# Title page

**Maternal and infant dietary patterns are not related to food allergy risk in Singapore children: GUSTO cohort study.**

**Short running title: Maternal and infant diet and childhood food allergy risk**

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**Abbreviations**

AHEI-P – Alternate Healthy Eating Index for Pregnancy

APAPARI – Asia Pacific Academy of Pediatric Allergy, Respirology & Immunology

EAACI – European Academy of Allergy and Clinical Immunology

DQI – Diet Quality Score

DQI-I – International DQI

GUSTO – Growing Up in Singapore Towards healthy Outcomes

HEI-SGP – Healthy Eating Index for Pregnant women in Singapore

RCT – Randomised Controlled Trial

SPT – Skin Prick Test

# Abstract

## Background

We previously reported that delayed allergenic food introduction in infancy did not increase food allergy risk until age 4 years within our prospective cohort. However, it remains unclear whether other aspects of maternal or infant diet play roles in the development of childhood food allergy.

## Objective

Here we examined the relationship between maternal pregnancy and infant dietary patterns and the development of food allergies until age 8 years.

## Methods

Among 1152 Singapore GUSTO study mother-infant dyads, the infant’s diet was ascertained using food frequency questionnaires at 18 months (M). Maternal dietary patterns during pregnancy were derived from 24-hour diet recalls. Food allergy was determined through interviewer-administered questionnaires at regular time points from infancy to age 8 years (Y) and defined as a positive history of allergic reactions, alongside skin prick tests at M18, Y3, Y5 and Y8.

## Results

Food allergy prevalence was 2.5% (22/883) at 12 months and generally decreased over time by 8 years (1.9%; 14/736). Higher maternal dietary quality was associated with increased risk of food allergy (p≤0.016), however, odds ratios were modest. Offspring food allergy risk up until 8 years showed no associations with measures of infant diet including timing of solids/food introduction [aOR 0.90 (0.42-1.92)], infant’s diet quality [aOR 0.93 (0.88-0.99)] or diet diversity [aOR 0.84 (0.6-1.19)]. Most infants (89%) were first introduced to cow’s milk protein within the first month of life, while egg and peanut introduction were delayed (58.3% introduced by mean age 8.8 months and 59.8% by mean age 18.1 months, respectively).

## Conclusions

Apart from maternal diet quality showing a modest association, infant’s allergenic food introduction, diet quality and dietary diversity were not associated with food allergy development in this Asian paediatric population. Interventional studies are needed to evaluate the efficacy of these approaches to food allergy prevention across different populations.

**Keywords**

Allergenic food introduction; Allergy prevention; Asian children; Food allergy; Solids introduction

# INTRODUCTION

Various infant and maternal dietary intervention strategies have been explored as a means of food allergy prevention. Recent evidence suggests that in areas with high peanut allergy prevalence, early peanut introduction may reduce the burden of peanut allergy in high-risk patients with pre-existing severe eczema or food allergy (1, 2). Timing of allergenic food introduction has been shown to reduce the risk of peanut and egg allergies(3, 4). However, as raised by a recent meta-analysis of randomised controlled trials (RCT), rates of non-compliance to such interventions are relatively high (5). While several of the included studies were carried out in Japan, the meta-analysis did not make comparisons between timing of introduction in different populations, and there is currently no data from other Asian populations, with only one ongoing RCT in China (ChiCTR2100053552) and two in Japan (UMIN000030214 and jRCTs041190089). Some studies have shown that maternal avoidance of allergenic foods during pregnancy does not prevent and may in fact increase the risk of food allergy in the offspring (6, 7). Recent studies also suggest that maternal consumption of peanuts or milk during pregnancy and lactation might reduce specific food sensitization or allergy in their offspring (8).

Alongside this key factor, overall nutrition and diet of mothers and infants have also been shown to potentially play a role. A systematic review by De Silva et al and Garcia-Larsen reported no major effect of maternal avoidance of allergenic food during pregnancy or breastfeeding on food allergy in children (9, 10). Meta analyses of vitamin supplementation, including vitamin D showed no association with any allergic outcomes (10). De Silva et al also consolidated various interventions to prevent food allergy in children. The authors found that prebiotics, vitamin supplementations and breastfeeding had little to no effect on food allergy in early childhood (9). However, there is some evidence of fish oil supplementation during pregnancy and continuing during breastfeeding having a slightly protective effect on child’s food allergy risk.

Additionally, research in assessing holistic markers of diet such as diet diversity, diet variety and diet indices in both mothers and infants are gaining traction(11). Their role in food allergy prevention is postulated given that nutrients and food are often not taken in isolation. It has been posited that a diverse diet increases the intake of essential nutrients, modulating the gut microbiome positively and thereby allergic outcomes as well (12). However, insufficient studies on maternal diet are available to conclusively determine their role in food allergy prevention (13).

As studies from various parts of the world have demonstrated variability in the patterns of prevalence and allergen triggers for food allergy and anaphylaxis across different populations (14), risk factors and the effectiveness of prevention strategies for food allergy may differ between populations. We have previously found that delayed allergenic food introduction in infancy was not associated with an increased risk of food allergy development (particularly peanut allergy) up to age 4 years in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort (15). However, as peanut and egg introduction were delayed, there remains the question of whether food allergy onset may manifest much later in this cohort. This study aimed to analyse associations between maternal and infant diet quality, diet diversity and allergenic food exposure and food allergy development up to age 8 years.

# METHODS

## Study Population

The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study is a longitudinal birth cohort study in Singapore. Pregnant women aged 18-50 years (n=1247), with spouses of homogenous ethnicity from the main ethnic groups in Singapore - Chinese, Malay, or Indian - were recruited from two major public maternity hospitals in Singapore, namely KK Women’s and Children’s Hospital (KKH) and National University Singapore (NUH), between June 2009 and September 2010. Mother-infant dyads were followed up antenatally and throughout childhood at multiple time-points. Detailed methodology of the GUSTO study has been described previously.(16)

The study received ethics approval from the Domain Specific Review Board of Singapore National Healthcare Group (D/2009/021; 26/02/2009) and the Centralised Institutional Review Board of SingHealth (2018/2767; 02/03/2009). Written informed consent was collected from all mothers.

## Maternal Data Collection and Identification

A total of 1152 women with singleton, naturally conceived pregnancies were included in this study. Parental socio-demographic characteristics such as age, ethnicity, educational level, smoking status, and family history of atopy, were collected upon recruitment (< 14 weeks of gestation) via questionnaires. Several maternal dietary measures were collected during pregnancy. These include maternal plasma vitamin D concentrations measured at 26-28 weeks of gestation, maternal consumption of allergenic food, namely peanut, egg, milk and shellfish.

### Maternal Dietary Patterns

Maternal consumption of allergenic food was captured using 3-day food diaries administered during mid-late trimester. Maternal dietary patterns during pregnancy were derived from interviewer-administered 24-hour recall diets using exploratory factor analysis resulting in three dietary patterns, namely vegetable - fruit - rice pattern; seafood - noodle pattern; and pasta - cheese - meat pattern. Trained clinical staff conducted the 24-hour recalls using a 5-stage, multiple-pass interviewing technique. To ensure better accuracy of data collection, visual aids such as food photos and portion sizes were incorporated during the interviews (17). Detailed methods on the dietary patterns derivation (18) have been described previously.

### Maternal Healthy Eating Index

Additionally, to evaluate diet quality, a maternal Healthy Eating Index for Pregnant women in Singapore (HEI-SGP) was calculated using dietary intake collected using 24-hour recalls and validated using 3-day food diaries. Detailed description of the HEI-SGP and its scoring has been described previously (19). The HEI-SGP was developed to assess diet quality of pregnant women in the GUSTO cohort. It is an adaptation of the Healthy Eating Indices (HEI) and Alternate Healthy Eating Index for Pregnancy (AHEI-P), modified to be aligned with recommendations from the Singapore dietary guidelines for pregnant women. A detailed comparison of included components in HEI-SGP compared to HEI and AHEI-P can be found in Han et al (19). The HEI-SGP is made up of 11 components (total fruit, whole fruit, total vegetables, dark green leafy and orange vegetables, total rice and alternatives, whole grains, dairy, total protein foods, use of antenatal supplements, total fat, saturated fat) reflecting dietary adequacy, quality of food groups, nutrients intake and adherence to antenatal supplementations. With a total possible score of 90, the raw HEI-SGP was then converted to a scale of 0-100. The nutrient analyses for 24-hour recalls were conducted using a nutrient software (Dietplan, Forestfield Software). The software comprises a database of locally available foods. For foods not available in the database, nutrient information was obtained from food labels or the US Department of Agriculture’s national nutrient database. The individual food components in each 24-hour recall were assigned into one of 68 food groups that were grouped according to nutrient composition.

## Infant Data Collection and Identification

Information on birth and delivery, child health, pet ownership, feeding practices such as breastfeeding, timing of introduction of solids and formula, allergenic food, infant supplementation in first year of life as well as allergic outcomes were collected from interviewer-administered questionnaires at multiple time-points from birth up to age 8 years. Breastfeeding pattern was characterized from type of infant feeding from 3 weeks to 12 months of age.

Data on breastfeeding patterns and infant formula feeding were captured from interviewer-administered questionnaires from 3 weeks to 12 months postnatally(20). Full breastfeeding was defined as a combination of exclusive and predominantly breastfeeding, the latter comprising breastmilk alongside other liquids like water or water-based drinks(21). Any breastfeeding was defined as any reported breastfeeding alongside liquid (including infant formula) and solid foods. World Health Organization (WHO) guidelines promote exclusive breastfeeding for the first 6 months of life, and complementary solid food introduction at approximately 6 months (22). Using this guidance, breastfeeding status were categorized as “Full Breastfeeding > 6 months”, “Any Breastfeeding < 6 months”, and “Any Breastfeeding > 1 year”.

Data on the infant’s age of weaning to solids was obtained at 9 and 12 months postpartum. Timing of introduction of solids was categorized into < 4 months, 4-<6 months and ≥ 6 months. Timing of introduction of specific allergenic foods (milk, egg, peanut, prawn) was grouped into ≤ 9 months or > 9 months, suggesting appropriate and delayed introduction respectively.

***Food Allergy and Eczema***

Skin prick tests (SPT) to food allergens (egg, peanut, cow’s milk and shellfish) and house dust mite allergens (*Dermatophagoides pterynossinus*, *Dermatophagoides farinae*, and *Blomia tropicalis*) were offered to all children at age 18 months, 3, 5 and 8 years, while food allergy data was obtained via questionnaires at ages 12, 15, 18 months and thereafter yearly from 2 years up to 8 years. Food allergy was defined by a convincing history of anIgE-mediated reaction (hives, angioedema, vomiting, diarrhea, etc) within four hours of ingestion of the specific allergenic food (namely the major allergens milk, egg, peanut, tree nuts, fish, wheat, soy and crustaceans). For timepoints whereby SPT was carried out, the definition of food allergy also included a positive SPT with an average wheal size of 3mm or larger. Prevalence of any food allergies and specific food allergies (cow’s milk, egg, peanut, and seafood) were categorized cumulatively: “By 18 months”, “By 3 years”, “By 5 years”, and “By 8 years”. For each of these cumulative timepoints, at least 60% of the timepoints would need to have complete food allergy data in order to be classified as a control or a food allergic. Participants were otherwise classified as having a missing food allergy status (by 18 months both timepoints with complete data required; by 3 years 3/4 timepoints completed; by 5 years 4/6 timepoints completed, by 8 years 6/9 timepoints completed).

Early onset eczema was defined as parental-reported doctor's diagnosis of eczema at any time in the first 6 months of life.

***Infant Supplementation***

Data on supplementation feeding practices were collected via interviewer-administered questionnaires at the 6, 9- and 12-month postnatal visits. Dietary supplements were categorized into probiotics (probiotic drops/powder or probiotic-enriched foods) and vitamins and mineral supplements (multivitamins, such as iron or calcium, fish oil, and individual vitamins (A, B12, C and D))(23).

### Infant Diet Quality Index and Diet Diversity Score

A Diet Quality Index (DQI) was previously developed by the GUSTO cohort (24) to assess the overall diet quality in Asian toddlers. Development of the DQI is primarily based on Singapore’s dietary guidelines for children from 1-2 years of age, while also taking into consideration guidelines from other Asian and Western countries. Detailed methodology pertaining to the derivation of the DQI has been previously explained (24). In summary, the DQI comprises 7 components – Total rice, bread, and alternatives; Total fruit; Total vegetables; Total meat and alternatives; Total milk and dairy products; Whole grains; Foods high in sugar. Participants were scored for each component and a raw DQI score was eventually derived by adding the individual scores. The score was then adjusted by standardizing to an energy intake of 845 kcal per day, based on average daily energy requirements for 1-year olds in Singapore (25). A higher DQI score correlates with a better diet quality which is associated with higher consumption of several nutrients and food groups, but no standard cutoffs exist in literature (theoretical range 0-65).

Diet diversity score on the other hand was defined as per the Infant and Young Children Feeding Practices (22); which is the total count of different food groups consumed by the infant at 18 months over an average of 28 days 24-hour period (irrespective of amount consumed). Maximum score possible is 8 based on the following food groups: breastmilk; grains, roots and tubers; legumes, nuts and seeds; dairy products (milk, yoghurt, cheese); flesh foods (meat, fish, poultry, liver or other organs); eggs; vitamin A rich fruits & vegetables; other fruits & vegetables.

## Statistical Analyses

All data were analyzed with SPSS Version 26 (IBM Corp, New York, NY, USA) and/or STATA I/C 16. Results with p values <0.05 were considered statistically significant. The prevalence of food allergy by 8 years was estimated as the observed proportion with 95% confidence intervals generated using the normal approximation to the binomial distribution. We adjusted for differences in demographics and other potential risk factors between participants included in the analyses and those who were excluded due to missing food allergy status as a result of loss to follow up/uncertain food allergy status. Re-weighting was carried out using the inverse probability weighting method described by Little and Rubin (26).

Chi-squared and Fisher’s exact test were used to assess the significance between food allergy by 8 years and socio-demographic characteristics, infant characteristics, maternal and infant dietary patterns, and feeding practices.

Associations between maternal and infant exposures and food allergy were analyzed using both univariate and adjusted logistic regression. To assess potential confounding factors, directed acyclic graphs (DAGs) were developed using a browser-based interface environment, DAGitty (version 3.0)(27) based on confounders chosen *a priori* (28, 29). Logistic regression models were then adjusted for a minimum set of confounders reflected by the curated DAGs (see Supplementary Figures 1 – 5). Potential confounders considered in the DAGs were collected from interviewer-administered questionnaire at every timepoint; these comprised maternal highest education (Primary & Secondary/Pre-Tertiary/Tertiary), maternal ethnicity (Chinese/Malay/Indian/Mixed), siblings (binary), breastfeeding, mode of birth (vaginal/caesarean), childcare attendance in first year of life (binary), maternal history of atopy which included asthma, rhinitis, eczema (binary), infant’s early onset eczema (binary), pet ownership in first year of life (binary), sex (Male/Female), maternal smoking during pregnancy (Non-smoker/Ex-smoker/Current Smoker), household smoking exposure (binary), maternal body mass index during pregnancy (continuous), maternal age at delivery (continuous).

# RESULTS

## Characteristics of study participants

Of the 1152 singletons, naturally conceived infants in the cohort, food allergy outcome data was available for 822 (18 months), 826 (3 years), 794 (5 years) and 728 (8 years) children who were included in the final analysis. The cumulative prevalence of any food allergy by age 8 years was 8.1% (95% CI 6.3%-10.3%): – milk 0.4% (3/700), egg 4.2% (30/710), shellfish 3.5% (25/716), peanut 1.1% (8/704). An initial peak food allergy prevalence of 2.5% (22/883) was observed at age 12 months and this generally decreased over time, with a prevalence of 1.9% (14/736) at 8 years. Another peak in prevalence of 2.9% (23/790) was recorded at 4 years, primarily due to shellfish and peanut allergy.

Comparison between participants who were included in analysis versus those with missing data showed significant differences in maternal education, ethnicity, and breastfeeding duration of less than 6 months (**Supplementary** **Table 1**). A sensitivity analysis which included sampling weights to adjust for these differences found no change in cumulative food allergy prevalence: 8.2%, 95% CI 6.4%-10.5%.

The demographic factors of the study population at 8 years are shown in **Table 1**. Notably, children with food allergies tended to have early onset eczema (before 6 months of age) and a maternal history of atopy. Early onset eczema and maternal history of atopy were also associated with an increased risk of food allergy in the univariate analyses (**Supplementary** **Table 2**). Of those with eczema by 6 months (8.5%, n=61/716), 29.5% developed food allergy by 8 years).

## Maternal diet during pregnancy

The majority of mothers consumed egg and milk (75.8% and 91.1%, respectively) during pregnancy, but fewer than half consumed peanut (27.7%) and shellfish/crustaceans (41.4%). Of the 405 mothers who avoided at least one allergenic food during pregnancy, only 37 (9.1%) had offspring with food allergy. 33/628 mothers consumed all four allergenic foods and of these, 4/33 (12.1%) had children with food allergy.

While the mothers of the three children with peanut allergy had not consumed peanut during pregnancy, the majority of peanut-avoiding mothers (99%) nevertheless had healthy children. Similarly, only 3.2% of egg-avoiding mothers had egg-allergic children, compared to 5.4% in infants of egg-consuming mothers. However, none of these reached statistical significance, likely due to very small numbers (**Supplementary Table 3**).

Maternal dietary patterns and vitamin D status also did not impact infant’s food allergy risk (**Supplementary Table 4**). Although a statistically significant association (p≤0.016) was reported between higher maternal dietary quality (HEI-SGP score) and increased risk of infant food allergy at every cumulative timepoint, the odds ratios were small and clinical significance is uncertain (Supplementary Table 4). Results were similar when models were adjusted for maternal food allergy status. Mean HEI-SGP scores also did not differ significantly by maternal food allergy status (54.1 and 52.6 in mothers with, and without, food allergy respectively).

## Breastfeeding and vitamin, probiotics supplementation in first year of life

More than half of the infants were breastfed for less than 6 months and this proportion was similar in both allergic (61.1%) and non-food allergic (59.8%) infants (Table 1). Generally, no associations were observed between breastfeeding duration and food allergy until 8 years of age in both univariate (Supplementary Table 2) and adjusted analyses (**Table 2**). Although statistically significant in univariate model, probiotics consumption between 6 to 12 months of life was no longer associated with food allergy status after adjusting for confounders (Table 2).

## Timing of introduction of solids and allergenic food

**Figure 1** depicts patterns in the timing of introduction of allergenic foods into the infants’ diet. The weaning age (age at first solid introduction) ranged from 0.75 to 9 months (mean age of introduction 5.7 ± 1.1 months) (Figure 1A). The majority of infants were introduced to cow’s milk protein within the first month of life (median 0 months, IQR 0.25 months, range 0 to 16 months) (Figure 1B). However, introduction of other allergenic foods such as eggs (mean age 8.8 ± 3.7 months) and particularly peanut (18.1 ± 7.0 months) was delayed. The mean age of prawn introduction was not able to be calculated as data for age at prawn introduction was only collected up to age 1 year. However, data from the first 12 months of life showed that only 8.9% infants had been introduced to prawn by this age.

 The timing of introduction of specific cow’s milk products such as milk formula and dairy products and milk allergy outcomes were assessed further. The majority of infants were introduced to cow’s milk protein in the form of infant formula within the first month of life (86.7%; n=880/1015) with only 2.6% introducing cow’s milk protein (infant formula) beyond 9 months (n=26/1015). By 9 months of age, 99.4% of infants had already been introduced to cow’s milk protein (n=1015/1021) in various forms such as dairy, formula, cheese, or yoghurt.

We next assessed patterns of cow’s milk protein consumption over the first year of life, in particular whether this was continued or ceased after initial introduction in early life, as cessation of cow’s milk protein consumption after an initial exposure has been reported to increase the risk of milk allergy development (30). Similar proportions of infants were introduced to cow’s milk formula early in life (≤1 month) followed by continuation, as opposed to cessation of cow’s milk formula consumption until dairy-containing solid foods were introduced during weaning [217/898 (24.2%) vs 232/844 (27.5%) respectively]. Only 15.3% (137/898) of infants were not introduced to cow’s milk protein (exclusively breastfed) until the time of dairy solid food introduction.

No associations were observed between food allergy and timing of introduction of any of the allergenic foods in both univariate (**Supplementary** **Table 5**) and adjusted analyses (Table 2). There were also no differences when stratified by eczema status (data not shown).

## Diet quality index score and diet diversity score at 18 months of age

 The energy adjusted DQI and diet diversity score was available for 514 children. The DQI scores did not differ significantly at each individual time-point or by food allergy status: median DQI score was 44.4 (IQR 11.5) in non-food-allergic subjects compared to 41.6 (IQR 11.8) in food allergic subjects (Table 1). At least 45% had a diet diversity score of 5 regardless of food allergy status (Table 1). Higher DQI scores were associated with a reduced risk of food allergy by 18 months and by 8 years, although odds ratios crossed the null (Table 2). No associations were observed between diet diversity score and food allergy at any time point (Table 2).

# DISCUSSION

In a high income tropical Asian country, we examined potential exposures proposed to affect food allergy risk in children up to age 8 years. As a follow-up to our previous work (31), we analyzed the impact of maternal and infant diet quality, diversity and allergenic food exposure on food allergy development up to age 8 years. Contrary to studies in mainly Western populations showing that timing of allergenic food introduction (1, 3, 32, 33), dietary diversity (11, 34) and maternal allergic food consumption (35) impact food allergy risk in children, these factors showed no clinically important associations with food allergy development in this Asian child population.

## Maternal diet

Our findings suggest that maternal dietary patterns do not significantly impact food allergy risk in populations where food allergy prevalence is low. A systematic review by Venter et al similarly found no consistent evidence for the role of maternal dietary factors on offspring food allergy, although there were only a small number of studies on food allergy and there was high heterogeneity among the included studies(36). Additionally, the Nutrition Evidence Systematic Review in the USA (37) concluded that there is currently insufficient evidence to determine associations between dietary patterns during pregnancy and lactation on offspring food allergy risk. Nevertheless, some individual studies which showed positive associations reported so only among mothers with high levels of consumption of the relevant allergenic foods (highest quartile of milk consumption and peanut/tree nut consumption of ≥ 5 times per month) (38, 39). As data on levels of allergenic food consumed in pregnancy were not collected in our study, we were not able to conduct subgroup analyses to examine the impact of this particular factor on infant food allergy risk, which is an area for future research. While we observed that higher maternal diet quality was associated with a small increased risk of food allergy in their offspring, it is not certain if this is mediated through specific nutrients instead of overall dietary quality, or if unmeasured confounders might be responsible. It is also currently unclear if the small effect sizes reported bear meaningful clinical implications and further research is required to elucidate the specific pathways through which this might occur.

## Infant diet

Results from RCTs such as Learning Early About Peanut Allergy (LEAP) (1), Enquiring About Tolerance (EAT) (2) and Prevention of Egg Allergy in Tiny Amount Intake (PETIT) (40) collectively showed a reduction in risk of allergy with early introduction of allergenic food. Here, we found that peanut allergy rates remained very low even up to age 8 years, further strengthening the hypothesis that timing of allergenic food introduction plays a small role in food allergy inception in this low-risk population. Our results are further corroborated by recent findings from an Australian study which showed reduced risk of peanut allergy with early peanut introduction in infants of Australian ancestry but not among those of East Asian ancestry (41).

We found that although a quarter of infants were introduced to cow’s milk formula within the first month of life followed by a period of cessation (due to exclusive breastfeeding), this did not translate to an increased risk of cow’s milk allergy, with cow’s milk allergy prevalence remaining very low, ranging from just 0.1-0.44%. across the cohort. This is despite recent studies suggesting an increased risk of cow’s milk allergy with irregular consumption or discontinuation of formula within the first year of life. An RCT carried out in Japan illustrated the introduction of cow’s milk formula daily between 1 and 2 months of life for prevention of cow’s milk allergy (42). Further analyses indicated that early discontinuation of cow’s milk formula in the first month of life increased the risk of cow’s milk allergy at age 6 months (43), suggesting that cow’s milk formula supplementation as a bridge to breastfeeding in the first few days of life should be avoided if possible and donor breastmilk may be a viable alternative, although no studies have been done on the latter.

Previous studies reported that a higher diet diversity score in the first year of life was linked to a reduced risk of food sensitization up to 2 years (44), parental report of food allergy up to 6 years (45) and food allergy outcomes over the first 10 years of life (34). Our study, however, did not find any associations with diet diversity score but reported similar associations between DQI and food allergy at 2 timepoints - by 18 months and by 8 years. Effect sizes though, were small and included the null. Differences in reported findings may be due to the lack of power in this study or a result of varied definitions used to curate diet diversity scores or indices.

Collectively, our findings are aligned with current guidelines by the European Academy of Allergy and Clinical Immunology (EAACI) task force which makes no recommendation for early peanut introduction in countries with a low prevalence of peanut allergy (46). The Asia Pacific Academy of Pediatric Allergy, Respirology & Immunology (APAPARI) consensus statement on timing of allergenic food introduction suggested that in low risk populations, allergenic foods are recommended to be introduced as per family preferences and cultural practices and there should just be no delay in introduction (47). In high-risk infants with moderate to severe eczema and/or pre-existing food allergy, early introduction of peanut and/or egg under allergist supervision may still be beneficial at an individual level. There remains little guidance on the ideal timing of cow’s milk protein introduction and continuation in a low-risk population.

## Strengths and limitations

One limitation of this study was the lack of confirmatory food challenges for the diagnosis of food allergy. However, data was collected at close intervals (3-6 monthly) and reported symptomatology were also examined in detail to ensure they fulfilled a convincing history of an IgE-mediated reaction to a food trigger; the addition of corroborative skin prick tests further mitigated this bias. This study has also been designed to focus on IgE-mediated food allergy and findings are not applicable to non-IgE mediated food allergy. Another limitation of this study was that infant DQI and diet diversity data was only obtained after the first year of life and not during weaning as solid food diversity is expected to be low in the first few months of weaning and earlier data collection would likely not be meaningful.

Nonetheless, one of the strengths of this study lies in its extensive longitudinal follow up which allows analyses for temporality and reverse causality to be performed. The standardized ISAAC questionnaire used for the study for the evaluation of food allergy is a well-established instrument that has been internationally validated for the assessment of allergenic outcomes and associated risk factors.

# Conclusion

Approaches to allergy prevention strategies are complex and multi-layered, lacking a universally recommended approach. Differences in infant and maternal dietary patterns such as delayed introduction of allergenic foods, dietary quality or maternal allergenic food avoidance did not appear to confer any significant additional risks for food allergy in this population. To affirm our findings, there is a pressing need for comparative studies on the efficacy of allergy prevention strategies on food allergy risk across different populations. It may be plausible that dietary guidelines for infants be tailored according to food allergy risk factors and burden, and interventions should be customized at an individual patient level rather than across the whole population (15).

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# Tables

**Table 1: Demographic variables of children included in analyses stratified by food allergy status by 8 years (N=728)1**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Non-Food Allergic by 8Y (%)****N=669** | **Food Allergic by 8Y (%)****N=59 (8.1% of total population n=728)** | **P-value7** |
| **Maternal Demographics** |  |
| Ethnicity |  |  |  |
| *Chinese* | 378 (56.5) | 37 (62.7) |  |
| *Malay* | 177 (26.5) | 17 (28.8) |  |
| *Indian* | 113 (16.9) | 5 (8.5) |  |
| *Others* | 1 (0.2) | 0 (0.0) | 0.30 |
| Maternal highest education |  |  |  |
| *Primary & Secondary* | 195 (29.4) | 18 (30.5) |  |
| *Pre-Tertiary* | 241 (36.3) | 15 (25.4) |  |
| *Tertiary* | 228 (34.3) | 26 (44.1) | 0.19 |
| Maternal history of atopy (eczema, rhinitis, wheeze) | 185 (28.5) | 28 (50.0) | **0.001** |
| Smoking exposure at pregnancy W26 |  |
| *Non-smoker* | 572 (86.5) | 53 (91.4) |  |
| *Ex-smoker* | 72 (10.9) | 5 (8.6) |  |
| *Current Smoker* | 17 (2.6) | 0 (0.0) | 0.53 |
| **Children’s Demographics** |  |
| Male | 336 (50.2) | 36 (61) | 0.11 |
| Having siblings | 352 (56.0) | 28 (48.3) | 0.26 |
| Mode of delivery |  |  |  |
| *Vaginal* | 471 (70.4) | 42 (71.2) |  |
| *Caesarean* | 198 (29.6) | 17 (28.8) | 0.90 |
| Childcare attendance | 49 (8.8) | 6 (13.6) | 0.29 |
| Early onset eczema (<6M) | 43 (6.5) | 18 (31.6) | **<0.001** |
| Pet ownership in first year of life | 56 (13.9) | 5 (14.7) | 0.90 |
| Smoking exposure in first year of life | 215 (47.4) | 13 (37.1) | 0.24 |
| **Children’s Dietary Variables** |  |
| Solid food introduction < 4M | 15 (2.7) | 2 (4.1) | 0.64 |
| Solid food introduction 4-5M | 193 (34.3) | 17 (34.7) | 0.95 |
| Solid food introduction ≥ 6M | 355 (63.1) | 30 (61.2) | 0.80 |
| Full breastfeeding2 > 6M | 49 (7.6) | 4 (7.3) | 1.00 |
| Any breastfeeding < 6M | 386 (59.8) | 33 (61.1) | 0.86 |
| Any breastfeeding > 1Y | 138 (21.4) | 14 (25.9) | 0.44 |
| Dietary supplements – vitamins & minerals consumption up to 3M 3 | 30 (8.4) | 2 (6.7) | 1.00 |
| Dietary supplements – vitamins & minerals consumptions from 6-12M 3 | 110 (19.5) | 13 (26.5) | 0.24 |
| Probiotics consumption up to 3M | 13 (2.1) | 2 (3.9) | 0.34 |
| Probiotics consumption from 6-12M | 22 (3.9) | 6 (12.2) | **0.007** |
| DQI score at 18M (median (IQR))4 | 44.39 (11.58) | 41.6 (11.84) |  |
| Diet diversity score at 18M (binary)5 |  |  |  |
|  ≥ 5 items6 | 194 (50) | 15 (45.5) | 0.63 |

DQI: Diet Quality Index; M: months; Y: years % in brackets are column percentages with the number of cases (N=59) or controls (N=669) respectively being the denominator.

1 424 participants were classified as missing as they had missing food allergy status for at least one of the timepoints in the first 8 years of life.

2Full Breastfeeding: Exclusive and predominant breastfeeding without solids introduction but may be alongside other liquids like water or water-based drinks.

3 Vitamins and Minerals included the consumption of multivitamins, Vitamins A, B12, C and D, fish oils and other minerals from 6-12 months.

4Diet Quality Index (DQI): Reflect overall diet quality in Asian children based on scoring of 7 components. Total score was then adjusted by standardizing to energy intake of 845 kcal per day. A higher DQI score correlates with a better diet quality.

5Diet diversity score: Defined as per the Infant and Young Children Feeding Practices (IYCF)(48), based on the total count of different food groups consumed by the infant at 18 months over ”an average of 28 days”. Possible maximum score of 8.

6 WHO IYCF recommended minimum dietary diversity score of ≥ 5 (48).

7P values were obtained from Chi-Square test except where cells with sample sizes < 5, p-values from Fisher’s exact test were quoted.

**Table 2: Adjusted analyses of the association between infant risk factors and food allergy at various timepoints (by 18M, 3Y, 5Y and 8Y)**

|  |  |
| --- | --- |
|   | **Any Food Allergy** |
|  | **By 18M** | **By 3Y** | **By 5Y** | **By 8Y** |
|  | **aOR (95% CI)** | **P-value** | **aOR (95% CI)** | **P-value** | **aOR (95% CI)** | **P-value** | **aOR (95% CI)** | **P-value** |
| **Any Breastfeeding < 6M1** | 0.62 (026-1.52) | 0.301 | 1.01(0.46-2.21) | 0.988 | 1.01 (0.51-2.37) | 0.809 | 1.00 (0.49 -2.05) | 0.995 |
| **Any Breastfeeding > 1Y1** | 2.15 (0.89-5.22) | 0.09 | 1.55 (0.70-3.48) | 0.283 | 1.52 (0.69-3.36) | 0.299 | 1.39 (0.65-2.96) | 0.394 |
| **Full Breastfeeding > 6M1** | 1.65 (0.50-5.47) | 0.412 | 1.17 (0.37-3.70) | 0.793 | 1.17 (0.37 -3.69) | 0.790 | 1.06 (0.34-3.31) | 0.913 |
| **Weaning < 4M2** | NA | NA | NA | NA | NA | NA | 1.34 (0.16-11.38) | 0.787 |
| **Weaning 4-5M2** | 1.05 (0.39-2.82) | 0.917 | 1.13 (0.47-2.69) | 0.790 | 0.94 (0.40-2.22) | 0.895 | 1.08 (0.50-2.31) | 0.848 |
| **Weaning ≥ 6M2** | 1.04 (0.39-2.80) | 0.934 | 1.02 (0.43-2.44) | 0.963 | 1.22 (0.52-2.86) | 0.650 | 0.90 (0.42-1.92) | 0.782 |
| **Vitamins and Minerals consumption up to 3M 3,4** | NA | NA | NA | NA | NA | NA | NA | NA |
| **Vitamins and Minerals consumption from 6-12M3,4** | 0.82 (0.23-2.85) | 0.750 | 0.89 (0.30-2.65) | 0.839 | 1.09 (0.40-3.00) | 0.865 | 0.76 (0.29-2.02) | 0.589 |
| **Total probiotics consumption up to 3M 3,4** | 1.71 (0.18-16.10) | 0.640 | 1.26 (0.14-11.08) | 0.838 | 2.88 (0.55-15.01) | 0.211 | 2.33 (0.46-11.88) | 0.309 |
| **Total probiotics consumption from 6-12M3,4** | 3.14 (0.68-14.46) | 0.142 | 3.11 (0.83-11.66) | 0.093 | 2.61 (0.72-9.46) | 0.145 | 2.32 (0.65-8.26) | 0.192 |
| **DQI Score at 18M5** | 0.91 (0.84-0.98) | **0.013** | 0.94 (0.88-1.00) | 0.066 | 0.94 (0.88-1.00) | 0.058 | 0.93 (0.88-0.99) | **0.016** |
| **Diet diversity score at 18M5** | 0.83 (0.54-1.28) | 0.394 | 0.94 (0.64-1.37) | 0.751 | 0.90 (0.62-1.31) | 0.587 | 0.84 (0.6-1.19) | 0.333 |
|  | **Specific Food Allergy10** |
|  | **By 18M6** | **By 3Y7** | **By 5Y8** | **By 8Y9** |
| **Milk introduction2** |  |  |  |  |  |  |  |  |
| **≤ 9M** | NA | NA | NA | NA | NA | NA | NA | NA |
| **> 9M** | REF |
| **Egg introduction2** |  |  |  |  |  |  |  |  |
| **≤ 9M** | 0.53 (0.15-1.94) | 0.338 | 0.78 (0.26-2.30) | 0.648 | 0.70 (0.24-2.10) | 0.526 | 0.83 (0.28-2.42) | 0.734 |
| **> 9M** | REF |
| **Peanut introduction2** |  |  |  |  |  |  |  |  |
| **≤ 9M** | NA | NA | NA | NA | NA | NA | NA | NA |
| **> 9M** | REF |
| **Prawn introduction2** |  |  |  |  |  |  |  |  |
| **≤ 9M** | 17.98 (0.64-501.61) | 0.089 | 2.05 (0.21-20.02) | 0.538 | 1.15 (0.13-9.98) | 0900 | 1.63 (0.33-8.03) | 0.548 |
| **> 9M** | REF |

aOR: adjusted odds ratios; DQI: diet quality index; M: months; NA: Not Applicable (due to small sample size after adjusting for confounders); Y: year. Confounders were included based on directed acyclic graphs (DAGs) provided in the Supplementary.

1 Adjusted for childcare attendance in first year of life, maternal education, mode of delivery, maternal ethnicity, siblings, and maternal history of atopy.

2 Adjusted for childcare attendance in first year of life, maternal history of atopy, infant's early onset eczema, maternal education, maternal ethnicity, presence of siblings, breastfeeding duration, and mode of delivery.

3 Adjusted for childcare attendance in first year of life, infant's early onset eczema, maternal education, maternal ethnicity, breastfeeding duration, maternal history of atopy and mode of delivery.

4 Vitamins and Minerals supplementation included multivitamins, Vitamins A, B12, C and D, fish oils and other minerals.

5 Adjusted for childcare attendance in first year of life, child’s sex, maternal education, maternal ethnicity, siblings, breastfeeding duration, mode of delivery and maternal history of atopy.

6 By 18M: Milk (n=14); Egg (n=513); Peanut (n=3); Prawn (n=78)

7 By 3Y: Milk (n=13); Egg (n=505); Peanut (n=45); Prawn (n=421)

8 By 5Y: Milk (n=12); Egg (n=483); Peanut (n=46); Prawn (n=405)

9 By 8Y: Milk (n=12); Egg (n=448); Peanut (n=42); Prawn (n=476)

10 As respective outcomes at each timepoint, milk introduction was analysed with milk allergy, egg introduction with egg allergy, peanut introduction with peanut allergy and prawn introduction with shellfish allergy.

# Figure Legend

**Figure 1:** Timing of introduction of A) solids and B) egg, peanut, cow’s milk protein and prawn over 3 years.

Among the four main allergens, cow’s milk protein was introduced into infant’s diet the earliest - beginning from birth, while peanut and egg introduction into infant’s diet occurred later in life at around 18 months and 8 months respectively. While data on egg, peanut and cow’s milk protein was collected up to the 3 years follow up, data on timing of prawn introduction was only collected up to 1 year. // indicates the timepoint when data collection for timing of prawn introduction stopped. Those who had yet to introduce prawn by 12 months were classified as 0 months in order to not exclude these participants from the total sample size in the graph.