

Journal Pre-proof

Comparative study of food allergies in children from China, India and Russia: The EuroPrevall-INCO surveys

Jing Li, MD, Ludmila M. Ogorodova, MD, Padukudru Anand Mahesh, MD, Maggie Haitian Wang, PhD, Olga Sergeevna Fedorova, MD PhD, Ting Fan Leung, MD, Montserrat Fernandez-Rivas, MD, EN Clare Mills, PhD, James Potts, PhD, Ischa Kummeling, PhD, Serge A. Versteeg, PhD, Ronald van Ree, MD, Maria Yazdanbakhsh, PhD, Peter GJ. Burney, MD, Gary WK. Wong, MD, FRCPC



PII: S2213-2198(19)31032-3

DOI: <https://doi.org/10.1016/j.jaip.2019.11.042>

Reference: JAIP 2596

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 29 April 2019

Revised Date: 30 October 2019

Accepted Date: 21 November 2019

Please cite this article as: Li J, Ogorodova LM, Mahesh PA, Wang MH, Fedorova OS, Leung TF, Fernandez-Rivas M, Mills EC, Potts J, Kummeling I, Versteeg SA, van Ree R, Yazdanbakhsh M, Burney PG, Wong GW, Comparative study of food allergies in children from China, India and Russia: The EuroPrevall-INCO surveys, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2019.11.042>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Comparative study of food allergies in children from China, India and Russia: The EuroPrevall-INCO surveys

Jing Li MD,^{a*} Ludmila M. Ogorodova MD,^{b*} Padukudru Anand Mahesh MD,^{c*} Maggie Haitian Wang PhD,^d Olga Sergeevna Fedorova MD PhD,^b Ting Fan Leung MD,^e Montserrat Fernandez-Rivas MD,^f EN Clare Mills PhD,^g James Potts PhD,^h Ischa Kummeling PhD,ⁱ Serge A. Versteeg PhD,ⁱ Ronald van Ree MD,^{ij} Maria Yazdanbakhsh PhD,^k Peter GJ Burney MD,^h Gary WK Wong MD, FRCPC^e

a. Department of Allergy and Clinical Immunology, State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

b. Department of Pediatrics, Siberian State Medical University, Tomsk, Russia

c. Department of TB and Respiratory Medicine, JSS Medical College, JSS University and Allergy Asthma Associates, Mysore, India

d. School of Public Health, Chinese University of Hong Kong, Shatin, NT, Hong Kong

e. Department of Pediatrics, Chinese University of Hong Kong, Hong Kong, China

f. Allergy Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

g. School of Translational Medicine, Manchester Academic Health Science Centre and Manchester Interdisciplinary Biocentre, The University of Manchester, UK

- h. Department of Respiratory Epidemiology and Public Health, National Heart and Lung Institute, Imperial College London, SW3 6LR, London, UK
- i. Department of Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands
- j. Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, The Netherlands
- k. Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands

Key words: children, food allergy, EuroPrevall, comparison, China, India, Russia.

***Drs Li, Ogorodova, and Mahesh contributed equally to this article.**

Conflicts of interest

We declare that we have no conflicts of interest.

Correspondence:

Gary WK Wong, Lui Che Woo Clinical Sciences Building, Department of Pediatrics, Prince of Wales Hospital, Faculty of Medicine, Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, China

Phone: +852 35052981

Fax: +852 26451570

Email; wingkinwong@cuhk.edu.hk

ABSTRACT

BACKGROUND: A clear understanding of the differences of the epidemiology of food allergy between rural and urban populations may provide insights to the causes of increasing prevalence of food allergy in the developed world.

OBJECTIVE: We used a standardized methodology to determine the prevalence and types of food specific allergic sensitisation and food allergies in schoolchildren from urban and rural regions of China, Russia, and India.

METHODS: The current study is a multicentre epidemiological survey of children recruited from five cities in China (Hong Kong, Guangzhou), Russia (Tomsk), India (Bangalore, Mysore), and one rural county in Southern China (Shaoguan). A total of 35,549 children aged 6 to 11 years from three countries participated in this survey. Random samples of children from three countries were first screened by the Europrevall screening questionnaire. Children with and without history of adverse reactions to foods were then recruited for the subsequent case-control comparative studies. We determined the prevalence rates of food specific IgE sensitization and food allergies using the pre-defined criteria.

RESULTS: The prevalence rates of food-specific IgE sensitisation (≥ 0.7 kU/L) to at least one food were 16.6% in Hong Kong, 7.0% in Guangzhou, 16.8% in rural Shaoguan, 8.0% in Tomsk, and 19.1% in India. Using a definition of probable food allergy as reporting allergic symptoms within 2 hours of ingestion of a specific food plus the presence of allergic sensitization to the specific food (positive IgE and/or positive skin-prick-test), the prevalence of food allergy was highest in Hong Kong (1.50%), intermediate in Russia

(0.87%), lowest in Guangzhou (0.21%), Shaoguan (0.69%) and India (0.14%). For children recruited from Hong Kong, both sensitization and food allergy were significantly higher in children who were born and raised in Hong Kong when compared to those who were born in mainland China and migrated to Hong Kong highlighting the importance of early life exposures in affecting the subsequent development of food sensitization and food allergy.

CONCLUSIONS: There are wide variations in the prevalence of food specific IgE sensitization and food allergy in the three participating countries. Food allergy appears to be less common when compared to developed countries. The variations of the prevalence of food allergen sensitization cannot be explained by the differences in the degree of urbanization. Despite the high prevalence of food-specific IgE sensitization in India and rural China, food allergy is still extremely uncommon. In addition to IgE sensitization, other factors must play important roles resulting in the clinical manifestations of food allergies.

Key words: Food allergy, children, epidemiology, China, Russia, India, rural population

What is already known about this topic?

IgE mediated food allergy and food induced anaphylaxis have been found to be increasing in developed countries. Very little is known regarding the prevalence of food allergies in developing countries.

What does this article add to our knowledge?

Our study is the first comparative study to evaluate food allergies in India, China and Russia. The protection observed in migrants from mainland China to Hong Kong highlighted the important role of early environmental exposures.

How does this study impact current management guidelines?

Most children with food allergen IgE sensitization in rural areas do not have symptoms of food allergy. Additional evaluations are important for diagnosing allergies in the small fraction of rural children with food allergy.

Abbreviations used

95% CI: 95% confidence intervals

IgE: Immunoglobulin E

SPT: Skin-prick test

86
87
88
89 Food allergy has become a major worldwide problem affecting a large proportion of
90 children and adults especially those in developed countries, and food allergy is one of the
91 most common causes of anaphylaxis. There is evidence of an increase in the prevalence of
92 food allergy in the last two decades (1-4). However, food allergy has been perceived to be
93 less common in developing countries (5). The exact pathophysiology of food allergy
94 remains poorly understood and currently the cornerstone of the management for this
95 potentially fatal condition is still avoidance of the relevant foods and the use of rescue
96 medication for an accidental exposure. The rise of the prevalence of peanut allergy has
97 been alarming and we are beginning to understand the possible underlying reasons for such
98 increase (6). Recent data from the United States, United Kingdom and Australia
99 documented an increasing trend of food induced anaphylaxis-related hospitalization (7-9).
100 Epidemiological studies in the US revealed that up to 8% of children and adolescents
101 suffered from food allergy (10). Although there are many published reports of food allergy

from the western world, it has been difficult to accurately determine the prevalence because of the lack of objective measures in many of these studies (11,12). The European Union funded the multidisciplinary Integrated Project, EuroPrevall, aiming to evaluate the prevalence, basis and costs of food allergy in different European countries using the same standardized and validated methodology (12).

Despite many studies in North America, Europe and other developed countries, the exact determinants of food allergy are still largely unknown. Similar to other atopic conditions such as allergic rhinitis and asthma, food allergy appears to be relatively less common in developing or underdeveloped countries (13-16). Comparative studies of Chinese children from different environments revealed a wide variation of prevalence of asthma, and differences in environmental exposures may explain such disparity found in children with similar genetic background (17). Therefore, careful comparative studies of children from these communities and those from western countries may reveal possible causal factors responsible for the higher prevalence in the West. The EuroPrevall project was extended to study food allergies in urban and rural China, India, and Russia, countries that are emerging economies where rapid urbanization and changes of lifestyle are taking place (18).

Although there have been many epidemiology studies of food allergy around the world, the use of non-standardized methodology and the lack of objective assessments in the studies made it difficult to compare the results. Data from the European Community Respiratory Health Survey (ECRHS) (19) revealed that 12% of the population reported

adverse reactions caused by eating certain foods (20), with the lowest rate of 4.6% in Spain to the highest of 19.1% in Melbourne, Australia. In the current study, the combined population of the three participating countries, namely China, India and Russia, represents about 40% of the world population. Yet, there have been very few epidemiology studies of food allergies in these countries (13, 21-22). The limited evidence available suggested that the prevalence of food allergy might be very low and some of the common food allergens are different from those in developed countries (13-16). In the past two decades, many studies from around the world have confirmed that children from rural areas have much lower prevalence of asthma and related atopic conditions (23-26). Many factors in the rural environment including microbial exposure and dietary factors may exert epigenetic effects thereby modulating the immature immune system in early life (27-28). Careful studies in rural regions may help to understand the possible driving force behind the rise of food allergy in urban environment.

The current study aims to determine the prevalence of food allergies, and the distribution of food sensitization using standardized EuroPrevall protocol in random samples of primary school children aged 7-10 years recruited from urban and rural regions of China, Russia, and India. Given the transient nature of food allergy in a large proportion of younger children and the difficulty of performing multiple SPT and blood taking in preschool children, school age children were chosen for this large-scale comparative study. The results can be used to compare with data collected by the same standardized protocol in children recruited from different regions of Europe. This set of data will also form the baseline dataset for monitoring the trend of food allergies in these three countries.

METHODS

Study design and data collection

The EuroPrevall-INCO survey was a multi-center, cross-sectional study in random samples of children from the general populations with a nested case-control design conducted in China, India, and Russia. The studies were performed between September 2009 and June 2016. The details of the study methodology including sampling strategies, skin-prick test (SPT), serum IgE analyses, and sample size calculation have been published previously (18). The sample sizes were estimated based on pilot studies from China and estimation of prevalence of food allergies in urban and rural centres of the participating countries (18). In brief, primary school children from grade 2 to grade 5 (aged 7-10 years) were screened for the presence of adverse reactions to foods by a standardized screening questionnaire. The EuroPrevall questionnaires were developed based on relevant pre-existing questionnaires (19), and the questions inquired about possible adverse reactions to specific food and obtained information related to possible risk factors for food allergy. The screening and case-control questionnaires are included as online repository text.

To estimate the prevalence of food allergies among children from the three participating countries, a multi-staged approach was used and we concentrated on IgE-mediated allergies to a panel of foods most commonly reported to result in Type I allergic reactions. Objective assessments of sensitization by skin prick test (SPT) or measurement

of serum specific immunoglobulin E (IgE) were performed. A total of 25 EuroPrevall priority foods were assessed in the three countries (29). These foods were hen's egg, cow's milk, peanut, soy, hazelnut, walnut, celery, kiwi, apple, peach, sesame, mustard, wheat, fish, shrimp, buckwheat, corn, carrot, rice, tomato, melon, banana, lentils, sunflower seeds and poppy seeds. In addition, foods perceived to be of local importance were also included for assessment with SPT and/or IgE measurements. These were mango (IgE and SPT) and crab (IgE and SPT) for China, jackfruit (SPT only), eggplant (SPT only), orange (SPT only) and chickpea (SPT) for India, and carrot (SPT) for Russia. Random samples of school children were recruited from Hong Kong, Guangzhou (urban), Shaoguan (rural), Tomsk (Russia), and the two Indian cities of Mysore and Bangalore. Guangzhou is one of the largest metropolitan cities with a population of 15 million located in Southern China approximately 200 kilometers north-west of Hong Kong and Shaoguan is a rural area involved mostly in agricultural farming located 240 kilometers north-east of Guangzhou. Two cities in Karnataka State, South India took part in this study. Bangalore, the capital of Karnataka State, is a metropolitan city with a population of 8.5 million. Mysore is a smaller city of Karnataka state with a population of 0.9 million. It is 140 kilometers south-west of Bangalore and the population retains a traditional lifestyle including habits of food consumption when compared with people in Bangalore. Tomsk Oblast is located at the Western Siberia - middle part of the Russian Federation with the total number of the population around 1 million. The capital of Tomsk Oblast comprises the territory of 294.6 sq. km on the River Tom, a confluent of Ob, and the weather is typical of the region of Siberia with very low temperature in the winter.

All recruited subjects were first screened by a standardized one-page questionnaire. Subsequently, a case-control sample was recruited for completion of a face-to-face questionnaire, skin-prick test (SPT), and blood collection for serum specific IgE measurement. Those who reported adverse reactions to food in the screening stage would be considered as 'cases' while those without reported adverse reaction to food were 'controls'. The questionnaire used in the second stage included questions on potential risks and exposures as well as symptoms of other allergic conditions such as asthma, allergic rhinitis, and eczema along with a detailed enquiry of the timing and symptoms of the possible reactions to the suspected foods and how the foods were processed. Ethical approval was given by the ethical review board of the Chinese University of Hong Kong and all relevant ethical review boards in other participating centers.

Objective measures of sensitization

Standardized allergen extracts and control solutions were obtained from ALK-Abelló (Madrid, Spain) for SPT. All measurement of serum specific IgE were performed using an ImmunoCAP 250 system (ThermoFisher Scientific, Uppsala, Sweden), following the manufacturer's instructions. As in other EuroPrevall centres (29), serum IgE to twenty-five foods were determined (Figure 1). The sera were first tested on five mixtures (two commercially available and three custom-made). Samples testing positive (≥ 0.35 kU_A/L) to a mix was tested on the individual foods of that mix. Additional serum specific IgE measurements or SPT were performed because such foods were perceived to be of local

importance as described previously. We also measured serum specific IgE against the common environmental aeroallergens including house dust mite, cat, birch, grass, mugwort, and *Parietaria* pollen. Ethical approval was given by the relevant ethical review board in all participating centers. A positive response in replying to the initial screening questionnaire was taken to imply consent to the subsequent case-control study if they were selected. Written informed consents were obtained from the parents or legal guardians prior to subsequent clinical studies including SPTs and blood testing. Less than 2% of the questionnaires had one or more missing data, we then contacted the parents or guardians to provide answers to the missing variables. The case-control questionnaires were done face-to-face and there was no missing data. Only 6 cases (0.3%) and 11 controls (0.7%) were unable to provide sera for IgE measurements.

Statistical analyses

For the determination of clinically relevant sensitization and probable food allergy, positive serum specific IgE was defined as ≥ 0.7 kU_A/L, and positive SPT was defined as a weal size of ≥ 3 mm after subtraction of the negative control. “Probable food allergy” was defined as reporting allergic symptoms within 2 hours of ingestion plus the presence of serum specific IgE and/or positive SPT to that specific food. The prevalence rates of IgE sensitization and probable food allergy in each population or subgroup were estimated as the prevalence rates of those specific food among the ‘cases’ and ‘controls’ weighted back

to the population participating in the initial screening survey. We used R (R Foundation for Statistical Computing, version 3.4.3) for all statistical analyses. The 95% confidence intervals of the prevalence rates were calculated based on the pooled variance of the outcomes of the case-control samples in each population group. A *P*-value of <0.05 was considered significant.

RESULTS

Overall, 35,549 children took part in the screening survey, of whom 2,891 participated in the second stage of case-control study. Tables 1 summarises the demographic characteristics of the study population and the prevalence of parental reported adverse food reactions. The participation rates were very high ranging from 91% in Hong Kong to almost 100% in Russia and India. The prevalence of reporting adverse reaction to food at least once in the subjects' lifetime varied widely from the highest of 38% in Russia to the lowest of 1.8% in India. The reported prevalence rates were similar among the three centers from China. Table 2 shows the number of subjects recruited in the subsequent case-control study along with their demographic information. As the number of subjects reported to have adverse food reactions was very low in India, we recruited more control subjects for comparison in the subsequent case-control study.

To give a better picture of the relationship of sensitization and food allergy, we first report the prevalence of sensitization (SPT, sIgE) and then the prevalence of food allergy in

the 5 participating centers. Table 3 shows the estimated prevalence of IgE sensitization to different foods. The prevalence rate of IgE sensitization to at least one food was highest in India (19.1%) and lowest in Guangzhou (7.0%). The most common foods associated with sensitization in Hong Kong were egg, milk, and shrimp. Hong Kong has the highest rates of sensitization against milk and egg when compared to all other centres ($P < 0.05$). With the exception of India, sensitization against peanuts was very low, ranging from 0% in Guangzhou to 2.7% in Hong Kong. Despite having a very low prevalence of reported adverse reaction to food, India has the high prevalence of IgE sensitization (19.1%) when compared to other cities. Positive sensitization against shrimp was highest in India (10.3%) and rural Shaoguan (13.1%). Table 4 shows the estimated prevalence of sensitization to different foods in the participating centres by SPT. Although the overall rates of positive SPT were much lower than those of IgE sensitization, the SPT results are in line with those of IgE sensitization with the highest rate in Shaoguan and India (Table 3).

Using the predefined criteria, the prevalence of probable food allergy was highest in Hong Kong (1.50%; 95% CI: 1.23-1.84) and the rate was significantly higher than the two other Chinese centers, Guangzhou and Shaoguan (Table 5). Tables E1 and E2 show the prevalence of IgE sensitizations and probable food allergy if the lower cut-off of specific IgE (≥ 0.35 kU_A/L) was used. In Russia, in addition to fish, probable food allergies for fruits and vegetables such as apple, peach, carrot, and tomato were significantly higher than the other centers as these plant allergies are non-existent in China or India. The prevalence rate of probable food allergy was intermediate in Guangzhou and was lowest in India despite having very high rates of IgE sensitization. Among the 6194 participants from

Hong Kong, 5015 were born and raised in Hong Kong while 1049 were born in mainland China and subsequently migrated to Hong Kong. The rest were born outside of mainland China and Hong Kong. Among those born in mainland China, their mean $\pm$ SD age of migration to Hong Kong was 4.9 ± 2.9 years. When compared with children born in mainland China, those born and raised in Hong Kong were 4 times more likely to be sensitized against at least one food as measured by serum specific IgE (Table 6). IgE sensitization against most food allergens including egg, milk, fish, and shrimp were all more common in children who were born and raised in Hong Kong ($P < 0.01$). As shown in Table 7, the prevalence of probable food allergy in those born in Hong Kong was 1.68% while the rate for those born in mainland China was only 0.48% ($P < 0.01$). Table 8 shows the prevalence of IgE sensitization against common aeroallergens in the three participating countries. House dust mite sensitization was very high in Hong Kong (66.3%) while birch sensitization was highest in India (14.3%) and Russia (3.7%).

DISCUSSION

Using the standardized EuroPrevall methodologies, we have conducted the first comparative study of food allergies in children from China, India and Russia. Both rural and urban children were successfully recruited for study and the participation rates were extremely high. We documented a wide variation in the rates of sensitization to different foods. The results showed that the prevalence of probable food allergies were higher in children from the highly urbanized city of Hong Kong when compared to regions of lesser

degree of urbanization such as the participating cities in Russia and India. However, the prevalence of sensitization alone cannot be adequately explained by the difference in levels of urbanization among the study centers. The strength of this study is the use of standardized and objective methodology in a large sample of children. Participation rates were very high (91- 99%) with little missing values.

Among the different Chinese populations, we have documented that the prevalence of childhood asthma was highest in Hong Kong when compared to children from mainland China. In a large study with more than 10,000 participants from three Chinese cities, we confirmed that environmental and dietary factors could explain the disparity of asthma prevalence among Chinese children from different cities (17). The results of the current studies are in line with data on asthma epidemiology, children from Hong Kong have the highest rates of probable food allergies when compared with children from mainland China. Early life exposures most likely have significant effects on the early immune system affecting the subsequent development of food sensitization and food allergy as children born in mainland China and migrated to Hong Kong had much lower prevalence of food sensitization and allergies when compared to children who were born and raised in Hong Kong. These results corroborate with our previous studies that children born and raised in Hong Kong had significantly higher prevalence of wheeze in the past year (1.6 times) and symptom of rhinoconjunctivitis in the past year (1.3 times) when compared with children born in mainland China and migrated to Hong Kong subsequently (30). The numbers of children recruited from the two Indian cities were relatively small and the occurrence of probable food allergy was also very low in India such that we do not have enough statistical

power to detect possible differences among children from the urban centre of Bangalore and the less developed city of Mysore.

IgE mediated food allergy is common affecting both children and adults in developed countries. Recent literature also suggested that the prevalence of food allergy is increasing in the western world. Data from national databases in England and Wales revealed significant increase in the hospital admissions of anaphylaxis (8). Hospitalization data of anaphylaxis and other severe allergic reactions have also increased in the US Australia (8,9). In Australia, the increase was particular steep in children under 5 years and there has been a 5.5-fold increase of hospitalisation rate for food induced anaphylaxis in this age group (31). One of the major areas of allergy research has been allergies to peanuts. These allergies are commonly associated with food induced anaphylaxis and the disease in a large proportion of these patients with peanut allergy tends to persist into adulthood (32). Despite possible exposure to peanuts as a common ingredient in different foods among Indian and Chinese children, peanut allergy was very uncommon. Peanut consumption in the form of boiled peanuts and the use of peanut oil are common in Southern China. A comparative study revealed that the prevalence of peanut allergy among Jewish children in the United Kingdom was 10-fold higher than that of Jewish children from Israel (33). Their findings suggested that high consumption of peanuts in early life might be an important factor explaining the difference. A recent randomised control trial of high risk UK infants confirmed that frequent peanut consumption from infancy to 5 years of age could reduce the risk of peanut allergy (34). Another study from Australia also documented that the prevalence of challenge proven peanut allergy in Asian children born

in Australia was three times higher than that of children with parents born in Australia (35). This argues against the notion that Asian children have lower genetic risk in developing peanut allergy. Summing up these findings and our findings in Chinese children, environmental exposures including factors related to the timing and amount of peanut consumption are likely to be crucial in protecting the subsequent development of peanut allergy in the Chinese population. Similar to peanut exposure, cow's milk and egg are usually introduced around 4 to 6 months as protein sources when Chinese infants are weaned off breast milk. Such early exposure may also contribute to the low prevalence of cow's milk and egg allergy in this population. Furthermore, among the Chinese children who are sensitized to cow's milk, the majority (96%) of them have low levels of sensitization ($<3.5\text{kU}_A/\text{L}$). Although 6.7% of the children from Hong Kong were sensitized to cow's milk, very few of them had cow's milk allergy as such low level of sensitization is usually not associated with true milk allergy.

The patterns of food sensitization and food allergy in Russia were very different from those of China. Sensitizations and probable food allergy to hazelnut, fruits and vegetables such as apples, carrot, tomato, and peach were rather common in Russia. Such fruit and vegetable allergies may be related to cross reactivity to birch pollen in Russian children (36). In our study, birch sensitization as reflected by positive specific IgE in Russian children was 6 times higher than that in children from Hong Kong (Table 8). However, the high rate of sensitization to birch in Indian children did not translate into high prevalence of allergies against fruits and vegetables.

Children from India had very low prevalence of food allergy despite of their high rates of sensitization. Such findings were similar to our recent reported results in adults from India (37). Additional factors other than IgE sensitization must be important for clinical food allergies to develop. In contrast with epidemiological data from Western countries, the prevalence rates of shrimp allergy and IgE sensitization were found to be very high in Chinese children. A recent questionnaire based study conducted in Singapore also suggested that the prevalence of shrimp allergy was higher among Asian children when compared with expatriate children of other racial groups (38). There is accumulating evidence suggesting that shellfish allergy may be related to dust mite allergy. Early studies suggested that primary sensitizing agent might be tropomyosin found in dust mites, while recent molecular studies revealed that α -actinin and arginine kinase could also be responsible for the cross reactivity between mite and shrimp allergy (39). Our epidemiological data from the Chinese centres corroborated with these findings. In a large series of patients presented to an emergency department in Hong Kong with anaphylaxis, seafood was found to be the most common precipitating factor responsible for 71% of all food induced anaphylaxis (40). In our studies, we have also measured serum specific IgE against dust mite in addition to food specific IgE, the prevalence rates of mite sensitization (ImmunoCap, Thermofisher, Sweden) were 65.4 % in Hong Kong, 30.1% in Guangzhou, 23.0% in Shaoguan, 18.2% in India, and only 8.4% in Russia. We have repeatedly documented very high prevalence of mite sensitization in Chinese school children from Hong Kong and Guangzhou (17,41). Such high prevalence rate of mite sensitization may be one of the reasons resulting in the high prevalence of shrimp allergy in Chinese children. There are other possible reasons for the high prevalence of shrimp allergy. Exposure to

cockroach or exposure to shrimp allergen through skin contact may also result in subsequent sensitization leading to manifestation of shrimp allergy (42). Detailed studies of our shrimp allergic individuals are needed to determine if dust mite proteins may be the primary sensitizing agents for these patients or if other possible mechanisms may explain their shrimp allergy.

This study has several limitations. Although we have use objective assessment including SPT and IgE measurements to determine sensitization in addition to symptoms after ingestion of a specific food, it was not possible for us to conduct food challenges in all subjects with suspected food allergy to confirm “true” food allergy. The true prevalence rates of food allergies are likely to be even lower than our reported rates of probable food allergy. Geographically, the three participating countries are very large. We have only sampled a small number of cities. There are marked regional differences regarding environmental exposures and dietary habits in different regions of these three countries such that data from the participating cities may not reflect all the regional variations within the participating countries. Furthermore, only a relatively small number of Indian children were recruited. According to our questionnaire data on dietary habits, approximately 60% of the Indian children were vegetarians who do not eat egg or meat. The absence of many foods in their vegetarian diet is likely one of the major reasons for their low rate of sensitization and food allergy. Non-vegetarian children from other regions of India most likely have different patterns of sensitization and food allergy.

In conclusion, this is the most comprehensive study of food allergy in large randomly selected samples of children using a standardised approach along with objective measurement of food specific sensitization recruited from China, Russia and India. Compared with developed countries, food allergy is much less common in these three countries and the prevalence of food allergy appears to increase with the level of urbanization with the highest prevalence in Hong Kong. Despite the high rate of IgE sensitization in rural China and India, the prevalence of food allergies was very low highlighting that other factors in addition to sensitization are needed for inducing clinical manifestations of food allergies. Our earlier analysis showed that serological markers of orofecal infections such as hepatitis A and salmonella were not associated with food allergen sensitization (43). Using the big data approach such as the current study, we can further evaluate the possible role of lifestyle factors as well as dietary exposures in the development of food allergy in children.

Contributors:

GWKW, JL, LMO, PAM, MFR, ENCM, IK, RVR, MY, PGJB were involved in the study concept and design. TFL, MHW, OF, and JP were involved in the acquisition and analysis of the data. All authors were involved in the interpretation of the data. GWKW and JL drafted the manuscript, and all authors critically revised in every step of the revision process. GWKW, MHW, and JP did the statistical analysis. GWKW and PGJB are the guarantors.

Funding

This work was funded by the EU through EuroPrevall (FP6- FOOD-CT-2005-514000), HK Research Grant Council CUHK GRF477110, Specific Funds of Chinese Medical Association for Clinical Research (08020510129), National Natural Science Foundation of China (81261130023) and China Postdoctoral Science Foundation (2014M552186), TS Lo Foundation. The study sponsors had no role in the study design, data collection, analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The authors had the responsibility to write and submit the paper for publication. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The authors wish to thank all the subjects and their parents in taking part in the EuroPrevall-INCO surveys. We also like to acknowledge the generous supply of food allergen extracts for skin-prick test by ALK-Abelló (Madrid, Spain). We also thank Lucia Jimeno and Domingo Barber of ALK-Abelló (Madrid, Spain) for preparation of the allergen extracts. We also thank Jonas Lidholm, Asa Marknell DeWitt, Caroline Pettersson, and Hakan Molander (Phadia, Uppsala) for their development of the custom food mix IgE tests.

REFERENCES

1. Eggesbo M. The prevalence of CMA/CMPI in young children. *Allergy* 2001;56;393–402.

2. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;16;567–573.
3. Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 2004;34;1534–1541.
4. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110;784–789.
5. Wong GW. Epidemiology: international point of view, from childhood to adults, food allergens. *Chem Immunol Allergy* 2015;101:30-37.
6. Rinaldi M, Harnack L, Oberg C, Schreiner P, St Sauver J, Travis LL. Peanut allergy diagnoses among children residing in Olmsted County, Minnesota. *J Allergy Clin Immunol* 2012;130:945-50.
7. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, Pumphrey R, Boyle RJ. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol* 2015;135:956-963.
8. Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990 -2006. *Ann Allergy Asthma Immunol* 2008 ;10:387-93.
9. Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol* 2015;136:367-375.
10. Gupta RS, Springston EE, Warriar MR, Smith B, Kumar R, Pongracic J, Holl JL. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9-17.
11. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638-646.
12. Mills EN, Mackie AR, Burney P, Beyer K, Frewer L, Madsen C et al. The prevalence, cost and basis of food allergy across Europe. *Allergy* 2007;62:717-722.

13. Leung TF, Yung E, Wong YS, Lam CW, Wong GW. Parent-reported adverse food reactions in Hong Kong Chinese pre-schoolers: epidemiology, clinical spectrum and risk factors. *Pediatr Allergy Immunol* 2009;20:339-346.
14. Chiang WC, Kidon MI, Liew WK, Goh A, Tang JP, Chay OM. The changing face of food hypersensitivity in an Asian community. *Clin Exp Allergy* 2007;37:1055-1061.
15. Kim JS, Ouyang F, Pongracic JA, Fang Y, Wang B, Liu X et al. Dissociation between the prevalence of atopy and allergic disease in rural China among children and adults. *J Allergy Clin Immunol* 2008;122:929-935.
16. Oh JW, Pyun BY, Choung JT, Ahn KM, Kim CH, Song SW et al. Epidemiological change of atopic dermatitis and food allergy in school-aged children in Korea between 1995 and 2000. *J Korean Med Sci* 2004;19:716-723.
17. Wong GW, Ko FW, Hui DS, Fok TF, Carr D, von Mutius E, Zhong NS, Chen YZ, Lai CK. Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey. *BMJ* 2004;329:486-489.
18. Wong GW, Mahesh PA, Ogorodova L, Leung TF, Fedorova O, Holla AD, Fernandez-Rivas M, Clare Mills EN, Kummeling I, van Ree R, Yazdanbakhsh M, Burney P. The EuroPrevall-INCO surveys on the prevalence of food allergies in children from China, India and Russia: the study methodology. *Allergy* 2010;65:385-390.
19. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-960.
20. Woods RK, Abramson M, Bailey M, Walters EH. International prevalences of reported food allergies and intolerances. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991-1994. *Eur J Clin Nutr* 2001;55:298-304.
21. Dey D, Ghosh N, Pandey N, Gupta Bhattacharya S. A hospital-based survey on food allergy in the population of Kolkata, India. *Int Arch Allergy Immunol* 2014;164:218-221.
22. Eriksson NE, Möller C, Werner S, Magnusson J, Bengtsson U, Zolubas M. Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia. *J Invest Allergol Clin Immunol* 2004;14:70-79.

23. Downs SH, Marks GB, Mitakakis TZ, L  ppli JD, Car NG, Peat JK. Having lived on a farm and protection against allergic diseases in Australia. *Clin Exp Allergy* 2001;31:570-575.
24. von Ehrenstein OS, von Mutius E, Illi S, Baumann L, B  hm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000;30:187-193.
25. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever asthma and allergic sensitization. *Clin Exp Allergy* 2000;30:194-200.
26. Yu M, Jing Z, Han ZR, Chen YZ, Leung TF, Wong GWK. Very low prevalence of asthma and allergies in schoolchildren from rural Beijing, China. *Pediatr Pulmonol* 2009;44:793-799
27. Elliott AM, Mpairwe H, Quigley MA, Nampijja M, Muhangi L, Oweka-Onyee J et al. Helminth infection during pregnancy and development of infantile eczema. *JAMA* 2005;294:2032-2034.
28. Wong GW, Chow CM. Childhood asthma epidemiology: insights from comparative studies of rural and urban populations. *Pediatr Pulmonol* 2008;43:107-116.
29. Kummeling I, Mills EN, Clausen M, Dubakiene R, P  rez CF, Fern  ndez-Rivas M et al. The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology. *Allergy* 2009;64:1493-1497.
30. Wong GW, Leung TF, Ko FW, Lee KK, Lam P, Hui DS, Fok TF, Lai CK. Declining asthma prevalence in Hong Kong Chinese schoolchildren. *Clin Exp Allergy* 2004;34:1550-1555.
31. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *J Allergy Clin Immunol* 2007;120:878-884.
32. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, Lowe A, Tang ML, Gurrin LC; HealthNuts Study. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. *J Allergy Clin Immunol* 2015;135:1257-1266.
33. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, Fox AT, Turcanu V, Amir T, Zadik-Mnuhin G, Cohen A, Livne I, Lack G. Early consumption of

- peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-991.
34. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, Turcanu V, Sever ML, Gomez Lorenzo M, Plaut M, Lack G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-813.
 35. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, Dharmage SC, Allen KJ; HealthNuts Study Group. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 2014;69:1639-1647.
 36. Ballmer-Weber BK, Hoffmann-Sommergruber K. Molecular diagnosis of fruit and vegetable allergy. *Curr Opin Allergy Clin Immunol* 2011;11:229-235.
 37. Mahesh PA, Wong GW, Ogorodova L, Potts J, Leung TF, Fedorova O, Holla AD, Fernandez-Rivas M, Clare Mills EN, Kummeling I, Versteeg SA, van Ree R, Yazdanbakhsh M, Burney P. Prevalence of food sensitization and probable food allergy among adults in India: the EuroPrevall INCO study. *Allergy* 2016;71:1010-9.
 38. Shek LP, Cabrera-Morales EA, Soh SE, Gerez I, Ng PZ, Yi FC, Ma S, Lee BW. A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations. *J Allergy Clin Immunol* 2010;126:324-331.
 39. Gámez C, Zafra M, Boquete M, Sanz V, Mazzeo C, Ibáñez MD, Sánchez-García S, Sastre J, del Pozo V. New shrimp IgE-binding proteins involved in mite-seafood cross-reactivity. *Mol Nutr Food Res* 2014 ;58:1915-1925.
 40. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med* 2005;28:381-388.
 41. Li J, Wang H, Chen Y, Zheng J, Wong GW, Zhong N. House dust mite sensitization is the main risk factor for the increase in prevalence of wheeze in 13- to 14-year-old schoolchildren in Guangzhou city, China. *Clin Exp Allergy* 2013;43:1171-1179.
 42. Yang Z, Zhao J, Wei N, Feng M, Xian M, Shi X, Zheng Z, Su Q, Wong GWK, Li J. Cockroach is a major cross-reactive allergen source in shrimp-sensitized rural children in southern China. *Allergy* 2018;73:585-592.

43. Janse JJ, Wong GW, Potts J, Ogorodova LM, Fedorova OS, Mahesh PA, Sakellariou A, Papadopoulos NG, Knulst AC, Versteeg SA, Kroes AC, Vossen AC, Campos Ponce M, Kummeling I, Burney P, van Ree R, Yazdanbakhsh M. The association between foodborne and orofecal pathogens and allergic sensitisation - EuroPrevall study. *Pediatr Allergy Immunol* 2014;25:250-256.

Figure 1: Foods tested in CAP analysis

Table 1 **Demographic characteristics of subjects and prevalence of parental reports of adverse food reactions from all participating centers**

	Hong Kong	Guangzhou	Shaoguan	Tomsk	India
N	6194	5542	5139	12997	5677
Participated rate (%)	91	94	92	99	99
Males: N (%)	3004 (48)	2835 (51)	2615 (51)	6417 (47)	2914(51)
Age (years) $\pm$ SD	8.6 $\pm$ 1.6	9.3 $\pm$ 1.7	10.4 $\pm$ 2.0	8.9 $\pm$ 1.1	8.8 $\pm$ 1.5
Adverse food reaction					
at least once	734 (12%)	809 (15%)	880 (17%)	4187 (38%)	102 (1.8%)
2-4 times	269 (4.3%)	254 (4.6%)	225 (4.4%)	1964 (15%)	40 (0.7%)
>4 times	242 (3.9%)	128 (2.3%)	68 (1.3%)	1741 (13%)	56 (1.0%)

Table 2 **Number of subjects participated in the second stage case-control study**

	Hong Kong	Guangzhou	Shaoguan	Tomsk	India
Cases:	194	189	124	652	82
Control	207	213	225	637	368
Male	211	209	183	624	230
Female	190	193	166	665	220
Age (Years)±SD	8.5±1.6	9.1±1.5	9.1±1.5	8.9±1.1	9.1±1.8

Table 3 Percentage (95% CI) of subjects with positive serum specific IgE (≥ 0.7 kU/L) to various food allergens in participating centers

	Hong Kong	Guangzhou	Shaoguan	Tomsk [95%CI]	India [95%CI]
IgE food at least 1	16.6 [15.7-17.6]	7.0 [6.3-7.7]	16.8 [15.8-17.8]	8.0 [7.6-8.5]	19.1 [18.1-20.1]
Egg	5.4 [4.9-6.0]	1.5 [1.2-1.8]	0.4 [0.3-0.7]	0.5 [0.4-0.7]	1.7 [1.4-2.1]
Milk	6.7 [6.1-7.4]	3.4 [3.0-3.9]	1.0 [0.7-1.3]	1.2 [1.1-1.4]	2.1 [1.8-2.5]
Fish	1.2 [0.9-1.5]	0.0 [0.00-0.07]	0.0 [0.00-0.07]	0.5 [0.4-0.6]	0.4 [0.3-0.6]
Shrimp	4.7 [4.2-5.3]	2.0 [1.7-2.4]	13.1 [12.2-14.0]	1.8 [1.6-2.0]	10.3 [9.5-11.1]
Crab	2.4 [2.1-2.9]	0.8 [0.6-1.1]	3.3 [2.8-3.8]	N/D	N/D
Apple	1.0 [0.8-1.3]	0.0 [0.01-0.13]	1.9 [1.6-2.4]	2.9 [2.6-3.2]	4.2 [3.7-4.7]
Peach	1.5 [1.2-1.8]	0.0 [0.00-0.07]	1.9 [1.6-2.4]	2.5 [2.3-2.8]	5.0 [4.5-5.6]
Mango	1.5 [1.2-1.8]	0.0 [0.00-0.07]	2.0 [1.7-2.5]	N/D	N/D
Melon	1.5 [1.2-1.8]	0.0 [0.00-0.07]	2.0 [1.7-2.5]	0.9 [0.8-1.1]	6.7 [6.1-7.4]
Banana	3.1 [2.7-3.6]	0.5 [0.3-0.7]	2.8 [2.4-3.3]	1.7 [1.5-1.9]	5.0 [4.5-5.6]
Kiwi	3.3 [2.9-3.8]	1.0 [0.8-1.3]	1.9 [1.6-2.4]	1.6 [1.4-1.9]	5.5 [4.9-6.1]
Tomato	2.0 [1.7-2.4]	0.0 [0.00-0.07]	2.5 [2.1-3.0]	1.6 [1.4-1.8]	7.5 [6.9-8.3]
Carrot	1.5 [1.3-1.9]	0.0 [0.00-0.07]	2.0 [1.7-2.5]	2.5 [2.2-2.7]	6.7 [6.1-7.4]
Celery	1.0 [0.8-1.3]	0.0 [0.00-0.07]	2.0 [1.7-2.5]	2.2 [1.9-2.4]	5.9 [5.3-6.5]
Hazelnut	1.6 [1.3-1.9]	0.0 [0.00-0.07]	2.0 [1.6-2.4]	3.2 [2.9-3.5]	3.8 [3.3-4.3]
Walnut	1.0 [0.8-1.3]	0.0 [0.00-0.07]	2.1 [1.7-2.5]	0.7 [0.5-0.8]	4.2 [3.7-4.8]
Mustard	0.1 [0.07-0.26]	0.0 [0.00-0.07]	1.0 [0.8-1.3]	0.9 [0.8-1.1]	3.3 [2.9-3.8]
Poppy	0.1 [0.05-0.21]	0.0 [0.00-0.07]	2.0 [1.7-2.5]	1.1 [1.0-1.3]	5.9 [5.3-6.5]
Sunflower	1.6 [1.3-1.9]	0.0 [0.00-0.07]	2.0 [1.6-2.4]	1.0 [0.9-1.2]	5.5 [4.9-6.1]
Sesame	2.2 [1.9-2.6]	0.0 [0.01-0.13]	3.3 [2.8-3.8]	2.3 [2.0-2.6]	8.0 [7.3-8.7]
Peanut	2.7 [2.3-3.1]	0.0 [0.01-0.13]	2.4 [2.0-2.8]	1.6 [1.4-1.9]	6.3 [5.7-7.0]
Soya	2.9 [2.5-3.3]	0.0 [0.00-0.07]	2.0 [1.6-2.4]	1.2 [1.0-1.4]	5.4 [4.9-6.1]
Lentils	0.7 [0.5-1.0]	0.0 [0.00-0.07]	2.4 [2.0-2.9]	1.6 [1.4-1.8]	4.7 [4.2-5.3]
Buckwheat	2.0 [1.7-2.4]	0.0 [0.00-0.07]	2.8 [2.4-3.3]	0.9 [0.8-1.1]	7.5 [6.9-8.3]
Rice	2.1 [1.7-2.4]	0.0 [0.00-0.07]	2.8 [2.4-3.3]	1.2 [1.0-1.4]	5.4 [4.9-6.1]
Corn	2.5 [2.1-2.9]	0.0 [0.01-0.13]	1.9 [1.6-2.4]	1.4 [1.2-1.6]	5.9 [5.3-6.5]
Wheat	3.4 [3.0-3.9]	0.0 [0.00-0.07]	2.0 [1.7-2.5]	1.6 [1.4-1.9]	6.7 [6.1-7.4]

N/D = not done

Table 4 Percentage [95% CI] of subjects with positive skin-prick test in participating centers

	Hong Kong	Guangzhou	Shaoguan	Tomsk	India
Food at least 1	3.04 [2.64-3.50]	3.19 [2.76-3.69]	8.58 [7.84-9.37]	4.11 [3.78-4.47]	4.48 [3.97-5.05]
Egg	0.09 [0.04-0.20]	0.00 [0.00-0.07]	0.04 [0.01-0.15]	0.52 [0.41-0.66]	0.10 [0.05-0.23]
Milk	0.04 [0.01-0.14]	0.00 [0.00-0.07]	0.48 [0.33-0.71]	0.21 [0.15-0.31]	1.35 [1.08-1.68]
Fish	0.22 [0.13-0.37]	0.00 [0.00-0.07]	0.04 [0.01-0.15]	0.91 [0.76-1.08]	N/D
Shrimp	2.43 [2.07-2.84]	1.14 [0.89-1.45]	4.53 [3.99-5.13]	N/D	N/D
Crab	0.94 [0.73-1.21]	1.31 [1.04-1.65]	5.06 [4.49-5.69]	N/D	N/D
Mussel	0.04 [0.01-0.14]	0.92 [0.70-1.21]	0.22 [0.13-0.40]	N/D	N/D
Beef	0.09 [0.04-0.20]	0.00 [0.00-0.07]	0.13 [0.06-0.28]	N/D	N/D
Apple	0.09 [0.04-0.20]	0.00 [0.00-0.07]	0.04 [0.01-0.15]	0.29 [0.21-0.40]	0.34 [0.22-0.52]
Peach	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.48 [0.33-0.71]	N/D	N/D
Mango	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.53 [0.37-0.77]	N/D	N/D
Melon	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.10 [0.06-0.17]	0.03 [0.01-0.11]
Orange	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	N/D	1.01 [0.78-1.30]
Banana	N/D	N/D	N/D	N/D	0.36 [0.24-0.56]
Jackfruit	N/D	N/D	N/D	N/D	2.46 [2.09-2.89]
Tomato	0.04 [0.01-0.14]	0.44 [0.30-0.66]	0.00 [0.00-0.07]	0.12 [0.07-0.19]	0.36 [0.24-0.56]
Carrot	N/D	N/D	N/D	1.17 [1.00-1.37]	N/D
Eggplant	N/D	N/D	N/D	N/D	1.05 [0.82-1.35]
Hazelnut	0.04 [0.01-0.14]	0.00 [0.00-0.07]	0.04 [0.01-0.15]	0.54 [0.43-0.68]	N/D
Walnut	0.04 [0.01-0.14]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	N/D	N/D
Mustard	N/D	N/D	N/D	N/D	0.36 [0.24-0.56]
Sunflower	N/D	N/D	N/D	0.14 [0.09-0.22]	0.36 [0.24-0.56]
Peanut	0.26 [0.16-0.43]	0.44 [0.30-0.66]	0.53 [0.36-0.77]	1.23 [1.05-1.43]	0.08 [0.03-0.19]
Soybean	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.46 [0.36-0.59]	0.67 [0.49-0.92]
Lentil	N/D	N/D	N/D	N/D	0.05 [0.02-0.15]
Chickpea	N/D	N/D	N/D	N/D	0.08 [0.03-0.19]
Wheat	0.04 [0.01-0.14]	0.04 [0.01-0.13]	0.09 [0.04-0.22]	0.34 [0.26-0.46]	0.67 [0.49-0.92]

*N/D = not done

Table 5 Probable food allergy as defined by reported symptoms and positive SPT/IgE (≥ 0.7 kU/L) to the specific food (% [95% CI]) in different centers

	Hong Kong	Guangzhou	Shaoguan	Tomsk	India
At least one food	1.50 [1.23-1.84]	0.21 [0.12-0.38]	0.69 [0.50-0.95]	0.87 [0.73-1.05]	0.14 [0.07-0.27]
Egg	0.20 [0.11-0.34]	0.04 [0.01-0.13]	0.00 [0.00-0.07]	0.10 [0.06-0.17]	0.05 [0.02-0.16]
Milk	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.04 [0.01-0.15]	0.05 [0.02-0.11]	0.00 [0.00-0.07]
Fish	0.20 [0.11-0.34]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.34 [0.25-0.45]	0.00 [0.00-0.07]
Shrimp	1.05 [0.82-1.33]	0.18 [0.10-0.33]	0.65 [0.46-0.90]	0.02 [0.00-0.06]	0.00 [0.00-0.07]
Crab	0.20 [0.11-0.34]	0.07 [0.03-0.18]	0.43 [0.28-0.65]	-	-
Apple	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.27 [0.19-0.37]	0.00 [0.00-0.07]
Peach	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.05 [0.02-0.11]	0.00 [0.00-0.07]
Mango	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	-	-
Melon	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.03 [0.01-0.08]	0.00 [0.00-0.07]
Banana	*0.00 [0.00-0.06]	*0.00 [0.00-0.07]	*0.00 [0.00-0.07]	*0.03 [0.01-0.08]	0.00 [0.00-0.07]
*Kiwi	0.07 [0.03-0.17]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.00 [0.00-0.03]	0.00 [0.00-0.07]
Tomato	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.07 [0.03-0.13]	0.00 [0.00-0.07]
Carrot	*0.00 [0.00-0.06]	*0.00 [0.00-0.07]	*0.00 [0.00-0.07]	0.15 [0.10-0.23]	*0.00 [0.00-0.07]
Eggplant	-	-	-	-	[†] 0.04 [0.01-0.14]
Hazelnut	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.05 [0.02-0.11]	0.00 [0.00-0.07]
Walnut	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	*0.03 [0.01-0.08]	*0.00 [0.00-0.07]
Sunflower	*0.00 [0.00-0.06]	*0.00 [0.00-0.07]	*0.00 [0.00-0.07]	0.03 [0.01-0.08]	0.00 [0.00-0.07]
Peanut	0.10 [0.05-0.21]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.08 [0.05-0.15]	0.03 [0.01-0.12]
Chickpea	-	-	-	-	[†] 0.03 [0.01-0.11]
Wheat	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.02 [0.00-0.06]	0.00 [0.00-0.07]

* IgE measurement only

[†] SPT only

Table 6 Percentage (95% CI) of subjects with positive IgE (≥ 0.7 kU/L): Subjects recruited from Hong Kong with birth place in Hong Kong vs mainland China

	Hong Kong	Mainland China	P	OR	[95%CI]
N	5015	1049			
At least one food	18.8% [17.8-19.9]	5.2% [4.0-6.7]	<0.001	4.3	[3.2-5.7]
Egg	5.8% [5.2-6.4]	4.4% [3.3-5.9]	0.087	1.3	[1.0-1.8]
Milk	7.8% [7.1-8.5]	0.2% [0.1-0.8]	<0.001	34.7	[10.1-119.7]
Fish	1.3% [1.0-1.6]	0.2% [0.1-0.8]	0.003	5.3	[1.5-18.8]
Shrimp	5.5% [4.9-6.2]	0.5% [0.2-1.1]	<0.001	12.0	[5.0-28.9]
Crab	2.9% [2.4-3.4]	0.0% [0.00-0.36]	<0.001	-	
Apple	1.1% [0.9-1.5]	0.0% [0.00-0.36]	<0.001	-	
Peach	1.7% [1.4-2.1]	0.0% [0.00-0.36]	<0.001	-	
Mango	1.7% [1.4-2.1]	0.0% [0.00-0.36]	<0.001	-	
Melon	1.7% [1.4-2.1]	0.0% [0.00-0.36]	<0.001	-	
Banana	3.5% [3.1-4.1]	0.2% [0.08-0.77]	<0.001	15.1	[4.4-52.2]
Kiwi	3.9% [3.4-4.4]	0.2% [0.1-0.8]	<0.001	16.6	[4.8-57.5]
Tomato	2.3% [1.9-2.7]	0.0% [0.00-0.36]	<0.001	-	
Carrot	1.8% [1.4-2.2]	0.0% [0.00-0.36]	<0.001	-	
Celery	1.2% [0.9-1.5]	0.0% [0.00-0.36]	<0.001	-	
Hazelnut	1.8% [1.5-2.2]	0.2% [0.1-0.8]	<0.001	7.6	[2.2-26.5]
Walnut	1.2% [0.9-1.5]	0.0% [0.00-0.36]	<0.001	-	
Mustard	0.1% [0.06-0.28]	0.0% [0.00-0.36]	0.242	-	
Poppy	0.1% [0.03-0.21]	0.0% [0.00-0.36]	0.34	-	
Sunflower	1.7% [1.4-2.1]	0.2% [0.1-0.8]	<0.001	7.2	[2.1-25.2]
Sesame	2.5% [2.1-3.0]	0.2% [0.1-0.8]	<0.001	10.6	[3.1-36.9]
Peanut	3.1% [2.6-3.6]	0.0% [0.00-0.36]	<0.001	-	
Soya	3.4% [2.9-3.9]	0.0% [0.00-0.36]	<0.001	-	
Lentils	0.8% [0.6-1.1]	0.0% [0.00-0.36]	0.004	-	
Buckwheat	2.3% [2.0-2.8]	0.0% [0.00-0.36]	<0.001	-	
Rice	2.4% [2.0-2.8]	0.0% [0.00-0.36]	<0.001	-	
Corn	2.9% [2.4-3.4]	0.0% [0.00-0.36]	<0.001	-	
Wheat	4.0% [3.5-4.5]	0.0% [0.00-0.36]	<0.001	-	

**Table 7 Subjects recruited from Hong Kong with probable food allergy (percentage with 95% CI):
Birth place in Hong Kong vs mainland China**

	Hong Kong	Mainland China			
	5015	1049	P	OR	[95% CI]
Probable food allergy	1.68% [1.32-2.08]	0.48% [0.21-1.12]	0.003	3.53	[1.44-8.67]
Shrimp	1.21% [0.94-1.55]	0.24% [0.08-0.77]	0.005	5.07	[1.44-17.84]
Crab	0.26% [0.15-0.44]	0.00% [0.00-0.36]	0.100	-	
Fish	0.13% [0.06-0.27]	0.24% [0.08-0.77]	0.387	-	
Egg	0.26% [0.15-0.44]	0.00% [0.00-0.36]	0.100	-	
Milk	0.00% [0.00-0.08]	0.00% [0.00-0.36]	-	-	
Peanut	0.13% [0.06-0.27]	0.00% [0.00-0.36]	0.245	-	
Kiwi	0.09% [0.03-0.21]	0.00% [0.00-0.36]	0.343	-	

Prevalence of probable allergy of the other foods was zero and was not listed in this table.

Table 8 Prevalence of aero-allergen sensitization (specific IgE $\geq$ 0.7kU/L), percentage positive (95% CI)

	Hong Kong	Guangzhou	Shaoguan	Tomsk	India
At least 1 Aeroallergen	66.3 [65.1-67.4]	30.6 [29.4-31.9]	26.7 [25.5-27.9]	13.6 [13.0-14.2]	26.2 [25.1-27.3]
HDM	65.4 [64.2-66.5]	30.1 [28.9-31.3]	23.0 [21.8-24.1]	8.4 [7.9-8.8]	18.2 [17.2-19.2]
Cat	9.0 [8.4-9.8]	3.4 [3.0-3.9]	0.1 [0.03-0.21]	5.4 [5.0-5.8]	11.8 [11.0-12.7]
Grass	2.1 [1.7-2.4]	0.5 [0.3-0.7]	2.9 [2.5-3.4]	2.5 [2.2-2.8]	18.4 [17.4-19.5]
Mugwort	1.1 [0.9-1.4]	0.2 [0.12-0.38]	3.7 [3.2-4.3]	3.3 [3.0-3.6]	15.9 [15.0-16.9]
Birch	0.6 [0.4-0.8]	0.0 [0.01-0.13]	2.0 [1.7-2.5]	3.7 [3.4-4.1]	14.3 [13.4-15.2]
Parietaria	1.6 [1.3-1.9]	0.1 [0.03-0.18]	2.0 [1.7-2.5]	1.7 [1.5-2.0]	16.1 [15.2-17.1]

Table E1 Percentage (95% CI) of subjects with positive serum specific IgE (≥ 0.35 kU/L) to various food allergens in different centers

	Hong Kong	Guangzhou	Shaoguan	Tomsk [95%CI]	India [95%CI]
IgE food at least 1	29.4 [28.3-30.6]	14.7 [13.8-15.7]	25.8 [24.6-27.0]	13.2 [12.7-13.8]	28.4 [27.3-29.6]
Egg	14.1 [13.2-14.9]	6.3 [5.7-7.0]	3.9 [3.4-4.4]	2.4 [2.1-2.6]	4.2 [3.7-4.8]
Milk	14.6 [13.7-15.5]	7.2 [6.6-7.9]	1.9 [1.6-2.3]	3.7 [3.4-4.0]	4.3 [3.8-4.8]
Fish	1.7 [1.4-2.1]	0.0 [0.01-0.13]	0.0 [0.00-0.07]	0.8 [0.6-0.9]	0.4 [0.3-0.6]
Shrimp	7.2 [6.5-7.8]	3.1 [2.7-3.6]	19.2 [18.2-20.3]	2.6 [2.4-2.9]	14.6 [13.7-15.6]
Crab	5.8 [5.2-6.4]	1.5 [1.2-1.8]	5.3 [4.7-5.9]	N/D	N/D
Apple	2.6 [2.2-3.0]	0.0 [0.01-0.13]	2.0 [1.7-2.5]	3.4 [3.1-3.8]	7.9 [7.3-8.7]
Peach	2.7 [2.4-3.2]	0.0 [0.00-0.07]	2.4 [2.0-2.9]	3.4 [3.1-3.7]	8.8 [8.1-9.5]
Mango	2.2 [1.9-2.6]	0.5 [0.3-0.7]	3.0 [2.6-3.5]	N/D	N/D
Melon	2.5 [2.1-2.9]	0.0 [0.00-0.07]	3.0 [2.5-3.5]	1.6 [1.4-1.8]	10.5 [9.7-11.3]
Banana	6.2 [5.6-6.8]	2.4 [2.0-2.8]	4.2 [3.7-4.8]	3.9 [3.6-4.3]	10.5 [9.7-11.3]
Kiwi	6.2 [5.6-6.8]	1.0 [0.8-1.3]	2.9 [2.5-3.4]	3.1 [2.9-3.5]	9.6 [8.9-10.4]
Tomato	2.7 [2.3-3.1]	0.0 [0.00-0.07]	3.4 [2.9-3.9]	2.6 [2.3-2.8]	10.9 [10.1-11.8]
Carrot	1.8 [1.5-2.2]	0.0 [0.00-0.07]	3.4 [2.9-3.9]	3.0 [2.7-3.3]	10.5 [9.7-11.3]
Celery	2.1 [1.8-2.5]	0.0 [0.00-0.07]	3.4 [2.9-3.9]	2.8 [2.5-3.1]	10.0 [9.3-10.8]
Hazelnut	2.2 [1.9-2.6]	0.0 [0.00-0.07]	2.5 [2.1-3.0]	3.7 [3.4-4.1]	8.0 [7.3-8.7]
Walnut	2.1 [1.7-2.4]	0.0 [0.00-0.07]	3.1 [2.6-3.6]	1.2 [1.1-1.4]	7.2 [6.5-7.9]
Mustard	2.0 [1.7-2.4]	0.0 [0.01-0.13]	2.5 [2.1-3.0]	1.5 [1.3-1.7]	5.1 [4.5-5.7]
Poppy	1.7 [1.4-2.0]	0.0 [0.00-0.07]	3.4 [2.9-3.9]	1.6 [1.4-1.8]	8.8 [8.1-9.6]
Sunflower	2.3 [1.9-2.7]	0.0 [0.01-0.13]	3.8 [3.3-4.4]	2.5 [2.2-2.8]	9.6 [8.9-10.4]
Sesame	3.0 [2.6-3.5]	0.1 [0.03-0.18]	4.7 [4.2-5.3]	3.0 [2.7-3.3]	12.6 [11.8-13.5]
Peanut	3.9 [3.4-4.4]	0.1 [0.03-0.18]	3.8 [3.3-4.4]	2.8 [2.5-3.1]	9.3 [8.5-10.0]
Soya	4.0 [3.6-4.6]	0.5 [0.36-0.75]	3.3 [2.8-3.8]	2.0 [1.8-2.3]	8.4 [7.7-9.2]
Lentils	3.3 [2.8-3.7]	0.0 [0.01-0.13]	3.4 [2.9-3.9]	2.6 [2.4-2.9]	9.7 [9.0-10.5]
Buckwheat	2.7 [2.3-3.1]	0.0 [0.01-0.13]	4.2 [3.7-4.8]	2.3 [2.0-2.5]	11.7 [10.9-12.6]
Rice	2.2 [1.9-2.6]	0.0 [0.01-0.13]	4.2 [3.7-4.8]	2.4 [2.2-2.7]	10.1 [9.3-10.9]
Corn	2.7 [2.4-3.2]	0.0 [0.01-0.13]	3.8 [3.3-4.3]	2.6 [2.3-2.9]	10.1 [9.3-10.9]
Wheat	7.5 [6.9-8.2]	0.6 [0.39-0.79]	2.5 [2.1-3.0]	3.3 [3.0-3.7]	13.0 [12.2-13.9]

N/D = not done

Table E2 Probable food allergy as defined by reported symptoms and positive SPT/IgE (≥ 0.35 kU/L) to the specific food (% in population [95% CI])

	Hong Kong	Guangzhou	Shaoguan	Tomsk	India
At least one food	1.99 [1.67-2.37]	0.25 [0.15-0.42]	0.69 [0.50-0.95]	1.02 [0.86-1.21]	0.14 [0.07-0.27]
Egg	0.23 [0.14-0.38]	0.04 [0.01-0.13]	0.00 [0.00-0.07]	0.12 [0.07-0.19]	0.05 [0.02-0.16]
Milk	0.45 [0.32-0.66]	0.00 [0.00-0.07]	0.04 [0.01-0.15]	0.07 [0.03-0.13]	0.00 [0.00-0.07]
Fish	0.20 [0.11-0.34]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.34 [0.25-0.45]	0.00 [0.00-0.07]
Shrimp	1.08 [0.85-1.37]	0.21 [0.12-0.38]	0.65 [0.46-0.90]	0.02 [0.00-0.06]	0.00 [0.00-0.07]
Crab	0.20 [0.11-0.34]	0.07 [0.03-0.18]	0.43 [0.28-0.65]	-	-
Apple	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.27 [0.19-0.37]	0.00 [0.00-0.07]
Peach	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.08 [0.05-0.15]	0.00 [0.00-0.07]
Mango	0.03 [0.01-0.12]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	-	-
Melon	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.03 [0.01-0.08]	0.00 [0.00-0.07]
Banana	*0.00 [0.00-0.06]	*0.00 [0.00-0.07]	*0.00 [0.00-0.07]	*0.03 [0.01-0.08]	0.00 [0.00-0.07]
*Kiwi	0.07 [0.03-0.17]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.00 [0.00-0.03]	0.00 [0.00-0.07]
Tomato	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.07 [0.03-0.13]	0.00 [0.00-0.07]
Carrot	*0.00 [0.00-0.06]	*0.00 [0.00-0.07]	*0.00 [0.00-0.07]	0.15 [0.10-0.23]	*0.00 [0.00-0.07]
Eggplant	-	-	-	-	[†] 0.04 [0.01-0.14]
Hazelnut	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.20 [0.13-0.29]	0.00 [0.00-0.07]
Walnut	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	*0.03 [0.01-0.08]	*0.00 [0.00-0.07]
Sunflower	*0.00 [0.00-0.06]	*0.00 [0.00-0.07]	*0.00 [0.00-0.07]	0.03 [0.01-0.08]	0.00 [0.00-0.07]
Peanut	0.10 [0.05-0.21]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.08 [0.05-0.15]	0.03 [0.01-0.12]
Chickpea	-	-	-	-	[†] 0.03 [0.01-0.11]
Wheat	0.00 [0.00-0.06]	0.00 [0.00-0.07]	0.00 [0.00-0.07]	0.02 [0.00-0.06]	0.00 [0.00-0.07]

* IgE measurement only

[†] SPT only

Figure 1

Commercial mixes

CAP mix 1 (commercial, fx5): hen's egg, cow's milk, soy, peanut, wheat, fish

CAP mix 2 (commercial, fx6): sesame seed, wheat, buckwheat, corn, rice

EuroPrevall custom mixes

CAP mix 3 (custom made): hazelnut, tomato, walnut, carrot, celery

CAP mix 4 (custom made): shrimp, poppy seed, lentil, mustard, sunflower