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This week's issue was organized by Guest Editor Yongning Wu.

Methods and Applications

A Methodology of Epidemiologic Study in the General Population Focusing on Food Allergy — China, 2020

Hua Feng^{1,2}; Yan Chen^{3,*}; Hongbing Chen¹; Chengwei Liu⁴; Wei Zhou⁵; Lianglu Wang^{6,*}; Yongning Wu^{1,3,*}

ABSTRACT

Introduction: Adverse reactions to food (ARF) are a major worldwide public health and food safety problem. Among the various causes of ARF, food allergies (FA) are particularly serious as the immune response that is triggered can be fatal even at very low doses. However, the prevalence of ARF and FA in the general population in China is presently unclear. This study aims to determine the epidemiological characteristics and risk factors for ARF and FA, which can be a basis for estimating thresholds for major food allergens.

Methods: This is a multicenter, cross-sectional, epidemiologic survey with a case-control study nested among a selected population in China. Random individuals were recruited using stratified cluster random sampling; ARF and FA were comprehensively assessed using modified EuroPrevall FA Project questionnaires as well as structured interviews, sensitization testing, and double-blind placebo-controlled food challenges (DBPCFC).

Results: This method of epidemiologic study on ARF and FA was a pilot application in Jiangxi Province from January 2020; among the total 21,273 children and adults that completed the questionnaire, 5.8% reported ARF and 4.3% reported FA. ARF were determined to be associated with age, gender, and region. Animal-derived foods were the dominant offending foods, especially shrimp, and skin symptoms were the most commonly reported ARF.

Discussion: This is the first multi-center, large-scale, epidemiologic study on ARF and FA using standardized methods, including DBPCFC, in the Chinese general population. This study presents an important approach to assessing ARF and FA, provides significant insights about the prevalence of ARF and FA, and facilitates support for updating the list of allergenic food labels: which will be essential for improving ARF prevention and management in China.

Adverse reactions to food (ARF) are a major, worldwide public health and food safety problem. Among the various causes of ARF, food allergies (FA) are particularly serious as the immune response that is triggered can be fatal even at very low doses. FA usually occur as an adverse immune response arising from exposure to a specific given food; it is often the first clinical allergy appearance and the first link in the so-called “march of atopy” (1), representing one of the most common causes of anaphylaxis (2). Previous studies have shown that FA generally affects about 5% of adults and 8% of children — and can even manifest in up to 10% of children in high-income countries (3–5). The prevalence of FA has risen in the past 10 years (6); the types of foods causing allergies and serious allergic reactions are growing. FA can cause many physical and psychological disorders. It is a very serious problem, not only for patients and their families, but also for medical staff and local communities. Today, FA has become a well-recognized, major public health and food safety issue of global concern (7).

Due to allergenic agents being extremely heterogeneous in eliciting allergens, symptoms, and clinical signs (8), validly assessing FA has been difficult. Many studies on FA have used outpatients as subjects to investigate the clinical aspects of FA. However, only a fraction of the individuals who actually experience a food allergy visit a medical doctor. Therefore, it is presently unclear how representative these results are of the general population (9).

Very little is known regarding global variations in the prevalence of food allergies. Data about FA in most low- and middle-income countries are quite scarce (4). Limited, small-scale research shows that the confirmed FA prevalence is about 6% among children in China, which also demonstrates an upward trend consistent with the upward trend in global prevalence (10).

Food allergen labelling of the “Big-8” recommended by the Codex Alimentarius Commission (gluten, crustaceans, eggs, fish, milk, peanuts, soybeans, and tree nuts) (11) lacks support from Chinese

epidemiologic data on FA, as their prevalence is poorly defined in the Chinese population. Epidemiologic studies on FA confirmed with double-blind placebo-controlled food challenges (DBPCFC) in the general population are thus necessary to be conducted in China.

This study aims to assess the unknown, epidemiological feature of ARF and FA in China. The results will form the baseline dataset for monitoring the trend of FA, provide support for updating the allergenic food labelling list in China, estimate the thresholds for food allergens where feasible, present scientific evidence for effective control measures, and inform policies for FA prevention and diagnosis.

METHODS

Sampling Strategies

Eight provincial-level administrative divisions (PLADs) were selected as study centers by random cluster sampling in China; three prefectures were selected randomly from each selected PLAD, then one county/district was selected from each prefecture as a sub-survey center.

Children were recruited from primary schools in both rural and urban regions, of which 4–6 schools generated by computer randomization were obtained for each sub-survey center. In these schools, children aged 6–11 years old were recruited from grades 1–5. For adults, towns or street districts were ranked according to their population size; 2 townships and 2 street districts were randomly selected in each sub-survey center, with adults aged 18–70 randomly recruited. Exclusion criteria of participants included: age outside of the aforementioned ranges; difficulty in completing the survey due to severe disease; and respondents or their parents (guardians) not providing consent.

Sample Size

Sample size estimation was mainly based on the case-control study: assuming the case-control study had 90% power to find an odds ratio of 2; 15% population were exposed to the risk factors (12). One control per case (e.g., 240 cases and 240 controls) was used. Given a 20% non-response rate in the case-control study, 5% and 3% prevalence rates of IgE-mediated FA were estimated in primary schoolchildren and adults, respectively. In total, 9,000 children and 12,000 adults for FA screening in each study center were estimated to

be sufficient, i.e., 3,000 children and 4,000 adults for each sub-survey center. Each subject was coded uniformly, concealing his/her residence and personal information. Data were collected from 2020, and this research is expected to continue to be completed in the following ten years.

Questionnaires

Modifications based on the habits and characteristics of the Chinese population were made to the translated EuroPrevall FA questionnaires before this methodology was applied. The questionnaires focused on demographic characteristics and adverse reactions to food: including food allergies, risk factors, and exposures.

Multistage of Study

This study mainly focused on IgE-mediated allergies to 20 priority foods (cow's milk, hen's eggs, fish, shrimp, crab, shellfish, beef, peanuts, sesame, soy, wheat, buckwheat, rice, peaches, oranges, mangos, hazelnuts, walnuts, almonds, and cashews) reported to commonly cause FA reactions and frequently consumed in China. The epidemiologic study consisted of three main consecutive stages.

In Stage I, subjects were screened using an FA questionnaire that focused on demography, ARF, causative foods, diagnosis methods of FA and other allergic diseases. For children, the screening questionnaires were completed by their parents or legal guardians; adults completed screening questionnaires themselves.

In Stage II, subjects who reported ARF symptoms to 1 of the 20 priority foods were regarded as cases (suspected FA); those who had “no reaction” to foods reported in Stage I were randomly matched to suspected FA cases with similar demographics as controls. All cases and controls were invited to the local hospital for clinical evaluation of FA, which involves skin prick testing (SPT), collection of serum for IgE testing, and clinical interviews. The face-to-face interviews were conducted by well-trained clinicians with detailed questionnaires that focused on socio-demographics, FA, living environments, lifestyle behaviors, and presence of any family history of allergy. SPT was performed with 20 food allergens, along with negative and positive controls, standardized allergen extracts, and control solutions obtained from GREER (Madrid, German). Valid controls and largest wheal diameter ≥ 3 mm were regarded as positive. All serum

samples were sent to the laboratory of Peking Union Medical College Hospital to test for total IgE and specific IgE (sIgE) using the commercially available ImmunoCAP 250 (Phadia, Uppsala, Sweden): this study followed the manufacturer's instructions, whereby an sIgE value of ≥ 0.35 kU_A/L is considered positive (9).

In Stage III, an individual with probable FA who self-reported an ARF (Stage I and/or Stage II) and matched food sensitization (positive SPT or sIgE) (12) to one of 9 priority foods (milk, eggs, fish, shrimp, peanuts, hazelnuts, peaches, mangos, or apples) was scheduled for a comprehensive clinical evaluation, including DBPCFC (13). Subjects with a history of anaphylactic food reactions were excluded. DBPCFC was performed on two separate days with subjects and medical staff blinded to the order of food/placebo given. Gradually, the dose of placebo or causative food was increased at 20-minute intervals, and the test was ended until the participant either exhibited objective symptoms, exhibited significant subjective symptoms lasting >45 minutes, or consumed all the food samples (13). Participants who had a reaction of any duration on the active day (but not on the placebo day) were considered positive. Participants who did not react either on the active or placebo days were classified as tolerant, and participants who reacted on the placebo day were considered placebo responders (9). FA threshold information was recorded during DBPCFCs.

Definition and Clinical Evaluation

ARF is defined as reporting illness or trouble after consuming food. Self-reported FA was referred to as FA in the questionnaires. Doctor-diagnosed FA was referred to as FA diagnosed by a doctor. Food sensitivity (FS) was considered to be positive results for SPT or sIgE. Probable FA refers to a clinical history matched with IgE sensitization to the same food. Confirmed FA was defined as positive results in the DBPCFC.

Statistical Analyses

Continuous variables were expressed as mean \pm standard deviation and compared by a t-test or analysis of variance. Categorical variables were presented with frequencies and percentages: compared by a Chi-square test. Single factor and multivariate regression analysis were used to evaluate the relationship between food allergies and potential risk factors, as well as analyze possible confounding factors. FA prevalence in the

case-control stage or confirmation stage were weighted back to the population in FA screening. Statistical analysis was performed with SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). *P* values of <0.05 were considered significant.

Study Management

The expert group formulated a Manual of Procedures, including standard operating procedures (SOP). All staff members were trained in SOP and all study centers followed the Manual of Procedures and standardized methodology. Each study center identified strategies to maximize response rates, such as mobilization meetings, text messages, phone calls, or emails. Data were cross-checked and verified by two people, which formed a database accessible via a web APP (Information Management System of Chinese FA Epidemiological Investigation) specifically designed for this project.

Ethical Approval

Ethical approval (Number 2019027) was obtained from the China National Center for Food Safety Risk Assessment ethical committee, and written, informed consent was obtained from the participants or their legal guardians.

RESULTS

This methodology of epidemiologic study on FA was implemented in Jiangxi, China in 2020.

Subjects

The sub-survey centers were described in Figure 1A. Figure 1B showed a sampling flow chart. A total of 21,273 FA screening questionnaires were distributed in Jiangxi Province. The valid response rate was 97.8%. A total of 11,935 adults and 8,856 children were screened for FA; the mean age was 45 ± 13 years and 8.7 ± 1.3 years, respectively.

Self-reported ARF and FA

Among all participants, 5.8% of responders reported ARF and 4.3% reported FA. Table 1 described the demographic characteristics of those who self-reported ARF and FA. Doctor-diagnosed FA was 2.20%, of which, 11.3% were diagnosed by oral food challenges where the main verifier of doctor-diagnosed FA was sIgE testing. This 3 stages of study across Jiangxi

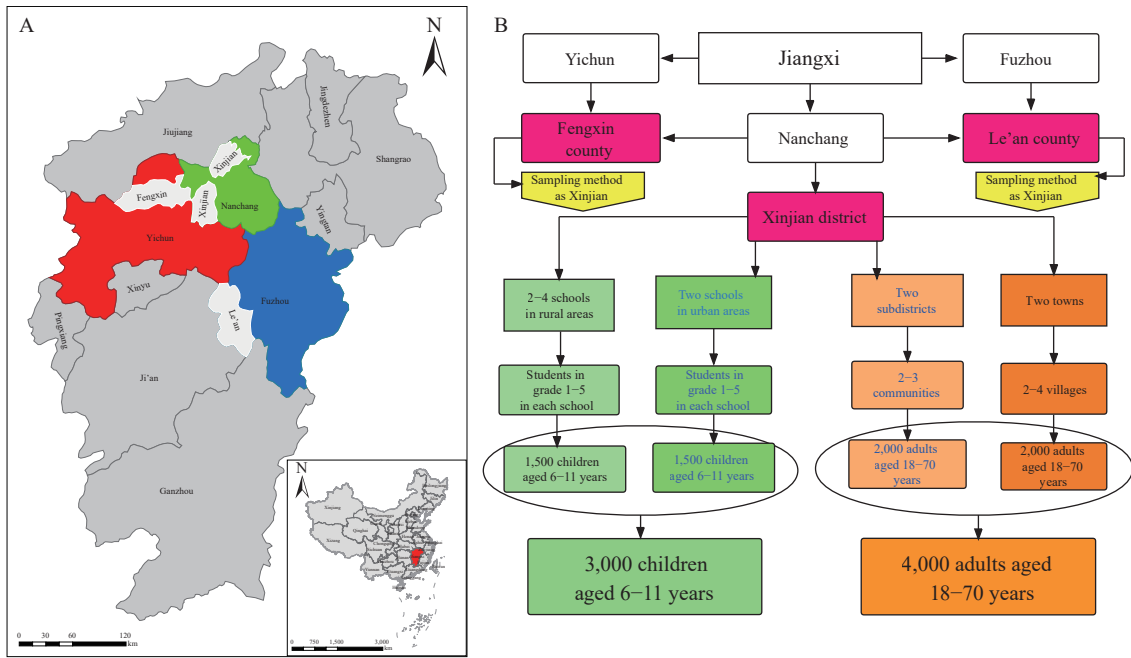


FIGURE 1. Distribution of sub-survey centers and sampling flow chart in the study center of Jiangxi Province, 2020. (A) Distribution of sub-survey centers. (B) Sample size and sampling flow chart among adults and school children.

Note: In panel A, three prefectures were randomly selected in Jiangxi Province, they are Yichun, Nanchang, and Fuzhou, respectively, then Fengxin, Xinjan, and Le'an were randomly selected from the three prefectures as the sub-survey centers. In panel B, three prefectures were randomly selected in Jiangxi as sub-survey centers, and then about 3,000 school children and 4,000 adults were selected from each sub-survey centers by stratified cluster random sampling.

TABLE 1. The demographic characteristics and prevalence of self-reported ARF and FA among children and adults in the study center of Jiangxi Province, 2020.

Variables	Population		ARF			FA		
	N	Percentage (%)	Percentage (%)	χ^2	P	Percentage (%)	χ^2	P
Total	20,791	100.00	5.79	/	/	4.29	/	/
Age								
Adult	11,935	42.60	8.21	165.35	0.00	2.90	145.71	0.00
Child	8,856	57.40	4.00			6.15		
Gender								
Male	10,517	50.58	5.47	4.09	0.04	4.06	2.71	0.09
Female	10,274	49.42	6.12			4.52		
Residence								
Rural area	10,755	51.76	5.74	0.09	0.76	4.12	2.10	0.15
Urban area	10,030	48.24	5.84			4.47		
Sub-survey center								
Fengxin	6,670	32.08	6.99	40.98	0.00	5.53	57.36	0.00
Le'an	7,005	34.13	5.99			4.48		
Xinjian	7,026	33.79	4.45			2.96		
Ethnic								
Han	20,754	99.82	5.79	0.06	0.80	4.28	0.78	0.38
Others	37	0.18	8.11			8.11		

Abbreviation: FA=food allergy; ARF=adverse reaction to food.

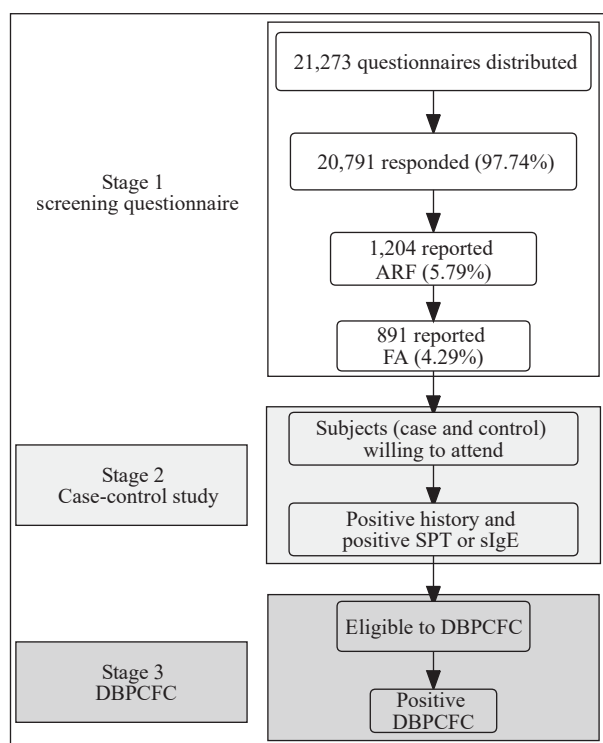


FIGURE 2. Study population and multilevel assessment of FA among adults and school children in the study center of Jiangxi Province, 2020.

Note: The comprehensive clinical assessment of food allergy consists of three stages; the main research includes food allergy screening, structured interview, IgE sensitivity test, and oral food challenge test.

Abbreviation: ARF=adverse reaction to food; FA=food allergy; SPT=skin prick test; slgE=Specific IgE; DBPCFC=double blind placebo-controlled food challenge.

survey centers were presented in Figure 2.

Common Causative Foods and Symptoms

The 8 most common causative foods were, in descending order, shrimp, mangos, shellfish, eggs, fish, beef, milk, and mutton; their prevalence was 1.95%, 1.22%, 1.07%, 0.68%, 0.49%, 0.35%, 0.34%, and 0.25%, respectively. Figure 3A shows the distribution of incriminated foods. Unlike in Europe, beef and mutton as offending foods were more common than peanuts and soybeans. Skin symptoms, such as rash or pruritus (itching), were the most frequently reported manifestation. Oral allergy symptoms were reported by 20.6% of subjects. Figure 3B presents the common symptoms of this self-reported FA.

DISCUSSION

The epidemic characteristics of FA are diverse across

different countries and regions. In this study, the prevalence of self-reported ARF and FA was 5.79% and 4.29%, respectively, where shrimp was the most common offending food. Peanuts as a causative food was uncommon, unlike in America or Europe. Animal-derived foods were dominant as causative foods in China, but plant foods were dominant among adults with FA in most other countries (13). The most common FA in this study are different from those in high-income countries; this difference may mean that cultural, dietary, industrialization (1), and biological factors (14) play important roles in FA.

This is the first and largest multicenter, population-based cross-sectional study on FA with case-control nested in China, as well as the first to use a multilevel technical approach, including DBPCFC, to assess FA and threshold value, which ensures better comparability of data on FA across different countries or regions. The potential for non-response in different stages will be assessed and weighted back to the population of the FA screening so that results can more accurately reflect prevalence among the general population, including those not assessed (8).

This methodology also has limitations: the possible FA and the DBPCFC-confirmed FA are mainly focused on 20 priority foods and 9 common foods, respectively. Other foods are not considered and allergies to other types of foods could not be included. Geographically, there are regional differences in the effects of environmental exposure and dietary habits on food allergens; only eight PLADs were randomly selected as study centers, and the results may not completely reflect FA prevalence and variation across China overall.

This study provides baseline information about FA in China. The results will contribute to updating the labelling list of allergenic food, identifying the risk factors for the occurrence and development of food allergies, and estimating thresholds for the major food allergens. The study will also contribute to the improvement of preventive, administrative, and treatment strategies for food allergies in China.

Conflicts of interest: No conflicts of interest.

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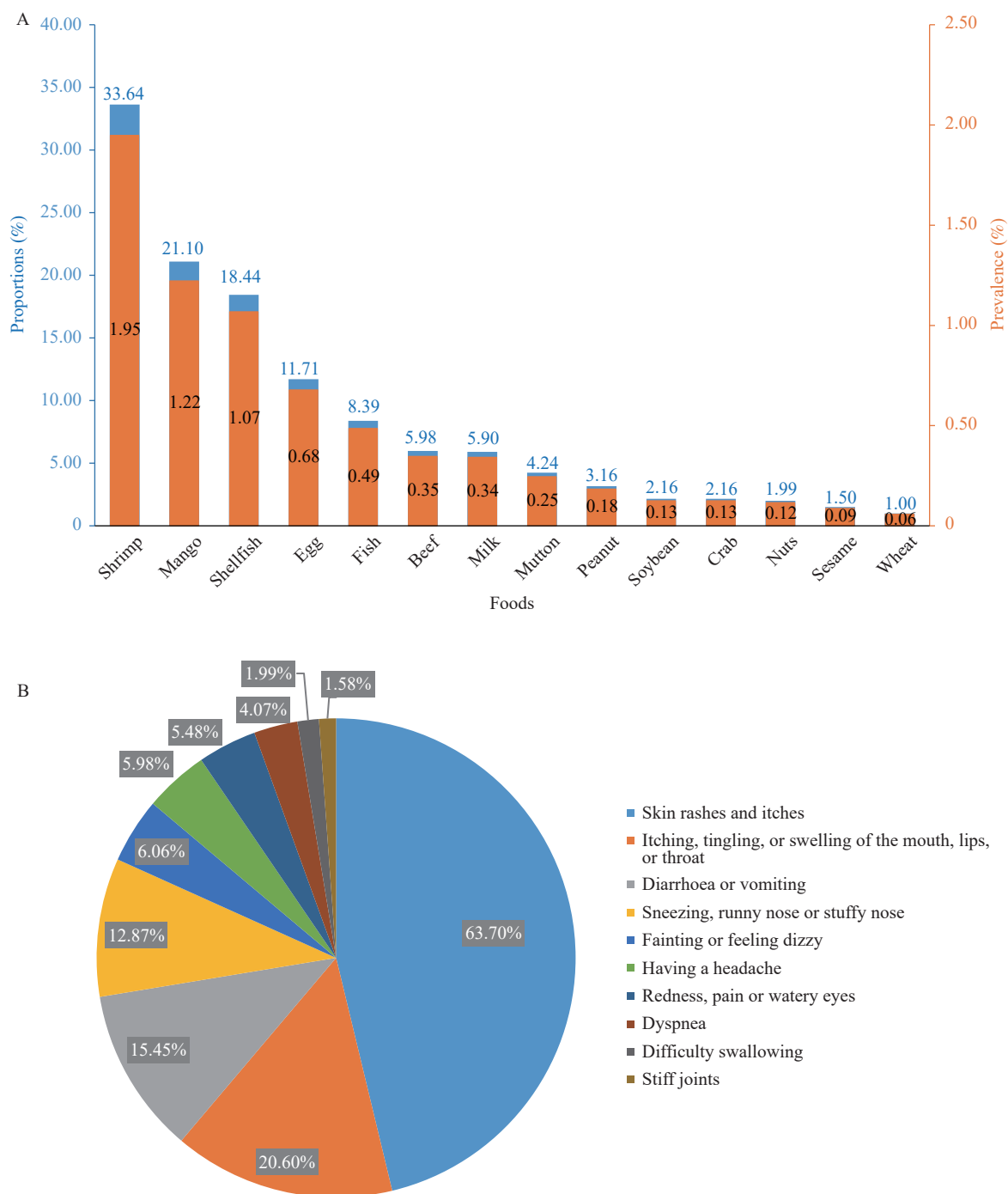


FIGURE 3. Common causative foods and symptoms in the study center of Jiangxi Province, 2020. (A) Distribution of causative foods among adults and school children. (B) Percentage of common symptoms among adults and school children with food allergy.

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Preplanned Studies

A Chinese-Specific Reference Amounts Study With TNO Food Allergen Risk Assessment Models — China, 2022

Jinfang Sun^{1,2}; Di Wu³; Yiyun Zhang⁴; Yongning Wu^{4,*}

Summary

What is already known about this topic?

There are no consistent regulations on possible unintended allergen presence in food. The Netherlands Organization for Applied Scientific Research (TNO) has been committed to developing a quantitative risk assessment methodology for the unintentional intake of allergens.

What is added by this report?

This study aims to derive the optimal food consumption point for a deterministic food allergy risk assessment under the TNO framework based on Chinese national consumption data. A case study has been presented as an illustration.

What are the implications for public health practice?

A robust evidence-based food consumption input in quantitative risk assessment of unintended allergens is necessary for future public policy on Precautionary Allergen Labeling for specific products to meet the safety objectives and to be adequately conservative.

Unintended allergen presence (UAP) not only poses risks for the food allergic population but is also a regular cause of food recalls with considerable costs associated with such actions. To enable food producers to make evidence-based decisions on the utility of Precautionary Allergen Labeling (PAL), it is necessary to determine the risk of the product to allergic consumers. The Netherlands Organization for Applied Scientific Research (TNO) developed a methodology to support authorities and industries in establishing reference amounts (R_fA) when assessing the risk from UAP in food products (1). A case study was performed on the TNO framework based on Chinese national consumption data to derive the optimal food consumption point for a deterministic food allergy risk assessment (RA). It showed that the 95th–99th percentiles of the food consumption distribution per eating occasion for both Condiments and Chocolates

were the optimal point estimates for use in meeting the safety objective of protecting 99% of allergic individuals from unintended peanut allergic reactions. This study provides an illustration of a good evidence-based study for consumption parameters in food allergen RA, and it is suggested more food groups should be analyzed applying this framework to verify the optimal point estimate for Chinese-specific R_fAs .

A sensitivity analysis was performed to establish the optimal percentile of food consumption on a single eating occasion for food groups Condiments and Chocolates to meet the defined food safety objective for unintended peanut allergic reactions. Within this framework, exposure was calculated by both deterministic and probabilistic modeling and outcomes of the two RAs were compared. Optimal consumption percentiles in deterministic RA were defined as those which predicted an intake below the relevant reference dose (R_fD) and met the defined acceptable risk level confirmed by probabilistic RAs. (Figure 1) (1–2) The R_fD of 0.2 mg peanut protein in allergic food was proposed by Taylor et al. from the eliciting dose of 1% risk (ED01) from a large dataset of bibliographic data and unpublished clinical data (3). The deterministic RA provides an initial quantitative test, offering a binary answer: if the amount of peanut protein consumed is at or below the R_fD , a product is considered to “pass” (green box), and the allergy risk is not deemed to require further mitigation; otherwise, the product “fails” (red box). The cut-off for probabilistic RA is the estimated percentage of allergic responders either at or below (green box) or above (red box) the defined risk level at the R_fD (here indicated as $\leq 1\%$ and $> 1\%$). The sensitivity analysis shows that, underestimation or overestimation of the risk by the deterministic RA occurs if too low or too high food consumption percentiles were used in the deterministic modeling. This allows us to verify that consumption percentiles do not lead to under- or over-estimation of the predefined risk level.

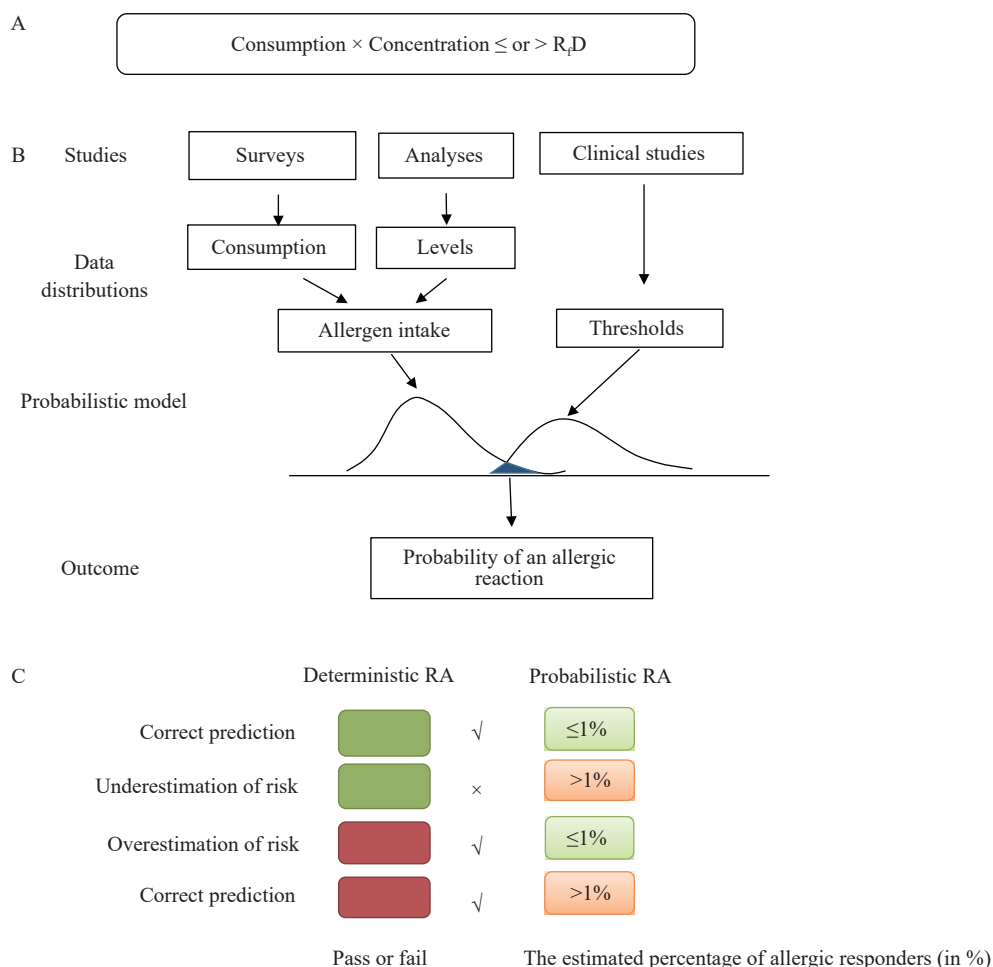


FIGURE 1. Description of the sensitivity analysis to derive an optimal point estimate for allergen RA. (A) The formula for deterministic RA. (B) The schematic description of probabilistic RA. (C) The sensitivity analysis in which the outcomes of the two RAs are compared.

Note: The deterministic outcome is a binary answer: a product is considered to “pass” (green box in C) or “fail” (red box in C) by comparing the amount of allergenic protein consumed with the relevant R_pD ; The cut-off for probabilistic RA is the estimated allergic responders either at or below (light green box in C) or above (light red box in C) the defined risk level (here is 1%) at the R_pD .

Abbreviation: RA=risk assessment; R_pD =reference dose.

The food consumption data were obtained from Chinese National Nutrition and Health Survey in 2002 by 24 h recall method on three consecutive days. Multistage and random cluster samplings were used in the survey and 30 provincial-level administrative divisions (PLADs) were covered. This food consumption database provided the food consumption amount for each food item per eating occasion from 65,915 consumers aged 2–100 years in total. In this study, 4,290 eating occasions for Condiments and 144 eating occasions for Chocolates were included. The percentiles (P50 to maximum) of the consumption distribution for each food group were calculated as input values in the deterministic RA, while food

consumption distribution from both parametric and non-parametric simulations was used for the probabilistic RA. As the contamination happens unintentionally during production, the concentration level is unknown. Ranges from 1 to 1,000 mg/kg of theoretical concentration (1, 3, 10, 30, 100, 300, 600, or 1,000 mg peanut protein/kg food products) were selected. These levels are typical concentrations found for UAP in food products in published surveys (1,4) and were chosen with a wide range to ensure that the allergen intakes would be both below and above the R_pD . SAS (version 9.4, SAS Institute Inc., Cary, North Carolina 27513, USA.) was used to conduct all analyses.

The deterministic RA outcomes for the food group Condiments contaminated with different concentrations of peanut are shown in Figure 2A. The binary outcome predicts either that there is risk above (red) or at or below (green) the intended risk level. Figure 2B provides the risk estimated by both parametric and non-parametric probabilistic RA. For each concentration of peanut protein in Condiments, the percentage (%) of intakes exceeding the R_fD in the population is estimated and the conclusion whether it is at or below (green) or exceeds (red) the given risk level (1%) is shown.

Then, the optimal percentile of food consumption is identified that produces a deterministic RA outcome in compliance with the predefined risk level. In Figure 2, the estimated risk at 1 mg peanut protein per kilogram condiments is below the pre-defined risk level for both probabilistic models. Whereas, at 3 mg/kg both probabilistic models estimated a risk above the cut-off value, and the conclusion is that the product “fails” the RA according to the pre-defined criteria. The deterministic RA predicted this conclusion consistently for the percentiles 95th–100th at 3 mg/kg, whereas using P50 to P90 of the food consumption distribution would pose an underestimated exposure. At 1 mg/kg, the deterministic RA prediction was in agreement for

the P50 to P99 of the food consumption distribution. Using the consumption values of P100 combined with 1 mg/kg, the deterministic RA was more conservative and predicted a risk above the pre-defined risk level.

The RA outcomes for peanut in Chocolates are presented in Figure 3. At 3 mg/kg peanut in chocolates, the estimated risk in the probabilistic approach is above the pre-defined risk level for both models. The deterministic RA predicted this conclusion consistently for the percentiles 85th–100th at 3 mg/kg, whereas using P50 to P80 of the food consumption distribution would pose an underestimate of exposure. At 1 mg/kg, the deterministic RA prediction was in agreement for the P50 to P99 of the food consumption distribution. Using the consumption values of P100 combined with 1 mg/kg, the deterministic RA was more conservative and predicted a risk above the pre-defined risk level.

In terms of this case study, it is concluded that the 95th–99th percentiles of food distribution could be the optimal points for use in deterministic RA, with which the outcome is in compliance with the probabilistic RA meeting the safety objective of protecting 99% of allergic individuals from objective allergic reactions to unintended allergic peanut presence and be adequately conservative from a public health context.

A Food consumption		Concentration of allergen (mg/kg)							
Percentiles	grams	1	3	10	30	100	300	600	1,000
P50	25	Green	Green	Red	Red	Red	Red	Red	Red
P55	25	Green	Green	Red	Red	Red	Red	Red	Red
P60	25	Green	Green	Red	Red	Red	Red	Red	Red
P65	25	Green	Green	Red	Red	Red	Red	Red	Red
P70	40	Green	Green	Red	Red	Red	Red	Red	Red
P75	50	Green	Green	Red	Red	Red	Red	Red	Red
P80	50	Green	Green	Red	Red	Red	Red	Red	Red
P85	50	Green	Green	Red	Red	Red	Red	Red	Red
P90	50	Green	Green	Red	Red	Red	Red	Red	Red
P95	75	Green	Red	Red	Red	Red	Red	Red	Red
P97.5	100	Green	Red	Red	Red	Red	Red	Red	Red
P99	125	Green	Red	Red	Red	Red	Red	Red	Red
P100	250	Red	Red	Red	Red	Red	Red	Red	Red

B Models		1	3	10	30	100	300	600	1,000
Nonparametric (%)		0.11	5.20	62.31	88.59	100.00	100.00	100.00	100.00
Weibull (%)		0.00	8.05	59.24	88.28	97.44	99.32	99.72	99.87

FIGURE 2. Example peanut in Condiments for determination of the optimal percentile of the food consumption distribution. (A) Deterministic RA for peanut protein in Condiments. (B) The estimated risk for allergic responders (in %) at the different concentrations of peanut protein in Condiments using parametric and non-parametric probabilistic RA.

Note: The intake by deterministic model at or below the R_fD dose of 0.2 mg peanut protein is shown in the green box. Otherwise, the red box is shown. For probabilistic models, in terms of green, the estimated risk is at or below the defined risk level (1%), and in terms of red, it is exceeding 1%.

Abbreviation: RA=risk assessment; R_fD =reference dose.

A Food consumption		Concentration of allergen (mg/kg)							
Percentiles	grams	1	3	10	30	100	300	600	1,000
P50	25								
P55	40								
P60	50								
P65	50								
P70	50								
P75	50								
P80	50								
P85	90								
P90	100								
P95	100								
P97.5	100								
P99	150								
P100	250								

B Models		1	3	10	30	100	300	600	1,000
Nonparametric (%)		0.61	17.52	64.58	93.81	100.00	100.00	100.00	100.00
Weibull (%)		0.22	20.31	69.4	90.61	97.66	99.4	99.77	99.91

FIGURE 3. Example peanut in Chocolates for determination of the optimal percentile of the food consumption distribution. (A) Deterministic RA for peanut protein in Chocolates. (B) The estimated risk for allergic responders (in %) at the different concentrations of peanut protein in Chocolates using parametric and non-parametric probabilistic RA.

Note: The intake by deterministic model at or below the relevant R_D of 0.2 mg peanut protein is shown in the green box. Otherwise, the red box is shown. For probabilistic models, in terms of green, the estimated risk is at or below the defined risk level (1%), and in terms of red, it is exceeding 1%.

Abbreviation: RA=risk assessment; R_D=reference dose.

DISCUSSION

Methods proposed by TNO on recommendations for R_fAs for foods based on allergen RA are applied to Chinese consumption data and the results show that the 95th–99th percentiles of the food consumption distribution per eating occasion for Condiments and Chocolates are the optimal point estimates for use in deterministic allergen RA meeting the safety objective of protecting 99% of allergic individuals from objective allergic reactions to unintended allergic peanut presence. This provides an illustration of a robust evidence-based study for food consumption parameters in food allergen RA. A diverse range of inputs is seen in practice, such as the large portion or maximum amounts to be “on the safe side”. These diverse formulations of consumption amounts lead to highly divergent quantitative risk estimates and substantial confusion in RA. To achieve one cohesive, agreed quantitative risk assessment approach has become a global trend for allergen management.

Blom et al. conducted such a sensitivity analysis with consumption data from three European countries, where the procedure was repeated for all food groups and allergens (480 combinations) and in total 1,344 RAs were performed and concluded that the 75th

percentile of the food consumption distribution per eating occasion is the optimal estimate for use in meeting the safety objective of protecting 97%–99% of allergic individuals from objective allergic reactions to UAP (1). In addition, Blom et al. found the P75 of Ice cream consumption (100 grams) with an action level of 1 mg/kg hazelnut and the P70 of Spices and Salts consumption (2 grams) with an action level of 100 mg/kg peanut posed an allergy risk which did not require further mitigation. The R_fA at 1 mg/kg was close to that in this study but with different percentiles.

Future public policy on PAL for specific products should consider both reference amounts and action levels that would trigger such labeling. In the present study, only the food groups Condiments and Chocolates with theoretical concentration levels were taken for an illustration of choosing evidence-based consumption parameters. Due to the differences of diet consumption patterns and potential changes, and the R_fAs are food- and region- or country-specific, future studies need to broaden the scope to include more food groups consumed by Chinese consumers and allergens in this framework, where possible with update database, to verify the optimal point estimate for Chinese-specific R_fAs. Besides, it was assumed that the food consumption pattern of allergic persons does not

differ from that of the general population, which has been validated in the Dutch population (5). More studies are necessary for the Chinese population and emphasis should also be put on grouping food consumption data for use in food allergen RA under different circumstances (6). In addition, further recommendations and guidance for determination of the concentration of allergen for input to the RA could be beneficial for all stakeholders (1).

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Preplanned Studies

Self-Reported Food Allergy Prevalence Among Elementary School Children — Nanchang City, Jiangxi Province, China, 2021

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Summary

What is already known about this topic?

The prevalence of food allergy (FA) among the general population has been increasing in recent decades, and seriously affects the physical and mental health and the quality of life of many people — especially children.

What is added by this report?

The survey estimated self-reported FA prevalence using a standardized FA questionnaire among school children in Nanchang City, Jiangxi Province, China in 2021.

What are the implications for public health practice?

Based on the local, epidemiological characteristics of food allergy, public policies on the prevention and management of FA should be developed and preventive practices should be promoted to decrease the overall prevalence of FA.

The prevalence of food allergy (FA) is rising rapidly worldwide; it has become a major health burden in many jurisdictions, especially in children, but little is known about its prevalence in Jiangxi Province in China. Thus, this survey aimed to estimate the FA prevalence in school children across Nanchang City, Jiangxi Province. A cross-sectional survey on FA was performed using a standardized questionnaire of FA among school children in Nanchang in 2021. Children whose parents or legal guardians reported the children had or have FA were considered FA individuals. FA accounted for 67.3% of adverse reaction to food (ARF) and the prevalence of FA was 4.9%. The main foods triggering allergies were shrimp and mango: while severe food allergic reactions accounted for 26.0% of those reported. The prevalence of other allergic diseases was significantly higher in children with existing FA than in children without FA. Further epidemiological studies on FA in Jiangxi are warranted; and preventive strategies such as a comprehensive FA labeling system should be developed and implemented in line with the

findings of epidemiological studies. In addition, preventive practices such as public awareness campaigns about FA should be conducted to increase people's awareness of FA and assist them in recognizing the signs and symptoms of allergic reactions, especially among high-risk groups. A subset of susceptible individuals could have life-threatening FA anaphylactic reactions and, in many cases, may require urgent medical attention.

Geographical variability in the prevalence, the major allergenic food triggers, and the clinical presentation of FA — as well as differences in symptoms and clinical phenotypes due to race, ethnicity, age, and concomitant allergic disease — suggest that gene-environment interaction may play an important role in the development and presentation of FA (1–2). FA affects about 2 children in an average-sized classroom of 25 children; about 30.0% of allergic reactions occurred in children who were not previously known to have had FA (3). Moderate and severe reactions co-occur frequently: 42.3% of food-allergic children reported ≥ 1 severe FA (4). Living with FA is well recognized to impair one's quality of life in childhood, parenthood, and adulthood (5) and has also been implicated in increasing pediatric asthma morbidity and life-threatening exacerbations (6). FA is becoming a major health burden in many countries, especially in children (7). To fill the gap in the epidemiological study on FA among children in Jiangxi Province and obtain a list of allergenic foods, this survey on FA was conducted in school children in Nanchang, Jiangxi Province in 2021.

Xinjian District was selected randomly from the six districts in Nanchang. All schools in the district were numbered, and five schools were selected randomly by computer; a representative sample of 6–11-year-old children was selected from the 5 elementary schools.

Ethical approval was obtained from the ethical committee of the China National Center for Food Safety Risk Assessment and written informed consent was obtained from the children's legal guardians.

The survey was mainly based on the EuroPrevall FA screening questionnaire, and included demographic variables, ARF, FA, and other allergic diseases, etc. The questionnaires were distributed to the recruited children in school and completed at home by their parents or other guardians. Upon completion, they were collected and checked by teachers and investigators. Based on the response to the question of whether your child has/had a FA, if one reported “yes” to it, they were defined as a FA individual.

Data were double entered using EpiData (version 3.1, EpiData Association, Odense, Denmark) and statistical analysis was performed using SPSS (version 25.0, IBM Corp., NY, USA). Percentage rate was used to express the count data, and mean±standard deviation was used to describe the continuous data. Body mass index (BMI) was graded by the Chinese BMI grading standard. The chi-square (χ^2) test and t test were used to evaluate the significance of the data: $P < 0.05$ was considered a statistically significant difference.

A total of 3,003 questionnaires were distributed to the 5 selected schools. Ultimately, 2,997 valid questionnaires were collected with a valid response rate of 99.8%. There were 1,512 males and 1,485 female, 1,475 rural children and 1,522 urban children among the participants. Their mean age was 8.40 ± 1.23 years, and mean family size was 5.28 ± 1.41 . The reported

prevalence of FA was 4.9%. 3.9% of the participants did not know if they had FA; differences in reported FA prevalence were not significant for gender, age, or BMI, as shown in Table 1. Doctor-diagnosed FA prevalence was 3.0%, and the major method of FA diagnosis used by doctors was the serum special immunoglobulin E (sIgE) test (35.6%) with oral food challenge (OFC) and skin prick test (SPT): 16.7% and 10%, respectively.

Shrimp (28.1%), mango (22.6%), and shellfish (18.5%) were the top 3 allergenic foods, while peanut was No. 8 on the list of allergenic foods with a reported rate of 5.3%. Among the 8 major allergenic foods, mango and beef were not included in the 8 categories of allergenic substances in the China National Food Labeling Standard (GB 7718-2011), as shown in Table 2. The main manifestations of FA were skin symptoms such as rash or itching (63.0%), severe allergic reactions (8) accounted for 26.0%. Figure 1 describes the main food allergic symptoms.

The prevalence of atopic dermatitis, allergic rhinitis, and allergic asthma was 2.5%, 3.3% and 0.4%, respectively. All of these were lower than FA prevalence in school children. The distribution of other allergic diseases was significantly higher in the FA group than that in the non-FA group. Supplementary Table S1 (available in <http://weekly.chinacdc.cn/>) describes the prevalence of other allergic diseases.

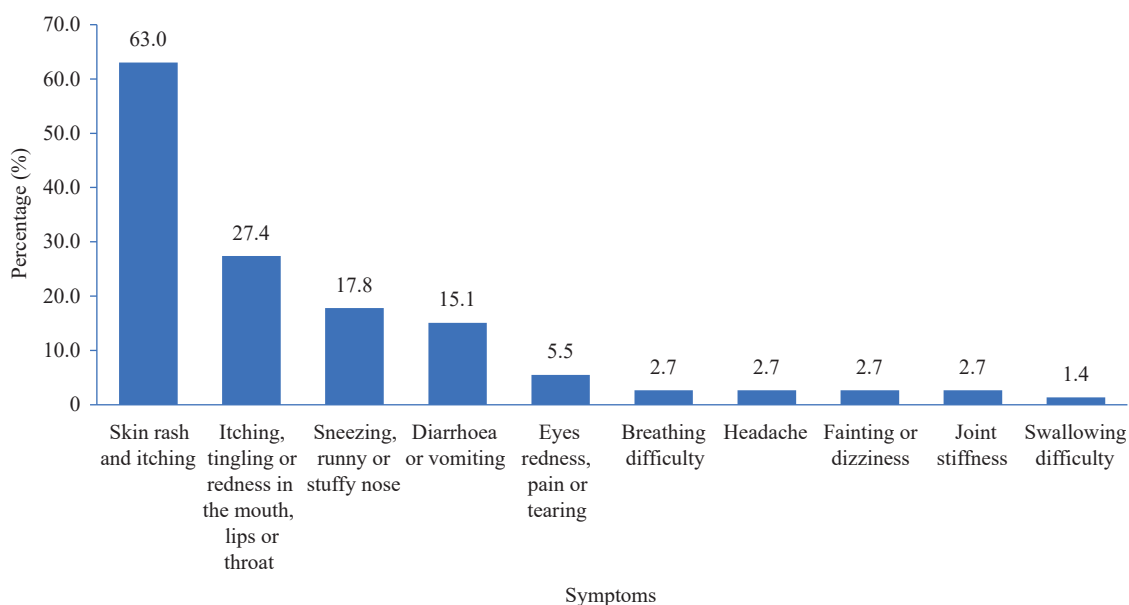


FIGURE 1. Major symptoms of food allergy among the school children in Nanchang City, Jiangxi Province, China in 2021. Note: The most common manifestations of FA in the children were skin symptoms such as rash or itching with 63.0% proportion, followed by itchy tingling or redness in the mouth, lips, throat, sneezing, runny or stuffy nose, diarrhea or vomiting, etc.

TABLE 1. Demographic characteristics and prevalence of food allergy among the school children in Nanchang, Jiangxi, China in 2021.

Variable	FA (n=146)	No FA (n=2,734)	χ^2/t	P	FA (%)	Total (N=2,997)
Age (Mean±SD)	8.41±1.26	8.42±1.23	-0.990	0.921	4.9	8.40±1.23
Gender			0.093	0.760		
Male	75	1,369			5.0	1,512
Female	71	1,365			4.8	1,485
Residence			1.966	0.161		
Rural	81	1,354			5.5	1,475
Urban	65	1,380			4.3	1,522
Ethnic			0.000	1.000		
Han	146	2,732			4.9	2,994
Others	0	2			0	3
BMI			2.587	0.274		
Thin	25	365			6.1	407
Normal	85	1,758			4.5	1,908
Overweight and obesity	36	611			5.3	682
Family size (Mean±SD)	5.29±1.34	5.29±1.41	-0.026	0.979	4.9	5.28±1.41

Abbreviation: FA=food allergy; BMI=body mass index; SD=standard deviation.

TABLE 2. Common allergenic foods among the school children in Nanchang, Jiangxi, China in 2021.

Allergenic foods	N (%)	Rural	Urban	Included in GB 7718-2011
Shrimp	41 (28.1%)	24 (29.6%)	17 (26.2%)	Yes
Mango	33 (22.6%)	15 (18.5%)	18 (27.7%)	No
Shellfish	27 (18.5%)	14 (17.3%)	13 (20.0%)	Yes
Egg	19 (13.0%)	11 (13.6%)	8 (12.3%)	Yes
Milk	15 (10.3%)	8 (9.9%)	7 (10.8%)	Yes
Fish	7 (4.8%)	2 (2.5%)	5 (7.7%)	Yes
Beef	7 (4.8%)	3 (3.7%)	4 (6.2%)	No
Peanuts	7 (4.8%)	4 (4.9%)	3 (4.6%)	Yes
Nuts	5 (3.4%)	3 (3.7%)	2 (3.1%)	Yes
Soybeans	4 (2.7%)	2 (2.5%)	2 (3.1%)	Yes
Mutton	3 (2.1%)	0 (0.0%)	3 (4.6%)	No
Total	146 (100.0%)	81 (100%)	65 (100%)	-

DISCUSSION

This is the first population-based survey that attempts to estimate reported FA (by parents/guardians) prevalence among school children in Nanchang, Jiangxi, China. The results showed the prevalence of reported FA among school children in Nanchang to be 4.9%: higher than the 1.8% reported in India, and lower than the 38% reported in Russia, 15% reported in Guangzhou, and 13% reported in Hong Kong (8). These differences in FA prevalence are probably due to differences in dietary exposures, early-

life environment, and socioeconomic factors.

Allergenic foods vary in different countries or regions. Although the consumption of peanuts and peanut products is widespread in China, there have been fewer reports of peanut allergies; however, peanut allergy is the most common FA in the U.S. and Europe (4,9). This may reflect the differences that genetic background makes in susceptibility to the same food across different countries and races. In addition, mango was one of the primary reported allergenic foods in this study; however, it is not included in the Chinese GB 7718-2011, which was developed with

reference to the International Codex Alimentarius Commission standards. This study suggests that key allergens differ between geographical jurisdictions and that standards should be specific to the Chinese population.

The common symptoms of FA reported in this study were skin and oral mucosal symptoms. However, a survey in 8 European countries showed the most common symptoms to be rash or gastrointestinal symptoms in children with FA (9). The variance of allergenic foods may cause differences in common FA symptoms; for example, the main allergenic foods are milk and eggs in European countries, which are different from the shrimp and mango primary allergens found in this survey. Previous studies have reported that FA was the first step of “allergy march”, and could increase the risk of other allergic diseases (10). Furthermore, this survey showed that the prevalence of other allergic diseases was significantly higher in the FA group than in the non-FA group.

Avoiding allergenic foods through diet and management of acute allergic reactions with antihistamines or epinephrine is the current standard of care for those diagnosed with FA (4). Managing FA in school children requires cooperation amongst school administrators, teachers, and families. Resources for managing FA should be provided to parents, school administrators, and teachers, and they should be offered information about planning and implementing strategies for preventing and reducing allergic reactions and treating life-threatening FA reactions (11).

Further epidemiological studies on FA should be conducted in Jiangxi; prevention strategies such as comprehensive relevant food allergen labeling systems should be developed according to the epidemic characteristics of prevalent food allergens; public awareness campaigns to increase FA knowledge should be conducted to assist people in recognizing the signs and symptoms of allergic reactions, especially among high-risk groups. Early detection and comprehensive prevention and control are important to reduce the health risks associated with FA in the population.

One potential limitation of this study is that using parent/guardian reported FA without objective indicators may not accurately estimate FA prevalence; Another disadvantage is that the selected school children only came from five primary schools, which may not be representative of all school children aged 6–11 years in Nanchang. However, preliminary results need to be confirmed in further studies with accurate diagnosis of FAs to confirm the reported

epidemiological findings. The high response rate and strict quality control in this survey suggest the results reflect a problem among school children in Nanchang worthy of further investigation.

Increased doctor-diagnosed FA prevalence and tests to confirm FA such as SPT and sIgE test are ongoing. The next step will be to use DBPCFC to confirm suspected FA.

This study contributes to improving awareness of FA, filling in the gap in the epidemiological data on FA in school children. It also presents scientific evidence for updating the list of food allergens for China and developing policies for FA prevention and management in Jiangxi and other regions.

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SUPPLEMENTARY TABLE S1. Other allergic diseases prevalence and distribution among the school children with food allergy in Nanchang, Jiangxi, China in 2021.

Other allergic diseases	FA, n (%)	No FA, n (%)	χ^2	P
Allergic dermatitis	30 (20.5%)	37 (1.4%)	224.729	0.000
Allergic rhinitis	22 (15.1%)	65 (2.4%)	76.199	0.000
Allergic asthma	3 (2.1%)	6 (0.2%)	9.674	0.002
Else	6 (4.1%)	17 (0.6%)	21.282	0.000
Total	61 (41.8%)	125 (4.6%)	317.632	0.000

Abbreviation: FA=food allergy.

Preplanned Studies

Meta-Analysis: Prevalence of Food Allergy and Food Allergens — China, 2000–2021

Jiangzuo Luo¹; Qiuyu Zhang¹; Yanjun Gu¹; Junjuan Wang¹; Guirong Liu¹; Tao He¹; Huilian Che^{1,†}

Summary

What is already known about this topic?

In recent decades, the prevalence of food allergy has increased worldwide; however, a comprehensive estimate of the prevalence of food allergy and allergens in China is not yet available.

What is added by this report?

By searching the English databases PubMed, Embase, Cochrane Library, and Chinese databases CNKI, Wanfang Data, and VIP Chinese epidemiological studies on food allergy, the probability of food allergy in China and related influencing factors were determined.

What are the implications for public health practice?

The findings of this study provide up-to-date estimates of the prevalence of food allergy rates in China in terms of age, gender, and the eight major food allergens.

Food allergy is a pathological, potentially fatal, immune response induced by food protein antigens (1). In recent decades, the prevalence of food allergy has increased worldwide, but there is no comprehensive estimation of the prevalence of food allergy and food allergens in Chinese scientific literature. To evaluate the above content, we searched for Chinese epidemiological studies of food allergy in different databases. We selected 24 cross-sectional studies from 9,767 publications and extracted data for statistical analysis. Our results show that different regions, ages, gender, food types, and other factors can cause different food allergy rates. These reviews provide up-to-date estimates of the frequency of food allergy in China in general and in particular, indicating that the prevalence of specific food allergy in China is significantly different from that in the West.

The Codex Alimentarius Commission (CAC) has stipulated the food or ingredients that must be marked on the label of prepackaged food, including gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, and

nuts (2). These special food substances are often referred to as “priority food allergens” because they account for more than 90% of all food allergic reactions (3). In Asia, allergic reactions to shellfish and fish are more common than those to nuts, peanuts, and wheat (4). Most of the allergens proposed by China and other countries and regions have been modified based on the eight categories proposed by CAC, and less consideration is given to the prevalence of different food allergens in different geographical regions. Considering the different dietary habits of different countries and races, determining food allergens for the management of allergic patients is vital and can prevent extensive dietary restrictions. In this systematic review and meta-analysis, we aimed to determine the prevalence of food allergy and allergenicity of specific food allergens in the Chinese population.

We searched PubMed, EMBASE, and Cochrane Library in English and CNKI, Wanfang Data, and VIP databases in Chinese for the epidemiological studies of food allergy in China, published from January 1, 2000 to 2021. There were no limits to the type of literature and the language. Key words include allergen, allergy, hypersensitivity, China, Chinese, prevalence, and epidemiology. To select the most suitable articles and to extract the data of the selected articles, evaluation tables and data extraction tables were respectively applied. The expert committee finally evaluated the article and ruled out inappropriate articles after discussing the dispute (Supplementary Figure S1, available in <http://weekly.chinacdc.cn>).

The following data were extracted from the final selected articles: study date, region, sample size, age range, gender, result evaluation method, number of food allergy, and allergic food (Supplementary Table S1, available in <http://weekly.chinacdc.cn>). The American Health Care Quality and Research Institution scale was used to evaluate the quality of the literature. Stata State (version 15.0; Institute Stata Corp LLC. U.S.) was used for data analysis. Detailed experimental methods are in Supplementary Materials,

available in <http://weekly.chinacdc.cn>.

We selected 24 studies from 9,767 publications in this field, with data from 138,740 children and adults who met the inclusion criteria for the meta-analysis. Participants included infants, children, and adults of all ages. The combined prevalence of self-reported and hospital-diagnosed food allergy was 8% [95% confidence interval (CI): 6%–10%, $P < 0.05$] (Figure 1A). The self-reported prevalence rate of food allergy was 12% (95% CI: 8%–15%), while that of hospital-diagnosed food allergy was 5% (95% CI: 4%–7%) (Figure 1B). In addition, the prevalence of food allergy in males and females were 9% (95% CI: 5%–13%) and 10% (95% CI: 5%–15%), respectively (Figure 1C). According to the scope of sample cities, we divided them into Northeast, North China, Central China, East China, South China, and Southwest for

analysis. Owing to data limitations, no effective studies on Northeast, North, and Central China were observed (Figure 1D). The prevalence of food allergy in East China was 11% (95% CI: 6%–15%), higher than that in South China (8%; 95% CI: 4%–12%) and Southwest China (8%; 95% CI: 4%–11%). Furthermore, the prevalence of food allergy in children aged 4–17 years was the highest (10%; 95% CI: 7%–14%), followed by that in adults (7%; 95% CI: 2%–11%) and infants 6% (95% CI: 4%–8%) (Figure 1E). The results also showed that the prevalence of food allergy from 2009–2018 was 8% (95% CI: 6%–11%), higher than that in 1999–2008 (5%; 95% CI: 3%–7%) (Figure 1F), indicating that the prevalence of food allergy in China is on the rise.

The proportion of different types of food allergies to the total number of patients with food allergies in

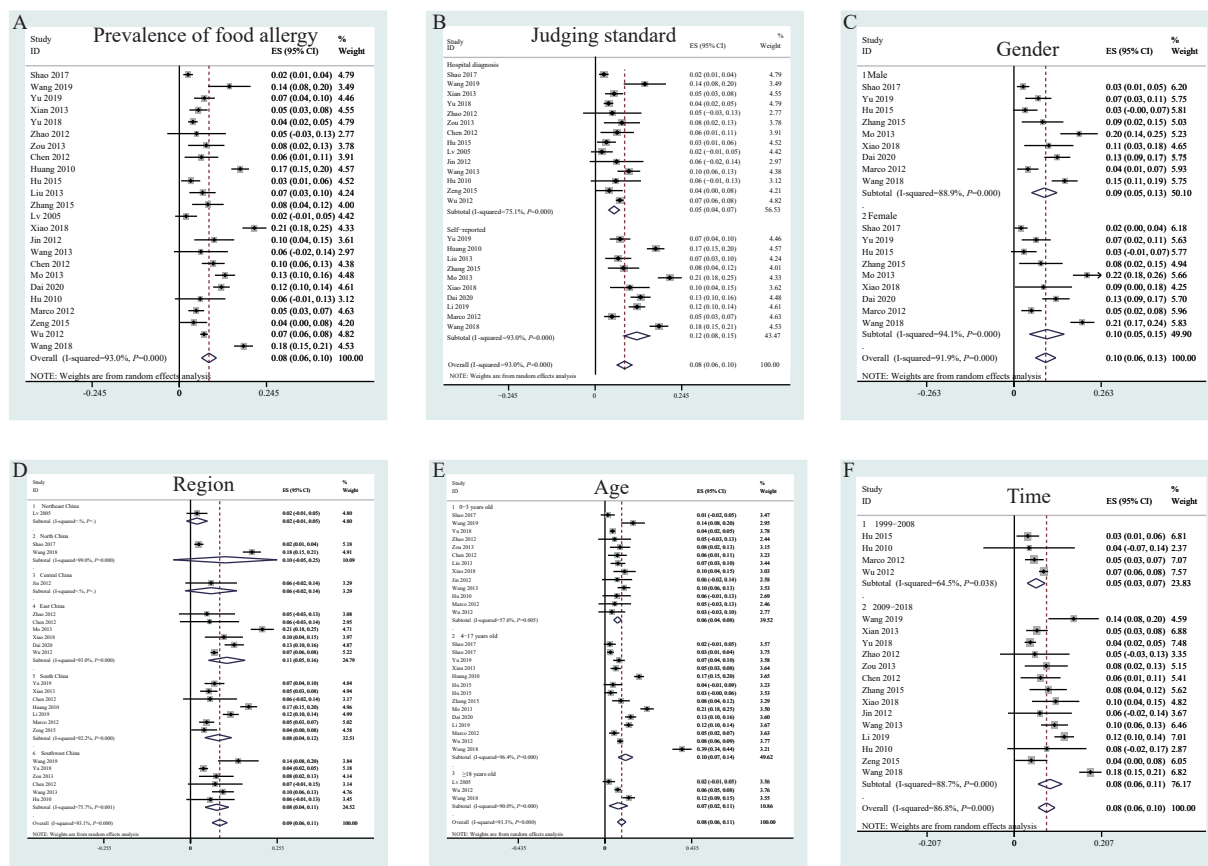


FIGURE 1. Prevalence of food allergy in Chinese. (A) Overall prevalence of food allergy. (B) The difference between the prevalence of self-report (questionnaire survey) and hospital confirmed food allergy. (C) Prevalence of food allergy in male and female. (D) Prevalence of food allergy in different regions. (E) Prevalence of food allergy in different ages. (F) Prevalence of food allergy in different time periods.

Note: In the figure, group 1 represents questionnaire survey, and group 2 represents hospital diagnosis. Diagnosis methods include SPT, sIgE, FE, ET, OFC, or clinical history of hospital diagnosis.

Abbreviation: SPT=skin prick test; sIgE=serum-specific immunoglobulin E; FE=food elimination test; ET=Allergic patients Exclusion Diet Test; OFC=Open Food Challenge; ES=effect size; CI=confidence interval.

China was measured. A total of 22% of the patients have cow's milk allergy (Figure 2A). Furthermore, 0–3 year old infants were more likely to be allergic to milk than to all kinds of food allergens (95% CI: 18%–41%) (Figure 2B). In addition, 27% (95% CI: 22%–31%) of the patients have egg allergy (Figure 2C). Infants were more likely to be allergic to eggs than children (Figure 2D). Fish allergy was observed in 15% (95% CI: 10%–20%) of the total patients with food allergy (Figure 2E), while shrimp allergy was observed in 16% (95% CI: 3%–30%) of the patients (Figure 2F). Crab allergy accounted for 27% (95% CI: 12%–41%) (Figure 2G), while shellfish allergies accounted for 19% (95% CI: 6%–32%) (Figure 2H). A total of 16% (95% CI: 11%–21%) of the patients have fruit allergies (Figure 3A). Contrary

to egg and milk allergies, fruit allergies were more common in children than in infants (Figure 3B). Specifically, we extracted the data for mango allergy, the most studied allergic fruit. The proportion of patients with mango allergy was 15% (95% CI: 9%–22%) (Figure 3C). Furthermore, patients with meat allergies accounted for 5% (95% CI: 3%–8%) (Figure 3D). Patients with peanut allergies accounted for 4% (95% CI: 2%–7%) of the total food allergy patients (Figure 3E), while those with nut allergies accounted for 2% (95% CI: 2%–3%) (Figure 3F). Soybean allergies were observed in 3% (95% CI: 2%–4%) of the patients (Figure 3G), whereas wheat allergies were observed in 1% (95% CI: 1%–2%) of the patients (Figure 3H).

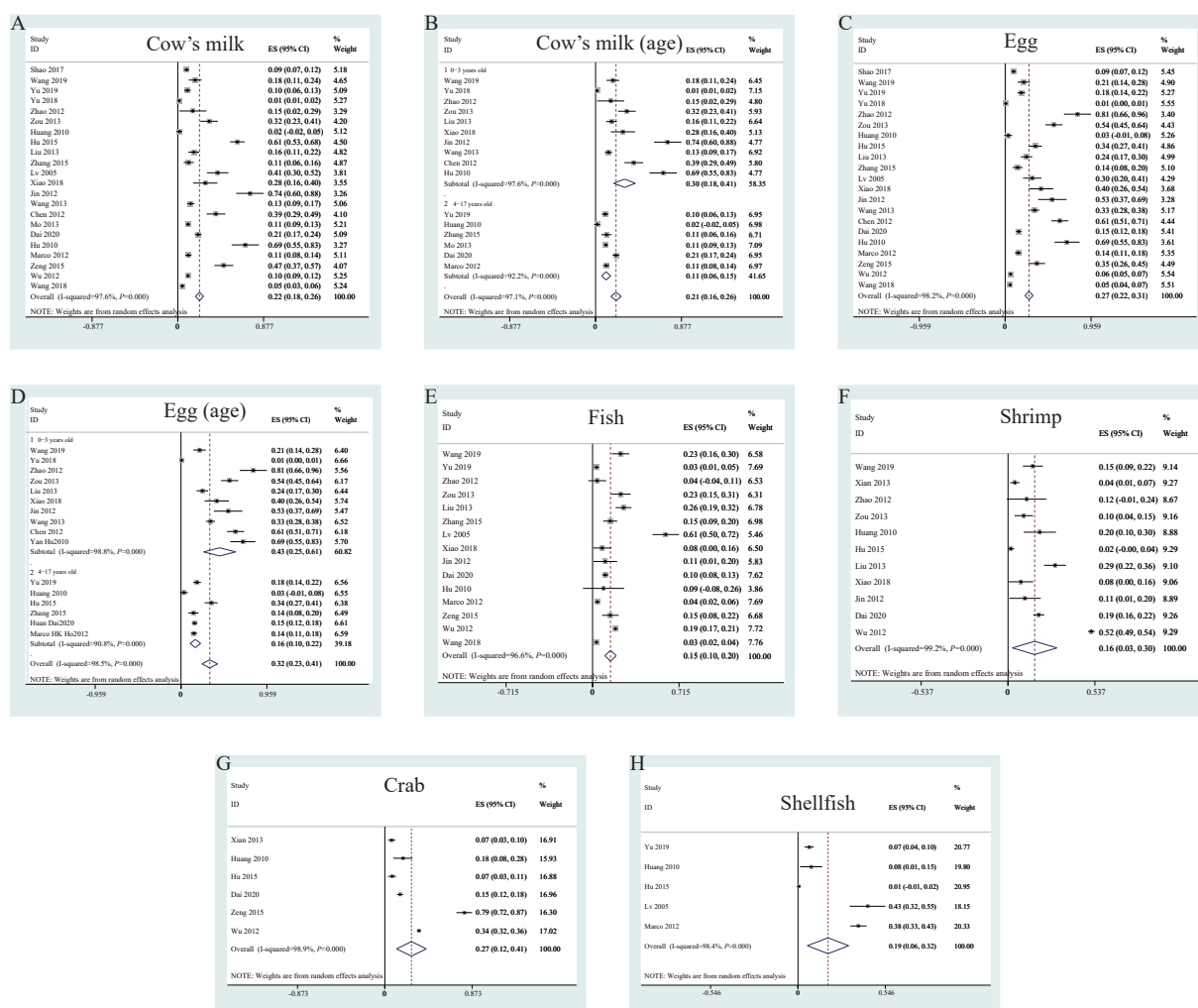


FIGURE 2. Prevalence of milk, egg, and aquatic product allergy in patients with food allergy. (A) Cow's milk. (B) Different ages of cow's milk allergy patients. (C) Egg. (D) Egg allergy rates in different age groups. (E) Fish. (F) Shrimp. (G) Crab. (H) Shellfish.

Abbreviation: ES=effect size; CI=confidence interval.

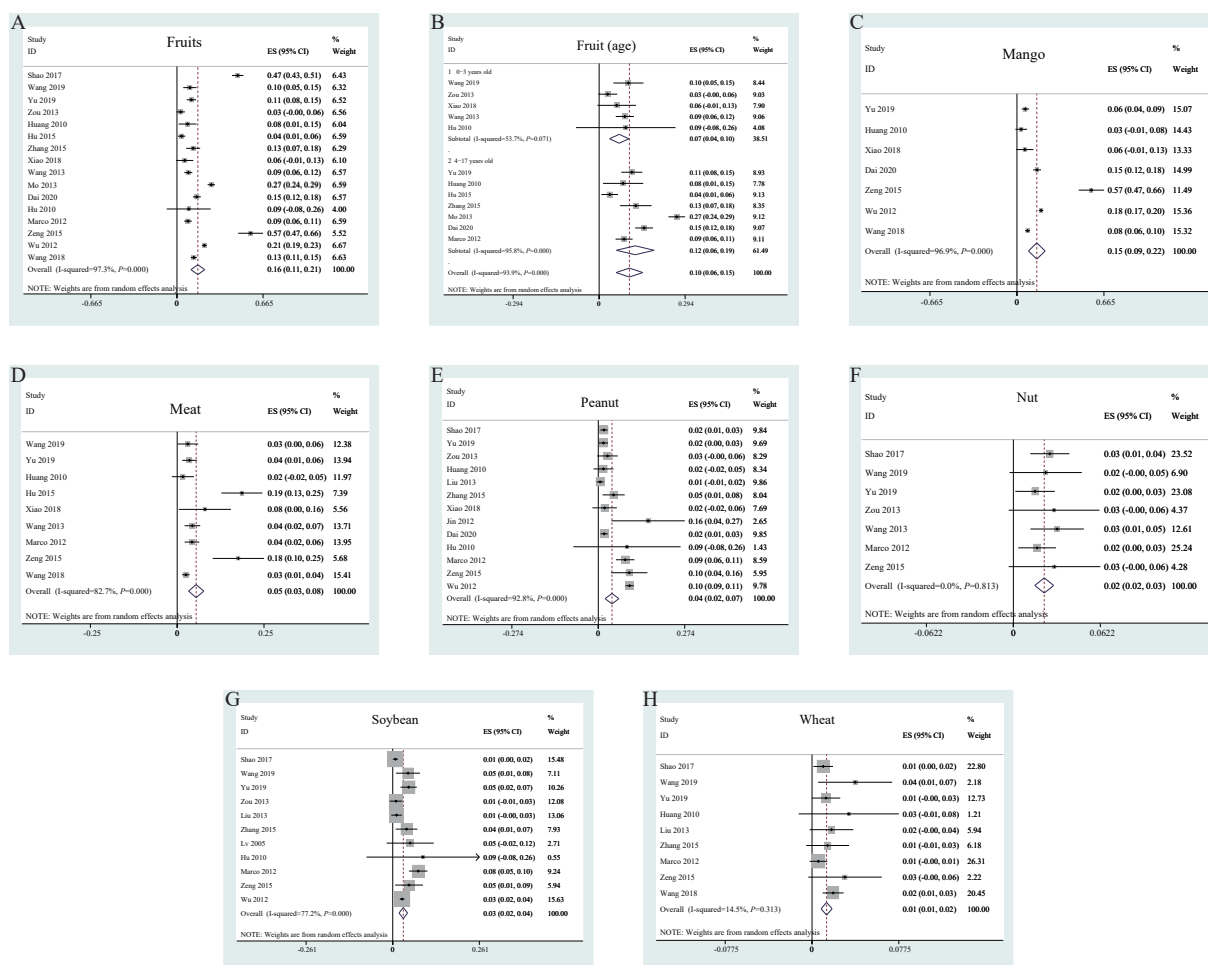


FIGURE 3. Prevalence of fruit, meat, peanut, nut, soybean, and wheat allergy in patients with food allergy. (A) Fruits, including mangoes, peaches, pineapples, oranges, dates, apples, cherries, tomatoes, kiwifruit, and other. (B) Different ages of fruit allergy patients. (C) Mango. (D) Meat, including beef, mutton, chicken. (E) Peanut. (F) Nut. (G) Soybean. (H) Wheat. Abbreviation: ES=effect size; CI=confidence interval.

DISCUSSION

In our survey, milk allergy was found to be one of the most important food allergens for infant food allergies. In the study of Chen et al., milk is the main allergen of children under two years old, and children with milk allergy will exhibit “milk refusal” and other manifestations in the process of OFC (5). Although milk allergy is more common in children, it does not mean that there are no milk allergy in adults. In a study in Taiwan, China, 7.5% of the people over 19 years old with food allergy still had milk allergy (6). In our study, egg allergy accounted for 27% of the total food allergy patients.

According to CAC, fish and crustaceans are two of the eight allergens in aquatic products. In western countries, allergy to crab aquatic products is more common in crab processing workers who are sensitized by inhalation (7). In China, a large number of aquatic

product allergies have been reported in infants under one year old. Studies have shown that up to 42.3% of children with food allergy are allergic to aquatic products (8). Compared with eggs, milk, peanuts, and other allergic foods, fruit allergy is not common in the West, and no fruits are classified as allergens requiring identification by CAC. In our study, fruit allergy accounted for 16% of the total food allergies patients. In our study, the proportion of mango allergy patients of the total food allergy patients was 15%, which was much higher than that of common western allergens such as peanuts and nuts. In our study, meat allergy patients accounted for 5% of the total food allergy patients, mainly beef allergy patients. Although the prevalence of meat allergy is not high, there are great differences among the studies included in this paper. These differences may be due to different criteria for determining food allergy, or to different meat ranges defined in different studies. Studies have shown that

Asian children have relatively low rates of allergy to peanuts and nuts (9), which is confirmed by our study. In our study, peanut and nut allergies accounted for 4% and 2% of the total food allergy patients, respectively. Soybean is considered to be one of the eight most important food allergens. Population based meta-analysis of European countries showed that the prevalence of soybean allergy was 0.4% (10). In our study, soybean allergy patients accounted for 3% of the total food allergy patients.

This study was subject to some limitations. In order to accurately calculate the prevalence of food allergy in the general population of China, this paper only includes community-based studies, excluding hospital-based studies, limiting the statistical analysis of specific food allergens, and lacking the statistics of the prevalence of specific food allergy in allergic diseases.

This study shows that different regions, ages, gender, food types, and other factors can cause different food allergy rates. This study provides some reference information for dealing with food allergy symptoms caused by different influencing factors and provides reference for formulating relevant food allergy prevention policies.

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SUPPLEMENTARY MATERIAL

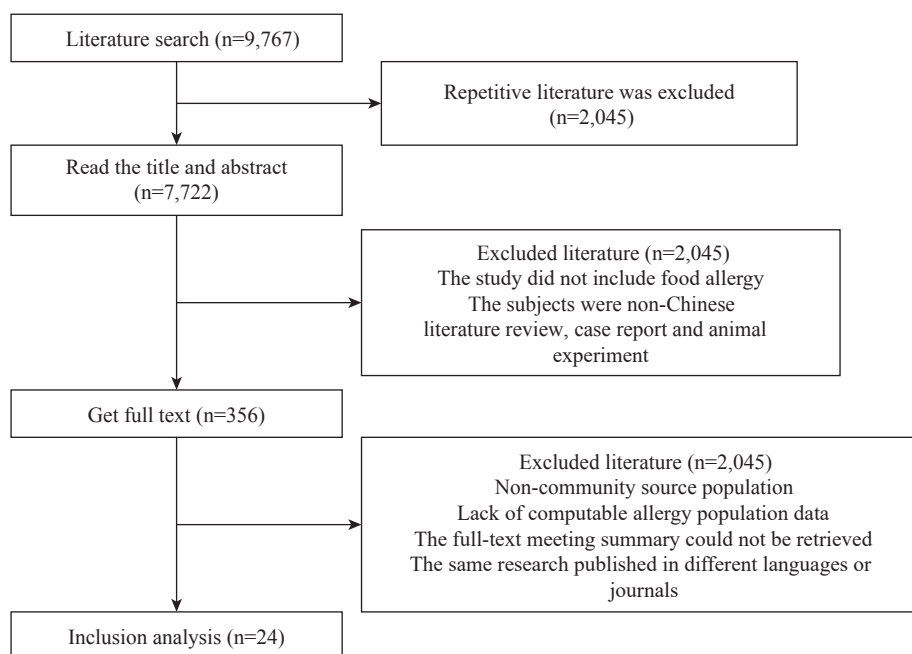
Search Strategy and Research Selection

We searched PubMed, EMBASE, and Cochrane Library in English and CNKI, Wanfang Data, and VIP databases in Chinese for the epidemiological studies of food allergies in China, published from January 1, 2000, to January 1, 2021. There was no limit to the type of literature and the language. Key words include the following: allergen, allergy, hypersensitivity, China, Chinese, prevalence, and epidemiology.

Inclusion criteria: 1) The subjects of the study were Chinese people, and the source was the community; 2) study diseases included food allergies; and 3) included computable data for people with specific allergens. Exclusion criteria: 1) The study population was from hospitals; 2) literature review, case report, and animal experiment; and 3) the research topic was the prevention and treatment of food allergies. For meeting abstracts or other items that do not have full text, we used the author's name and/or title word combination to search for relevant full-text articles. We included self-reported data (participants or their parents reported whether they had any food allergies), skin prick test (SPT) positive, serum-specific immunoglobulin E (sIgE) positive, food elimination test (FE) positive, allergic patients with positive exclusion diet test (ET), open food challenge (OFC) positive, or clinical history of hospital diagnosis. In addition, we also reviewed the reference list of related articles to increase sensitivity and reduce missing articles. We only keep one of the different documents published in the same population sample research. The literature was screened independently by two researchers at the same time, and when there was a disagreement on the inclusion and exclusion of the literature, it was discussed and a third party made a ruling (Supplementary Figure S1).

Data Extraction

Before data extraction, members of the research group jointly developed excel tables suitable for data extraction, which were independently carried out by two researchers at the same time. The following data were extracted from the final selected articles: study date, region, sample size, age range, gender, result evaluation method, number of food allergies, and allergic food (Supplementary Table S1).



SUPPLEMENTARY FIGURE S1. Flow chart of literature retrieval and screening.

SUPPLEMENTARY TABLE S1. Summary of research features.

Author	PLADs/Cities	No. of participants	No. of participants with food allergies
Shao, 2017 (1)	Beijing	20,186	499
Wang, 2019 (2)	Chengdu	923	130
Yu, 2019 (3)	Foshan	4,166	294
Xian, 2013 (4)	Guangzhou	5,542	298
Yu, 2018 (5)	Qiannan Prefecture, Guizhou	19,787	751
Zhao, 2012 (6)	Hangzhou	536	26
Zou, 2013 (7)	Panzhihua	1,359	103
Chen, 2012 (8)	Chongqing, Zhuhai, Hangzhou	1,604	100
Huang, 2012 (9)	Shaoguan	5,139	880
Hu, 2015 (10)	Beijing, Shanghai, Chongqing, and other 26 places	5,190	166
Liu, 2013 (11)	Beijing, Suzhou, Guangzhou, and other 8 cities	2,632	172
Zhang, 2015 (12)	Beijing, Suzhou, Guangzhou, and other 8 cities and rural areas	1,792	144
Lv, 2005 (13)	Liaoning	3,974	76
Mo, 2013 (14)	Shanghai	2,626	555
Xiao, 2018 (15)	Shanghai	1,100	108
Jin, 2012 (16)	Wuhan	626	38
Wang, 2013 (17)	Yunnan, Guizhou, Sichuan	3,344	319
Dai, 2020 (18)	Wenzhou	4,151	534
Li, 2019 (19)	Hong Kong SAR	6,194	734
Hu, 2017 (20)	Chongqing	715	42
Marco, 2012 (21)	Hong Kong SAR	7,393	352
Zeng, 2015 (22)	Guangdong	2,540	102
Wu, 2012 (23)	Taiwan, China	30,018	2,086
Wang, 2018 (24)	Inner Mongolia	4,441	802

Abbreviation: PLAD=provincial-level administrative division; SAR=special administrative region.

Literature Quality Assessment

The American Health Care Quality and Research Institution scale was used to evaluate the quality of the literature. The scale consists of eleven questions: 1) define the source of information (survey, record review); 2) list inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; 3) indicate time period used for identifying patients; 4) indicate whether or not subjects were consecutive if not population-based; 5) indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; 6) describe any assessments undertaken for quality assurance purposes (e.g. test/retest of primary outcome measurements); 7) explain any patient exclusions from analysis; 8) describe how confounding was assessed and/or controlled; 9) if applicable, explain how missing data were handled in the analysis; 10) summarize patient response rates and completeness of data collection; 11) clarify what follow-up, if any, was expected and the percentage of patients for whom incomplete data or follow-up was obtained. After evaluation, all the literatures were of medium quality.

Statistical Analysis

Stata State (version 15.0; Institute Stata Corp LLC. U.S.) was used for data analysis. Heterogeneity between studies was determined using I^2 and analyzed using the χ^2 test. Significance was set at $P < 0.05$. When $I^2 < 50\%$, the fixed-effect model was used in the meta-analysis; otherwise, the random-effects model was used.

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Perspectives

Risk Assessment of Food Allergens

Hongbing Chen^{1,2}; Yongning Wu^{3,#}

GLOBAL STRATEGIES FOR RISK ASSESSMENT OF FOOD ALLERGENS

Held on the 8th of July every year, World Allergy Day is a global joint initiative launched by the World Health Organization (WHO) and the World Allergy Organization (WAO) as well as other national allergy agencies, which aims to raise the general public awareness of the importance of managing and preventing allergic diseases. Food allergies are a major source of exposure to allergens and a significant public health problem globally with increasing prevalence (1). Importantly, there is currently no effective cure for food allergies and the only strategy for preventing food allergic reactions is to practice a strict avoidance diet. Notably, implementation and adherence to a diet that is free of allergenic foods is challenging because a consumer may be allergic to more than one food or food ingredient and must face a wide variety of food

choices in daily life. Therefore, the labeling of allergenic foods and food ingredients on pre-packaged foods can play a critical role in protecting food-allergic individuals. Based on the recommendations of an expert consultation convened by WHO and the Food and Agriculture Organization of the United Nations (FAO), the labeling of the eight most common allergenic foods (commonly known as the “Big Eight”) was incorporated into the Codex General Standard for the Labeling of Packaged Foods (GSLPF) in 1999 (2). Subsequently, member countries of the Codex Alimentarius Commission developed their own national lists for labeling of allergens in pre-packaged food based on the Codex list and on evidence of allergenicity of other foods and food ingredients (Figure 1).

Since the original drafting of the GSLPF, scientific understanding of food allergens and their management have evolved. In response, Codex requested the WHO/FAO to provide updated advice, and a series of

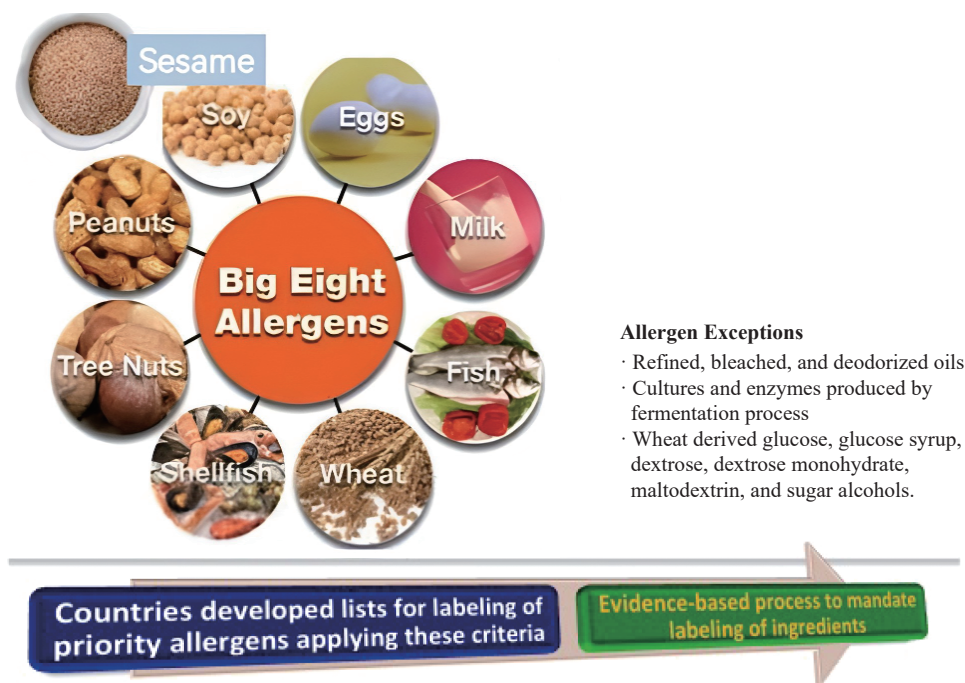


FIGURE 1. The eight most common food allergens (i.e., “Big Eight” or “Big 8”) in the Codex with evidence-based process to mandate labeling of ingredients.

meetings of the Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens were held during 2020 and 2022 (2).

The establishment of priority allergenic foods recommended by the Expert Consultation was based on three criteria: 1) prevalence (e.g., the proportion of a defined population known to have experienced an immune-mediated adverse reaction to the specific food); 2) potency (e.g., the amount of the total proteins from the food/ingredient required to cause objective symptoms in a specified proportion of the population allergic to that specific food); and 3) severity (e.g., frequency or proportion of severe objective reactions to a food/ingredient, such as anaphylaxis). After a systematic and thorough assessment based on these three criteria, the Expert Consultation recommended the following allergenic foods should be listed as priority allergens in the GSLPF:

- cereals containing gluten
- crustacean shellfish
- eggs
- fish
- milk
- peanuts
- sesame

• specific tree nuts (hazelnut, walnut, pecan, cashew, pistachio, and almond).

It is worth noting that soybeans have been excluded from the list of global priority allergens, which has been replaced by sesame as a new member among the “Big Eight”. In addition, some potential allergens, such as buckwheat, mustard, soybean, lupin, Brazil nut, oat, molluscan shellfish, and others may still be considered for inclusion in priority allergen lists in individual countries or regions (Figure 2).

PRACTICAL ACTIONS FOR RISK ASSESSMENT OF FOOD ALLERGENS IN CHINA

China has gradually established a research framework for risk assessment of food allergens. Research efforts have included work on the three key criteria of food allergy needed to implement a risk assessment framework — namely, prevalence, potency, and severity. Regarding food allergy epidemiology, more than 60 articles on the prevalence of food allergy in China have been published since 1996. These epidemiological studies were geographically distributed, including Beijing, Shanghai, Hangzhou,

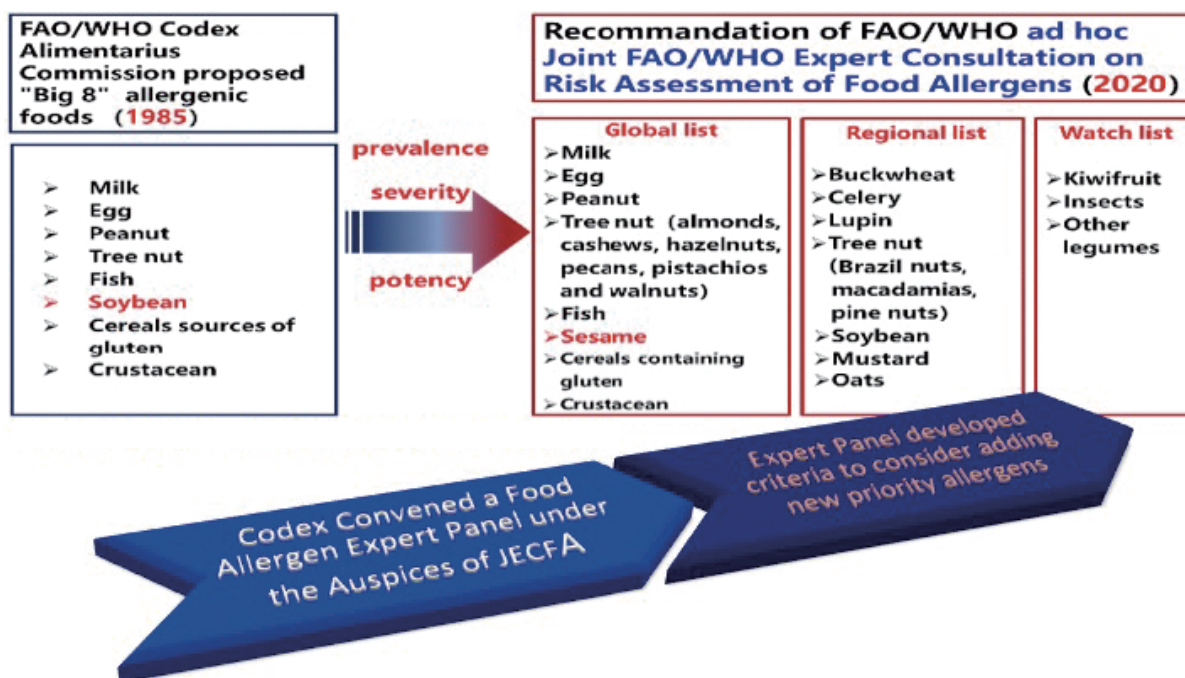


FIGURE 2. The list of global priority allergens by ad hoc Joint FAO/WHO expert consultation on risk assessment of food allergens: sesame has replaced soybeans as a new member among “Big Eight”.

Abbreviation: FAO=Food and Agricultural Organization of the United Nations; WHO=World Health Organization; WAO=World Allergy Organization; JECFA=FAO/WHO Joint Expert Committee on Food Additives.

Guangzhou, Shenzhen, Wenzhou, Chongqing, and other cities. Interestingly, research on the prevalence of celiac autoimmunity disease (0.36%; 95% CI: 0.28%–0.46%) was first reported in the general Chinese youth population (3). This was followed by a report on the prevalence of celiac disease (0.35%; 95% CI: 0.11%–0.59%) in Xinjiang Uyghur Autonomous Region (4). To evaluate the allergenic potency of specific allergenic foods among the Chinese population, oral food challenge testing (OFC) is essential. Thankfully, ten tertiary grade A hospitals have established a base for conducting OFC in China. Peking Union Medical College Hospital was the first to release a ranking of the causes of food-related anaphylaxis among Chinese people and validated that there were significant regional differences in the causes of anaphylaxis (5). This clinical research will also help to fill a void of information on the severity of food allergy in China (5). Furthermore, the Chinese government has financed special projects, including the National Key Basic Research Program (“973” Program), the National High Technology Research and Development Program (“863” Program) and the National Science and Technology Supporting Program to support scientific research on the risk assessment of food allergens, leading to the formulation of more than 20 national standards. Meanwhile, many national and international conferences on food allergy were held in China during the past 5 years, which strengthened multidisciplinary collaboration, innovation and academic exchange in food science, basic immunology, clinical medicine, public health nutrition and sociology.

Although China has carried out some relevant research on risk assessment of allergenic foods, certain limitations still remain. Most studies on the prevalence of food allergy were restricted to specific regions, and high-quality data on prevalence were limited, in part, due to the lack of a uniform diagnostic protocol based on OFC using well-defined food challenge materials. The determination of the threshold doses for specific allergenic foods among Chinese food-allergic individuals has not been conducted and presents clinical challenges in China. Furthermore, allergen risk assessment also requires detailed information on eating patterns of Chinese consumers and sub-groups of those consumers. There are no specific dietary surveys based on consumers with food allergy in China even though total diet databases were established for dietary exposure assessment purposes. Under the circumstances, a list of priority allergenic foods based

upon the actual situation of the Chinese population is not currently available. Accordingly, the relevant provisions on allergenic food labeling in China’s General Rules for the Labeling of Pre-Packaged Foods (GB 7718) were basically the same as the corresponding Codex provisions.

FUTURE STRATEGIES FOR RISK ASSESSMENT OF FOOD ALLERGENS IN CHINA

Risk assessment techniques provide a scientific basis for governments to make scientifically sound regulatory decisions, for companies to set appropriate safety standards, and for populations to make safe consumption choices. Regarding risk assessment of food allergens, regulators need to consider the current quality assurance practices of food companies and balance those practices against the desired level of protection of allergic populations. Companies are concerned with the products they produce in light of “farm-to-table” safety assurance and the need to prevent/minimize cross and carry-over contamination of allergens during the transportation of raw materials, product processing, and packaging and to assess the risk of their products according to safety limits. Ultimately, food allergy risk assessment is about safeguarding food safety for consumers.

The future scientific development of food allergen risk assessment in China must address several different aspects of the current situation. The first step is to carry out a nationwide epidemiological survey on the prevalence and incidence of food allergy to understand the existing level of risk faced by food-allergic Chinese consumers. This survey should lead to knowledge of the most common allergenic foods in China and a realistic gauge of the severity of food allergic reactions that happen within China. The survey should focus on the risk factors for food-allergic reactions within the Chinese population and determine which of those factors can be better controlled with improved and targeted interventions.

Moreover, based on the best practice for food allergy diagnosis, a double-blind placebo-controlled food challenge trial in multi-center hospitals should be conducted to establish individual and population thresholds, and further quantitative risk assessment should be carried out based on the thresholds of the major allergens. The monitoring of individual clinical symptoms should be strengthened and the severity of

allergic reactions at various doses used in the clinical challenges could be recorded. That clinical data can then be compared to the symptoms reported by food-allergic consumers to better assess the nature of the symptoms occurring within the community versus the doses administered in the clinical challenges. Based on the epidemiology of food allergies, allergen thresholds and severity of allergic reactions in the Chinese population, the decisions on what and how to label food allergens in China will be effectively addressed based on sound clinical and scientific information, providing benefits to relevant stakeholders.

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