-42.58)	0.001	0.463
After 6 months	23 (82.1)	5 (17.9)	68 (97.1)	2 (2.9)	2.59 (0.85-7.95)	0.096	5.05 (0.91-28.09)	0.064	0.523
<b>Eczema diagnosis with steroid use</b>									
No eczema	155 (92.3)	13 (7.7)	632 (99.5)	3 (0.5)	1	-	1	-	-
Eczema + steroids	45 (65.2)	24 (34.8)	62 (95.4)	3 (4.6)	6.36 (3.00-13.49)	<0.001	10.19 (2.01-51.58)	0.005	0.605
Eczema + no steroids	10 (76.9)	3 (23.1)	37 (92.5)	3 (7.5)	3.58 (0.87-14.63)	0.076	17.08 (3.33-87.55)	0.001	0.156
<b>Infant Diet</b>									
<b>Type of milk feeding</b>									
Mixed feeding	165 (63)	29 (63)	705 (87.9)	5 (55.6)	1	-	1	-	-
Fully formula feed	9 (3.4)	3 (6.5)	40 (5.0)	0 (0)	1.9 (0.48-7.43)	0.358	NA	NA	NA
Fully breastfed	88 (33.6)	14 (30.4)	57 (7.1)	4 (44.4)	0.91 (0.45-1.8)	0.777	9.89 (2.59-37.87)	0.001	0.002
<b>Maternal Diet during pregnancy</b>									
<b>Egg consumption</b>									
No	10 (4)	6 (13.6)	370 (43.4)	6 (66.7)	1	-	1	-	-
Yes	239 (96)	38 (86.4)	483 (56.6)	3 (33.3)	0.26 (0.09-0.77)	0.015	0.38 (0.10-1.54)	0.177	0.681
<b>Soy consumption</b>									
No	25 (10.5)	10 (24.4)	514 (60.3)	5 (55.6)	1	-	1	-	-
Yes	212 (89.5)	31 (75.6)	339 (39.7)	4 (44.4)	0.37 (0.16-0.83)	0.017	1.21 (0.32-4.55)	0.775	0.131

NA- not applicable. Where no children fall into one particular group of a variable (n=0), ORs were not able to be obtained and rows are indicated as NA.

**Table 3** Adjusted models for the risk factors of food allergy in Australia and Singapore.

	Australia (n=278)		Singapore (n=666)		P interaction
<b>Model 1<sup>†</sup>: Eczema</b>	<b>aOR (95% CI)</b>	<b>P-value</b>	<b>aOR (95% CI)</b>	<b>P-value</b>	
No eczema	1	-	1	-	-
< 6 months	5.11 (2.34-11.14)	<0.001	4.00 (0.62-25.8)	0.145	0.920
≥ 6 months	2.34 (0.75-7.34)	0.145	4.16 (0.65-26.49)	0.132	0.412

aOR – adjusted odds ratio. <sup>†</sup>Adjusted for maternal history of atopy, child’s sex and pet ownership.

	Australia (n=294)		Singapore (n=622)		P interaction
<b>Model 2<sup>‡</sup>: Hygiene hypothesis</b>	<b>aOR (95% CI)</b>	<b>P-value</b>	<b>aOR (95% CI)</b>	<b>P-value</b>	
<b>Use of antibiotics</b>	1.27 (0.64-2.53)	0.497	1.64 (0.35-7.78)	0.532	0.857
<b>Dog ownership</b>	0.68 (0.17-2.69)	0.579	1.98 (0.21-18.34)	0.547	0.294
<b>Cat ownership</b>	4.87 (0.95-24.95)	0.058	NA	NA	NA
<b>Childcare attendance</b>	0.87 (0.34-2.23)	0.772	1.07 (0.12-9.68)	0.955	0.729
<b>Any siblings</b>	1.50 (0.75-3)	0.251	1.36 (0.28-6.58)	0.699	0.736
<b>Household exposure to tobacco smoke</b>	1.15 (0.49-2.71)	0.745	0.21 (0.02-1.83)	0.157	0.178
<b>Caesarean delivery</b>	1.04 (0.50-2.16)	0.911	0.45 (0.05-3.98)	0.473	0.486

aOR – adjusted odds ratio

<sup>‡</sup> model adjusted for sex and maternal history of atopy

	Australia (n=238)		Singapore (n=204) <sup>§</sup>		P interaction
<b>Model 3<sup>¶</sup>: Diet</b>	<b>aOR (95% CI)</b>	<b>P-value</b>	<b>aOR (95% CI)</b>	<b>P-value</b>	
<b>Age of solid introduction</b>					
≤ 6 months	1	-	1	-	-
> 6 months	1.45 (0.42-5.07)	0.560	NA	NA	NA
<b>Age of egg introduction</b>					
≤ 10 months	1	-	1	-	-
10-12 months	0.94 (0.31-2.88)	0.915	NA	NA	NA
Not yet given	2.06 (0.46-9.19)	0.343	NA	NA	NA
<b>Age of peanut introduction</b>					
Not yet given	1	-	1	-	-
≤ 10 mths	0.73 (0.21-2.45)	0.605	NA	NA	NA
> 10 mths	0.50 (0.06-4.32)	0.531	1.51 (0.27-8.46)	0.639	0.531

<b>Duration of breastfeeding</b>					
< 1 mths	1.62 (0.34-7.73)	0.546	NA	NA	NA
1-2 mths	1.07 (0.24-4.67)	0.930	0.92 (0.08-10.4)	0.946	0.550
3-5 mths	1.79 (0.65-4.92)	0.261	0.52 (0.05-5.39)	0.581	0.203
6-11 mths	1.28 (0.46-3.53)	0.634	1.01 (0.16-6.26)	0.991	0.523
≥ 12 mths	1	-	1	-	-

aOR – adjusted odds ratio, NA – not applicable. Odds ratios could not be obtained as there were no children in that particular group. For example, in model 3, for egg introduction, there were no children introduced to egg between 10 to 12 months with food allergy in the GUSTO study.

§sample size greatly reduced due to missing maternal atopy data which was a confounder in the model and low food allergy cases that have introduced solids, egg and peanut by the first year of life.

¶model adjusted for sex, eczema diagnosis (<6 months, >=6 months or no eczema) and maternal history of atopy



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