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Relation of infant dietary patterns to allergic outcomes in early childhood

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To the Editor

Allergic disorders result from the complex interplay between genetic predisposition and environmental influences. According to the Developmental Origins of Health and Disease

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hypothesis, environmental pressures at critical or early periods of development can evoke persisting changes in gene regulation and expression (1), affecting disease development. Infant nutrition is a major environmental influence in early life as the immature gut is exposed to a variety of food proteins. However, results from studies examining the early introduction of allergenic food and allergic outcomes have been conflicting. In addition, the current literature, describing associations between different types of diet or nutrients and allergic outcomes, consists mainly of either cross-sectional studies or case-control studies that examine children during pre-school or school-going ages (2). Moreover, studies that have examined the contribution of infant nutrition to the development of paediatric allergic outcomes in a prospective birth cohort setting in Asia have mainly focused on breastfeeding and its effects on allergic diseases (3). In this study, we analysed the influence of infant dietary patterns in the first year of life on allergic outcomes (allergen sensitization, eczema, rhinitis and wheeze with use of nebuliser) until the age of 5 years in the Growing Up in Singapore towards healthy Outcomes (GUSTO) mother-offspring cohort, potentially offering insights into the effects of infant diet on allergic outcomes in early life.

The methodology of the GUSTO study has been described previously (4). Briefly, we recruited healthy pregnant mothers who agreed to enrol their offspring for future follow-up. Interviewers gathered information on demographic characteristics, family history of allergy, social data and lifestyle factors. Definitions of allergic outcomes were standardized in the questionnaires administered at 3, 6, 9, 12, 15, 18, 24, 36, 48 and 60 months to ensure consistency during interviews and home visits. We used the ISAAC modified questionnaire as used in other studies. Physician-diagnosed atopic eczema was based on a positive answer to the written question: “Has your child ever been diagnosed with eczema?”, “Wheezing” was based on a positive answer to both “Has your child ever wheezed?” and “Has your child ever been prescribed with nebulizer/inhaler?”, while “rhinitis” was based on a positive response to the question “Has your child ever had sneezing, running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks duration?”. Study team members questioned the subjects who reported rhinitis to collect information on the number of episodes of rhinitis and the duration of each episode. A case of rhinitis prior to 18 months required a single episode that lasted for at least 4 weeks or two or more episodes, each lasting at least 2 weeks. New cases of rhinitis after 18 months were defined by one or more episodes lasting at least 2 weeks. Allergen sensitization was determined by skin prick testing (SPT) to house dust mite allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis*) and food allergens (egg, peanut and cow’s milk) at 18, 36 and 60 months. At 60 months, skin prick testing was also carried out to shrimp and crab allergens. The allergens for skin prick testing were obtained from Greer Laboratories (Lenoir, NC, USA), except for *B. tropicalis*, which was obtained from our laboratory. Tests were interpreted as positive if the wheal was at least 3 mm above the negative control (saline) and a child was considered as SPT-positive if any one or more of the individual tests was positive. For allergic outcomes by 18 months, the allergic outcome was classified as absent when the answers for all visits were “no.” For allergic outcomes by 36 and 60 months, the allergic outcome was classified as absent when the answers for the visits were “no” for at least 70% of the visits with no answer of “yes” at any

point in time. Sensitivity analysis was also performed by replacing the missing visits with best and worse scenarios (for example either positive or negative).

Family history of allergy was defined as positive if the mother, father or an older sibling ever had eczema, asthma or allergic rhinitis.

Ethics approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group and the Centralised Institutional Review Board of SingHealth.

The detailed methodology used to identify dietary patterns of the GUSTO cohort has been previously described (5). Briefly, cross-sectional dietary patterns were derived by factor analysis using 24-hour recalls and food diaries of infants at ages 6-, 9- and 12-months. There were 486 subjects with complete infant dietary data from 6-12 months; a schematic diagram of the selection of subjects has been previously published (6). Four main dietary patterns were established from 6- to 12-months (6): *Predominantly breastmilk* - mainly breastmilk and less formula milk; *According to Guidelines* - rice porridge, vegetables, fruits and low-fat fish and meat; *Easy-to-prepare foods* - infant cereals, juices, cake and biscuits; and *Noodles (in soup) and seafood* - rice and wheat noodles and common accompaniments such as fish and shellfish. A fifth pattern emerged at age 12-months: *Pulses and grains* - characterised by high intake of nuts and seeds, grains, legumes and lentils and high energy-dense confectionaries. The factor loading scores of the dietary patterns are available as Supplementary Tables 1-3. Statistical analysis was carried out using SPSS version 20.0 (IBM SPSS Statistics, Armonk, NY). Associations between infant dietary pattern scores and subsequent allergic outcomes (eczema, rhinitis, wheeze and use of nebulizer) in the offspring were examined using multivariable logistic regression adjusting for sex, ethnicity, maternal education and family history of allergy. Associations between infant dietary pattern scores and allergen sensitization in the offspring were estimated using multivariable logistic regression adjusting for sex, ethnicity, maternal education and family history of allergy and eczema.

A schematic diagram of the subjects with information on allergic outcomes is shown in Supplementary Figure 1. There were generally no differences in characteristics such as sex, ethnicity, maternal education levels and family history of allergy between those with information on allergic outcomes and those without, with the exception of ethnicity differences between those that complete skin prick testing at 18 months and 36 months compared to those without (data not shown). In addition, subjects who did not complete skin prick testing at 60 months had higher level of maternal education compared to those who completed (data not shown).

Adjusting for sex, ethnicity, maternal education levels, family history of allergy and eczema “*Noodles and seafood*” dietary pattern at month 12 which consists of consumption of rice and wheat noodles, prawn, scallop and cuttlefish was associated with reduced odds of developing allergen sensitization at ages 18 months [Adjusted OR (95% CI): 0.5 (0.3-0.98)], and at 60 months [Adjusted OR (95% CI) : 0.7 (0.4-0.98)].

Further analysis showed that a “*Noodles and seafood*” dietary pattern at month 12 was also associated with reduced odds of developing house dust mite allergen sensitization at ages 18

months [Adjusted OR (95% CI): 0.4 (0.2-0.9), data not shown] and 60 months [Adjusted OR (95% CI): 0.7 (0.4-0.99), data not shown]. There were no associations between a “*Noodles and seafood*” dietary pattern at month 12 and development of food allergen sensitization at 18, 36 and 60 months (data not shown). In addition, no associations were observed between a “*Noodles and seafood*” dietary pattern at month 12 and eczema, rhinitis and wheeze with use of nebulizer.

“Predominantly breastfeeding” dietary pattern at month 6 and 9 was associated with increased odds of developing allergen sensitization at 18 months [Adjusted OR (95% CI) : 1.6 (1.01-2.5) and Adjusted OR (95% CI): 1.5 (1.01-2.1) respectively] after adjusting for sex, ethnicity, maternal education levels, family history of allergy and eczema. There were no changes in trend upon performing sensitivity analysis.

Our study examined the influence of infant dietary patterns on allergic outcomes until 5 years in a Multi-Ethnic Asian cohort. We observed that a “*Noodles and seafood*” pattern, in the first year of life was protective against allergen sensitization, particularly house dust mite allergen sensitization at 18 months and at 5 years of age. This finding supports the finding from other studies (e.g. The LEAP study(7)) that early (between 6 to 12 months) introduction of allergenic foods, such as shellfish and wheat in early life may induce immune tolerance. Several local studies have found that seafood (crustaceans and molluscs) is the most common cause of immediate food hypersensitivity and anaphylaxis in older children and adults. In a study that surveyed children from Singapore and Philippines (n=25,692) comparing allergies, it was found that in local schoolchildren, and not in expatriate children, shellfish allergy predominated, instead of the peanut or tree nut allergy found in Western children (8).

A possible underlying mechanism for a preventive effect of a “*Noodles and seafood*” diet may be due to the high sequence similarity (81%) between tropomyosin found in dust mites and shrimp (9). Tropomyosin is the major allergen found in shellfish and house dust mites. House dust mite immunotherapy has been reported to improve shrimp tolerance. Our study results raise the possibility that early exposure to shrimp or seafood may protect against subsequent dust mite allergen sensitization. Interestingly, the protective effect from a “*Noodles and seafood*” pattern was observed at 5 years of age, and it is at the age of 5 years that most allergy is made up by house dust mite allergy.

The “*Predominantly Breastfeeding*” pattern was associated with higher risk of allergen sensitisation. This could be attributed to the lack of diversity in the aforementioned dietary pattern, which consists of mostly breast milk and less of formula milk in the infant’s diet. In agreement with our findings, a Finnish birth cohort study involving 3781 children found that less food diversity even at 3 months of age may increase the risk of atopic sensitization, and is most evident among high-risk children with atopic history (10).

The merit of this study lies in the analysis of a dietary pattern of food consumption, and not just in analysing individual food items. This allows holistic analyses of the synergistic effects of singular dietary components, and thus makes it more applicable and relatable to the clinical practice. In addition, this is a prospective cohort study with regular collection of

information at multiple time points. The collection of infant dietary patterns by 24 hour recall also reduces recall and response bias as this information is collected prior to the assessment of infant allergic outcomes. To further reduce misrepresentation of day-to-day variation of infant diet, a high correlation of dietary pattern scores across the 3-days of the food diaries was observed, signifying good reproducibility of 1-day dietary records. In addition, although the Singaporean diet is influenced by multiple cultures and several ethnic groups, namely the Chinese, Malays and Indians, the staple food still remain rice and noodles, being highly representative of an Asian diet. Hence the findings in this study may be extrapolated as potentially representative of Asia. Limitation of this study is that as this is an observational study, further supporting data from other prospective birth cohorts will be needed to confirm this.

In conclusion, we found that infant “noodles and seafood” dietary pattern is protective against house dust mite allergen sensitization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association between infant dietary patterns and allergic outcomes by 18 months

	Adjusted OR (95% CI)			
Month 6	Allergen sensitization	Eczema	Rhinitis	Wheeze and use of nebuliser/inhaler
Guidelines	1.1 (0.7-1.6)	1.1 (0.8-1.6)	1.2 (0.7-1.8)	1.1 (0.8-1.6)
Predominantly Breastmilk	1.6 (1.01-2.5)	1.2 (0.8-1.8)	1.0 (0.6-1.6)	1.2 (0.7-1.9)
Easy to prepare food	0.5 (0.3-0.99)	0.8 (0.5-1.5)	0.6 (0.2-1.5)	0.8 (0.3-1.7)
Noodles and seafood	0.8 (0.5-1.5)	1.1 (0.8-1.5)	1.0 (0.7-1.4)	0.9 (0.6-1.5)
Month 9				
Guidelines	0.7 (0.5-1.1)	1.0 (0.6-1.5)	#	1.1 (0.6-1.7)
Predominantly Breastmilk	1.5 (1.01-2.1)	1.1 (0.7-1.7)	#	0.8 (0.5-1.3)
Easy to prepare food	1.1 (0.7-1.5)	1.4 (1.02-2.0)	#	1.1 (0.7-1.6)
Noodles and seafood	0.6 (0.3-1.3)	0.5 (0.2-1.4)	#	0.4 (0.1-1.4)
Month 12				
Guidelines	0.7 (0.5-1.1)	1.0 (0.6-1.7)	#	0.8 (0.4-1.6)
Predominantly Breastmilk	1.4 (1.0-2.0)	1.9 (1.1-3.1)	#	0.6 (0.3-1.5)
Easy to prepare food	1.2 (0.8-1.6)	0.7 (0.3-1.5)	#	1.5 (1.0-2.4)
Noodles and seafood	0.5 (0.3-0.98)	0.8 (0.4-1.8)	#	0.6 (0.3-1.3)
Pulses and grains	0.8 (0.5-1.3)	1.3 (0.8-1.9)	#	0.5 (0.2-1.4)

* Odds ratio for allergen sensitization adjusted for sex, ethnicity, maternal education levels, family history of allergy and eczema. Odds ratio for eczema, rhinitis and wheeze with use of nebulizer/inhaler adjusted for sex, ethnicity, maternal education levels and family history of allergy

Not estimable, owing to insufficient number of children with studied outcomes

Table 2

Association between infant dietary patterns and allergic outcomes by 36 months

	Adjusted OR (95% CI)			
Month 6	Allergen sensitization	Eczema	Rhinitis	Wheeze and use of nebuliser/inhaler
Guidelines	1.5 (1.1-2.0)	1.1 (0.8-1.5)	1.2 (0.9-1.6)	1.4 (1.1-1.8)
Predominantly Breastmilk	1.4 (1.0-1.9)	1.1 (0.8-1.6)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Easy to prepare food	0.7 (0.4-1.2)	1.0 (0.7-1.6)	0.7 (0.5-1.1)	0.9 (0.6-1.3)
Noodles and seafood	0.9 (0.6-1.2)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.1 (0.8-1.4)
Month 9				
Guidelines	0.9 (0.6-1.2)	0.8 (0.5-1.3)	1.0 (0.7-1.4)	1.3 (1.0-1.8)
Predominantly Breastmilk	1.3 (0.9-1.8)	0.9 (0.7-1.4)	1.0 (0.7-1.4)	0.8 (0.5-1.1)
Easy to prepare food	0.9 (0.6-1.3)	1.3 (1.0-1.8)	1.1 (0.8-1.5)	1.0 (0.7-1.4)
Noodles and seafood	0.8 (0.5-1.3)	0.5 (0.2-1.2)	1.1 (0.9-1.4)	0.8 (0.5-1.3)
Month 12				
Guidelines	0.7 (0.5-1.0)	1.0 (0.6-1.6)	1.1 (0.8-1.7)	0.9 (0.6-1.3)
Predominantly Breastmilk	1.1 (0.8-1.5)	1.4 (0.9-2.1)	1.0 (0.7-1.4)	0.9 (0.6-1.3)
Easy to prepare food	1.1 (0.8-1.3)	1.0 (0.6-1.6)	1.2 (0.8-1.6)	1.1 (0.8-1.6)
Noodles and seafood	0.7 (0.4-1.1)	0.9 (0.6-1.6)	0.8 (0.5-1.2)	0.8 (0.5-1.4)
Pulses and grains	1.0 (0.7-1.4)	1.1 (0.8-1.6)	0.7 (0.4-1.1)	0.9 (0.6-1.3)

* Odds ratio for allergen sensitization adjusted for sex, ethnicity, maternal education levels, family history of allergy and eczema. Odds ratio for eczema, rhinitis and wheeze with use of nebulizer/inhaler adjusted for sex, ethnicity, maternal education levels and family history of allergy

Table 3

Association between infant dietary patterns and allergic outcomes by 60 months

	Adjusted OR (95% CI)			
Month 6	Allergen sensitization	Eczema	Rhinitis	Wheeze and use of nebuliser/inhaler
Guidelines	1.4 (1.0-1.8)	1.1 (0.8-1.5)	1.2 (0.9-1.6)	1.2 (0.9-1.6)
Predominantly Breastmilk	1.0 (0.7-1.4)	1.0 (0.7-1.5)	1.0 (0.8-1.4)	1.2 (0.9-1.7)
Easy to prepare food	0.9 (0.7-1.3)	1.0 (0.7-1.6)	0.7 (0.5-1.1)	0.9 (0.6-1.3)
Noodles and seafood	1.2 (0.9-1.7)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.1 (0.8-1.4)
Month 9				
Guidelines	1.2 (0.9-1.6)	0.9 (0.6-1.3)	1.0 (0.8-1.4)	1.1 (0.8-1.6)
Predominantly Breastmilk	1.0 (0.8-1.3)	1.0 (0.7-1.4)	1.0 (0.8-1.4)	0.8 (0.6-1.2)
Easy to prepare food	1.1 (0.9-1.4)	1.3 (1.0-1.7)	1.0 (0.8-1.4)	1.1 (0.8-1.4)
Noodles and seafood	1.2 (0.9-1.6)	0.8 (0.4-1.4)	1.1 (0.8-1.4)	0.4 (0.2-0.9)
Month 12				
Guidelines	0.8 (0.6-1.1)	1.1 (0.7-1.8)	1.3 (0.9-1.9)	0.8 (0.5-1.1)
Predominantly Breastmilk	1.0 (0.7-1.3)	1.2 (0.8-1.8)	1.1 (0.8-1.5)	1.1 (0.8-1.6)
Easy to prepare food	0.9 (0.7-1.2)	1.1 (0.7-1.6)	1.1 (0.9-1.5)	0.8 (0.6-1.3)
Noodles and seafood	0.7 (0.4-0.98)	0.9 (0.6-1.5)	0.8 (0.5-1.1)	0.9 (0.6-1.4)
Pulses and grains	1.2 (0.9-1.5)	1.0 (0.7-1.5)	1.0 (0.8-1.3)	1.0 (0.7-1.5)

* Odds ratio for allergen sensitization adjusted for sex, ethnicity, maternal education levels, family history of allergy and eczema. Odds ratio for eczema, rhinitis and wheeze with use of nebulizer/inhaler adjusted for sex, ethnicity, maternal education levels and family history of allergy