

Effect of Maternal Dietary Patterns during Pregnancy on Self-Reported Allergic Diseases in the First 3 Years of Life: Results from the GUSTO Study

Evelyn Xiu Ling Loo^a Lynn Ong^b Anne Goh^c Ai-Ru Chia^d Oon Hoe Teoh^e
Marjorelee T. Colega^a Yiong Huak Chan^f Seang Mei Saw^g Kenneth Kwek^h
Peter D. Gluckman^{i,l} Keith M. Godfrey^{m,n} Hugo Van Bever^{j,k} Bee Wah Lee^j
Yap Seng Chong^{a,d} Mary Foong-Fong Chong^{g,a} Lynette Pei-chi Shek^{a,j,k}

^aSingapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), ^bNational University of Singapore, ^cAllergy Service, Department of Paediatrics, KK Women's and Children's Hospital, ^dDepartment of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, ^eRespiratory Service Medicine, Department of Paediatrics, KK Women's and Children's Hospital, ^fBiostatistics Unit, Yong Loo Lin School of Medicine, National University Health System, ^gSaw Swee Hock School of Public Health, National University of Singapore, ^hDepartment of Maternal Fetal Medicine, KK Women's and Children's Hospital, ⁱGrowth, Development and Metabolism Programme, SICS, A*STAR, ^jDepartment of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, and ^kKhoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, Singapore, Singapore; ^lLiggins Institute, University of Auckland, Auckland, New Zealand; ^mNIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, and ⁿMedical Research Council Lifecourse Epidemiology Unit, Southampton, UK

Keywords

Maternal dietary patterns · Allergic diseases · Pregnancy · Birth cohorts

Abstract

Background: Maternal diet during pregnancy has been suggested to be an important early-life exposure that influences immune tolerance and the development of allergic diseases in offspring. **Methods:** We examined the relationship between maternal dietary patterns assessed using 24-h recalls and food diaries at 26–28 weeks of pregnancy and the subsequent development of allergic outcomes in the offspring in the Growing Up in Singapore towards Healthy Outcomes

(GUSTO) birth cohort. Exploratory factor analysis was used to characterize maternal dietary patterns during pregnancy. During repeated visits in the first 36 months of life, questionnaires were administered to ascertain allergic symptoms, namely, eczema, rhinitis, and wheeze. At ages 18 and 36 months, we administered skin-prick testing to inhalant and food allergens. **Results:** Of the 3 maternal dietary patterns that emerged, the seafood and noodles pattern was associated with a reduced risk of developing allergen sensitization at both 18 months (odds ratio [95% confidence interval]: 0.7 [0.5–0.9]) and 36 months (0.7 [0.6–0.9]) after adjustment for a family history of allergy, and ethnicity, sex, and maternal education levels. No associations between the patterns vegetables, fruit, and white rice or pasta, cheese, and processed

M.F.-F.C. and L.P.S. are senior authors and contributed equally to the work.

Correspondence to: Dr. Lynette Shek
Department of Paediatrics, Yong Loo Lin School of Medicine
National University of Singapore
1E Kent Ridge Road, Level 12, NUHS Tower Block, Singapore 119228 (Singapore)
E-Mail lynette_shek@nuhs.edu.sg

Dr. Mary Chong
Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research
Brenner Centre for Molecular Medicine
30 Medical Drive, Singapore 117609 (Singapore)
E-Mail mary_chong@sics.a-star.edu.sg

meat were observed with any of the allergic outcomes in the first 18 and 36 months of life. **Conclusion:** Maternal diet during pregnancy can influence the subsequent development of allergic outcomes in offspring. © 2017 S. Karger AG, Basel

Introduction

In recent decades, increasing attention has been placed on the non-inheritable factors relating to the programming of immune function in the child as suggested by the DOHaD (Developmental Origins of Health and Disease) concept [1]. Besides genetic predisposition increasing the risk of development of diseases, environmental exposures also play a role in modifying the risk [2]. This is evident from a study on monozygotic twin pairs where DNA methylation was influenced by the maternal environment [3, 4]. The early onset of paediatric allergic diseases raises the possibility that maternal diet during pregnancy may contribute to later disease development [5]. Maternal diet during pregnancy not only provides nutrients to the developing foetus but has also been suggested to be an important early-life exposure that influences immune tolerance and the development of allergic diseases in offspring [6]. Research on early-life exposures such as maternal diet during pregnancy on the subsequent development of allergic disease can form preventive strategies and intervention plans to reduce childhood allergic diseases.

Maternal dietary patterns such as the Mediterranean diet, typically consisting of fruits and vegetables, low-to-moderate amounts of eggs and dairy products, and a minimal amount of red meat has been reported to have a protective effect on the development of allergic diseases such as asthma in children [7–10]. Most studies are either cross-sectional or case-control studies that recruit subjects in pre-school or school-going age [11–13]. In addition, some studies have addressed the effect of nutrition in an atopic population from which it is difficult to infer findings to the general population [14, 15]. Other studies have only looked at outcomes in the first year of life [16, 17]. Besides this, studies that have looked at the contribution of maternal nutrition to the development of paediatric allergic outcomes in a prospective birth cohort setting are very limited in Asia as most studies on this topic are conducted in European countries [18, 19], where dietary patterns and genetic constitutions differ [20].

Here, we aimed to analyse the associations between maternal dietary patterns during pregnancy and the de-

velopment of allergic diseases in the first 3 years of life in the Growing Up in Singapore towards Healthy Outcomes (GUSTO) study cohort.

Materials and Methods

Questionnaires and Allergic Outcomes

The methodology of the GUSTO study has been described previously [21, 22]. Briefly, we recruited 1,247 healthy pregnant mothers who agreed to enrol their offspring for future follow-up. The interviewers gathered information on demographics, a family history of allergy, social data, and lifestyle factors. Definitions of allergic outcomes were standardized in questionnaires administered at 3, 6, 9, 12, 15, 18, 24, and 36 months to ensure consistency during interviews and home visits.

Diagnoses of physician-diagnosed atopic eczema, wheeze, and rhinitis were based on positive answers to the written questions “Has your child ever been diagnosed with eczema?”; “Has your child ever wheezed?”; and “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?”; with study team members calling the subjects who reported rhinitis to collect information on the number of episodes of rhinitis and the duration of each episode. A case prior to 18 months required a single episode that lasted for at least 4 weeks or ≥ 2 episodes each lasting at least 2 weeks. New cases of rhinitis after 18 months were defined by ≥ 1 episodes lasting at least 2 weeks.

Allergen sensitization was determined by skin-prick testing (SPT). SPT to inhalant allergens (the house dust mites *Dermaphagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis*) and food allergens (egg, peanut, and cow’s milk) was carried out at both 18 and 36 months. All of the allergens were obtained from Greer Laboratories (Lenoir, NC, USA), except for *B. tropicalis*, which was obtained from our laboratory. All tests were interpreted as positive if the wheal diameter was at least 3 mm, and a child was considered as SPT-positive if ≥ 1 of the individual tests was positive with a positive reaction to the positive control (histamine) and a negative reaction to the negative control (saline).

Allergic clinical outcomes until 18 months were defined as positive responses to the above-noted written questions in the first 18 months combined with a positive SPT at 18 months. Allergic clinical outcomes until 36 months were defined as positive responses to the questions in the first 36 months combined with a positive SPT at 36 months. Allergic outcome was classified as absent when the answers at all visits were “No.” A family history of allergy was defined as positive if the mother, father, or an older sibling had ever had eczema, asthma, or allergic rhinitis.

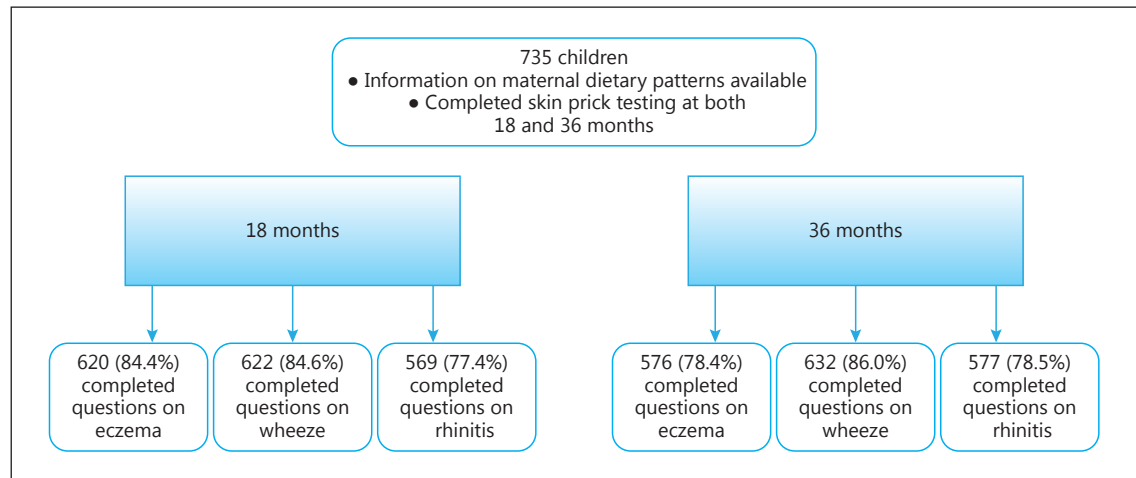
Ethics approval was obtained from the Domain-Specific Review Board of Singapore National Healthcare Group and the Centralised Institutional Review Board of SingHealth. The conduct of this study was based on the guidelines in the Declaration of Helsinki.

Identifying Maternal Dietary Patterns

The methods for maternal dietary assessment have been described previously [23]. Dietary intake was assessed at 26–28 weeks of pregnancy and conducted by trained clinical staff with the use of the 5-stage multiple-pass interviewing technique [24]. Visual aids such as pictures of food portion sizes were presented to assist

Table 1. Sensitization rates to allergens in the children in the first 3 years of life

Follow-up time point	Cow's milk	Peanut	Egg	<i>D. pteronyssinus</i>	<i>D. farinae</i>	<i>B. tropicalis</i>
Month 18	6 (0.8%)	8 (1.1%)	24 (3.3%)	65 (8.8)	53 (7.2%)	8 (1.1%)
Month 36	1 (0.1%)	8 (1.1%)	6 (1.1%)	144 (19.6)	117 (15.9%)	20 (2.7%)

**Fig. 1.** Schematic diagram of the study population that we included in our analysis, showing the number of subjects with responses to different allergic outcomes at 18 and 36 months.

women in their quantification of food and beverage intake. Exploratory factor analysis was used to characterize maternal dietary patterns during pregnancy. The patterns were derived by principal component extraction with varimax rotation on the 68 food groups. Three factors (i.e., dietary patterns) were retained and the pattern was determined by the breakpoint of the Scree plot and factor interpretability. The dietary pattern score for each participant was calculated by summing the standardized intake of food groups (as grams/day) weighted by their factor loadings, using dietary records from 24-h recall. Factor loadings are correlation coefficients between each food group and the dietary pattern, so higher dietary pattern scores indicate a greater adherence to the derived pattern. Three maternal dietary patterns emerged: vegetable, fruit, and white rice (VFR), seafood and noodles (SfN), and pasta, cheese and processed meat (PCP) [25]. Details of the food items and factor-loading scores of the dietary patterns are presented in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000475497).

Statistical Analysis

Statistical analysis was carried out using SPSS v20.0 (IBM SPSS Statistics, Armonk, NY, USA). Associations between maternal dietary pattern scores and subsequent allergic outcomes in offspring were estimated using univariable as well as multivariable logistic regression and adjusting for sex, ethnicity, maternal education, and a family history of allergy. These confounders were selected by a review of the literature [26, 27].

Results

Description of the Study Cohort

In this study, there were 735 children with information on maternal dietary patterns and who had completed SPT at both 18 and 36 months. At 18 months, 620 (84.4%) had completed questions on eczema, 622 (84.6%) had completed questions on wheeze, and 569 (77.4%) had completed questions on rhinitis. At 18 months, 103 subjects (14.0%) had a positive SPT: 6 (0.8%) to cow's milk, 8 (1.1%) to peanut, 24 (3.3%) to egg, 65 (8.8%) to *D. pteronyssinus*, 53 (7.2%) to *D. farinae*, and 8 (1.1%) to *B. tropicalis* (Table 1); 132 (21.3%) had eczema, 36 (5.8%) had eczema with a positive SPT; 107 (18.8%) had rhinitis, 22 (3.9%) had rhinitis with a positive SPT; 179 (28.8%) had wheeze, and 26 (4.2%) had wheeze with a positive SPT.

At 36 months, questions had been completed for 576 children (78.4%) on eczema, for 577 (78.5%) on rhinitis, and for 632 (86.0%) on wheeze. At this time point, 172 subjects (23.4%) had a positive SPT: 1 (0.1%) to cow's milk, 8 (1.1%) to peanut, 6 (1.1%) to egg, 144 (19.6%) to *D. pteronyssinus*, 117 (15.9%) to *D. farinae*, and 20 (2.7%)

Table 2. Comparison of study subjects who completed questionnaires and SPT at 18 months versus other GUSTO subjects

	SPT questions				Eczema questions				Eczema and SPT questions				Wheeze questions				Wheeze and SPT questions				Rhinitis questions				Rhinitis and SPT questions			
	compl.	excl.	p value		compl.	excl.	p value		compl.	excl.	p value		compl.	excl.	p value		compl.	excl.	p value		compl.	excl.	p value		compl.	excl.	p value	
Sex																												
Male	386 (52.5)	56 (57.1)	0.5		323 (52.1)	63 (54.8)	0.6		323 (52.1)	63 (54.8)	0.6		324 (52.1)	62 (54.9)	0.6		324 (52.1)	62 (54.9)	0.6		295 (51.8)	91 (54.8)	0.5		295 (51.8)	91 (54.8)	0.5	
Female	349 (47.5)	42 (42.9)			297 (47.9)	52 (45.2)			297 (47.9)	52 (45.2)			298 (47.9)	51 (45.1)			298 (47.9)	51 (45.1)			274 (48.2)	75 (45.2)			274 (48.2)	75 (45.2)		
Ethnicity																												
Chinese	415 (56.5)	57 (58.2)	0.2		367 (59.2)	48 (41.7)	<0.01		367 (59.2)	48 (41.7)	<0.01		364 (58.5)	51 (45.1)	<0.01		364 (58.5)	51 (45.1)	<0.01		338 (59.4)	77 (46.4)	0.01		338 (59.4)	77 (46.4)	0.01	
Malay	198 (26.9)	19 (19.4)			162 (26.1)	36 (31.3)			162 (26.1)	36 (31.3)			169 (27.2)	29 (25.7)			169 (27.2)	29 (25.7)			145 (25.5)	53 (31.9)			145 (25.5)	53 (31.9)		
Indian	122 (16.6)	22 (22.4)			91 (14.7)	31 (27.0)			91 (14.7)	31 (27.0)			89 (14.3)	33 (29.2)			89 (14.3)	33 (29.2)			86 (15.1)	36 (21.7)			86 (15.1)	36 (21.7)		
Maternal education																												
<12 years	295 (40.5)	36 (37.1)	0.6		236 (38.4)	59 (52.2)	<0.01		236 (38.4)	59 (52.2)	<0.01		243 (39.3)	52 (47.3)	0.1		243 (39.3)	52 (47.3)	0.1		212 (37.5)	83 (50.9)	<0.01		212 (37.5)	83 (50.9)	<0.01	
At least 12 years	433 (59.5)	61 (62.9)			379 (61.6)	54 (47.8)			379 (61.6)	54 (47.8)			375 (60.7)	58 (52.7)			375 (60.7)	58 (52.7)			353 (62.5)	80 (49.1)			353 (62.5)	80 (49.1)		
Family history of allergy																												
No	252 (48.5)	40 (61.5)	0.049		211 (48.3)	41 (49.4)	0.9		211 (48.3)	41 (49.4)	0.9		209 (48.2)	43 (50.0)	0.8		209 (48.2)	43 (50.0)	0.8		191 (47.0)	61 (53.5)	0.2		191 (47.0)	61 (53.5)	0.2	
Yes	268 (51.5)	25 (38.5)			226 (51.7)	42 (50.6)			226 (51.7)	42 (50.6)			225 (51.8)	43 (50.0)			225 (51.8)	43 (50.0)			215 (53.0)	53 (46.5)			215 (53.0)	53 (46.5)		

Values are expressed as n (%). compl., subjects who completed the questionnaire; excl., subjects excluded (i.e., other GUSTO subjects).

Table 3. Comparison of study subjects who completed questionnaires and SPT at 36 months versus other GUSTO subjects

	SPT questions			Eczema questions			Eczema and SPT questions			Wheeze questions			Wheeze and SPT questions			Rhinitis questions			Rhinitis and SPT questions		
	compl.	excl.	<i>p</i> value	compl.	excl.	<i>p</i> value	compl.	excl.	<i>p</i> value	compl.	excl.	<i>p</i> value	compl.	excl.	<i>p</i> value	compl.	excl.	<i>p</i> value	compl.	excl.	<i>p</i> value
<i>Sex</i>																					
Male	386 (52.5)	43 (45.7)	0.2	299 (51.9)	87 (54.7)	0.6	332 (52.5)	54 (52.4)	0.9	332 (52.5)	54 (52.4)	0.9	300 (52.0)	86 (54.4)	0.6	300 (52.0)	86 (54.4)		300 (52.0)	86 (54.4)	0.6
Female	349 (47.5)	51 (54.3)		277 (48.1)	72 (45.3)		300 (47.5)	49 (47.6)		300 (47.5)	49 (47.6)		277 (48.0)	72 (45.6)		277 (48.0)	72 (45.6)		277 (48.0)	72 (45.6)	
<i>Ethnicity</i>																					
Chinese	415 (56.5)	51 (54.3)	0.04	330 (57.3)	85 (53.5)	0.2	330 (57.3)	85 (53.5)		364 (57.6)	51 (49.5)	<0.01	364 (57.6)	51 (49.5)		341 (59.1)	74 (46.8)		341 (59.1)	74 (46.8)	0.02
Malay	198	18		158	40		158	40		176	22		176	22		145	53		145	53	
Indian	122 (16.6)	25 (26.6)		88 (15.3)	34 (21.4)		88 (15.3)	34 (21.4)		92 (14.6)	30 (29.1)		92 (14.6)	30 (29.1)		91 (15.8)	31 (19.6)		91 (15.8)	31 (19.6)	
<i>Years of maternal education</i>																					
<12 years	295 (40.5)	31 (34.1)	0.3	226 (39.6)	69 (43.9)	0.4	226 (39.6)	69 (43.9)	0.3	249 (39.7)	46 (45.5)		249 (39.7)	46 (45.5)		215 (37.5)	80 (51.6)		215 (37.5)	80 (51.6)	<0.01
At least 12 years	433 (59.5)	60 (65.9)		345 (60.4)	88 (56.1)		345 (60.4)	88 (56.1)		378 (60.3)	55 (54.5)		378 (60.3)	55 (54.5)		358 (62.5)	75 (48.4)		358 (62.5)	75 (48.4)	
<i>A family history of allergy</i>																					
No	252 (48.5)	39 (54.2)	0.4	195 (48.3)	57 (49.1)	0.9	195 (48.3)	57 (49.1)	0.1	207 (46.7)	45 (58.4)		207 (46.7)	45 (58.4)		190 (46.3)	62 (56.4)		190 (46.3)	62 (56.4)	0.1
Yes	268 (51.5)	33 (45.8)		209 (51.7)	59 (50.9)		209 (51.7)	59 (50.9)		236 (53.3)	32 (41.6)		236 (53.3)	32 (41.6)		220 (53.7)	48 (43.6)		220 (53.7)	48 (43.6)	
Values are expressed as <i>n</i> (%). compl., subjects who completed the questionnaire; excl., subjects excluded (i.e., other GUSTO subjects).																					

Table 4. Univariable and multivariable associations between maternal dietary patterns and allergic outcomes in offspring in the first 18 months of life

Maternal dietary pattern	Allergen sensitization	Eczema	Eczema with a positive SPT	Wheeze	Wheeze with a positive SPT	Rhinitis	Rhinitis with a positive SPT
<i>Univariable analysis</i>							
VFR	0.9 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.7–1.4)	0.8 (0.7–0.97)	0.8 (0.5–1.2)	0.8 (0.7–1.0)	1.0 (0.6–1.5)
SfN	0.8 (0.7–1.0)	1.1 (0.9–1.3)	0.8 (0.5–1.1)	0.9 (0.7–1.0)	0.8 (0.5–1.3)	0.9 (0.7–1.1)	0.8 (0.5–1.2)
PCP	0.9 (0.7–1.2)	1.1 (0.9–1.3)	0.7 (0.4–1.2)	0.9 (0.7–1.1)	0.7 (0.4–1.3)	1.1 (0.9–1.3)	1.0 (0.6–1.6)
<i>Multivariable analysis</i>							
VFR	1.1 (0.8–1.4)	0.8 (0.7–1.1)	1.1 (0.7–1.7)	0.9 (0.7–1.2)	0.8 (0.5–1.4)	0.8 (0.6–1.1)	1.1 (0.6–2.0)
SfN	0.7 (0.5–0.9)	0.9 (0.6–1.2)	0.6 (0.3–1.1)	0.8 (0.6–1.1)	0.6 (0.3–1.2)	0.9 (0.6–1.2)	0.8 (0.4–1.5)
PCP	0.9 (0.7–1.2)	1.1 (0.9–1.4)	0.8 (0.4–1.5)	0.8 (0.6–1.1)	0.7 (0.3–1.4)	1.1 (0.9–1.4)	1.1 (0.7–1.7)

Values are expressed as odds ratio (95% confidence intervals). Values in bold type denote significant associations between the dietary pattern and allergic outcome with a *p* value <0.05.

Table 5. Univariable and multivariable associations between maternal dietary patterns and allergic outcomes in offspring in the first 3 years of life

Maternal dietary pattern	Allergen sensitization	Eczema	Eczema with a positive SPT	Wheeze	Wheeze with a positive SPT	Rhinitis	Rhinitis with a positive SPT
Univariable analysis							
VFR	1.0 (0.9–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.4)	0.8 (0.7–0.96)	0.9 (0.7–1.1)	1.0 (0.8–1.1)	1.1 (0.8–1.4)
SfN	0.8 (0.7–1.0)	1.2 (1.0–1.4)	1.0 (0.8–1.3)	0.9 (0.7–1.0)	0.9 (0.7–1.1)	1.0 (0.8–1.1)	0.9 (0.7–1.2)
PCP	0.9 (0.7–1.1)	1.1 (0.9–1.3)	0.9 (0.6–1.2)	0.9 (0.8–1.1)	0.9 (0.7–1.2)	1.1 (0.9–1.3)	1.0 (0.7–1.3)
Multivariable analysis							
VFR	1.1 (0.9–1.4)	0.8 (0.6–1.1)	1.1 (0.8–1.6)	0.9 (0.7–1.1)	1.1 (0.8–1.5)	0.9 (0.7–1.1)	1.0 (0.7–1.5)
SfN	0.8 (0.6–0.98)	1.0 (0.7–1.3)	0.9 (0.6–1.4)	0.9 (0.7–1.2)	0.8 (0.5–1.2)	1.0 (0.7–1.2)	0.9 (0.6–1.3)
PCP	0.9 (0.8–1.2)	1.1 (0.9–1.4)	0.8 (0.6–1.3)	0.8 (0.7–1.0)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	1.0 (0.7–1.3)

Values are expressed as odds ratio (95% confidence intervals). Values in bold type denote significant associations between the dietary pattern and allergic outcome with a *p* value <0.05.

to *B. tropicalis* (Table 1); 157 (27.3%) had eczema, 59 (10.2%) had eczema with a positive SPT; 226 (39.2%) had rhinitis, 66 (11.4%) had rhinitis with a positive SPT; 258 (40.8%) had wheeze, and 75 (10.2%) had wheeze with a positive SPT.

A flow chart of the study population with the responses to allergic outcomes in the first 36 months of life is illustrated in Figure 1. There were very regular follow-up visits in this study, and the main reason for non-completion of the questionnaires was when the mothers could not be contacted, hence no home visit took place. The rates of the loss of follow-up in our study are similar to in other studies [28, 29].

We compared the characteristics of the children with complete information and those with missing data (Tables 2, 3). There were some differences in ethnicity and maternal education levels within the analysis groups.

Associations between Maternal Dietary Patterns and Allergic Outcomes in Offspring

The maternal dietary pattern SfN was associated with a reduced risk of developing allergen sensitization at both 18 months (odds ratio [95% confidence interval]: 0.7 [0.5–0.9]; Table 4) and 36 months (0.8 [0.6–0.98]; Table 5) after adjustment for a family history of allergy, and ethnicity, sex, and maternal education levels. There were no significant associations between the maternal dietary patterns VFR and PCP on the development of allergen sensitization, eczema, rhinitis, and wheeze at either 18 or 36 months.

Discussion

In this observational study, we evaluated the effect of early-life nutritional influences on allergic outcomes in infancy in a prospective birth cohort in Singapore. We found that maternal dietary patterns during pregnancy affect the risk of subsequent development of allergic diseases in the offspring.

Interestingly, we found that the maternal dietary pattern SfN reduced the risk of allergen sensitization in the children. There was also a trend of inverse association of this dietary pattern with other allergic outcomes, although it was not statistically significant. A possible reason for our observations could be due to the greater intake of fatty acids from the fish and seafood products consumed with this pattern. Fatty acids may play a role in the protective effect of early immunological development towards atopy sensitization and allergy development [30]. In addition, the SfN pattern contains legumes and pulses which are associated with a reduced risk of allergic disease development in offspring [31]. Supporting evidence for the protective effect of the maternal consumption of legumes such as peanuts during pregnancy was shown in a longitudinal birth cohort study from the USA on 1,277 mother-child pairs, which found that a higher maternal peanut intake was associated with a decreased peanut allergic reaction in children when serum-specific IgE levels were tested in mid-childhood (at a mean age of 7.9 years) [31]. In addition, the Danish Birth Cohort study also reported that the maternal intake of peanuts and tree nuts is associated with reduced odds of the development of asthma in children [19]. Maternal dietary antigens have

been reported to be able to cross the placenta and affect T helper (Th) cell differentiation [32, 33]. This protective effect may be particular to the food or dietary pattern due to the different composition of nutrients such as linolenic acid, which has also been linked with T cell signalling and the expression of MHC II molecules [30]. Due to the different nutrient profiles and synergistic effect between different foods in the SfN dietary pattern, the biological mechanism is complex and may involve many candidate nutrients that together confer this protective effect. Other candidate nutrients include selenium [34], zinc [35], and vitamin E [36] which have also been associated with a protective effect for allergic diseases, possibly by influencing the Th1/Th2 cell ratio through effects on cytokine production [37, 38].

There were findings similar to ours in another prospective cohort study conducted in France that analysed 1,500 children with follow-up until 2 years, and reported no associations between the maternal consumption of shellfish and childhood wheeze and eczema [39]. However, our findings were in contrast to a prospective study conducted in the Netherlands that recruited 2,976 mothers with follow-up of their offspring until 4 years that reported that the maternal consumption of shellfish in the first trimester increased the risk of development of wheeze and eczema in their children [40]. Possible reasons for this discrepancy could be that we analysed dietary patterns, taking into account a potential synergistic effect between food groups whereas the above-mentioned studies looked at single-food consumption in relation to the outcomes. In addition, there may also have been differences in the genetic constitution and lifestyle in these populations.

Although a high maternal intake of fruits and vegetables was found to be protective against developing asthma symptoms in 2 previous cohort studies [41, 42], we did not find any associations between the VFR maternal dietary pattern and allergic outcomes in our study. In agreement with our observations, another study which looked at birth cohorts from Spain and Greece that recruited 1,771 and 745 mother-child pairs, respectively, also showed no association between a maternal Mediterranean diet during pregnancy and infantile wheeze or eczema at the age of 1 year [43]. Besides this, a longitudinal cohort study which recruited 1,376 mother-child pairs from Project Viva in the USA also found no significant associations between “Prudent” and “Western” dietary patterns (comparable to a Mediterranean and a processed diet, respectively) during pregnancy with recurrent wheeze at 3 years of age [44]. Additionally, a birth cohort

with data from 2,832 children showed no associations between maternal vegetable consumption and childhood wheeze or asthma at 8 years old [45]. However, a Spanish birth cohort study showed that adherence to a Mediterranean diet in pregnancy was associated with a lower risk of persistent wheeze and atopy in 460 children who had SPT at the age 6.5 years [8]. This suggests there is merit in following up the children in our study in the longer term to track atopic sensitizations and allergic outcomes in the future.

The strengths of this study are that we analysed dietary patterns of food consumption, which enabled us to conduct holistic analyses of the synergistic effects of foods and nutrients. In addition, this is a prospective birth cohort study with a regular collection of information at multiple time points. The collection of maternal dietary information during pregnancy also reduced a recall and response bias, as this information was collected prior to the assessment of the infant allergic outcomes.

However, the weaknesses of this study are the incomplete response rates to the questionnaires due to subjects not being contactable at some point in the study. Another limitation is that some of the allergic outcomes reported by parents may have been subject to a recall bias and misclassification. We thus combined these with an objective assessment of allergen sensitization.

In conclusion, we found evidence that maternal diet during pregnancy plays a role in the subsequent development of allergic outcomes in offspring.

Acknowledgements

This research was supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Programme 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, NMRC/CSA/022/2010, and NRF370062-HUJ-NUS [Project 10]). Additional funding was provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore. K.M.G. is funded by the NIHR through the NIHR Southampton Biomedical Research Centre and by the European Union's Seventh Framework Programme (FP7/2007–2013), projects EarlyNutrition and ODIN under the grant agreement Nos. 289346 and 613977.

The co-authors acknowledge the contribution of the rest of the GUSTO study group which includes Pratibha Agarwal, Dennis Bier, Arijit Biswas, Shirong Cai, Jerry Kok Yen Chan, Cornelia Yin Ing Chee, Helen Y. H. Chen, Audrey Chia, Amutha Chinnadurai, Chai Kiat Chng, Shang Chee Chong, Mei Chien Chua, Chun Ming Ding, Eric Andrew Finkelstein, Doris Fok, Marielle Fortier, Yam Thiam Daniel Goh, Joshua J. Gooley, Wee Meng Han, Mark Hanson, Christiani Jeyakumar Henry, Joanna D Holbrook, Chin-Ying

Hsu, Hazel Inskip, Jeevesh Kapur, Birit Leutscher-Broekman, Sok Bee Lim, Seong Feei Loh, Yen-Ling Low, Iliana Magiati, Lourdes Mary Daniel, Michael Meaney, Susan Morton, Cheryl Ngo, Krishnamoorthy Niduvaje, Anqi Qiu, Boon Long Quah, Victor Samuel Rajadurai, Mary Rauff, Jenny L. Richmond, Anne Rifkin-Graboi, Allan Sheppard, Borys Shuter, Leher Singh, Wing Chee So, Walter Stunkel, Lin Lin Su, Kok Hian Tan, Soek Hui Tan, Rob M. van Dam, Sudhakar K. Venkatesh, Inez Bik Yun Wong, P.C. Wong, and George Seow Heong Yeo.

Disclosure Statement

P.D. Gluckman, K.M. Godfrey, L.P. Shek, and Y.S. Chong received reimbursement for speaking at conferences sponsored by companies selling nutritional products.

P.D. Gluckman, K.M. Godfrey, and Y.S. Chong are part of an academic consortium that has received research funding from Abbot Nutrition, Nestec, and Danone. L.P. Shek has received research funding from Danone.

References

- ▶ 1 Heindel JJ, Balbus J, Birnbaum L, Bruner-Drise MN, Grandjean P, Gray K, Landrigan PJ, Sly PD, Suk W, Cory Slechts D, Thompson C, Hanson M: Developmental origins of health and disease: integrating environmental influences. *Endocrinology* 2015;156:3416–3421.
- ▶ 2 Harb H, Amarasekera M, Ashley S, Tulic MK, Pfefferle PI, Potaczek DP, Martino D, Kesper DA, Prescott SL, Renz H: Epigenetic regulation in early childhood: a miniaturized and validated method to assess histone acetylation. *Int Arch Allergy Immunol* 2015;168:173–181.
- ▶ 3 Brodin P, Jovic V, Gao T, Bhattacharya S, Angel CJ, Furman D, Shen-Orr S, Dekker CL, Swan GE, Butte AJ, Maecker HT, Davis MM: Variation in the human immune system is largely driven by non-heritable influences. *Cell* 2015;160:37–47.
- ▶ 4 Waterland RA, Kellermayer R, Laritsky E, Rayco-Solon P, Harris RA, Travisano M, Zhang W, Torskaya MS, Zhang J, Shen L, Manary MJ, Prentice AM: Season of conception in rural Gambia affects DNA methylation at putative human metastable epialleles. *PLoS Genet* 2010;6:e1001252.
- ▶ 5 Khan TK, Palmer DJ, Prescott SL: In-utero exposures and the evolving epidemiology of paediatric allergy. *Curr Opin Allergy Clin Immunol* 2015;15:402–408.
- ▶ 6 West CE, D'Vaz N, Prescott SL: Dietary immunomodulatory factors in the development of immune tolerance. *Curr Allergy Asthma Rep* 2011;11:325–333.
- ▶ 7 Chatzi L, Apostolaki G, Bibakis I, Skypala I, Bibaki-Liakou V, Tzanakis N, Kogevinas M, Cullinan P: Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax* 2007;62:677–683.
- ▶ 8 Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, Kogevinas M, Sunyer J: Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax* 2008;63:507–513.
- ▶ 9 Chatzi L, Kogevinas M: Prenatal and childhood Mediterranean diet and the development of asthma and allergies in children. *Public Health Nutr* 2009;12:1629–1634.
- ▶ 10 Grieger JA, Clifton VL, Tuck AR, Wooldridge AL, Robertson SA, Gattford KL: In utero programming of allergic susceptibility. *Int Arch Allergy Immunol* 2016;169:80–92.
- ▶ 11 Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda Rojas JD, Valverde-Molina J, Sanchez-Solis M: Mediterranean diet as a protective factor for wheezing in preschool children. *J Pediatr* 2008;152:823–828, 828 e821–e822.
- ▶ 12 de Batlle J, Garcia-Aymerich J, Barraza-Villarreal A, Anto JM, Romieu I: Mediterranean diet is associated with reduced asthma and rhinitis in Mexican children. *Allergy* 2008;63:1310–1316.
- ▶ 13 Rice JL, Romero KM, Galvez Davila RM, Meza CT, Bilderback A, Williams DL, Breyse PN, Bose S, Checkley W, Hansel NN; GASP Study Investigators: Association between adherence to the Mediterranean diet and asthma in Peruvian children. *Lung* 2015;193:893–899.
- ▶ 14 Sicherer SH, Wood RA, Stablein D, Lindblad R, Burks AW, Liu AH, Jones SM, Fleischer DM, Leung DY, Sampson HA: Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. *J Allergy Clin Immunol* 2010;126:1191–1197.
- ▶ 15 Herrmann ME, Dannemann A, Gruters A, Radisch B, Dudenhausen JW, Bergmann R, Coumbos A, Weitzel HK, Wahn U: Prospective study of the atopy preventive effect of maternal avoidance of milk and eggs during pregnancy and lactation. *Eur J Pediatr* 1996;155:770–774.
- ▶ 16 Erkkola M, Nwaru BI, Kaila M, Kronberg-Kippila C, Ilonen J, Simell O, Veijola R, Knip M, Virtanen SM: Risk of asthma and allergic outcomes in the offspring in relation to maternal food consumption during pregnancy: a Finnish birth cohort study. *Pediatr Allergy Immunol* 2012;23:186–194.
- ▶ 17 Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, Arshad SH, Dean T: Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatr Allergy Immunol* 2009;20:320–327.
- ▶ 18 Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, Kronberg-Kippila C, Veijola R, Ilonen J, Simell O, Knip M, Virtanen SM: Maternal diet during pregnancy and allergic sensitization in the offspring by 5 years of age: a prospective cohort study. *Pediatr Allergy Immunol* 2010;21:29–37.
- ▶ 19 Maslova E, Granstrom C, Hansen S, Petersen SB, Strom M, Willett WC, Olsen SF: Peanut and tree nut consumption during pregnancy and allergic disease in children—should mothers decrease their intake? Longitudinal evidence from the Danish national birth cohort. *J Allergy Clin Immunol* 2012;130:724–732.
- ▶ 20 Hadley C: Food allergies on the rise? Determining the prevalence of food allergies, and how quickly it is increasing, is the first step in tackling the problem. *EMBO Rep* 2006;7:1080–1083.
- ▶ 21 Soh SE, Lee SS, Hoon SW, Tan MY, Goh A, Lee BW, Shek LP, Teoh OH, Kwek K, Saw SM, Godfrey K, Chong YS, Gluckman P, van Bever HP: The methodology of the GUSTO cohort study: a novel approach in studying pediatric allergy. *Asia Pac Allergy* 2012;2:144–148.
- ▶ 22 Soh SE, Tint MT, Gluckman PD, Godfrey KM, Rifkin-Graboi A, Chan YH, Stunkel W, Holbrook JD, Kwek K, Chong YS, Saw SM: Cohort profile: Growing Up in Singapore towards Healthy Outcomes (GUSTO) birth cohort study. *Int J Epidemiol* 2014;43:1401–1409.
- ▶ 23 Chong MF, Chia AR, Colega M, Tint MT, Aris IM, Chong YS, Gluckman P, Godfrey KM, Kwek K, Saw SM, Yap F, van Dam RM, Lee YS; GUSTO Study Group: Maternal protein intake during pregnancy is not associated with offspring birth weight in a multiethnic Asian population. *J Nutr* 2015;145:1303–1310.
- ▶ 24 Conway JM, Ingwersen LA, Vinyard BT, Moshfegh AJ: Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. *Am J Clin Nutr* 2003;77:1171–1178.

- ▶ 25 de Seymour J, Chia A, Colega M, Jones B, McKenzie E, Shirong C, Godfrey K, Kwek K, Saw SM, Conlon C, Chong YS, Baker P, Chong MF: Maternal dietary patterns and gestational diabetes mellitus in a multi-ethnic Asian cohort: the GUSTO study. *Nutrients* 2016;8:E574.
- ▶ 26 Miyake Y, Okubo H, Sasaki S, Tanaka K, Hirota Y: Maternal dietary patterns during pregnancy and risk of wheeze and eczema in Japanese infants aged 16–24 months: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2011;22:734–741.
- ▶ 27 Shaheen SO, Northstone K, Newson RB, Emmett PM, Sherriff A, Henderson AJ: Dietary patterns in pregnancy and respiratory and atopic outcomes in childhood. *Thorax* 2009;64:411–417.
- ▶ 28 Smithers LG, Brazionis L, Golley RK, Mittinty MN, Northstone K, Emmett P, McNaughton SA, Campbell KJ, Lynch JW: Associations between dietary patterns at 6 and 15 months of age and sociodemographic factors. *Eur J Clin Nutr* 2012;66:658–666.
- ▶ 29 Oddy WH, de Klerk NH, Sly PD, Holt PG: The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002;19:899–905.
- ▶ 30 Yaqoob P, Calder PC: Fatty acids and immune function: new insights into mechanisms. *Br J Nutr* 2007;98(suppl 1):S41–S45.
- ▶ 31 Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA Jr, Gillman MW, Gold DR, Litonjua AA: Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. *J Allergy Clin Immunol* 2014;133:1373–1382.
- ▶ 32 Devereux G: The increase in the prevalence of asthma and allergy: food for thought. *Nat Rev Immunol* 2006;6:869–874.
- ▶ 33 Loibichler C, Pichler J, Gerstmayr M, Bohle B, Kist H, Urbanek R, Szepefalusi Z: Materno-fetal passage of nutritive and inhalant allergens across placentas of term and pre-term deliveries perfused in vitro. *Clin Exp Allergy* 2002;32:1546–1551.
- ▶ 34 Devereux G, McNeill G, Newman G, Turner S, Craig L, Martindale S, Helms P, Seaton A: Early childhood wheezing symptoms in relation to plasma selenium in pregnant mothers and neonates. *Clin Exp Allergy* 2007;37:1000–1008.
- ▶ 35 Litonjua AA, Rifas-Shiman SL, Ly NP, Tantisira KG, Rich-Edwards JW, Camargo CA Jr, Weiss ST, Gillman MW, Gold DR: Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 years of age. *Am J Clin Nutr* 2006;84:903–911.
- ▶ 36 Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, Helms PJ, Seaton A: Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med* 2006;174:499–507.
- ▶ 37 Malmberg KJ, Lenkei R, Petersson M, Ohlun T, Ichihara F, Glimelius B, Frodin JE, Masucci G, Kiessling R: A short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer. *Clin Cancer Res* 2002;8:1772–1778.
- ▶ 38 Li-Weber M, Giaisi M, Treiber MK, Krammer PH: Vitamin E inhibits IL-4 gene expression in peripheral blood T cells. *Eur J Immunol* 2002;32:2401–2408.
- ▶ 39 Pele F, Bajeux E, Gendron H, Monfort C, Rouget F, Multigner L, Viel JF, Cordier S: Maternal fish and shellfish consumption and wheeze, eczema and food allergy at age two: a prospective cohort study in Brittany, France. *Environ Health* 2013;12:102.
- ▶ 40 Leermakers ET, Sonnenschein-van der Voort AM, Heppe DH, de Jongste JC, Moll HA, Franco OH, Hofman A, Jaddoe VW, Duijts L: Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: the Generation R Study. *Eur J Clin Nutr* 2013;67:353–359.
- ▶ 41 Fitzsimon N, Fallon U, O'Mahony D, Loftus BG, Bury G, Murphy AW, Kelleher CC, Lifeways Cross Generation Cohort Study Steering Group: Mothers' dietary patterns during pregnancy and risk of asthma symptoms in children at 3 years. *Irish Med J* 2007;100(suppl)27–32.
- ▶ 42 Willers SM, Devereux G, Craig LC, McNeill G, Wijga AH, Abou El-Magd W, Turner SW, Helms PJ, Seaton A: Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax* 2007;62:773–779.
- ▶ 43 Chatzi L, Garcia R, Roumeliotaki T, Basterrechea M, Begiristain H, Iniguez C, Vioque J, Kogevinas M, Sunyer J: Mediterranean diet adherence during pregnancy and risk of wheeze and eczema in the first year of life: INMA (Spain) and RHEA (Greece) mother-child cohort studies. *Br J Nutr* 2013;110:2058–2068.
- ▶ 44 Lange NE, Rifas-Shiman SL, Camargo CA Jr, Gold DR, Gillman MW, Litonjua AA: Maternal dietary pattern during pregnancy is not associated with recurrent wheeze in children. *J Allergy Clin Immunol* 2010;126:250–255, 255 e251–e254.
- ▶ 45 Willers SM, Wijga AH, Brunekreef B, Kerkhof M, Gerritsen J, Hoekstra MO, de Jongste JC, Smit HA: Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Respir Crit Care Med* 2008;178:124–131.

Supplementary Table 1:

Factor loading matrix for the 3 major dietary patterns identified by using 24 hour recall during the 26-28 weeks of pregnancy

	Vegetable, Fruit and white Rice (VFR) diet	Seafood and Noodles (SfN) diet	Pasta, Cheese and Processed Meat Diet (PCP)
Low fat red meat	0.21	0.39	
Red meat and poultry (Deep fried / in curry)	-0.26		
Processed meat		0.21	0.23
Non-fried fish	0.21		
seafood		0.28	
Fish and seafood products		0.43	
Cruciferous, red, yellow leafy vegetables	0.52		
Other Vegetables	0.44		
Fried potatoes	-0.43		
Fresh fruits	0.39		
Beancurd	0.21		
Legumes and pulses	0.22	-0.38	
White rice	0.37	-0.33	
Flavoured rice	-0.29		
Other grains		-0.23	
Noodles (in soup)		0.41	
Flavoured noodles		0.38	-0.2
Pasta			0.71
White bread			0.36
Wholegrain / wholemeal bread	0.31		
Ethnic bread	0.23	-0.44	
Low fat milk			0.22
Cheese			0.49
Carbonated drinks	-0.36		
Sweetened drinks	-0.31		
Local savoury snacks		0.21	
Margarine and peanut butter			0.21
Soup with meat and vegetable	0.35	0.5	
Tomato based gravies			0.66
Cream based gravies			0.38
Curry based gravies		-0.28	
Soya sauce based gravies		0.28	
Burger	-0.35		

- Absolute values <0.20 were not included in the table for simplicity
- Ethnic bread include Chinese steamed bun, tortilla, idli, puri, thosai, chapati and naan
- Sweetened drinks include non-carbonated, cordial, and fruit drinks