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Prenatal and perinatal risk factors of food allergy in Taiwanese young children

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ABSTRACT

Background: In recent decades, the prevalence of food allergy (FA) in children has increased in Western countries; however, there have been only limited studies on FA, especially among young children, in Asian countries, including Taiwan. In this study, we identified prenatal and perinatal risk factors associated with FA in young children in Taiwan.

Methods: For this prospective birth cohort study, we adopted the Southern Taiwan Allergy Research Alliance (STARA)-FA questionnaire to collect data related to prenatal and perinatal risk factors and self-reported allergic symptoms in children aged 1–3 years in the well-baby clinics of 4 medical centers located in 3 cities, Chia-Yi, Tainan, and Kaohsiung, Taiwan. The STARA-FA questionnaire consisted of 99 questions to investigate the association of prenatal and perinatal risk factors with FA.

Results: We recruited 903 young children aged 1–3 years in Taiwan. Among those, 95 (14.7%) children had allergic reactions to foods. The most common food allergens were eggs (26/95, 27.3%), milk (22/95, 23.2%), fruits (13/95, 13.7%), and seafood (12/95, 12.6%). We also found that there were 134 (14.8%) children with eczema, 86 (9.5%) with wheezing, and 240 (26.6%) with rhinitis. Children with a personal history of eczema (adjusted odds ratio [AOR], 2.48; 95% confidence interval [CI], 1.38–4.45) and a family allergy history (AOR, 2.06; 95% CI, 1.18–3.57) had a significantly increased risk of FA. Maternal peanut consumption during pregnancy was associated with a decreased risk of FA in children (AOR, 0.57; 95% CI, 0.33–0.98).

Conclusions: In this study, the prevalence of FA in a cohort of Taiwanese young children was 14.7%. Risk factors associated with FA were a personal eczema history and a family allergy history, which might serve as predictive or prevention factors for the development of FA in young children in Taiwan.

Keywords: Food allergy, Prevalence, Questionnaire, Risk factors, Atopy

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INTRODUCTION

Food allergy (FA) is defined as an adverse reaction occurring reproducibly upon exposure to a specific food. Severe FA, such as food-induced anaphylaxis, can often be life threatening.[1] FA is generally diagnosed in up to 10% of the population, mostly in children, and FA has become a major health problem in many countries around the world. In the United States, the prevalence of FA has been increasing in recent decades,[2–4] from approximately 5% in 2011 to 7.6% in 2016.[3,5] However, only limited population-based studies are available from Asia and other parts of the world.[6]

Furthermore, meta-analyses on FA studies across different populations have shown marked heterogeneity in the reported prevalence of food allergy.[7–11] This heterogeneity might be due to the wide variety of methodologies used across studies and differences in the cultural backgrounds and eating habits of different populations, which could limit the robustness of comparisons across different populations. Recent studies have focused on the prevalence of FA in preschoolers, because preschoolers have the highest burden of FA among childhood age groups. The reported prevalence of oral-challenge-proven FA was 1% in Thai children less than 5 years of age, 5.3% in Korean infants[12] and 11% in Australian infants.[2] Previous studies have indicated that the prevalence of food-induced anaphylaxis, particularly due to eggs and cow's milk, was found to be the highest in children less than 2 years of age.[13–15] At present, the prevalence of FA in children, particularly in those under 3 years old, in Taiwan remains unknown and has yet to be determined.

In fact, few prospective birth cohort studies are available on the effects of prenatal and perinatal early-life exposures on FA and other allergic disorders among Asian individuals.[16,17] One recent prospective birth cohort study conducted in China found that prenatal factors associated with FA and eczema are multifaceted and involve hereditary, environmental and nutritional exposures.[16] Thus, this study aimed to investigate prenatal and perinatal risk factors for FA and other related allergic symptoms, such as eczema, rhinitis, and wheezing, in children aged 1–3 years in the general population in Taiwan.

METHODS

Study populations

A birth cohort of young children in the southern part of Taiwan, the Southern Taiwan Allergy Research Alliance (STARA),[18] aged between one and three years, was recruited between March 2018 and Feb 2019. Children were recruited from four medical centers, National Cheng Kung University Hospital, Tainan; E-Da Hospital, Kaohsiung; Kaohsiung Chan Gung Memorial Hospital, Kaohsiung; and St. Martin De Porres Hospital, Chia-Yi, Taiwan, located in Chia-I, Tainan, and Kaohsiung cities in the southern part of Taiwan. In each medical center, 150–250 participants were enrolled from the well-baby clinic when they received their routine heath check-up and vaccination, and the questionnaires were completed by children's parents or caregivers. The informed consent form was signed by the children's parents or caregivers. Both the study questionnaire and consent forms were approved by the respective hospital's human research and ethics committee.

Questionnaire details and definitions

The STARA-FA questionnaires were translated and adapted from the Prevalence and Natural History of Cow's Milk and Hen's Egg Allergy questionnaires provided by the Department of Pediatrics, National Singapore University, which were used for investigating self-reported FA and identifying common food allergens in children aged 1–3 years. The STARA-FA questionnaire used in this study consisted of 99 questions to investigate the prenatal and perinatal risk factors that might be associated with FA and other allergic symptoms, such as eczema, rhinitis, and wheezing, in children aged 1–3 years old. The survey included questions related to the child's demographic and epidemiological information, such as the type of birth, maternal diet during pregnancy, breastfeeding, food introduction, and a section to assess whether the child had symptoms that were suggestive of cow's milk, hen's eggs, or peanut allergy. These questions regarding specific symptoms of FA were adapted from a questionnaire developed by Boyce et al[19] to

ascertain the presence of immediate-type (IgE-mediated) FA. Parent-reported FA was defined as an affirmative response to the question, "Has your child ever experienced allergic reactions to food, including the symptoms of skin rash, urticaria, swollen eyelid/lip, rhinorrhea, difficulty breathing, wheezing, dizziness, abdominal pain, diarrhea, vomiting, or low blood pressure?" Parents reporting a current FA were asked to complete additional, more detailed sections of the questionnaire regarding specific foods to which their children were allergic: peanuts, other nuts (nut type specified), hen's eggs, cow's milk, fish, shellfish, fruits, and other food (specified). Those parents who did not complete the additional FA questions and those who reported an FA that was unlikely to be IgE-mediated (celiac disease, lactose intolerance, or reactions to additives) were excluded from the current analyses. The remaining infants for whom an FA was reported by parents were classified as "possibly IgE-mediated food allergic". Parent-reported infantile wheezing was defined as affirmative responses to both of the questions "Has your child ever wheezed without fever?" and "Has your child ever had repeated bronchiolitis or asthma?" Parent-reported eczema was defined as affirmative responses to the following three questions: "Has your child at any time had an itchy rash other than a nappy rash?" If Yes, "Were topical steroids applied?", and "Does your child have eczema?" Parent-reported rhinitis was defined as an affirmative response to the question "Has your child had a runny nose, a stuffy or congested nose, snoring or noisy breathing during sleep or when awake that lasted for 2 or more weeks?"

Our questionnaire included questions for investigating maternal food consumption during pregnancy. The questions were as follows: "During pregnancy, did the child's mother consume eggs/cow's milk/peanuts/clam or shrimp/fish?" and the answer options were (1) Yes, (2) No, and (3) Not Sure. "If Yes, how often?" with answer options of (1) Less than Once/Week, (2) At Least Once/Week, and (3) Daily. If the answer was Yes with any frequency of specific food consumption, we defined these individuals as mothers who consumed the food during pregnancy. If the answer was No, we defined these individuals as mothers who did not consume the food during pregnancy. To investigate the consumption of maternal supplements during pregnancy, the parents were asked "Did the child's mother take any supplements, including fish oil, probiotics, vitamin D, or folic acid, during pregnancy?" The answer options were (1) Yes, (2) No, and (3) Not Sure. Moreover, for the assessment of maternal drug exposure, the questionnaire contained the question "Did the child's mother receive any drug treatment, especially antipyretic agents and antibiotics, during pregnancy?" and the answer options were (1) Yes, (2) No, and (3) Not Sure.

Statistical analysis

We tested the difference in demographic characteristics between children with and without the 4 examined allergic symptoms, FA, eczema, wheezing and rhinitis, using the chi-squared test for categorical variables and Student's *t*-test for continuous variables. Potential risk factors were considered for inclusion in the analyses, including those variables whose P value was less than 0.1 in univariate analyses or that were known important risk factors from already published reports. We created logistic regression models to examine the associations between each prenatal factor and four allergic symptoms with and without adjustment for the other prenatal factors. The prenatal factors examined in this study were as follows: the consumption of eggs, milk, peanuts, or shellfish during pregnancy; the consumption of any supplements or drugs during pregnancy; a household member who smoked during pregnancy; and the presence of pets in the home during pregnancy. We also applied logistic regression analyses to evaluate the associations between each perinatal factor and four allergic symptoms with and without adjustment for the other perinatal factors. The perinatal factors examined in this study were as follows: the child's sex; the type of delivery; gestational age; the season of birth; family income; exclusive breastfeeding for 6 months; a household member who smoked during pregnancy; the presence of pets in the home; and the personal allergic history, including FA, eczema, wheezing and rhinitis, and family allergic history. The relationship between the maternal diet during pregnancy and the sensitization to foods in the children was examined using either the chi-square test or Fisher's exact test. A P value less than 0.05 was declared statistically significant. All analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

The prevalence of allergic symptoms in young children

A total of 903 participants completed the questionnaire, and nearly all the responses to the questionnaires were provided by the children's parents (99.0%). The mean age of the children was 22.6 ± 7.9 months (12–47 months of age), and 51.5% of the studied children were males. Table 1 shows the demographic characteristics of the study children. The prevalence of FA was 14.7% (95/645), including 95 children with allergic reactions to food, 550 children without allergic reactions to food, 250 children for whom parents were not sure, and 8 children for whom parents did not answer the question. Fig. 1 shows the most common food allergens, such as eggs (26/95, 27.3%) and milk (22/95, 23.2%), in children with FA. Allergic reactions to fruits (kiwi, strawberry, peach, tomato, and cantaloupe, 13/95, 13.7%), seafood (shrimp, crab, clam and fish, 12/95, 12.6%), and peanuts (9/95, 9.5%) were also considered in this study. We also found that there were 134 (14.8%) children with eczema, 86 (9.5%) with wheezing, and 240 (26.6%) with rhinitis. The prevalence of none, 1 or more allergic symptoms of the above 4 allergic comorbidities among the study children is shown in Fig. 2. There were 336 (45.5%) children without any allergic symptoms, 278 (37.6%) children with any of the allergic symptoms, 103 (13.9%) with 2 of the allergic symptoms, 17 (2.3%) children with 3 of the allergic symptoms, and 5 (0.7%) children with all 4 allergic symptoms. We found no differences in any of the collected demographic data between children with FA and children without FA (Table 1). Children with eczema were older than those without eczema. Males tended to have a higher prevalence of wheezing than females. Similar to children with eczema, children with rhinitis were older than those without rhinitis.

Prenatal risk factors for food allergy and other allergic symptoms among children

Table 2 shows the association of prenatal risk factors with FA and other allergic symptoms, including eczema, wheezing, and rhinitis. We found that the maternal consumption of milk during pregnancy was not associated with FA but was associated with a decreased risk of rhinitis (adjusted odds ratio [AOR] = 0.53; 95% confidence interval [CI]: 0.31–0.93). The results also showed that maternal peanut consumption during pregnancy was negatively associated with a decreased risk of FA (AOR = 0.57; 95% CI: 0.33–0.98) but was not associated with the other allergic symptoms. We also found that maternal consumption of probiotics during pregnancy was associated with a risk of rhinitis in children (AOR = 1.58; 95% CI: 1.05–2.36).

Perinatal risk factors for FA and other allergic symptoms among children

Table 3 shows the association of perinatal risk factors with FA and other allergic symptoms, including eczema, wheezing, and rhinitis. We found a significant association of male sex with an increased risk of wheezing in the study children (AOR = 2.33; 95% CI: 1.2–4.51). Children born in the winter had an increased risk of eczema compared to children born in the summer (AOR = 2.05; 95% CI: 1.00–4.22). Regarding the environmental risk factors, having a household member who smoked was associated with an increased risk of wheezing (AOR = 2.44; 95% CI: 1.25–4.75). Furthermore, we found that child personal allergy history of eczema was significantly associated with FA (AOR = 2.48; 95% CI: 1.38–4.45); child personal allergy history of wheezing and child personal allergy history of FA, respectively, were significantly associated with eczema (AOR = 2.51; 95% CI: 1.24–5.09 for child personal allergy history of wheezing; and AOR = 2.53; 95% CI: 1.41–4.53 for child personal allergy history of FA); child personal allergy history of eczema and child personal allergy history of rhinitis, individually, were positively associated with wheezing (AOR = 2.64; 95% CI: 1.32–5.31 for child personal allergy history of eczema; and AOR = 2.43; 95% CI: 1.30–4.53 for child personal allergy history of rhinitis); and child personal allergy history of wheezing was associated with rhinitis (AOR = 2.38; 95% CI:

	Food allergy			Eczema			Wheezing			Rhinitis		
	Yes (n = 95)	No (n = 550)	*P**	Yes (n = 134)	No (n = 769)	*P*	Yes (n = 86)	No (n = 817)	*P*	Yes (n = 240)	No (n = 663)	*P*
	Mean ± SD or n (%)			Mean ± SD or n (%)			Mean ± SD or n (%)			Mean ± SD or n (%)		
Age	22.9 ± 7.9	23.6 ± 7.8	0.35	24.9 ± 8.4	22.2 ± 7.8	**< 10^{-3}**	23.9 ± 7.8	22.5 ± 7.9	0.09	23.6 ± 7.8	22.3 ± 7.9	**0.02**
Gender			0.76			0.83			**< 10^{-3}**			0.25
Female	45 (47.4)	270 (49.1)		64 (47.8)	375 (48.8)		29 (33.7)	410 (50.2)		109 (45.4)	330 (49.8)	
Male	50 (52.6)	280 (50.9)		70 (52.2)	394 (51.2)		57 (66.3)	407 (49.8)		131 (54.6)	333 (50.2)	
Types of delivery			0.62			0.67			0.24			0.60
NSD	55 (58.5)	336 (61.2)		79 (59.0)	467 (60.9)		47 (54.6)	499 (61.2)		142 (59.2)	404 (61.1)	
C/S	39 (41.5)	213 (38.8)		55 (41.0)	300 (39.1)		39 (45.4)	316 (38.8)		98 (40.8)	257 (38.9)	
Gestational age			0.09			0.31			0.98			0.84
Term	83 (88.3)	512 (93.3)		120 (89.6)	706 (92.2)		79 (91.9)	747 (91.8)		221 (92.1)	605 (91.7)	
Preterm	11 (11.7)	37 (6.7)		14 (10.4)	60 (7.8)		7 (8.1)	67 (8.2)		19 (7.9)	55 (8.3)	
Birth body weight			0.76			0.87			0.22			0.41
<1500 g	0	3 (0.6)		1 (0.8)	7 (1.0)		2 (2.3)	6 (0.8)		3 (1.3)	5 (0.8)	
1500-2499 g	8 (9.1)	43 (8.3)		10 (7.8)	66 (9.1)		10 (11.8)	66 (8.6)		16 (7.1)	60 (9.6)	
≥2500 g	80 (90.9)	469 (91.1)		117 (91.4)	648 (89.9)		73 (85.9)	692 (90.6)		208 (91.6)	557 (89.6)	
Season of birth			0.50			0.14			0.72			0.32
Spring	28 (29.5)	136 (24.7)		34 (25.4)	192 (25.0)		20 (23.3)	206 (25.2)		60 (25.0)	166 (25.0)	
Summer	18 (18.9)	137 (24.9)		29 (21.6)	208 (27.0)		25 (29.1)	212 (26.0)		53 (22.1)	184 (27.8)	
Autumn	20 (21.1)	127 (23.1)		26 (19.4)	179 (23.3)		22 (25.6)	183 (22.4)		61 (25.4)	144 (21.7)	
Winter	29 (30.5)	150 (27.3)		45 (33.6)	190 (24.7)		19 (22.1)	216 (26.4)		66 (27.5)	169 (25.5)	
Siblings			0.09			0.37			0.14			0.37
0	45 (47.4)	189 (34.6)		58 (43.3)	287 (37.6)		31 (36.1)	314 (38.7)		89 (37.2)	256 (38.9)	
1	39 (41.1)	265 (48.5)		58 (43.3)	356 (46.7)		35 (40.7)	379 (46.7)		105 (43.9)	309 (47.0)	
2	10 (10.5)	75 (13.7)		17 (12.7)	99 (13.0)		18 (20.9)	98 (12.1)		37 (15.5)	79 (12.0)	
≥3	1 (1.0)	17 (3.1)		1 (0.7)	21 (2.7)		2 (2.3)	20 (2.5)		8 (3.4)	14 (2.1)	
Family's income			0.43			0.72			0.94			0.63
< NT60,000	42 (49.4)	220 (46.5)		55 (46.2)	314 (47.0)		34 (47.9)	335 (46.8)		102 (49.8)	267 (45.9)	
NT60,000-100,000	32 (37.7)	164 (34.7)		39 (32.8)	234 (35.0)		25 (35.2)	248 (34.6)		67 (32.7)	206 (35.4)	
≥ NT100,000	11 (12.9)	89 (18.8)		25 (21.0)	120 (18.0)		12 (16.9)	133 (18.6)		36 (17.6)	109 (18.7)	

Table 1. Demographic characteristics of study population by food allergy and three other allergic symptoms. *Note: Abbreviation: SD, standard deviation; NSD, normal spontaneous delivery; C/S, cesarean section. P values < 0.05 are in bold*

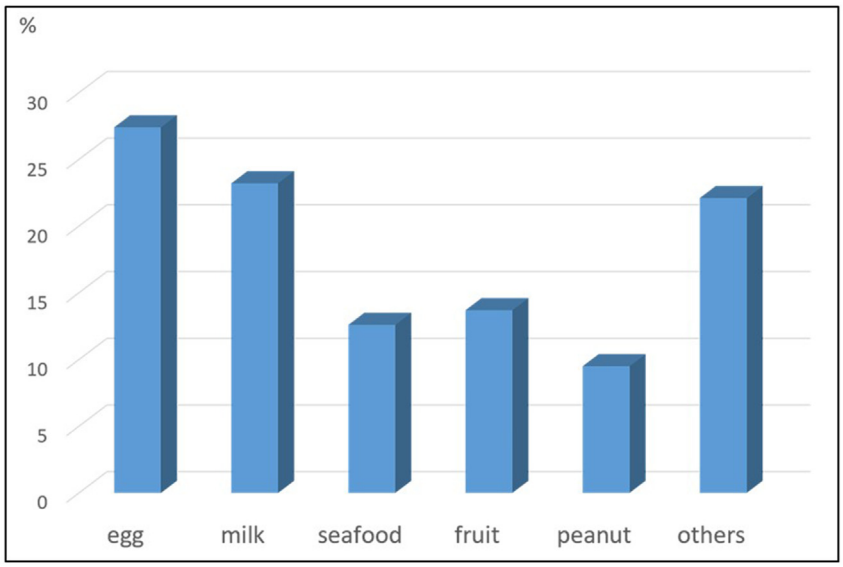

Fig. 1 The most common food allergens in young children in southern Taiwan (N = 95)

1.28–4.43). Furthermore, family allergy history was significantly associated with all four allergic symptoms of the offspring.

Relationship between maternal diet during pregnancy and the sensitization of foods in children with food allergy

In this study, we explored the relationship between maternal diet during pregnancy and the sensitization of foods in children. Table 4 shows the significant difference between maternal peanut consumption during pregnancy and egg allergy in young children. The consumption of milk by mothers during pregnancy also showed a significant difference in young children with or without peanut allergy. However, it was noted that the sample size was too small for conclusions to be made.

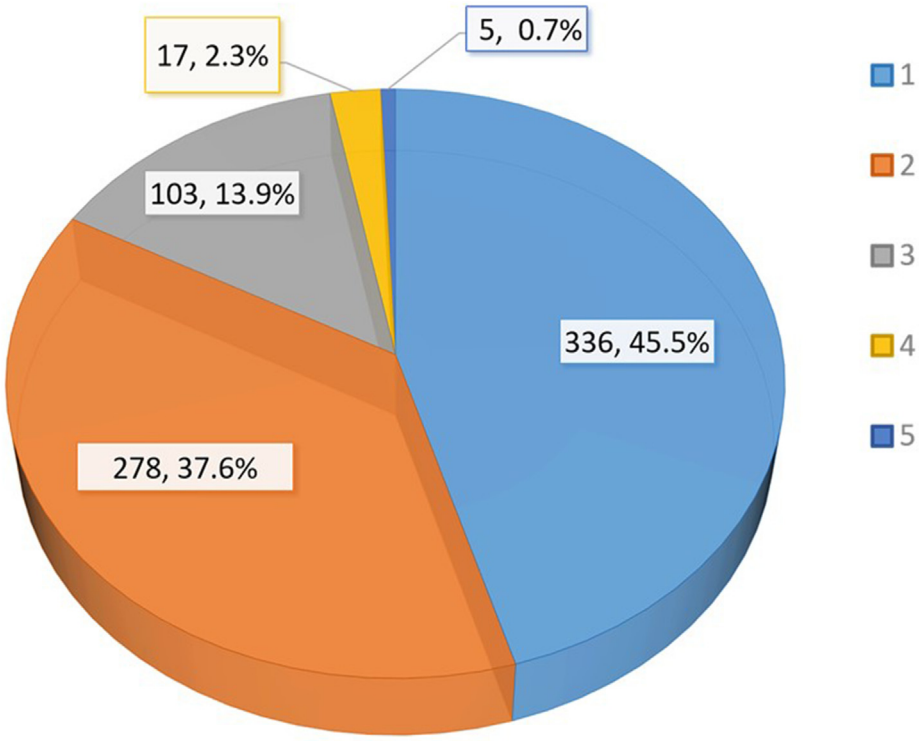

Fig. 2 The prevalence of none, one, or more than one allergic symptom (food allergy, eczema, wheezing, allergic rhinitis) among allergic young children. 1: no allergic symptoms; 2: any of the four allergic symptoms; 3: two of the four allergic symptoms; 4: three of the four allergic symptoms; 5: all four allergic symptoms

During pregnancy	Food allergy COR (95% CI)	Food allergy AOR (95% CI)[a]	Eczema COR (95% CI)	Eczema AOR (95% CI)	Wheezing COR (95% CI)	Wheezing AOR (95% CI)	Rhinitis COR (95% CI)	Rhinitis AOR (95% CI)
Maternal diet								
Egg	0.52 (0.05-5.04)	0.40 (0.03-5.07)	1.05 (0.13-8.81)	0.47 (0.04-4.86)	0.63 (0.07-5.26)	0.27 (0.03-2.82)	2.2 (0.26-18.39)	1.76 (0.16-18.84)
Milk	1.12 (0.53-2.35)	1.60 (0.59-4.30)	**2.87 (1.23-6.70)**	2.76 (0.97-7.86)	0.99 (0.48-2.05)	0.94 (0.38-2.36)	0.72 (0.46-1.14)	**0.53 (0.31-0.93)**
Peanut	**0.62 (0.38-0.99)***	**0.57 (0.33-0.98)**	1.11 (0.72-1.70)	1.05 (0.66-1.68)	1.56 (0.90-2.69)	1.84 (0.98-3.45)	0.80 (0.58-1.11)	0.79 (0.54-1.15)
Clam/shrimp	1.06 (0.58-1.96)	1.35 (0.58-3.11)	1.22 (0.71-2.08)	1.09 (0.55-2.15)	0.69 (0.40-1.20)	1.09 (0.47-2.54)	0.91 (0.61-1.36)	0.78 (0.46-1.31)
Fish	0.71 (0.23-2.16)	0.49 (0.13-1.80)	1.95 (0.59-6.45)	2.78 (0.59-13.09)	**0.34 (0.15-0.77)**	0.38 (0.12-1.2)	0.62 (0.31-1.25)	0.89 (0.37-2.16)
Maternal supplements								
Fish oil	0.84 (0.54-1.33)	1.10 (0.63-1.93)	0.88 (0.60-1.28)	0.75 (0.46-1.21)	0.97 (0.62-1.53)	0.83 (0.46-1.51)	0.86 (0.64-1.17)	0.68 (0.46-1.02)
Probiotics	0.79 (0.49-1.26)	0.73 (0.40-1.32)	1.17 (0.80-1.71)	1.59 (0.98-2.59)	1.11 (0.70-1.76)	1.65 (0.92-2.98)	1.25 (0.92-1.70)	**1.58 (1.05-2.36)**
Vitamin D	0.92 (0.58-1.45)	0.96 (0.53-1.71)	1.11 (0.76-1.62)	1.06 (0.65-1.73)	1.05 (0.66-1.67)	1.04 (0.56-1.9)	0.89 (0.65-1.21)	0.77 (0.51-1.15)
Folic acid	1.00 (0.53-1.88)	1.52 (0.61-3.82)	0.84 (0.50-1.41)	0.98 (0.49-1.94)	0.94 (0.49-1.78)	1.05 (0.44-2.49)	1.20 (0.76-1.88)	1.53 (0.85-2.75)
Maternal drugs								
Yes	1.24 (0.78-1.97)	1.28 (0.74-2.21)	1.14 (0.77-1.68)	1.38 (0.87-2.17)	1.21 (0.76-1.93)	1.11 (0.63-1.95)	**1.37 (1.00-1.87)**	1.38 (0.94-2.01)
Environmental factors								
Smoker at home	0.74 (0.46-1.20)	0.71 (0.41-1.25)	1.20 (0.82-1.76)	1.19 (0.75-1.87)	1.49 (0.94-2.35)	1.40 (0.81-2.45)	1.17 (0.86-1.60)	1.00 (0.68-1.45)

(continued)

	Food allergy		Eczema		Wheezing		Rhinitis	
	COR (95% CI)	AOR (95% CI)[a]	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)
During pregnancy								
Pets at home	0.71 (0.42–1.19)	1.01 (0.56–1.85)	**0.56 (0.35–0.88)**	0.64 (0.38–1.09)	1.17 (0.72–1.89)	0.84 (0.45–1.57)	1.05 (0.76–1.46)	1.00 (0.66–1.51)

Table 2. (Continued) Association of prenatal factors with food allergy and three other allergic symptoms, respectively, among the children. *Note: Abbreviation: COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval.* [a] *Maternal diet (egg, milk, peanut, clam/shrimp and fish), maternal supplements (fish oil, probiotics, vitamin D and folic acid), whether maternal subjects taking drugs during pregnancy, whether family member(s) smoke, having pets at home are included in the adjusted analysis. P values < 0.05 are in bold*

DISCUSSION

It is known that allergy disorders that involve the gastrointestinal tract, respiratory tract, and skin are common in young children, but the prevalence and timing of the occurrence of these allergy disorders vary due to geographical and cultural differences.[20] The significance of our study was that we used a general survey to recruit study participants from multiple medical centers in the southern part of Taiwan, and the focus of the study was on 3 aspects, ie, the family allergy history and the environmental and demographic risk factors in 2 time periods: the prenatal and perinatal periods.

The obtained results showed that 14.7% of young children under 4 years of age in the southern part of Taiwan had allergic reactions to food. A previous questionnaire-based survey in Taiwan showed that the prevalence of FA was 3.44% in children under 3 years of age and 7.65% in children aged 4–18 years.[21] The Japan Environment and Children's Study (JECS) revealed that the prevalence of caregiver-reported immediate FA was 7.6%, 6.7%, and 4.9% at ages 1, 2, and 3 years, respectively.[9] A study in Vietnam showed that the prevalence of FA among children 2–6 years of age was 9.8% in Hue and 7.9% in Tien Giang.[22] A study across Europe showed that the prevalence of self-reported FA among 7- to 10-year-old children ranged from 13.1% to 45.6% for any food and from 6.5% to 24.6% for symptoms in response to at least 1 of 24 foods often implicated in FA (priority foods).[4] Our study demonstrated a higher prevalence of parent-reported FA in southern Taiwan than in previous studies and other countries.

In our study, the most common food allergens were egg (2.9%) and milk (2.4%). Most FA prevalence studies conducted in Asian regions have been based on personal responses to FA history questions.[3] A Chinese study showed that the most common food allergens in preschool age children were shrimp, crab, mango, cow's milk, dairy products, and eggs.[23,24] The JECS reported that the most common food allergens were hen's eggs, cow's milk, and wheat in young Japanese children.[9] A Korean study reported the prevalence of egg and cow's milk

	Food allergy		Eczema		Wheezing		Rhinitis	
	COR (95% CI)	AOR (95% CI)[a]	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)
Demographic factors								
Gender (male vs. female)	1.07 (0.69–1.66)	1.19 (0.72–1.97)	1.04 (0.72–1.50)	0.93 (0.56–1.52)	**1.98 (1.24–3.16)***	**2.33 (1.2–4.51)**	1.19 (0.89–1.60)	1.20 (0.81–1.78)
Delivery (C/S vs. NSD)	1.12 (0.72–1.75)	0.90 (0.52–1.54)	1.08 (0.75–1.57)	1.28 (0.76–2.16)	1.31 (0.84–2.05)	1.29 (0.67–2.48)	1.08 (0.80–1.47)	1.12 (0.74–1.69)
Gestational age (preterm vs term)	1.83 (0.90–3.74)	1.84 (0.76–4.48)	1.37 (0.74–2.53)	1.02 (0.4–2.61)	0.99 (0.44–2.23)	0.44 (0.09–2.09)	0.95 (0.55–1.63)	0.58 (0.25–1.37)
Season of birth								
Summer (1)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Autumn (2)	1.20 (0.61–2.37)	0.84 (0.39–1.81)	1.04 (0.59–1.83)	1.35 (0.61–3.01)	1.02 (0.56–1.87)	0.77 (0.32–1.85)	1.47 (0.96–2.26)	1.47 (0.83–2.62)
Spring (3)	1.57 (0.83–2.96)	1.33 (0.67–2.64)	1.27 (0.75–2.16)	1.88 (0.91–3.89)	0.82 (0.44–1.53)	0.66 (0.29–1.52)	1.25 (0.82–1.92)	1.26 (0.72–2.19)
Winter (4)	1.47 (0.78–2.77)	1.07 (0.52–2.17)	**1.70 (1.02–2.82)**	**2.05 (1.00–4.22)**	0.75 (0.40–1.39)	0.42 (0.17–1.05)	1.36 (0.89–2.06)	1.22 (0.70–2.12)
Family income								
< NT60,000	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
NT60,000–100,000	1.02 (0.62–1.69)	0.89 (0.52–1.54)	0.95 (0.61–1.48)	1.06 (0.6–1.85)	0.99 (0.58–1.71)	1.20 (0.59–2.44)	0.85 (0.60–1.22)	0.70 (0.45–1.09)
≥ NT100,000	0.65 (0.32–1.31)	0.47 (0.22–1.04)	1.19 (0.71–2.00)	1.32 (0.67–2.61)	0.89 (0.45–1.77)	1.45 (0.61–3.46)	0.86 (0.56–1.34)	0.87 (0.50–1.50)
Exclusive breastfeeding for six months	0.96 (0.61–1.53)	0.95 (0.55–1.63)	0.91 (0.61–1.35)	0.95 (0.56–1.62)	1.42 (0.90–2.24)	1.34 (0.7–2.57)	1.09 (0.80–1.49)	0.96 (0.63–1.47)
Environmental factors								

(continued)

	Food allergy		Eczema		Wheezing		Rhinitis	
	COR (95% CI)	AOR (95% CI)[a]	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)
Smoker at home	0.74 (0.46–1.20)	0.58 (0.33–1.02)	1.20 (0.82–1.76)	1.15 (0.68–1.96)	1.49 (0.94–2.35)	**2.44 (1.25–4.75)**	1.17 (0.86–1.60)	1.21 (0.80–1.84)
Pets at home	0.71 (0.42–1.19)	0.80 (0.44–1.45)	**0.56 (0.35–0.88)**	0.70 (0.39–1.26)	1.17 (0.72–1.89)	0.93 (0.46–1.88)	1.05 (0.76–1.46)	0.98 (0.63–1.53)
Personal allergy history								
Eczema	**2.87 (1.73–4.76)**	**2.48 (1.38–4.45)**	-	-	**2.32 (1.38–3.90)**	**2.64 (1.32–5.31)**	**1.49 (1.00–2.21)**	1.15 (0.68–1.96)
Wheezing	**1.92 (1.03–3.58)**	1.25 (0.57–2.74)	**2.32 (1.38–3.90)**	**2.51 (1.24–5.09)**	-	-	**2.68 (1.71–4.22)**	**2.38 (1.28–4.43)**
Rhinitis	1.45 (0.91–2.30)	1.47 (0.86–2.51)	**1.49 (1.00–2.21)**	1.17 (0.69–1.98)	**2.68 (1.71–4.22)**	**2.43 (1.30–4.53)**	-	-
Food allergy	-	-	**2.87 (1.73–4.76)**	**2.53 (1.41–4.53)**	**1.92 (1.03–3.58)**	1.25 (0.57–2.75)	1.45 (0.91–2.30)	1.41 (0.83–2.40)
Family allergy history	**1.99 (1.24–3.19)**	**2.06 (1.18–3.57)**	**2.46 (1.62–3.74)**	**1.99 (1.15–3.43)**	**2.38 (1.43–3.96)**	**2.52 (1.20–5.27)**	**1.61 (1.18–2.20)**	**1.60 (1.06–2.42)**

Table 3. (Continued) Association of perinatal factors with food allergy and other allergic symptoms, respectively, among the children. *Note: Abbreviation: COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; Ref, reference group. [a]Gender, types of delivery, gestational age, season of birth, family's income, exclusive breastfeeding for 6 months, whether family member(s) smoke, having pets at home, personal allergic history and family allergic history are included in the adjusted analysis. P values < 0.05 are in bold*

Maternal diet	Egg allergy Yes *n* (%)	No	*P* *n* (%)	Milk allergy Yes	No *n* (%)	*P*	Peanut allergy Yes	No	*P*
Egg[a]		0.15		1.0		1.0			
Yes	25 (3.9)	613 (96.1)		22 (3.5)	611 (96.5)		9 (1.5)	600 (98.5)	
No	1 (25)	3 (75)		0 (0)	4 (100)		0 (0)	4 (100)	
Milk			0.10			0.49			**0.05**
Yes	26 (4.6)	546 (95.4)		19 (3.4)	548 (96.6)		6 (1.1)	541 (98.9)	
No	0 (0)	66 (100)		3 (4.6)	63 (95.4)		3 (4.8)	59 (95.2)	
Peanut			**0.03**			0.99			0.71
Yes	11 (2.8)	378 (97.2)		13 (3.4)	373 (96.6)		5 (1.3)	369 (98.7)	
No	12 (6.7)	166 (93.3)		6 (3.4)	171 (96.6)		3 (1.8)	165 (98.2)	

Table 4. Relationship between maternal diet in the pregnancy and the sensitization of foods in study children. *[a]Fisher's exact test is performed if cell count is less than 5. P values < 0.05 are in bold*

allergy to be 0.21% and 0.18%, respectively, however these were reported for older children aged 6–7 years.[25] A study from the United States reported that the most common food allergens in children under 2 years of age were milk, peanuts, and eggs. In children 3–5 years of age, the most common food allergens were peanuts, milk, tree nuts, eggs, and shellfish.[26] Hence, it was suggested that even within Asia, further detailed study is needed to determine the rates of egg and cow's milk allergies, and these rates of food allergies might vary across regions.

In our study, children with eczema and rhinitis were older than those without eczema and rhinitis. The mean age of our study population was 22.6 ± 0.26 months. However, the JECS and a population-based study in England showed the highest prevalence of eczema in children aged 1 (16.8%) and 2 (16.5%), respectively.[9,27] The prevalence of rhinitis increases with age.[9] Our result is likely directly due to age data collection and not any biological characteristics of the participants.

Recently, several studies have evaluated the influence of prenatal and perinatal risk factors on early allergic disorders, particularly associations of maternal diet and allergic outcomes in their children.[28] Several systematic reviews and randomized trials have suggested that there were no benefits from restricting common allergenic foods among pregnant mothers.[29] Moreover, it was concluded that dietary restriction during pregnancy might compromise maternal and fetal health.[30] There are limited data regarding the association between FA and maternal consumption of supplements during pregnancy, including fish oil, probiotics, vitamin D, and folic acid. In a systematic review, a meta-analysis showed no association between the consumption of vitamin supplements and the risk of allergic diseases.[31] Probiotic and fish oil supplementation during pregnancy may reduce the risk of eczema but have no protective effects against FA.[31,32] A prospective birth cohort study showed no evidence of associations between maternal red blood cell folate levels during the third trimester and FA.[33] Our findings also showed that maternal diet, the consumption of nutritional supplements, and medications during pregnancy had no effect on FA in the participants.

In contrast, maternal peanut consumption during pregnancy had a protective effect (AOR = 0.57, CI: 0.33–0.98) on FA in their children. This finding is consistent with the recent randomized trial of the Learning Early About Peanut (LEAP) study, which showed that high-risk infants in whom sustained peanut consumption was initiated in the first 11 months of life showed a sustained reduction in the proportion of children with peanut allergy at 60 months of age when compared with the children in whom peanut consumption was not initiated.[28,34] The Nurses' Health Study II, a large prospective cohort study, also showed that higher peri-pregnancy consumption of peanuts was associated with a lower risk of peanut allergy in their offspring.[35] These results support that maternal ingestion of peanuts in the prenatal period could have beneficial results in terms of FA prevention in their children, and further investigations are warranted.

Other than diet and nutrients, we found that environmental risk factors in the prenatal and perinatal periods, such as household members who smoked, had effects on wheezing in the perinatal period, while the presence of pets in the house had no effect on FA. The findings were in agreement with others' reports that having household members who smoked directly affected the lung development of children, increasing the chance of wheezing and respiratory infections in infants.[36]

Notably, the most important findings in this study were that FA in this cohort was closely related to personal allergy of eczema and allergic disorders in the family. These results suggested that a strong hereditary factor and atopic characteristics were related to the development of FA.[37] The relationship between eczema and FA was proposed by the dual-allergen exposure hypothesis by Lack, which suggested that low-dose cutaneous exposure to food allergens was a risk factor for FA, while early consumption of an allergen could induce oral tolerance.[38] The Enquiring About Tolerance (EAT) study showed that regular application of moisturizers to the skin of young infants may promote the development of FA through transcutaneous sensitization.[39] It was also stated that when the skin barrier was impaired, such as in atopic dermatitis, this skin exposure might be even greater, which might

also partly explain the frequent coexistence of atopic dermatitis and FA. The EuroPrevall-iFAAM birth cohort study showed that family allergy history had a large effect not only on single allergic diseases but also on allergic multimorbidity (the coexistence of asthma, eczema, and allergic rhinitis).[40] Children with a family allergy history, especially mothers, also had a higher risk of FA.[41] Our findings in this study were consistent with those of previous studies and further confirmed that not only the personal comorbidity of eczema but also a family allergy history could also strongly affect the development of FA. Hence, it was suggested that these 2 risk factors could serve individually or be combined as biomarkers in the prediction and/or prevention of the development of FA in infants.

The limitation of this questionnaire-based study was the lack of a validation of serum IgE measurements and challenge-proven FA tests, such as skin prick tests and oral challenge tests. These tests are all invasive to young children, and the high refusal rate by their parents prevented us from administering important tests to confirm our questionnaire results. Therefore, we suggest that future studies should focus on elucidating the epigenetic mechanism controlling the pathogenesis of FA and eczema using mother-child birth cohorts and gather biological samples and clinical information in the long-term follow-up to reveal the temporal effect of environmental and genetic risk factors and the development of FA.

In summary, our study found that the prenatal and perinatal risk factors associated with FA in our study cohort were a personal eczema history and a family allergy history, which might serve as predictive or prevention factors for the development of FA in young children in Taiwan.

Abbreviations

AOR, adjusted odds ratio; CI, confidence interval; FA, food allergy; JECS, Japan Environment and Children's Study; STARA, Southern Taiwan Allergy Research Alliance.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Authors' contributions

CWL, BHL, and JYW conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript. CWL, YTS, HRY, HJL, and CHH conducted survey questionnaires, data collection and entry. YFT, LFL, and HJT performed statistical and data analyses. All authors were responsible for drafting and revision of the final paper.

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Boards of the National Cheng Kung University Hospital (NCKUH), Taiwan (No. A-ER-106-015), E-Da Hospital (EDH), Taiwan (No. EMRP-106-015), Kaoshiung Chan Gung Memorial Hospital (KCGMH), Taiwan (No. 201700878B0), St Martin Hospital (STMH), Taiwan (No. 17B-017).

Consent for publication

All authors have read the final manuscript and consent for submission and publication.

Declaration of competing interest

The authors declare that they have no competing interests.

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