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Article type : Original

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TITLE PAGE

Original Article

A cross-sectional, population-based study on the prevalence of food allergies among children in two different socio-economic regions of Vietnam

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAI.13022](https://doi.org/10.1111/PAI.13022)

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Running title: Food allergy in Vietnamese children

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Word count: 2,979

Number of tables and figures

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Figure 2. Comparison of the distribution of reported food groups eliciting clinical reactions in participating children in Hue and Tien Giang: **A.** Reported food-induced adverse symptoms in Hue (number of participants $n = 911$); **B.** Self-reported FA in Hue; **C.** Doctor-diagnosed FA in Hue; **D.** Reported food-induced adverse symptoms in Tien Giang; **E.** Self-reported FA in Tien Giang; **F.** Doctor-diagnosed FA in Tien Giang. The total number of reported food groups is presented for each study area and symptom group.

Additional file

Appendix S1. Survey Questionnaire for child participants

Ethics approval

This study was approved by the Human Research Ethics Committee (HREC) at James Cook University (ID: H6437).

Consent for publication

All authors have approved the manuscript for submission.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was funded by grants from the Australian Research Council (ARC), and the National Health and Medical Research Council (ID: 1086656) to AL. TL is the recipient of the Endeavour Postgraduate Scholarship. TR is a PhD full-time scholar of the Centre for Food and Allergy Research, Australia.

Authors' contributions

TL and AL developed the concept and study design. DN and TL conducted the on-site survey. AV and TL processed survey data. TL performed the statistical analysis. TL wrote

the manuscript. AT, TR and AL edited the final manuscript. All authors contributed to the development of the manuscript and approved the final version.

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ABSTRACT PAGE

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A cross-sectional, population-based study on the prevalence of food allergies among children in two different socio-economic regions of Vietnam

Pediatr Allergy Immunol

Abstract

Background: There is a paucity of data on the prevalence of food allergy (FA) in Vietnam. A cross-sectional, population-based study was conducted to evaluate the current prevalence of FA among 2-6-year-old children in two different regions in Vietnam.

Method: A structured, anonymous questionnaire, modified from published FA epidemiological studies and based on EAACI guidelines, was distributed to parents/guardians of participating children in Hue City (urban area) and Tien Giang Province (rural area). Data collected from the survey were statistically analyzed to generate the prevalence of self-reported and doctor-diagnosed FA and overarching pattern of food allergens.

Results: A total of 8,620 responses were collected (response rate 81.5%). Children in Tien Giang reported more than twice the food-induced adverse reactions seen in children in Hue (47.8% vs. 20.5%). In contrast, children in Hue showed higher self-reported FA (9.8%) and doctor-diagnosed FA rates (8.4%) than children in Tien Giang (7.9% and 5.0%, respectively).

Crustacean was the predominant allergy-inducing food in both areas (330 of 580 cases, 56.9%), followed by fish, mollusk, beef, milk and egg. However, substantial variations of FA patterns were seen between the study sites. Geographic location and co-morbidities of other allergic diseases were key risk factors of FA ($P<0.001$).

Conclusions: The prevalence of FA in Vietnamese children seems to be higher than previously reported from other Asian countries. Crustacean is the predominant allergy-inducing food among participating preschool children in Vietnam. The variation of reported food allergen sources across different socio-economic locations could imply different eating habits or the participation of indoor and outdoor allergen exposure.

Key words: children, crustacean allergy, fish allergy, food allergy, prevalence, Vietnam.

Abbreviations

FA: Food allergy

EAACI: European Academy of Allergy and Clinical Immunology

IgE: Immunoglobulin E

CI: Confidence Interval

OFC: Oral Food Challenge

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Introduction

Food allergy (FA), an adverse immune reaction to food proteins, has a wide spectrum of clinical presentations, ranging from mild skin problems to severe systematic reactions. In the most severe case, FA can lead to anaphylaxis and might result in death within minutes. FA is estimated to affect about 8% of children and 5% of adults in the general population worldwide (1).

Children are more likely to develop food allergies than adults due to remaining controversial causes, including the immature immune system in childhood and/or the inappropriate food introductory practices (2, 3). Eight food groups, often referred as the “Big 8”, account for over 90% of food allergic reactions and include cow’s milk, egg, peanut, tree nuts, soy, wheat, fish and shellfish. Except for cow’s milk and egg allergy which are often outgrown, most other FAs often persist for life (1). So far, no cure is available and childhood FA imposes a substantial health and economic burden for children and their caregivers.

The common food commodities accounting for FA in children are cow’s milk, egg, peanut, tree nuts and fish (4), while the first three foods are the leading causes for paediatric anaphylaxis in Western countries (5). In Asia, the prevalence of paediatric FA seems to vary between 1.11-7.65% (6), and the patterns of FA showed marked difference from other parts of the world (1). Recent studies among 2-7-year-old children from Singapore, Thailand, the Philippines and Hong Kong demonstrated that shellfish allergy was dominant, but not milk, egg or peanut (7, 8). Furthermore, fish was reported to be the predominant allergen in adolescents in the Philippines, Singapore and Thailand (9). Within Asia, studies from Japan and Korea showed different FA patterns to most available FA data, with wheat allergy particularly common in East Asian countries (6). These data were supported by a recent study from Australia, where large differences in allergy/anaphylaxis risk and trigger were demonstrated between children born in Australia and children born in Asia (10). The

variation of FA patterns throughout Asia indicates that region specific and accurate data on FA prevalence and clinical patterns are crucial for an effective FA management program in any community.

In Vietnam, about 4.4 million children aged 2-6-year-old attend kindergartens, accounting over 90% of all children at this age group in 2016 (11). The first population-based study on FA in adults was recently performed by our group, revealing a high rate of FA in this population: self-reported FA (18.0%) and doctor-diagnosed FA (5.8%) (12), while no data on children is available so far. We sought to evaluate the epidemiologic and clinical features of FA in Vietnamese preschool children. The possible variations of childhood FA prevalence and its associated risk factors in socio-economically different regions in Vietnam were also investigated.

Methods

Study design and subjects

A cross-sectional, population-based study was conducted in preschool children aged from 2 to 6 years in 2016. Survey participants were randomly selected using the cluster sampling method from a list of 25 kindergartens in Hue city and 14 kindergartens in Cai Be district, Tien Giang province, representing a total of 104,602 preschool children in two regions (11). The paper-based questionnaires were distributed to parents/guardians of children at their kindergartens. Most of the answer sheets were collected on the same day. The response rate was calculated based on the number of returned answer-sheets divided by the total distributed questionnaires.

Sample size calculation

To obtain a statistical estimation of the prevalence of FA, the minimum sample size was calculated based on the current estimated prevalence of FA in children (8%) in the general population (13); the chosen precision of the estimation $d=1/5p$ was calculated with a statistical confidence of two standard errors of the mean $z=1.96$ (95% Confidence Interval (CI), $P<0.05$). The minimum necessary sample size calculated for children was 1,825 participants.

Study locations

The study was conducted in two different regions of Vietnam: Hue City and Cai Be District of Tien Giang Province. Hue City is in the Central region of Vietnam with a population density of 5,011 per square kilometer. The main economic activities in Hue are tourism, industry and aquaculture. Urbanisation has quickly taken place in this city due to the rapid development of tourism. Hue has an average temperature of 25.4°C, average humidity of 87% and a total of 1,754.2 hours of sunshine per year.

Cai Be District is a rural area in the Mekong Delta of southern Vietnam. This river-land mixed town has a population density of 657 per square kilometer. The major economic activities in Cai Be are aquaculture, rice and fruit farming. Cai Be-Tien Giang has an average temperature of 28.2°C, average humidity of 80.4% and a total of 2,104.6 hours of sunshine per year (14).

In this study, taking into consideration the effects of population density, living lifestyle and environmental conditions, we defined participants in Hue City as living in urban area and participants from Cai Be District as living in rural area.

Questionnaire design

The questionnaire, modified from published studies in the US and Asia (7, 9), had two parts: part I asked the participant demographic information, and part II contained ten questions on FA (Appendix S1, Supporting Information). The questionnaire was translated into Vietnamese. The content of the questionnaire and its translation were reviewed and approved by the Human Research Ethics Committee at James Cook University (ID: H6437). By answering the questionnaire, the parents/guardians gave the informed consent to the study and the permission to use obtained child health information for research publications and reports.

Definitions

We established a set of criteria to define self-reported and doctor-diagnosed FA in this survey based on the most recent European Academy of Allergy and Clinical Immunology (EAACI) guidelines on FA and anaphylaxis (15). In specific, the suggestive symptoms of FA were considered including persistent symptoms towards food ingestion and the co-occurrence of two or more different clinical presentations (16). The typical symptoms for IgE-mediated FA included hives/urticaria or angioedema or vomiting or gastrointestinal symptoms or anaphylactic reactions (i.e. reduced blood pressure, loss of consciousness, chest pain and

weak pulse) after food intake. In this study, children with only one symptom of hives/angioedema were also defined as food allergic and included.

Self-reported FA was the group of participants who fulfilled the above criteria and reported having FA.

Doctor-diagnosed FA was the group of participants with self-reported FA, which was clinically confirmed by a medical practitioner.

Food-induced adverse symptoms: any abnormal clinical response that occurs following ingestion of a food or food component.

Family history of FA was defined when the participant had in their immediate family a member with FA.

Coexisting other allergic diseases was defined when the participant had any other allergic diseases including pollen allergy, antibiotic allergy, asthma, eczema etc.

Statistical analysis

The survey data were analyzed and plotted using the IBM SPSS Statistics for Windows, version 24.0 and GraphPad Prism version 7.03. Continuous variables were presented as median and interquartile range (IQR). Categorical data were compared by using either Fisher's exact test or Chi-square test with a 2-tailed *P*-value. The Wilson/Brown method was performed to provide a 95% CI of proportions. Multiple logistic regression model was used to study the association between multiple risk factors and the incidence of having doctor-diagnosed FA. A *P*-value of <0.05 was considered as statistically significant for all tests.

Results

Participants

A total of 8,620 questionnaires were completed and returned from the two survey sites (response rate 81.5%). The survey in Hue gained a higher response rate (93.5%) than in Tien Giang (69.5%). Minimal difference in gender distribution was observed across the two survey sites. The age median (IQR) of the participants was 4 (2-6) years in Hue and 6 (2-6.5) years in Tien Giang. The demographic characteristics of participating children are presented in Table 1.

Comparison of reported food-induced adverse symptoms between children in Hue and Tien Giang

Children in Tien Giang were reported to have twice the food-induced adverse symptoms than children in Hue (47.8% vs. 20.5%) (Table 1). However, self-reported FA in Hue (9.8%) was higher than in Tien Giang (7.9%) (Table 2). In the perceived FA group, more children in Hue presented to doctors for medical advice, 91.6% compared to 76.7% in Tien Giang. Overall, the prevalence of life-time doctor-diagnosed childhood FA in Hue was 8.4%, nearly double the rate of 5.0% in Tien Giang ($P<0.0001$).

Suspected FA children in Hue reported less concurrent episodes than those in Tien Giang (an average of 1.4 episodes compared to 2.0 episodes, respectively). Hives, diarrhea and nausea or vomiting were the most predominant clinical presentations reported. Ten participants (0.2%) in Tien Giang experienced severe symptoms (i.e. loss of consciousness, drop in blood pressure, chest pain and weak pulse) due to FA while in Hue, only one case was reported (0.02%) (Figure 1).

Distribution of the major food allergens in FA children in Hue and Tien Giang

Most of the affected subjects (78.1%) reported food adverse symptoms to only one food item; 13.1% reported adverse reactions to two different food items and 7.1% had reactions to more than two different food groups. Crustacean was the most predominant allergy causing food type in both Hue (50.1%) and Tien Giang (30.6%), while the distribution of the remaining 'Big 8' food groups were very different (Figure 2). Statistically significant differences were seen in the prevalence of crustacean, mollusk, beef, milk, wheat and tree nut allergies between children in Hue and Tien Giang ($P<0.05$) (Table 2).

Contribution of environmental factors to FA incidence

Genetic and environmental factors are reported to play a role in the development of FA (1, 17). In this study, we analyzed the contribution of geographical location, gender and family history of FA as well as coexisting other allergic diseases to the FA incidence by using multivariable logistic regression model. A strong influence of participant location and atopic conditions to FA risk was observed in this study. Children living in Hue (urban area) have a higher risk of having FA than children living in Tien Giang ($OR: 3.902$, $P<0.001$). The FA

rate was found to be 3.428 times higher in participants with other existing allergic diseases ($P<0.006$). Gender and family history of FA showed no impact on FA risk in this study population (Table 3).

Discussion

This population-based survey is the first to establish the prevalence of self-reported FA (8.9%) and doctor-diagnosed FA (6.7%) in Vietnamese children. Our findings indicate large variations of FA prevalence between two survey sites with different socio-economic backgrounds. The population living in the urban area presented a higher prevalence of FA but also had a higher rate of doctor consultation to diagnose FA. Most participants (78.1%) reported adverse symptoms to only one food group, with crustacean the dominating food allergen. Hives and gastrointestinal tract problems were the most commonly reported clinical symptoms for both regions.

We observed a higher rate of self-reported FA (8.9%) than doctor-diagnosed FA (6.7%), consistent with previous assessments of questionnaire-based FA rates in Asian populations (1.11 - 7.65%) (6). This variation appears to be determined by the complex pathophysiology of adverse reactions to food and the perception of respondents of this disease. Common aetiology in paediatrics with food-related adverse symptoms are immune-mediated FAs and non-immune mediated food intolerance (18). There is lack of strong evidence to differentiate FA from food intolerance exclusively based on reported clinical history, especially in Asian communities. Among doctor-diagnosed milk allergic participants, two thirds of participants presented gastrointestinal symptoms which might imply the contribution of other food-induced disorders rather than true FA. A food outbreak, suspected to be an acute allergic reaction to a new formula product, was recorded in 19 out of 229 hospitalised children in 2009 (19). Unfortunately, no allergens were identified due to the constraint of diagnostic capacity in Vietnam. Further investigations will exclude other non-Immunoglobulin E (IgE)-mediated FAs, such as Food Protein-Induced Enterocolitis Syndrome and eosinophilic esophagitis in the paediatric population to give an accurate estimation of true FA prevalence (20).

Patient's clinical history of FA is the initial motive for further diagnostic analysis, however, only 4 to 5% of the self-reporting FA population is generally confirmed as true FA (4). Parent-reported FA in Thai children was found to be 9.3%, but reduced to 1.1% when confirmed by oral food challenge (OFC) (21). A survey of Singapore-born children aged 4-6 years showed the variation of self-reported FA to shellfish with 7.22 % as compared to a rate of 1.19 % with convincing history FAs (7). As it was consistently concluded in previous studies, an accurate diagnostic procedure of IgE-mediated FA must comprise of multiple tests including skin prick testing, measurement of serum specific IgE and OFC (22). However, only limited services are available in Vietnam for diagnosing FA, particularly in rural areas. Most commercial diagnostic tests that are readily available in Western countries, including IgE quantification and skin prick tests, are not registered or partially available to private patients and in specialized clinics. In the presented study, data could not be collected for the onset of adverse symptoms that might have better supported differentiating between IgE-mediated and non-IgE mediated FA. This is one of the biggest challenges in studying the prevalence of FA in a country where only a few people have access to correct FA diagnosis. This paper-based survey on health conditions was thought to be a rather new practice for most Vietnamese, so we aimed and succeeded at keeping the questionnaire as simple as possible to achieve a high response rate (81.5%).

This study revealed a distinct distribution of the “Big 8” food allergens in Vietnamese children. Unlike the patterns of childhood FA from Western populations, previous studies in Asian populations showed the predominance of shellfish and fish allergy rather than egg, cow's milk and peanut (6, 7, 9), and this tendency was also determined in this survey. Children from rural and urban Vietnam reported higher adverse reaction rates to seafood, then beef, milk and egg. The predominance of seafood allergy in Asia might be claimed for the availability and high consumption of this food commodity (23). In Vietnam, the average fish consumption is with 33 kg per capita per annum much higher than the world's average consumption of 21 kg (23). The impact of ethnic characteristics to seafood allergy in Asian communities was validated in a study among expatriate and local Singaporean children, revealing the predominance of shellfish allergy in local children compared with expatriate children (7).

Considering ethnic characteristics and cultural dietary practices, we found considerable variations of FA prevalence among urban and rural population in Vietnam. Crustacean and milk allergy are predominant in children in Hue (urban area). However, there was insufficient data on the consumption of these commodities between the two areas to postulate FA risk. The high incidence of shellfish allergy in urban children might be related to higher exposure to indoor allergens as discussed in the current literature (24). For instance, indoor mites were documented to cross-react with the major shellfish allergen tropomyosin (25), and storage mites were identified in indoor environments in the north of Vietnam (26). In contrast, children in the Tien Giang province showed a much higher prevalence to mollusk, wheat, tree nuts and beef. Recent studies in the US and Sweden documented the association of red meat allergy to tick bites (27, 28), which was explained by the cross-reactivity of a carbohydrate oligosaccharide galactose- α -1,3-galactose in mammalian meat and a similar component found in the saliva of tick. Children from rural areas are more likely to have tick bites than those in the city (29), and therefore environmental factors might contribute to the high rate of beef allergy in children in Tien Giang. Similarly, the high incidence of wheat and tree nut allergy in this subpopulation might be explained by the possible cross-reactivity of these food allergens with other aeroallergens abundant in the rural area. It should be noted that wheat is not a staple food in Vietnam and no data on gluten intolerance or Coeliac disease have been reported so far in this population. This will be of interest for further investigation on the influence of environmental factors to FA.

The data from the multivariable logistic regression analysis of demographic risk factors (gender, family history of FA, coexisting other allergic diseases and geographic location) demonstrated a strong contribution of coexisting other allergic diseases ($OR= 3.428$, $P<0.006$) to FA incidence, but not a family history of FA ($OR=1.018$, $P=0.961$). FA is thought to run in a family (17). However, the contribution of a family history of FA to the risk of FA development remains inconsistent among studies (30, 31). In the present study, we did not apply any additional logistic regression models to further assess individual risk factors for FA.

The strengths of this study are the large population-based dataset ($n = 8,620$) collected at two different socio-economical survey sites and the high response rate (81.5%). The limitations of

this study are the self-administered data on FA and therefore the response might contain recall bias. Our target population were children age from 2-6 years and the information on children outside this age group with potentially different FA rates have not been included. There are several factors such as the disparity of the medical facilities among rural and urban areas in Vietnam and the economic circumstances of participants that might contribute to the variation on reported FA rates among the two study sites.

In conclusion, this study contributes to the current paucity of FA data in the broader Asian population and is the first to profile this emerging epidemic in Vietnam. Our study clearly showed that FA is prominent in Vietnam, but unexpected patterns of food allergies are perceived. A large variation of FA incidence was observed in subpopulations from rural and urban regions, implying possible impacts of living conditions. Further investigations are necessary to confirm the true prevalence of FA and possible cross-reactivities between different allergen sources for a precise diagnosis and better management of this serious childhood illness.

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497 **TABLE 1.** Demographics of participating children in Hue and Tien Giang.

Variable, <i>n</i> (%)	Hue	Tien Giang	Difference, <i>P</i>	Total study population
Total	4,443	4,177		8,620
Female	2,206 (49.6)	2,120 (50.8)	0.2860	4,326 (50.2)
Male	2,239 (50.4)	2,055 (49.2)	0.2860	4,294 (49.8)
Age group (years)				
2 to <3	1,140 (25.7)	52 (1.3)	<0.0001	1,192 (13.8)
3 to <4	1,365 (30.7)	655 (15.7)	<0.0001	2,020 (23.4)
4 to 6	1,940 (43.6)	3,467 (83.0)	<0.0001	5,407 (62.7)
Age, Median (IQR)	4 (2-6)	6 (2-6.5)		
Reported adverse reactions to food	911 (20.5)	1,994 (47.8)	<0.0001	2,905 (33.7)
Self-reported FA	433 (9.8)	330 (7.9)	0.0026	763 (8.9)
Seeking medical advice for FA [†]	394 (91.6)	250 (76.7)	<0.0001	644 (84.4)
Doctor-diagnosed FA	373 (8.4)	207 (5.0)	<0.0001	580 (6.7)
<i>FA to 1 food group</i>	328 (87.9)	125 (60.4)	<0.0001	453 (78.1)
<i>FA to 2 different food groups</i>	40 (10.7)	36 (17.4)	0.9084	76 (13.1)
<i>FA to more than 2 different food groups</i>	4 (1.1)	37 (17.9)	<0.0001	41 (7.1)

498 [†] Among subjects with self-reported FA.

499 The Fisher's exact test was performed using GraphPad Prism for Windows (GraphPad
500 Software, La Jolla California USA) to obtain *P* values.

	Self-reported FA				Doctor-diagnosed FA			
	Hue	Tien Giang	Difference, <i>P</i>	Entire study population	Hue	Tien Giang	Difference, <i>P</i>	Entire study population
Any food	9.75 (8.91 – 10.65)	7.90 (7.12 – 8.76)	0.0027	8.85 (8.27 – 9.47)	8.40 (7.62 – 9.25)	4.96 (4.34 – 5.66)	<0.0001	6.73 (6.22 – 7.28)

TABLE 2: Comparison of the prevalence of self-reported FA and doctor-diagnosed FA in two survey populations.

Crustacean	5.22 (4.61 – 5.92)	4.29 (3.71 – 4.94)	0.0415	4.77 (4.34 – 5.24)	4.79 (4.20 – 5.46)	2.80 (2.34 – 3.35)	<0.0001	3.83 (.344 – 4.25)
Fish	1.55 (1.23 – 1.96)	1.70 (1.35 – 2.14)	0.6097	1.62 (1.38 – 1.91)	1.37 (1.07 – 1.76)	1.10 (0.83 – 1.47)	0.2845	1.24 (1.03 – 1.50)
Mollusk	0.90 (0.66 – 1.22)	2.13 (1.73 – 2.61)	<0.0001	1.50 (1.26 – 1.78)	0.72 (0.51 – 1.01)	1.36 (1.05 – 1.76)	0.0038	1.03 (0.84 – 1.27)
Beef	0.34 (0.20 – 0.56)	2.32 (1.91 – 2.82)	<0.0001	1.30 (1.08 – 1.56)	0.27 (0.15 – 0.47)	1.46 (1.14 – 1.87)	<0.0001	0.85 (0.67 – 1.06)
Milk	0.81 (0.59 – 1.12)	0.26 (0.15 – 0.47)	0.0006	0.55 (0.41 – 0.72)	0.70 (0.49 – 0.99)	0.22 (0.11 – 0.41)	0.0012	0.46 (0.34 – 0.63)
Egg	1.15 (0.87 – 1.51)	1.10 (0.83 – 1.47)	0.9187	1.13 (0.92 – 1.37)	0.95 (0.70 – 1.28)	0.74 (0.52 – 1.05)	0.3471	0.85 (0.67 – 1.06)
Wheat	0.07 (0.02-0.20)	0.50 (0.33 – 0.77)	0.0001	0.28 (0.19 – 0.41)	0.07 (0.02 – 0.20)	0.38 (0.24 – 0.62)	0.002	0.22 (0.14 – 0.34)
Peanut	0.47 (0.31 – 0.72)	0.36 (0.22 – 0.59)	0.5046	0.42 (0.30 – 0.58)	0.27 (0.15 – 0.47)	0.31 (0.18 – 0.53)	0.7226	0.29 (0.20 – 0.43)
Soy	0.18 (0.09 – 0.35)	0.26 (0.15 – 0.47)	0.4934	0.22 (0.14 – 0.34)	0.16 (0.08 – 0.32)	0.17 (0.08 – 0.35)	>0.9999	0.16 (0.10 – 0.27)
Tree nuts	0.07 (0.02 – 0.20)	0.43 (0.27 – 0.68)	0.0006	0.24 (0.16 – 0.37)	0.02 (0.00 – 0.13)	0.31 (0.18 – 0.53)	0.0007	0.16 (0.10 – 0.27)
Other foods	0.41 (0.26 – 0.64)	0.53 (0.35 – 0.80)	0.4314	0.46 (0.34 – 0.63)	0.25 (0.14 – 0.44)	0.29 (0.16 – 0.50)	0.8354	0.27 (0.18 – 0.40)

All data were analyzed using GraphPad Prism for Windows. The Wilson/Brown method was used to calculate the 95% CIs. Fisher's exact test and Chi-square test were used (where appropriate) to compare the prevalence in two study groups. A *P* value of <0.05 was denoted as statistical significance (highlighted in bold).

TABLE 3. Multivariable logistic regression analysis of demographic factors for FA.

Risk factor	OR	P value
Gender (<i>Female/ Male</i>)	1.567	0.172
Family history of FA (<i>Yes/ No</i>)	1.018	0.961
Co-existing other allergic diseases (<i>Yes/ No</i>)	3.428	0.006
Participant location (Hue/ Tien Giang)	3.902	<0.001

Binary logistic regression was performed in SPSS Statistics for Windows to generate ORs. A *P* value of <0.05 was considered as statistical significance.

FIGURE 1. Proportion of reported clinical symptoms in participating children in Hue and Tien Giang. **A.** Reported food-induced adverse symptoms ($n = 2,905$). **B.** Reported adverse symptoms in self-reported FA participants ($n = 763$). **C.** Reported adverse symptoms in doctor-diagnosed FA participants ($n = 580$).

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Title:

A cross-sectional, population-based study on the prevalence of food allergies among children in two different socio-economic regions of Vietnam

Date:

2019-05-01

Citation:

Le, T. T. K., Nguyen, D. H., Vu, A. T. L., Ruethers, T., Taki, A. C. & Lopata, A. L. (2019). A cross-sectional, population-based study on the prevalence of food allergies among children in two different socio-economic regions of Vietnam. PEDIATRIC ALLERGY AND IMMUNOLOGY, 30 (3), pp.348-355. <https://doi.org/10.1111/pai.13022>.

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