Published in final edited form as:

J Allergy Clin Immunol Pract. 2018 ; 6(2): 466–475.e1. doi:10.1016/j.jaip.2017.06.001.

Low food allergy prevalence despite delayed introduction of allergenic foods – data from the GUSTO Cohort

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Conflict of Interest Statement

Chong YS has received reimbursement for speaking at conferences sponsored by Abbott Nutrition, Nestle, and Danone. Godfrey KM has received reimbursement for speaking at conferences sponsored by Nestle and Shek LP has received reimbursement for speaking at conferences sponsored by Danone and Nestle and consulting for Mead Johnson and Nestle.

Godfrey KM, Chong YS are part of an academic consortium that has received research funding from Abbot Nutrition, Nestle and Danone. Shek LP has received research funding from Danone.

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Abstract

Background—There is mounting evidence that early introduction of allergenic food decreases the risk of food allergy development, especially in high-risk infants with eczema. However, there is a lack of data to suggest if this association holds true in Asian populations.

Objective—We investigated the relationship between timing of introduction of allergenic foods and food allergy outcomes in infants in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study.

Methods—The GUSTO cohort recruited 1152 mothers of Chinese, Malay and Indian ethnicity who had singleton, naturally conceived pregnancies and followed their offspring prospectively. Information on demographics, child health, infant feeding practices and a convincing history of IgE-mediated food allergy were obtained from interviewer-administered questionnaires at multiple time-points. Corroborative skin prick tests to food allergens were performed at 18 and 36 months.

Results—The majority of infants were introduced to egg (49.6%), peanut (88.7%) and shellfish (90.2%) after 10 months of age. Food allergy prevalence was however very low, egg 0.35% - 1.8%; peanut allergy 0.1% - 0.3% and shellfish 0.2 - 0.9% between 12 to 48 months. There were no significant associations between the timing of introduction of allergenic foods and the development of food allergy, adjusted for confounders including breastfeeding and eczema.

Conclusions—Food allergy rates in Singapore are low despite delayed introduction of allergenic foods. Early introduction of allergenic foods may thus not be necessary in populations where overall food allergy prevalence is low and infant feeding recommendations should thus be carefully tailored to individual populations.

Keywords

food allergy; allergy prevention; solids introduction; allergenic food introduction; complementary feeding; egg; milk; peanut

Background

The recent publication of several randomized controlled trials investigating the early introduction of allergenic foods for food allergy prevention has fuelled renewed interest in the long-standing debate on the optimal timing of introduction of allergenic foods (1–6).

Previous guidelines released in 2000 by the World Health Organization (WHO) recommended that solid foods should not be introduced into the diets of infants until 6 months of age (7). The American Academy of Pediatrics (AAP) further recommended maternal restriction of cow's milk, egg, fish, peanuts and tree nuts during lactation and that dairy products should be delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age for the prevention of food allergy (8). However, in the light of interim studies which failed to show protective benefits of the above measures, the American Academy of Pediatrics (AAP) and the National Institute of Allergy and Infectious Diseases

(NIAID) replaced these guidelines in 2008 with new recommendations that complementary foods should instead be introduced to infants no later than 4-6 months of age and that delayed introduction of allergenic foods was no longer necessary (9, 10). This was further corroborated by observational data from birth cohorts in Europe, UK and the United States published after 2008, which found no benefit in delaying solid food introduction (11, 12). In fact, a protective effect against food allergy was observed in infants with a parental history of atopy (13) and normal healthy infants in whom solids were introduced before 4 months (14).

Du Toit et al. observed that Israeli children who consumed peanuts in high quantities from early life had a significantly lower prevalence of peanut allergy compared to Jewish children living in the UK who avoided peanuts (15). A study of 13, 234 newborn infants in Israel found that infants exposed to cow's milk in the first 14 days of life were less likely to become cow's milk allergic compared with those with first exposure after 14 days (16). The Australian HealthNuts study observed that delayed introduction of cooked egg was associated with an increased risk of egg allergies at age 12 months (17) and Poole et al. also found that the delayed introduction of cereal grains after 6 months of life was associated with an increased risk of IgE-mediated wheat allergy (18). A case-control study of cow's milk allergic Japanese infants by Onizawa et al. (19) likewise observed a lower incidence of cow's milk allergy in infants in whom cow's milk had been introduced within the first month of life.

The Learning Early About Peanut allergy (LEAP) study was a landmark randomized controlled trial published in 2015. It showed a significant risk reduction of peanut allergy at age 5 years in high risk UK infants (with severe eczema and/or egg allergy and peanut skin prick test (SPT) responses of $<4\text{mm}$) who had consumed peanut regularly from 4-11 months of age (1). However, several other randomized controlled trials in Australia and Germany, which tested this hypothesis in egg allergy, failed to demonstrate convincing evidence that early egg introduction was able to reduce the risk of egg allergy in both high risk and normal risk infants (3-5, 20). The Enquiring About Tolerance (EAT) study also did not show any efficacy of early introduction of 6 allergenic foods to fully breastfed normal risk infants against food allergy development although some protection for peanut and egg allergy was observed in the per-protocol analysis only (2). A meta-analysis of these early introduction trials found that early introduction of peanut and egg was associated with a lower risk of respective food allergy, though it was acknowledged there were limitations such as imprecise effect estimates, indirectness and heterogeneity between the populations studied (21).

There are, however, scant data on the effects of the timing of complementary or allergenic food introduction and the development of food allergies in other Asian populations. Asia is the largest and most populous continent in the world, home to more than 4.4 billion people with enormous cultural, dietary and religious diversity. Food allergy rates in Asia are low, ranging from just 1.1% in Thailand(22) to 3.8% in China(23), the highest of which was 5% in Japan (24) and Korea (25); in comparison to 10% in Australia, 5% in the United States and 4-6% in the United Kingdom in children below 5 years of age (26). There is currently no published data on the overall prevalence of food allergy in Singapore, but a large population-based survey of school-children by Shek et al reported prevalences of shellfish and peanut

allergy, by convincing history alone, to be 1.19% and 0.64% respectively in 4-6 year old children; and 5.23% and 0.47% in 14-16 year old school children (27). The timing of complementary feeding has historically been postulated to be one of the major contributory factors towards the relatively lower food allergy rates in Asia (28). Between 25%-65% of Chinese infants were introduced to complementary foods before 4 months of age (29, 30), presumably reflected in their low food allergy risk, whereas only 3% of Australian infants and 10% of UK infants were weaned before 4 months (31, 32).

In this study, we sought to explore the associations between the timing of allergenic food introduction and the development of food allergy in the GUSTO (Growing Up in Singapore Towards healthy Outcomes) birth cohort.

Methods

The GUSTO cohort is a population based, birth cohort study in Singapore comprising extensive longitudinal assessments of mother-infant pairs from pregnancy and through childhood. The GUSTO study methodology has been previously described in detail (33). We recruited 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) - between June 2009 and September 2010, of whom 1152 had singleton, naturally conceived pregnancies and were included in this study. The ethics boards of both hospitals approved this study.

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 at recruitment using interviewer-administered questionnaires. Information on birth and delivery, child health, pet ownership, childcare attendance, eczema and food allergy of the offspring were obtained from interviewer-administered questionnaires, including the modified ISAAC questionnaire (34–36), at birth, 3, 6, 9, 12, 15, 18, 24, 36 and 48 months of age. Eczema was defined as a parental-reported doctor's diagnosis of eczema at any of the above time-points. Food allergy was defined as a convincing history of an IgE-mediated reaction to a food product at 12, 18, 24, 36 or 48 months; at 18 and 36 months, the definition included a positive skin prick test (SPT), with a wheal of 3mm or larger, in addition to a convincing history of an IgE-mediated reaction to the food allergen.

Breastfeeding, infant feeding and complementary food introduction practices were ascertained from interviewer-administered questionnaires at 3 weeks, 6 weeks, 3, 6, 9 and 12 months of age. Information on breastfeeding status at 6 months of age as well as the age of introduction of all solid foods, inclusive of allergenic foods such as cow's milk, egg, peanut and shellfish, were gathered from these questionnaires. The age of introduction of allergenic foods was determined from answers to the questions: "Has your child eaten the following (food)?": cow's milk (which included cow's milk based formulas), egg white, egg yolk, peanut", "How old was the child when he/she first ate the following (food)?" at each time-

point and at 36 months, the question “Is the child *currently* eating the following (food)?” was again asked to verify ongoing consumption of the food item.

Statistical analysis

All data collected were analyzed using SPSS Version 22.0 (IBM Corp, New York, NY, USA) for Windows. Fisher’s exact test was used to assess significance between food allergy and demographic characteristics, infant characteristics and feeding practices across each time point for data with values less than five counts. Risk factors for food allergy at the various time-points were analyzed using multivariate logistic regression with Bonferroni correction, adjusting for confounders such as ethnicity, gender, household income, maternal education status, breastfeeding and mode of delivery. Results with p values <0.05 were considered significant. Univariate analysis of the timing of introduction of each allergenic food (milk, egg, peanut and shellfish) in association with sensitization and food allergy outcomes were analyzed using Fisher’s exact test to indicate trends. Timing of introduction of egg was analyzed by early introduction (defined by introduction before 6 months of age) and delayed introduction (after 10 months of age) and further subgroup analysis of the high-risk infants who had eczema was also performed. Multivariate logistic regression adjusted for potential confounders including breastfeeding status and family history of atopy, where sample size allowed.

Results

Timing of complementary and allergenic food introduction

A total of 922 participants (80%) completed questionnaires at 6 months, 902 (78.3%) at 12 months, 769 (66.8%) at 18 months, 881 (76.4%) at 24 months, 855 (74.2%) at 36 months and 851 (73.9%) at 48 months.

Twenty infants (2.2%) were introduced to solids before 4 months of age and 281 (31.2%) were introduced to solids between 4-6 months of age. The majority of infants (66.6%) were weaned after 6 months of age (mean 5.6 months, range 1-10 months). The first solid foods introduced were rice cereal (53.7%), non-rice cereal (17.2%) and rice porridge (12.1%). Timing of introduction of allergenic foods such as egg, peanut and shellfish was delayed beyond 10 months of age in the majority of GUSTO infants ($p<0.001$) (Figure 1). The majority of infants were introduced to cow’s milk before 4 months of age (66.7%) - as 51.3% of the cohort received cow’s milk in the form of infant formula in the first month of life, the overall mean age of cow’s milk introduction was 3.8 ± 6.24 months. However, egg yolk (mean age at introduction 9.5 ± 3.54 months) and egg white (10.5 ± 4.10 months) were introduced much later. Data on timing of shellfish and peanut introduction were available up to 12 months and 36 months respectively. The majority of infants (84.3%) had still not consumed any shellfish by 12 months of age and 4.9% of infants had not yet been exposed to peanut by 36 months of age. Peanut was only introduced at a mean age of 19 ± 7.87 months in those who had been exposed by 36 months of age.

Food Allergy

The overall prevalence of food allergy at 12 months was 2.9% (26/902) and 2.7% (21/769) at 18 months but this dropped to 1.6% (14/881), 1.1% (9/855) and 1.5% (13/851) at 24, 36 and 48 months respectively (Figure 2). Egg was the most common allergenic food at 12 months (1.8%), 18 months (1.2%, SPT range 3-7mm) and 24 months (0.7%). Cow's milk was the next most common, affecting 0.1-0.44% of infants between 12 to 24 months (SPT 3mm). However in the older age group, shellfish was the predominant allergen though this prevalence was still low - 0.6% (5/855) at 36 months and 0.9% (8/851) at 48 months. Peanut allergy was exceedingly rare in the Singapore population, affecting only 0.1-0.3% of infants across all the time-points (SPT range 4-10mm). Wheat, soy, fish and tree nut allergies were rare in this population and were grouped under "Others" in Figure 2. A convincing history of wheat allergy was reported in only 0.1% (1/902) at 12 months, 0.1% (1/769) at 18 months and none at 24 months. A convincing history of soy-related reactions were reported in 2/769 (0.2%) at 18 months and none at 12 and 24 months. Skin prick tests to wheat and soy were not performed in this cohort because of the low prevalence of wheat and soy allergy in our population (unpublished data).

The cumulative incidence of eczema at 3 months was 3.8% (34/850), 9.6% (79/819) at 6 months, 15% (115/769) at 12 months, 20.7% (151/730) at 18 months and 23.1% (172/743) at 24 months. Baseline characteristics of food allergic and non-food allergic infants at 12 months of age are shown in Table 1. Food allergic infants were significantly more likely to have a family history of atopy ($p=0.006$), pre-existing eczema at 3 and 6 months of age ($p<0.001$) and came from families who owned cats ($p<0.001$). Multivariate analysis of demographic risk factors for food allergy at 12, 18, 24 and 36 months are summarized in Table 2.

Antecedent doctor-diagnosed eczema was a significant risk factor for food allergy at all time-points but after Bonferroni correction, eczema at 3, 6 and 12 months of age remained significant for food allergy at 12 months of age. Subjects who had required the use of topical steroids, used as a surrogate indicator of greater disease severity, had an even higher risk of developing food allergy by age 12 months. The use of topical steroids before ages 3, 6 and 12 months was associated with aOR of food allergy by age 12 months of 28.96 (95% CI 7.84 – 107, $p<0.001$), 23.54 (95% CI 7.54 – 73.50, $p<0.001$) and 8.30 (95% CI 2.75 – 25.10, $p<0.001$), respectively. Similar associations were also evident for food allergy at 24 months; the use of topical steroids for eczema before ages 3, 6 and 12 months had aOR of food allergy by age 12 months of 68.43 (95% CI 10.43 – 448.9, $p<0.001$), 12.87 (95% CI 2.82 – 58.82, $p=0.001$) and 8.49 (95% CI 1.84 – 39.16, $p=0.006$), respectively (Table 2).

Cat ownership at 6 months of age was associated with food allergy at 12 months of age even after Bonferroni correction, but this was not observed at 18, 24 and 36 months of age.

A family history of atopy was a risk factor for any food allergy at 12 months of age and specifically maternal rhinitis for food allergy at 18 months of age. Food allergy at 24 months of age was significantly associated with asthma in a sibling, maternal rhinitis and paternal eczema. These variables were however no longer significant after Bonferroni correction. There were no significant associations between food allergy and other demographic

variables such as ethnicity, gender, household income, maternal education status, mode of delivery and breastfeeding status at 6 months.

Infants in whom the introduction of egg was delayed beyond 10 months of age were more likely to become sensitized to egg (defined as SPT wheal of ≥ 3 mm) by 18 months of age (4.6%, SPT range 3-7mm, median 3mm) than those who had been introduced to egg before 10 months (1%, SPT range 0-3mm, median 3mm), $p=0.01$ (Supplementary Table 1).

A similar trend was observed at 36 months – 0.8% (4/519) of infants with delayed egg introduction were sensitized (SPT range 3-4mm, median 3mm) compared to none who had been introduced early, though this did not reach statistical significance. The trend towards increased sensitization was also seen in those who had delayed introduction of peanut, but not for milk, at both time-points but this was not statistically significant (Supplementary Table 1).

Timing of allergenic food introduction and food allergy development

We observed a trend between delayed introduction of egg (>10 months) and the development of egg allergy at 12, 18 and 24 months but this was not statistically significant (Supplementary Table 2). Food allergy outcomes were too small for multivariate analysis at 18 and 24 months. None of the infants who were introduced to egg early (<6 months) developed egg allergy, compared to those who were introduced to egg after 6 months of age – 1.7% at 12 months, 1.1% at 18 months and 0.8% at 24 months. The total number of infants who were introduced to egg before 6 months was very low ($N=21$), precluding further multivariate analysis.

Since infant onset eczema was a significant risk factor for food allergy, subgroup analysis was performed in this high-risk group (Supplementary Table 2). Likewise, a trend towards egg allergy at 18 (4.4%) and 24 months (3.3%) was observed in infants who were introduced to egg after 10 months of age compared to those who had been introduced earlier. The single infant who was introduced to egg before 6 months of age did not develop egg allergy at later time points. Multivariate analysis was again not possible due to small outcomes.

The trend for milk allergy was not consistent but numbers were very low: 0.6% (4/685) of infants introduced to cow's milk before 10 months of age became cow's milk allergic by 12 months of age, compared to none who were introduced to cow's milk late. The one infant who was milk allergic at 18 months had been given cow's milk before 10 months of age, but there were none in the late introduction group. At 24 months, 2/687 (0.3%) of infants introduced to cow's milk before 10 months of age were milk allergic, compared to 1/183 (0.5%) who were introduced to cow's milk late.

There were no significant associations between timing of introduction of peanut or shellfish with the development of these food allergies at later time-points. After adjustment for confounders, the timing of introduction of allergenic foods was also not significantly associated with antecedent eczema, family history of atopy, breastfeeding status at 6 months, childcare attendance or pet ownership (data not shown).

Discussion

This study demonstrates evidence contrary to the current belief that delayed allergenic food introduction increases the risk of developing food allergies. Food allergy rates in the GUSTO cohort were very low despite the delayed timing of allergenic food introduction. Infants were generally weaned in accordance to World Health Organization (WHO) infant weaning guidelines, which recommended introduction of complementary foods beginning at 6 months (37), but introduction of egg, peanut and shellfish were delayed beyond 10 months of age in the majority of infants. While we observed a small and non-significant trend towards an increased risk of egg allergy in infants who had been introduced to egg after 10 months of age, including those with eczema, the overall prevalence of egg allergy in the whole cohort was still very low. The highest prevalence was only 1.8% at 12 months of age, much lower than the Australian HealthNuts cohort (>10%) (38). The low numbers also precluded statistical adjustment for confounders and the large ORs and wide confidence intervals seen on multivariate analysis are a reflection of the small numbers.

There are scant data on timing of complementary or allergenic food introduction and food allergy outcomes in Asia. The recently published PETIT (Prevention of Egg allergy with Tiny amount InTake) study was the first randomized controlled trial in Asia, which investigated the effects of early introduction of heated egg powder in high risk Japanese infants with atopic dermatitis on the development of egg allergy (6). The intervention group received a 2-step protocol of 50mg heated whole egg powder between 6-9 months of age, which was increased to 250mg from 9-12 months of age. The authors showed a significantly reduced risk of hen's egg allergy through open food challenge at 12 months of age (8%, 5/60) compared to the placebo group (38%, 23/61) with a risk difference of 29.4% (95% CI 15.3 – 43.4) and a number needed to treat of 3.40 (2.30 – 6.52). There were, however, concerning significant differences between the intervention and placebo groups at baseline which could have biased the results towards significance: The mean SCORAD in the placebo group was higher than that in the intervention group [42.0 vs 27.5, $p=0.030$]. The egg white-specific IgE concentration was also higher at baseline in the placebo group compared to the intervention group [4.46 vs 0.73, $p=0.0051$], as was the total IgE [41.2 vs 16.5, $p=0.00024$]. The trial was also terminated early because the interim analysis of the first 100 participants showed a significant difference in the two groups, thus only a small number - 60 participants in each group - were included in the final analysis. A larger study without risk of bias would be needed before definite conclusions can be made about whether early introduction of allergenic food would be effective or even necessary in Asian populations.

Food allergy rates in Asia are generally lower than in the West (26) despite the adoption of Western lifestyles and dietary practices in many developed Asian countries like Singapore, Japan, Korea and Hong Kong. A previous study by Shek et al reported a low prevalence of peanut and shellfish allergy in 4-6 year old Singaporean infants at 0.64% and 1.19% respectively (27). This is the first and largest population based study on food allergy in Singapore. The overall incidence of food allergy in children aged 0-4 years was not higher than 3% and this does not appear to have changed significantly over the past decade. It is also unlikely that this study did not pick up peanut allergy due to late introduction beyond

the 4 year time-point as Shek et al has previously shown that the low prevalence of peanut allergy extends even to adolescents aged 14-16 years(27).

Genetic factors alone do not sufficiently explain the differences in food allergy rates between East and West. In the Australian HealthNuts study, children of Asian immigrant parents who were born in Australia had three times the risk of peanut allergy and between 2-3 times the risk of egg allergy at 1 year of age compared to their Caucasian peers, while children born in Asia who subsequently migrated to Australia were at relatively lower risk of nut and egg allergy, suggesting that epigenetic or environmental factors may modulate an individual's allergic risk (39, 40).

It could be contended that the common risk factors for food allergy in early childhood, such as eczema and breastfeeding rates, might be lower in Asia compared to the West. However, existing literature has shown that well-known risk factors for food allergy such as eczema are also common in Asia. The overall prevalence of eczema in this cohort was more than 20% (41) and similar rates have been reported in other Asian countries (42–44). In this cohort, pre-existing eczema was nonetheless still a strong predictor for the development of food allergy in the small number of subjects who were food allergic. Breastfeeding rates in Singapore are also low, which is similar to that reported in the US (45) – at 6 months less than 50% of infants in this cohort were receiving any breastmilk at all and only 2-11% of infants were still exclusively breastfed by this age (46). Despite this, there were no significant associations between breastfeeding status at 6 months and the development of food allergy at any time point.

Cat ownership appeared to be associated with food allergy in this cohort, despite adjustment for several potential confounders such as family history of atopy and pre-existing eczema. However, as total pet ownership in this cohort was very low – cat 1.1 – 4% and dog 5.6% – 6.1% at 6 and 12 months respectively and confidence intervals were wide, we reserve definite clinical conclusions regarding this observation.

Food allergy patterns in Asia also differ by age group. Shellfish allergy typically emerges later in life than cow's milk, egg and peanut allergies, and is in fact the leading cause of food allergies in adults in Asia (26). This study showed that by 3 years of age, shellfish allergy became the leading cause of food allergy, in contrast to egg and cow's milk allergies which were more prevalent in children below 2 years of age. It has been postulated that inhaled house dust mite tropomyosin might be the primary sensitizer for shellfish allergy in this region (47), especially in hot and humid climates such as South East Asia where dust mites are ubiquitous (48). House dust mite sensitization increases with age - 11.5% of children aged 18 months in this study were sensitized to house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Blomia tropicalis*), and this increased to 22.5% by 36 months of age. The house dust mite sensitization rates in atopic adults in Singapore have been shown in a separate study to be as high as 80% (49).

Compared to other populations with increased risks of peanut and egg allergies with delayed dietary introduction (15, 17), our population demonstrates an unusual inverse relationship between these two factors – low peanut and egg allergy prevalence despite delayed dietary

introduction of each. Singapore is a tropical Asian country with an inherently low food allergy prevalence, high relative humidity and a significant environmental house dust mite burden and sensitization rate – all of which may mitigate the effects of delayed allergenic food introduction in this population.

It is likely that the development of food allergy at various ages is driven by different factors unique to the individual's environmental influences in early life. It is tempting to postulate that in environments where competing environmental allergen loads, such as house dust mites, are low, cutaneous sensitization to food allergens in infants with atopic dermatitis and induction of oral tolerance through early dietary allergen introduction play more important roles. These may be less important in South East Asia where house dust mite allergens heavily outweigh other allergens as potential sensitizers for atopic disease. An alternative hypothesis is that house dust mite-related microbiome or endotoxins may play a role in modulating sensitization and clinical food allergy, but further studies are needed to investigate this.

One of the limitations in this study was the reliance on parental-reported symptoms as a convincing history of food allergy and the lack of confirmatory oral food challenges. Skin prick test positivity was used as an additional tool to verify the presence of a likely food allergy in this study. As self-reported outcomes typically inflate the true food allergy numbers, the true prevalence of food allergy would likely be even lower than was reported, lending support to the observation that food allergy (in particular peanut allergy) rates are truly low in Singapore despite the late introduction of allergenic foods. The low food allergy rates in this population, and the very small number of infants introduced to allergenic foods such as egg, peanut and shellfish before 6 months of age, limits the statistical power of this study to demonstrate an association between *early* introduction of allergic foods and protection against food allergy.

Further strengths of the GUSTO study lie in its large sample size, which was recruited from the general population, and the prospective capture of data at multiple time-points. This allowed for analysis of the associations of antecedent factors such as eczema and a positive family history with the timing of introduction of allergenic foods; as well as the latter with subsequent food allergy outcomes which removed the possibility of reverse causality – the timing of introduction of allergenic foods was not influenced by antecedent eczema or a known family history of atopy. The standardized ISAAC questionnaire used in this study for food allergy evaluation is also a well-established instrument that has been validated internationally for the assessment of allergic outcomes and associated risk factors (34–36).

Our study demonstrates that despite delayed introduction of allergenic foods in Singaporean infants, even in the high-risk groups with eczema; low exclusive breastfeeding rates and high overall eczema prevalence, the rates of food allergy in early childhood remain low – suggesting that these postnatal and environmental factors alone cannot account for this difference. The pathogenesis of food allergy is likely modulated by competing influences from multiple genetic and epigenetic factors in the antenatal period and early infancy. The primary prevention of food allergy thus requires a much more complex and multi-pronged approach than any single intervention alone. As in many aspects of precision medicine, some

interventions like the early introduction of allergenic food to high-risk infants may apply to specific populations or ethnic groups, such as the Caucasian population in UK and USA, but may not be effective or necessary in a different population such as Singapore.

More research in Asia is needed to inform the development of food allergy prevention guidelines in Asian populations with low food allergy prevalences and the adaptation of existing international guidelines should be carefully tailored to each country depending on its food allergy epidemiology and infant feeding practices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank the GUSTO study group, operational managers, research fellows, study coordinators, and data management team. The GUSTO study group includes: Pratibha Agarwal, Arijit Biswas, Choon Looi Bong, Birit F.P. Broekman, Shirong Cai, Jerry Kok Yen Chan, Yiong Huak Chan, Cornelia Yin Ing Chee, Yin Bun Cheung, Amutha Chinnadurai, Chai Kiat Chng, Mary Foong-Fong Chong, Shang Chee Chong, Mei Chien Chua, Doris Fok, Marielle V. Fortier, Anne Eng Neo Goh, Yam Thiam Daniel Goh, Joshua J. Gooley, Wee Meng Han, Mark Hanson, Christiani Jeyakumar Henry, Joanna D. Holbrook, ChinYing Hsu, Neerja Karnani, Jeevesh Kapur, Ivy Yee-Man Lau, Bee Wah Lee, Yung Seng Lee, Ngee Lek, Sok Bee Lim, Iliana Magiati, Lourdes Mary Daniel, Cheryl Ngo, Krishnamoorthy Niduvaje, Wei Wei Pang, Anqi Qiu, Boon Long Quah, Victor Samuel Rajadurai, Mary Rauff, Salome A. Rebello, Jenny L. Richmond, Anne Rifkin-Graboi, Lynette Pei-Chi Shek, Allan Sheppard, Borys Shuter, Leher Singh, Shu-E Soh, Walter Stunkel, Lin Lin Su, Kok Hian Tan, Oon Hoe Teoh, Mya Thway Tint, Hugo P S van Bever, Rob M. van Dam, Inez Bik Yun Wong, P. C. Wong, Fabian Yap, and George Seow Heong Yeo.

Sources of Funding

This research is supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Program and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC), Singapore—NMRC/TCR/004-NUS/2008; NMRC/TCR/012-NUHS/ 2014. Additional funding is provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore. K.M.G. is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre and by the European Union's Seventh Framework Program (FP7/2007–2013), projects EarlyNutrition and ODIN under grant agreement numbers 289346 and 613977.

Abbreviations

AAP	American Academy of Pediatrics
EAT	Enquiring About Tolerance
GUSTO	Growing Up in Singapore Towards healthy Outcomes
ISAAC	International Study of Asthma and Allergies in Childhood
LEAP	Learning Early About Peanut allergy
NIAD	National Institute of Allergy and Infectious Diseases
PETIT	Prevention of Egg allergy with Tiny amount InTake
SCORAD	Scoring Atopic Dermatitis – a clinical tool for the assessment of extent and severity of atopic dermatitis

SPT	Skin Prick Test
WHO	World Health Organization

References

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Highlights

What is already known about this topic?

- The LEAP study demonstrated the efficacy of early introduction of allergenic foods such as peanut for the primary prevention of peanut allergy.
- Consensus guidelines in UK and Europe now recommend the early introduction of peanut in high-risk infants to reduce the risk of developing peanut allergy.

What does this article add to our knowledge?

- The prevalence of food allergy (particularly that of peanut allergy) in Singapore, an Asian country, is low despite delayed introduction of allergenic foods such as peanut, shellfish and eggs, even in high risk infants with eczema.

How does this article impact current management guidelines?

- Changing current infant feeding practices to recommend early introduction of specific allergenic foods for food allergy prevention thus may not be applicable to all populations as a whole.
- Further studies in different ethnic groups and countries are needed before implementing new recommendations on early introduction of allergenic foods like peanuts for the prevention of food allergy universally.

Figure 1. Timing of introduction of allergenic foods to infants in the GUSTO Cohort

The age groups at which cow's milk, egg yolk, egg white, peanut and shellfish were each first introduced to infants is displayed.

Figure 2. Food Allergy in the GUSTO Cohort

The prevalence of food allergy at each time-point is displayed. Data labels indicate individual food allergy percentages in infants within each time-point. The absolute number of food allergy cases (n) and the total population (N) is shown above and below each bar respectively.

Table 1
Characteristics of Food Allergic subjects at 12 months

Demographic Variable N=902	Non Food Allergic (%) N=876	Food Allergic (%) N=26	P value
Gender			
Male	452 (96.8)	15 (3.2)	0.56
Female	424 (97.5)	11 (2.5)	
Ethnicity			
Chinese	486 (96.6)	17 (3.4)	0.27
Malay	222 (96.5)	8 (3.5)	
Indian	166 (99.4)	1 (0.6)	
Mode of Delivery			
Vaginal	610 (97.3)	17 (2.7)	0.88
Caesarean	265 (96.7)	9 (3.3)	
Maternal Education			
Non-tertiary	563 (97.4)	15 (2.6)	0.65
Tertiary	304 (96.5)	11 (3.5)	
Household income			
<\$4000	378 (97.4)	10 (2.6)	0.87
>\$4000	444 (96.9)	2 (3.6)	
Household smoking at 6 months			
No	412 (96.7)	14 (3.3)	0.56
Yes	253 (98.1)	5 (1.9)	
Breastfeeding at 6 months			
No	500 (97.3)	14 (2.7)	0.35
Yes	325 (96.4)	12 (3.6)	
Family history of atopy			
Yes	325 (95.0)	17 (5.0)	0.006
No	551 (98.4)	9 (1.6)	
Presence of sibling			
No	305 (97.8)	7 (2.2)	0.71
Yes	510 (96.8)	17 (3.2)	
Childcare attendance			
No	606 (97.1)	18 (2.9)	0.97
Yes	43 (97.7)	1 (2.3)	
Cat ownership			
No	821 (97.5)	21 (2.5)	<0.001
Yes	4 (50.0)	4 (50.0)	

Demographic Variable N=902	Non Food Allergic (%) N=876	Food Allergic (%) N=26	P value
Dog ownership			
No	613 (97.1)	18 (2.9)	0.98
Yes	39 (97.5)	1 (2.5)	
Eczema @ 3 months			
No	758 (98.3)	13 (1.7)	<0.001
Yes	22 (75.9)	7 (24.1)	
Eczema @ 6 months			
No	764 (98.3)	13 (1.7)	<0.001
Yes	48 (80.0)	12 (20.0)	

Table 2

Multivariate Analysis of Risk Factors for Food Allergy

Risk Factor		Food Allergy							
		12 months		18 months		24 months		36 months	
		Adj OR (95%CI)	Adj P value	Adj OR (95%CI)	Adj P value	Adj OR (95%CI)	Adj P value	Adj OR (95%CI)	Adj P value
Doctor Diagnosed Eczema	3 months								
		All cases	12.78 (2.53 - 64.28)	0.002*	3.36 (0.39 - 28.81)	0.27	46.10 (2.21 - 962.78) [†]	1.39 (0.011 - 173.51)	0.89
		Use of topical steroids	28.96 (7.84 - 107)	<0.001*	2.27 (0.23 - 21.9)	0.48	68.43 (10.43 - 448.9)	0.00	0.00
	6 months	All cases	7.55 (2.07 - 27.62)	0.002*	0.84 (0.12 - 6.12)	0.86	1.31 (0.106 - 17.54)	0.018 (0.00 - 4.24)	0.15
Family history of atopy		Use of topical steroids	23.54 (7.54 - 73.50)	<0.001*	9.02 (2.59 - 31.39)	<0.001*	12.87 (2.82 - 58.82)	0.00	0.00
	12 months	All cases	7.79 (3.02 - 20.10)	<0.001*	7.63 (1.13 - 50.90)	0.04	1.26 (0.04 - 40.77)	304.27 (1.98 - 46861.16) [†]	0.03
		Use of topical steroids	8.30 (2.75 - 25.10)	<0.001*	1.82 (0.34 - 9.78)	0.49	8.49 (1.84 - 39.16)	0.00	0.00
			6.69 (1.35 - 33.27)	0.02	1.17 (0.18 - 7.61)	0.87	0.05 (0.00-2.11)	2.06 (0.022 - 190.4)	0.75
Asthma	Paternal		0.23 (0.022 - 2.32)	0.21	1.023 (0.13 - 7.81)	0.98	24.14 (0.48 - 1206.80)	0.11 (0.00 - 49.77)	0.48
	Maternal		1.80 (0.48 - 6.79)	0.39	0.24 (0.02 - 3.15)	0.28	0.00	0.14 (0.00 - 54.73)	0.51
	Sibling		0.45 (0.04 - 5.05)	0.52	1.31 (0.12 - 14.9)	0.83	157.26 (2.49 - 9947.90) [†]	0.00	0.99
Rhinitis	Paternal		0.60 (0.13 - 2.86)	0.52	0.85 (0.16 - 4.61)	0.85	0.22 (0.10 - 10.17)	19.9 (0.224 - 1766.19)	0.19
	Maternal		1.13 (0.30 - 4.29)	0.86	5.56 (1.07 - 28.83)	0.04	35.38 (1.15 - 1092.40) [†]	0.22 (0.002 - 21.18)	0.52
	Sibling		0.00	0.99	0.000	0.99	0.183 (0.00 - 28.87)	43.68 (0.58 - 3270.39) [†]	0.09
Eczema	Paternal		0.44 (0.06 - 3.31)	0.43	2.43 (0.33 - 18.13)	0.39	77.72 (3.462 - 1744.58) [†]	11.69 (0.148 - 922.26) [†]	0.27

Risk Factor	Food Allergy									
		12 months		18 months		24 months		36 months		
		Adj OR (95%CI)	Adj P value	Adj OR (95%CI)	Adj P value	Adj OR (95%CI)	Adj P value	Adj OR (95%CI)	Adj P value	
	Maternal	0.50 (0.11 – 2.28)	0.37	1.08 (0.192 – 6.01)	0.93	13.68 (0.97 – 193.10)	0.05	26.33 (0.163 – 4240.87) [†]	0.21	
	Sibling	0.44 (0.05– 3.61)	0.44	3.57 (0.38 – 33.73)	0.27	1.12 (0.02 - 44.29)	0.96	0.00	0.99	
Childcare attendance		0.49 (0.04 – 6.67)	0.59	0.38 (0.012 – 7.89)	0.53	0.44 (0.01 – 16.59)	0.66	0.00	0.99	
Cat ownership @ 6 months		26.05 (3.09 – 220.01) [†]	0.003*	12.88 (1.05 – 157.43) [†]	0.05	8.67 (0.21 – 364.72)	0.26	0.000	0.99	
Dog ownership @ 6 months		1.11 (0.09 – 13.42)	0.93	1.12 (0.06 – 20.86)	0.94	0.03 (0.00 – 1124)	0.69	4354.40 (5.052 – 376123) [†]	0.02	

Adjusted for gender, ethnicity, household income, maternal education level, breastfeeding status, sibling and mode of delivery

^{*} still significant after Bonferroni correction

[†] large OR and Confidence intervals are due to small number of food allergy outcomes